GRADE tables for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode?

Table 70: Clinical evidence profile for comparison 1. Augmenting with cognitive and cognitive behavioural therapies versus continuing with antidepressant (+/ waitlist or attention-placebo)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with cognitive and cognitive behavioural therapies	Continuing with antidepressant (+/ waitlist or attention-placebo)	Relative (95% Cl)	Absolute	Quality	Importance
Depression symptomato by lower values)	ology endpoi	nt (follov	v-up 8-26 weeks	s; measured v	vith: Beck De	pression Invento	ory (BDI/BDI-II) o	or Hamilton Rating	Scale for	Depression	(HAMD); Bet	ter indicated
13 (Chan 2012, Chiesa 2015, Dozois 2009, Dunn 1979, Embling 2002, Kocsis 2009/ Klein 2011, Lynch 2007_study 2, Nakagawa 2017, Nakao 2018, Paykel 1999/ Scott 2000, Strauss 2012, Watkins 2011a, Wiles 2013/2016)	randomised trials	serious ¹	serious ²	no serious indirectness	serious ³	none	666	558	-	SMD 0.74 lower (1.03 to 0.45 lower)	VERY LOW	CRITICAL
Depression symptomato from baseline to endpoir					red with: Bec	k Depression In	ventory (BDI/BD	I-II) or Hamilton Ra	ting Scale	e for Depres	sion (HAMD)	change
10 (Chan 2012, Chiesa 2015, Dozois 2009, Dunn 1979, Embling 2002, Nakagawa 2017, Nakao 2018, Paykel 1999/ Scott 2000, Strauss 2012, Watkins 2011a)		serious ¹	very serious ⁴		no serious imprecision	none	265	259	-	SMD 1.36 lower (1.87 to 0.86 lower)	VERY LOW	CRITICAL
Depression symptomato	ology at 2-3 r	nonth fol	low-up (follow-	up 8-16 weeks	s; measured	with: Hamilton R	ating Scale for I	Depression (HAM-D); Better	indicated by	lower values	s)

2 (Chiesa 2015, Nakagawa 2017)	randomised trials		no serious inconsistency	no serious indirectness	serious ³	none	63	60	-	SMD 0.51 lower (0.87 to 0.15 lower)	MODERATE	CRITICAL
Depression symptomato); Better indicated by lo		nonth fo	llow-up (follow-	-up mean 4-6	months; mea	sured with: Ham	ilton Rating Scal	e for Depression (I	HAM-D)/B	eck Depress	sion Inventor	y (BDI/BDI
5 (Chiesa 2015, Dunn 1979, Nakagawa 2017, Paykel 1999/ Scott 2000, Viles 2013/2016)	randomised trials	no serious risk of bias	serious ²	no serious indirectness	serious ³	none	350	346	-	SMD 0.51 lower (0.77 to 0.24 lower)	LOW	CRITICAL
Depression symptomato	logy at 11-1	2 month	follow-up (follo	w-up 11-12 m	onths; meas	ured with: Hamilt	on Rating Scale	for Depression (H	AM-D); Be	tter indicate	ed by lower v	alues)
2 (Nakagawa 2017, Paykel 1999/ Scott 2000)	randomised trials	no serious risk of bias	very serious ⁴	no serious indirectness	serious ³	none	120	118	-	SMD 0.3 lower (0.93 lower to 0.33 higher)	VERY LOW	CRITICAL
Depression symptomato	ology at 40-m	nonth fol	low-up (follow-	up mean 40 m	onths; meas	ured with: Beck I	Depression Inve	ntory (BDI-II); Bette	r indicate	d by lower v	values)	
1 (Wiles 2013/2016)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	136	112	-	SMD 0.31 lower (0.56 to 0.06 lower)	LOW	CRITICAL
Remission (ITT) (follow- I))	up 8-26 weel	ks; asses	sed with: Num	ber of people	scoring =<7/	10 on Hamilton F	Rating Scale for I	Depression (HAM-E	0) or <10 o	on Beck Dep	pression Inve	entory (BDI
8 (Eisendrath 2016, Kocsis 2009/ Klein 2011, Lynch 2007_study 2, Nakagawa 2017, Nakao 2018, Paykel 1999/ Scott 2000, Watkins 2011a, Wiles 2013/2016)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	215/703 (30.6%)	101/590 (17.1%)	RR 1.76 (1.32 to 2.36)	130 more per 1000 (from 55 more to 233 more)	MODERATE	CRITICAL
Remission (ITT) at 3-mo	nth follow-u	o (follow	-up mean 3 moi	nths; assesse	d with: Numb	er of people sco	ring =<7 on Ham	ilton Rating Scale	for Depre	ssion (HAM	-D))	
l (Nakagawa 2017)	randomised trials		no serious inconsistency	no serious indirectness	serious ³	none	20/40 (50%)	12/40 (30%)	RR 1.67 (0.95 to 2.93)	201 more per 1000 (from 15 fewer to 579 more)	MODERATE	CRITICAL
Remission (ITT) at 6-mo Depression (HAM-D))	nth follow-u	o (follow	-up mean 6 moi	nths; assesse	d with: Numb	per of people sco	ring <10 on Bec	k Depression Inver	itory (BDI	-II)/≤7 on Ha	milton Ratin	g Scale for
2 (Nakagawa 2017, Wiles 2013/2016)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	106/274 (38.7%)	52/275 (18.9%)	RR 1.99 (1.52 to 2.62)	187 more per 1000 (from 98 more to 306 more)	MODERATE	CRITICAL

(Nakagawa 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ³	none	29/40 (72.5%)	17/40 (42.5%)	RR 1.71 (1.13 to 2.56)	302 more per 1000 (from 55 more to 663 more)	MODERATE	CRITICAL
Remission (ITT) at 40-m	onth follow-u	up (follov	v-up mean 40 n	nonths; asses	sed with: Nu	mber of people s	scoring <10 on B	eck Depression Ir	ventory (B	DI-II))		
(Wiles 2013/2016)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	38/234 (16.2%)	20/235 (8.5%)		77 more per 1000 (from 13 more to 186 more)	LOW	CRITICAL
tesponse (ITT) (follow-u Pepression Inventory (E		s; asses	sed with: Resp	onse: Numbe	r of people sl	nowing at least 5	0% improvement	on Hamilton Rat	ing Scale f	or Depressio	on (HAM-D)/I	Beck
6 (Eisendrath 2016, Vakagawa 2017, Nakao 2018, Watkins 2011a, Viles 2008, Wiles 2013/2016)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	189/416 (45.4%)	81/413 (19.6%)	RR 2.27 (1.83 to 2.83)	249 more per 1000 (from 163 more to 359 more)	MODERATE	CRITICAL
tesponse (ITT) at 3-moi)))	nth follow-up	(follow-	up mean 3 mor	nths; assessed	d with: Numb	er of people sho	wing at least 50%	6 improvement or	n Hamilton	Rating Scal	e for Depres	sion (HAM
(Nakagawa 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ³	none	28/40 (70%)	17/40 (42.5%)	RR 1.65 (1.09 to 2.49)	276 more per 1000 (from 38 more to 633 more)	MODERATE	CRITICAL
esponse (ITT) at 6-moi ating Scale for Depres			up mean 6 mor	nths; assessed	d with: Numb	er of people sho	wing at least 50%	6 improvement or	n Beck Dep	ression Inve	entory (BDI-I	I)/Hamiltor
! (Nakagawa 2017, Wiles !013/2016)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	143/274 (52.2%)	86/275 (31.3%)	RR 1.6 (1.27 to 2.01)	188 more per 1000 (from 84 more to 316 more)	MODERATE	CRITICAL
Response (ITT) at 12-mo HAM-D))	onth follow-u	p (follow	r-up mean 12 m	ionths; assess	sed with: Nur	nber of people s	howing at least 5	0% improvement	on Hamilto	on Rating So	ale for Depr	ession
(Nakagawa 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ³	none	33/40 (82.5%)	20/40 (50%)	RR 1.65 (1.17 to 2.32)	325 more per 1000 (from 85 more to 660	MODERATE	CRITICAL

1 (Wiles 2013/2016)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	59/234 (25.2%)	30/235 (12.8%)	RR 1.98 (1.32 to 2.95)	125 more per 1000 (from 41 more to 249 more)	MODERATE	CRITICAL
Discontinuation due to a	ny reason (f	follow-up	8-26 weeks; as	ssessed with:	Number of p	articipants who	dropped out for a	any reason (includi	ing adver	se events))		
13 (Chan 2012, Chiesa 2015, Dozois 2009, Eisendrath 2016, Kocsis 2009/ Klein 2011, Lynch 2007_study 2, Nakagawa 2017, Nakao 2018, Paykel 1999/ Scott 2000, Strauss 2012, Watkins 2011a, Wiles 2008, Wiles 2013/2016)			no serious inconsistency	no serious indirectness	serious ³	none	111/807 (13.8%)	103/687 (15%)		7 fewer per 1000 (from 39 fewer to 31 more)	MODERATE	CRITICAL
Discontinuation due to s	ide effects (follow-up	o mean 12 weel	ks; assessed v	with: Number	of participants	who dropped out	due to adverse ev	vents)			
1 (Kocsis 2009/ Klein 2011)	randomised trials		no serious inconsistency	no serious indirectness	very serious⁵	none	2/200 (1%)	2/96 (2.1%)	RR 0.48 (0.07 to 3.36)	11 fewer per 1000 (from 19 fewer to 49 more)	LOW	CRITICAL
Quality of life endpoint (follow-up me	ean 12 w	eeks; measure	d with: Europe	ean Quality o	f Life Questionn	aire-5 Dimension	s (EQ-5D); Better i	ndicated	by higher va	lues)	
1 (Nakao 2018)	randomised trials		no serious inconsistency	no serious indirectness	very serious⁵	none	20	20		SMD 0 higher (0.62 lower to 0.62 higher)	LOW	IMPORTANT
Quality of life physical c indicated by higher value		core (PC	S) endpoint (fo	llow-up 12-26	weeks; meas	sured with: 12-ite	em/36-item Short	-Form Survey (SF-′	12/SF-36):	Physical co	mponent sc	ore; Better
3 (Nakagawa 2017, Nakao 2018, Wiles 2013/2016)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	261	269		SMD 0.04 higher (0.17 lower to 0.26 higher)	MODERATE	IMPORTANT
Quality of life mental con indicated by higher value		ore (MCS) endpoint (foll	ow-up 12-26 w	veeks; measu	red with: 12-iten	n/36-item Short-F	orm Survey (SF-12	2/SF-36): I	Mental comp	onent score	; Better
3 (Nakagawa 2017, Nakao 2018, Wiles 2013/2016)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	261	269		SMD 0.26 higher (0.03 lower to 0.55 higher)	LOW	IMPORTANT
Quality of life physical c indicated by higher valu		core (PC	S) at 3-month f	ollow-up (follo	ow-up mean 3	3 months; measu	red with: 36-item	Short-Form Surve	ey (SF-36)	: Physical co	omponent so	core; Better
	randomised		no serious	no serious	serious ³	none	40	40				IMPORTANT

		risk of bias								lower to 0.27 higher)		
Quality of life mental cor ndicated by higher value		ore (MCS) at 3-month fol	low-up (follow	v-up mean 3 i	nonths; measur	ed with: 36-item	Short-Form Survey	(SF-36):	Mental com	ponent score	e; Better
(Nakagawa 2015)			no serious inconsistency	no serious indirectness	serious ⁶	none	40	40	-	SMD 0.15 lower (0.58 lower to 0.29 higher)	MODERATE	IMPORTAN
Quality of life physical co core; Better indicated b			S) at 6-month fo	ollow-up (follo	ow-up mean 6	i months; measu	red with: 12-iten	n/36-item Short-For	n Survey	(SF-12/SF-3	36): Physical	component
2 (Nakagawa 2015, Wiles 2013/2016)	randomised trials	serious ¹	serious ²	no serious indirectness	serious ³	none	234	235	-	SMD 0.07 higher (0.37 lower to 0.52 higher)	VERY LOW	IMPORTAN'
Quality of life mental cor core; Better indicated b) at 6-month fol	low-up (follow	v-up mean 6 i	nonths; measur	ed with: 12-item/	36-item Short-Form	Survey	(SF-12/SF-36	6): Mental co	mponent
2 (Nakagawa 2015, Wiles 2013/2016)	randomised trials	serious ¹	very serious ⁴	no serious indirectness	very serious⁵	none	234	235	-	SMD 0.01 higher (0.56 lower to 0.58 higher)	VERY LOW	IMPORTAN
Quality of life physical constraints and the second s		core (PC	S) at 12-month	follow-up (fol	low-up mean	12 months; mea	sured with: 36-it	em Short-Form Sur	vey (SF-3	36): Physica	l component	score;
l (Nakagawa 2015)			no serious inconsistency	no serious indirectness	no serious imprecision	none	40	40	-	SMD 0.05 higher (0.39 lower to 0.49 higher)		IMPORTAN
Quality of life mental cor ndicated by higher value		ore (MCS) at 12-month fo	ollow-up (follo	ow-up mean 1	2 months; meas	ured with: 36-ite	m Short-Form Surv	ey (SF-36	6): Mental co	mponent sc	ore; Better
(Nakagawa 2015)	randomised trials		no serious inconsistency	no serious indirectness	serious ⁶	none	40	40	-	SMD 0.2 lower (0.64 lower to 0.24 higher)	MODERATE	IMPORTANT
Quality of life physical constraints and the second s		core (PC	S) at 40-month	follow-up (fol	low-up mean	40 months; mea	sured with: 12-it	em Short-Form Sur	vey (SF-1	12): Physica	l component	score;
(Wiles 2013/2016)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	132	110	-	SMD 0.22 higher (0.03 lower to 0.47 higher)	MODERATE	IMPORTANT
Quality of life mental cor ndicated by higher value		ore (MCS) at 40-month fo	ollow-up (follo	ow-up mean 4	0 months; meas	ured with: 12-ite	m Short-Form Surv	ey (SF-12	2): Mental co	mponent sc	ore; Better
(Wiles 2013/2016)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	132	110	-	SMD 0.34 higher (0.09		IMPORTANT

										to 0.6 higher)		
Functional impairment e Scale (SAS); Better indic			· · · · · · · · · · · · · · · · · · ·	asured with:	Longitudinal	Interval Follow-u	p Evaluation Ra	nge of Impaired Fu	nctioning	Tool (LIFE-	RIFT)/Social	Adjustment
2 (Kocsis 2009/ Klein 2011, Paykel 1999/ Scott 2000)	randomised trials	no serious risk of bias	serious ²	no serious indirectness	serious ³	none	252	153	-	SMD 0.36 lower (0.67 to 0.05 lower)	LOW	IMPORTAN
Functional impairment a	t 11-month	follow-up	(follow-up me	an 11 months	; measured w	ith: Social Adjus	stment Scale (SA	S); Better indicated	l by lowe	r values)		
1 (Paykel 1999/ Scott 2000)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ³	none	80	78	-	SMD 0.3 lower (0.61 lower to 0.01 higher)	MODERATE	IMPORTAN
CI: confidence interval;	ITT: intentio	on to trea	at; RR: relative	risk; SMD: s	tandardised	mean differenc	е					

¹ Risk of bias is high or unclear across multiple domains

² Substantial heterogeneity

³ 95% CI crosses threshold for both clinically important benefit and no effect

⁴ Considerable heterogeneity

⁵ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm ⁶ 95% CI crosses threshold for both clinically important harm and no effect

Table 71: Clinical evidence profile for comparison 2. Augmenting with cognitive and cognitive behavioural therapies versus augmenting with counselling

Quality as	sessment						No of patients		Effect		Quellin	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with cognitive and cognitive behavioural therapies	Augmenting with counselling	Relative (95% Cl)	Absolute	Quality	Importance
Depressio	n symptomat	tology end	dpoint (follow-up	mean 12 week	ks; measured	with: Hamilton Ra	ating Scale for Depres	sion (HAM-D); B	etter indica	ated by lower va	lues)	
1 (Kocsis 2009/ Klein 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	174	168	-	SMD 0.18 lower (0.39 lower to 0.04 higher)	HIGH	CRITICAL
Remission HAM-D))	ı (ITT) (follow	-up mean	12 weeks; asse	ssed with: Num	nber of people	scoring <=7 on I	Hamilton Rating Scale	for Depression	(HAM-D) AI	ND responding (≥50% improv	vement on
1 (Kocsis 2009/ Klein 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	67/200 (33.5%)	52/195 (26.7%)	RR 1.26 (0.93 to 1.7)	69 more per 1000 (from 19 fewer to 187 more)	MODERATE	CRITICAL

no serious very serious ²													
ncy indirectness	none	25/200 (12.5%)	27/195 (13.8%)	RR 0.9 (0.54 to 1.5)	14 fewer per 1000 (from 64 fewer to 69 more)	LOW	CRITICAL						
up mean 12 weeks; assessed wit	h: Number of part	icipants who dropped	out due to adve	se events)									
, , , , , , , , , , , , , , , , , , ,	none	2/200 (1%)	1/195 (0.51%)	RR 1.95 (0.18 to 21.33)	5 more per 1000 (from 4 fewer to 104 more)	LOW	CRITICAL						
bias more) unctional impairment endpoint (follow-up mean 12 weeks; measured with: Longitudinal Interval Follow-up Evaluation Range of Impaired Functioning Tool (LIFE-RIFT); Better idicated by lower values)													
	none	172	162	-	SMD 0.15 lower (0.36 lower to 0.07 higher)	HIGH	IMPORTAN						
- Ser	-up mean 12 weeks; assessed witasno seriousvery serious²o mean 12 weeks; measured with:asno seriousno seriousno seriousno seriousno seriousindirectnessimprecision	-up mean 12 weeks; assessed with: Number of partsno seriousvery serious²nonesincyindirectnessvery serious²noneo mean 12 weeks; measured with: Longitudinal Intersno seriousnone	-up mean 12 weeks; assessed with: Number of participants who dropped s no serious very serious ² none 2/200 indirectness very serious ² none 2/200 o mean 12 weeks; measured with: Longitudinal Interval Follow-up Evaluati s no serious none 172 indirectness imprecision none 172	-up mean 12 weeks; assessed with: Number of participants who dropped out due to advert so no serious very serious² none2/2001/195sincyindirectnessvery serious²none2/2001/195o mean 12 weeks; measured with: Longitudinal Interval Follow-up Evaluation Range of Impose indirectnessnone172162	-up mean 12 weeks; assessed with: Number of participants who dropped out due to adverse events) s no serious very serious ² none 2/200 1/195 RR 1.95 indirectness very serious ² none 2/200 1/195 (0.51%) RR 1.95 o mean 12 weeks; measured with: Longitudinal Interval Follow-up Evaluation Range of Impaired Function none 172 162 -	-up mean 12 weeks; assessed with: Number of participants who dropped out due to adverse events) -up mean 12 weeks; assessed with: Number of participants who dropped out due to adverse events) s no serious very serious ² indirectness very serious ² none 2/200 (1%) (0.51%) (0.18 to 21.33) 5 more per 1000 (from 4 fewer to 104 more) o mean 12 weeks; measured with: Longitudinal Interval Follow-up Evaluation Range of Impaired Functioning Tool (LIF soncy no serious none indirectness none 172 162 - SMD 0.15 lower (0.36 lower to 0.07 higher)	-up mean 12 weeks; assessed with: Number of participants who dropped out due to adverse events) -up mean 12 weeks; assessed with: Number of participants who dropped out due to adverse events) s no serious indirectness very serious ² none 2/200 (1%) (0.51%) (0.18 to 21.33) 1000 (from 4 fewer to 104 more) p mean 12 weeks; measured with: Longitudinal Interval Follow-up Evaluation Range of Impaired Functioning Tool (LIFE-RIFT); Building indirectness s no serious indirectness no serious none 172 162 - SMD 0.15 lower (0.36 lower to 0.07 higher)						

¹ 95% CI crosses thresholds for both clinically important benefit and no effect
 ² 95% CI crosses threshold for no effect and thresholds for both clinically important benefit and harm

Table 72: Clinical evidence profile for comparison 3. Augmenting with counselling versus continuing with antidepressant

Quality ass	sessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	UTHER	Augmenting with counselling	Continuing with antidepressant	Relative (95% Cl)	Absolute		
Depressior	n symptomat	ology end	point (follow-up	mean 12 weeks	; measured wi	th: Hamilton Rati	ing Scale for Dep	pression (HAM-D); I	Better indic	ated by lower val	lues)	
1 (Kocsis 2009/ Klein 2011)	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	168	76	-	SMD 0.06 higher (0.21 lower to 0.33 higher)	HIGH	CRITICAL
Remission HAM-D))	(ITT) (follow-	up mean 1	12 weeks; asses	sed with: Numb	per of people s	coring <=7 on Ha	milton Rating So	cale for Depression	(HAM-D) A	ND responding (≥50% improv	vement on
1 (Kocsis 2009/ Klein 2011)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	52/195 (26.7%)	30/96 (31.3%)	RR 0.85 (0.59 to 1.24)	47 fewer per 1000 (from 128 fewer to 75 more)	MODERATE	CRITICAL
Discontinu	ation due to	any reasoi	n (follow-up mea	n 12 weeks; as	sessed with: N	lumber of partici	pants who dropp	bed out for any reas	on (includi	ng adverse even	ts))	

1 (Kocsis 2009/ Klein 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ²	none	27/195 (13.8%)	16/96 (16.7%)	RR 0.83 (0.47 to 1.47)	28 fewer per 1000 (from 88 fewer to 78 more)	LOW	CRITICAL
Discontinu	ation due to	side effec	ts (follow-up me	an 12 weeks; a	ssessed with:	Number of partic	ipants who dropp	ed out due to adve	erse events			
1 (Kocsis 2009/ Klein 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ²	none	1/195 (0.51%)	2/96 (2.1%)	RR 0.25 (0.02 to 2.68)	16 fewer per 1000 (from 20 fewer to 35 more)	LOW	CRITICAL
	impairment y lower valu		follow-up mean	12 weeks; mea	sured with: Lo	ngitudinal Interva	al Follow-up Eval	uation Range of Im	paired Fun	ctioning Tool (LIF	E-RIFT); B	etter
1 (Kocsis 2009/ Klein 2011)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	162	75	-	SMD 0.07 lower (0.34 lower to 0.21 higher)	HIGH	IMPORTAN

¹ 95% CI crosses thresholds for both clinically important harm and no effect

² 95% CI crosses thresholds for no effect and both clinically important benefit and harm

Table 73: Clinical evidence profile for comparison 4. Augmenting with IPT versus continuing with antidepressant

Quality assessmen	ıt						No of patients	i	Effect		Quality	Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with IPT		Relative (95% CI)	Absolute			
Depression sympto	ression symptomatology endpoint (follow-up 5-19 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
2 (Schramm 2007, Souza 2016)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	79	79	-	SMD 0.36 lower (0.68 to 0.05 lower)	LOW	CRITICAL	
Depression sympto by lower values)	omatology ch	ange score	e (follow-up 5-19	weeks; measu	red with: Ha	milton Rating Sc	ale for Depress	sion (HAM-D) chang	ge from bas	seline to endpoin	t; Better	indicated	
3 (Murray 2010, Schramm 2007, Souza 2016)	randomised trials	no serious risk of bias		no serious indirectness	serious ²	none	106	106	-	SMD 0.73 lower (1.38 to 0.08 lower)	LOW	CRITICAL	
Depression sympto	omatology at	1-3 month	follow-up (follov	v-up 1-3 month	s; measured	with: Hamilton F	Rating Scale fo	r Depression (HAM	-D); Better	indicated by low	er value	s)	
2 (Schramm 2007, Souza 2016)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	66	65	-	SMD 0.31 lower (0.79 lower to 0.16 higher)	LOW	CRITICAL	
Depression sympto	omatology at	12-month f	follow-up (follow	-up mean 12 m	onths; meas	ured with: Hamil	ton Rating Sca	lle for Depression (HAM-D); B	etter indicated by	lower v	values)	

1 (Schramm 2007)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	50	47	-	SMD 0.54 lower (0.94 to 0.13 lower)	LOW	CRITICAL
Remission (ITT) (fo	llow-up 5-19	weeks; as	sessed with: Nu	mber of people	scoring <=7	on Hamilton Rati	ng Scale for De	epression (HAM-D))			
4 (Murray 2010, Reynolds 2010, Schramm 2007, Souza 2016)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	83/176 (47.2%)	57/182 (31.3%)	RR 1.44 (1.12 to 1.86)	138 more per 1000 (from 38 more to 269 more)	LOW	CRITICAL
Response (ITT) (fo	llow-up 5-19 v	weeks; as	sessed with: Nur	nber of people	showing at	east 50% improve	ment on Hamil	ton Rating Scale fo	or Depress	ion (HAM-D))		
3 (Murray 2010, Schramm 2007, Souza 2016)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	62/116 (53.4%)	40/118 (33.9%)	RR 1.51 (1.14 to 1.99)	173 more per 1000 (from 47 more to 336 more)	LOW	CRITICAL
Discontinuation du	ie to any reas	on (follow	up 5-19 weeks;	assessed with:	Number of	participants who	dropped out fo	r any reason)				
4 (Murray 2010, Reynolds 2010, Schramm 2007, Souza 2016)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	none	31/176 (17.6%)	23/182 (12.6%)	RR 1.35 (0.81 to 2.23)	44 more per 1000 (from 24 fewer to 155 more)	LOW	CRITICAL
Global functioning	endpoint (fol	low-up me	ean 5 weeks; me	asured with: Gl	obal Assess	ment of Function	(GAF); Better i	ndicated by higher	values)			
1 (Schramm 2007)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	63	61	-	SMD 0.32 higher (0.03 lower to 0.68 higher)	LOW	IMPORTAN
Global functioning	at 3-month fo	ollow-up (f	follow-up mean 3	months; meas	ured with: C	Blobal Assessmer	t of Function (GAF); Better indica	ted by hig	her values)		
1 (Schramm 2007)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	50	47	-	SMD 0.44 higher (0.03 to 0.84 higher)	LOW	IMPORTAN
Global functioning	at 12-month	follow-up	(follow-up mean	12 months; me	asured with	: Global Assessm	ent of Function	n (GAF); Better indi	cated by h	igher values)		
1 (Schramm 2007)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	50	47	-	SMD 0.47 higher (0.06 to 0.87 higher)	LOW	IMPORTAN

CI: confidence interval; IPT: interpersonal therapy; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference ¹ Risk of bias is high or unclear across multiple domains ² 95% CI crosses thresholds for both clinically important benefit and no effect

³ Substantial heterogeneity

⁴ 95% CI crosses thresholds for both clinically important harm and no effect

Table 74: Clinical evidence profile for comparison 5. Augmenting with short-term psychodynamic psychotherapy versus continuing with antidepressant

Quality assessment	No of patients	Effect	Quality	Importance	
--------------------	----------------	--------	---------	------------	--

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with short-term psychodynamic psychotherapy	Continuing with antidepressant	Relative (95% Cl)	Absolute		
Depression	symptomato	logy end	lpoint (follow-up	mean 26 weel	ks; measured	with: Hamilton F	Rating Scale for Depress	sion (HAM-D); Bett	er indicate	ed by lower valu	ues)	
1 (Town 2017/2020)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	30	30	-	SMD 0.56 lower (1.07 to 0.04 lower)	MODERATE	CRITICAL
	symptomato y lower value		nge score (follo	w-up mean 26	weeks; measi	ured with: Hamil	ton Rating Scale for De	pression (HAM-D)	change fro	om baseline to	endpoint; Be	tter
1 (Town 2017/2020)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	30	30	-	SMD 0.71 lower (1.23 to 0.19 lower)	MODERATE	CRITICAL
Depression	symptomato	ology at 3	-month follow-u	p (follow-up m	ean 3 months	; measured with	: Hamilton Rating Scale	for Depression (H	IAM-D); Be	etter indicated b	y lower valu	es)
1 (Town 2017/2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	30	30	-	SMD 0.58 lower (1.1 to 0.07 lower)	MODERATE	CRITICAL
Depression	symptomato	ology at 6	-month follow-u	p (follow-up m	ean 6 months	; measured with	: Hamilton Rating Scale	for Depression (H	IAM-D); Be	etter indicated k	y lower valu	es)
1 (Town 2017/2020)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	30	30	-	SMD 0.56 lower (1.08 to 0.05 lower)	MODERATE	CRITICAL
Depression	symptomato	ology at 1	2-month follow-	up (follow-up i	nean 12 mont	hs; measured w	ith: Hamilton Rating Sc	ale for Depression	(HAM-D);	Better indicate	d by lower va	alues)
1 (Town 2017/2020)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	30	30	-	SMD 0.62 lower (1.14 to 0.1 lower)	MODERATE	CRITICAL
Remission ((ITT) (follow-	up mean	26 weeks; asses	ssed with: Nun	ber of people	scoring <=7 on	Hamilton Rating Scale	for Depression (H	AM-D))			
1 (Town 2017/2020)	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	11/30 (36.7%)	1/30 (3.3%)	RR 11 (1.51 to 79.96)	333 more per 1000 (from 17 more to 1000 more)	HIGH	CRITICAL
Remission ((ITT) at 12-m	onth follo	ow-up (follow-up	mean 12 mon	ths; assessed	with: Number o	f people scoring <=7 or	Hamilton Rating	Scale for D	epression (HA	M-D))	
1 (Town 2017/2020)	randomised trials	no serious	no serious inconsistency	no serious indirectness	very serious ²	none	12/30 (40%)	9/30 (30%)	RR 1.33 (0.66 to 2.69)	99 more per 1000 (from 102	LOW	CRITICAL

		risk of bias								fewer to 507 more)			
Response (ITT) at 12-month follow-up (follow-up mean 12 months; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))													
1 (Town 2017/2020)		no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ²	none	15/30 (50%)	12/30 (40%)	RR 1.25 (0.71 to 2.2)	100 more per 1000 (from 116 fewer to 480 more)	LOW	CRITICAL	
Discontinua	ation due to a	any reaso	n (follow-up me	an 26 weeks; a	ssessed with	: Number of part	icipants who dropped o	ut for any reason)					
1 (Town 2017/2020)		no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ²	none	5/30 (16.7%)	3/30 (10%)	RR 1.67 (0.44 to 6.36)	67 more per 1000 (from 56 fewer to 536 more)	LOW	CRITICAL	

¹ 95% CI crosses thresholds for both clinically important benefit and no effect ² 95% CI crosses thresholds for no effect and for both clinically important benefit and harm

Table 75: Clinical evidence profile for comparison 6. Augmenting with long-term psychodynamic psychotherapy versus continuing with antidepressant

Quality as	Quality assessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Improcision	Considerations	term hevenodynamic		Relative (95% Cl)	Absolute		
Depressio	on symptoma	tology er	ndpoint (follow-u	ip mean 78 wee	ks; measure	d with: Hamilton	Rating Scale for Depress	ion (HAM-D); Bette	r indicated	by lower values)		
1 (Fonagy 2015)	randomised trials			no serious indirectness	serious ²	reporting bias ³	53	46	-	SMD 0.23 lower (0.63 lower to 0.16 higher)	VERY LOW	CRITICAL
Depressio	on symptoma	tology at	6-month follow-	up (follow-up n	nean 6 mont	hs; measured wit	h: Hamilton Rating Scale	for Depression (HA	M-D); Bette	er indicated by lo	wer valu	es)
1 (Fonagy 2015)	randomised trials			no serious indirectness	serious ²	reporting bias ³	49	47	-	SMD 0.34 lower (0.75 lower to 0.06 higher)	VERY LOW	CRITICAL
Depressio	on symptoma	tology at	12-month follow	v-up (follow-up	mean 12 mo	nths; measured v	with: Hamilton Rating Sca	le for Depression (HAM-D); Be	etter indicated by	lower va	alues)
1 (Fonagy 2015)	randomised trials			no serious indirectness	serious ²	reporting bias ³	49	49	-	SMD 0.38 lower (0.78 lower to 0.02 higher)	VERY LOW	CRITICAL

Depressio	on symptomat	ology at	24-month follow	v-up (follow-up	mean 2 yea	rs; measured with	: Hamilton Rating Scale f	or Depression (HAI	M-D); Better	indicated by low	er value	es)		
1 (Fonagy 2015)	randomised s trials		no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	47	45	-	SMD 0.68 lower (1.1 to 0.26 lower)	VERY LOW	CRITICAL		
Remission	n (ITT) (follow	-up mea	n 78 weeks; ass	essed with: Nu	mber of peo	ple scoring <=8 o	n Hamilton Rating Scale f	or Depression (HAI	M-D))					
1 (Fonagy 2015)	randomised s trials		no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ³	6/67 (9%)	4/62 (6.5%)	RR 1.39 (0.41 to 4.69)	25 more per 1000 (from 38 fewer to 238 more)	VERY LOW	CRITICAL		
Remission	Remission (ITT) at 24-month follow-up (follow-up mean 2 years; assessed with: Number of people scoring <=8 on Hamilton Rating Scale for Depression (HAM-D))													
1 (Fonagy 2015)	randomised s trials		no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	10/67 (14.9%)	3/62 (4.8%)	RR 3.08 (0.89 to 10.69)	101 more per 1000 (from 5 fewer to 469 more)	VERY LOW	CRITICAL		
Discontin	uation due to	any reas	son (follow-up m	ean 78 weeks;	assessed w	ith: Number of pa	rticipants who dropped o	ut for any reason)						
1 (Fornagy 2015)	randomised s trials		no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ³	10/67 (14.9%)	8/62 (12.9%)	RR 1.16 (0.49 to 2.74)	21 more per 1000 (from 66 fewer to 225 more)	VERY LOW	CRITICAL		

¹ Statistically significant group difference at baseline

² 95% CI crosses thresholds for both clinically important benefit and no effect

³ Study partially funded by the International Psychoanalytic Association

⁴ 95% CI crosses thresholds for no effect and for both clinically important benefit and harm

Table 76: Clinical evidence profile for comparison 7. Augmenting with self-help versus continuing with the antidepressant (+/- attention-placebo)

Quality assessme	ent						No of patients		Effect		Quality	Importance		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with self-help	Continuing with the antidepressant (+/- attention-placebo)	Relative (95% Cl)	Absolute				
Depression symp lower values)	Depression symptomatology endpoint (follow-up 1.4-6 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) or Beck Depression Inventory (BDI-II); Better indicated by													
3 (Baert 2010_study 2, Dai 2019,	randomised trials			no serious indirectness	serious ¹	none	80	77	-	SMD 0.29 lower (0.61	MODERATE	CRITICAL		

Schlogelhofer 2014)		risk of bias								lower to 0.03 higher)		
Depression symp baseline to endpo					easured with:	Hamilton Rating	Scale for Dep	ression (HAM-D) or Be	eck Depres	ssion Inventor	y (BDI-II) cha	nge from
3 (Baert 2010_study 2, Dai 2019, Schlogelhofer 2014)		no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	80	77	-	SMD 0.39 lower (0.71 to 0.08 lower)	MODERATE	CRITICAL
Depression symp	tomatology	at 1-month	n follow-up (follo	ow-up mean 1	months; meas	sured with: Hami	Iton Rating Sca	ale for Depression (HA	AM-D); Bet	tter indicated b	oy lower valu	es)
1 (Dai 2019)	randomised trials	serious ²	no serious inconsistency	no serious indirectness	no serious imprecision	none	16	16	-	SMD 1.37 lower (2.15 to 0.59 lower)	MODERATE	CRITICAL
Discontinuation of	lue to any re	ason (follo	ow-up 1.4-6 wee	ks; assessed v	with: Number	of participants w	ho dropped ou	it for any reason)				
	randomised		no serious	no serious	very serious ³	nono	15/69	10/61	RR 1.32	52 more per	LOW	CRITICAL

¹ 95% CI crosses thresholds for both clinically important benefit and no effect
 ² Risk of bias is high or unclear across multiple domains
 ³ 95% CI crosses thresholds for no effect and for both clinically important benefit and harm

Table 77: Clinical evidence profile for comparison 8. Augmenting with self-help and switching to SSRI versus switching to SSRI-only

Quality as	sessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Augmenting with self-help and switching to SSRI	Switching to SSRI-only	Relative (95% Cl)	Absolute		
Depressio	on symptoma	tology endp	ooint (follow-up n	nean 9 weeks; i	measured with:	Patient Health Q	uestionnaire (PHQ-9);	Better indicat	ed by lower	values)		
1 (Mantani 2017)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ²	81	83	-	SMD 1.13 lower (1.46 to 0.8 lower)	LOW	CRITICAL
Depressio values)	on symptoma	tology char	nge score (follow	-up mean 9 wee	eks; measured	with: Patient Hea	Ith Questionnaire (PH	Q-9) change fr	om baseline	e to endpoint; Bette	er indicat	ed by lower
1 (Mantani 2017)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	reporting bias ²	81	83	-	SMD 0.76 lower (1.08 to 0.44 lower)	VERY LOW	CRITICAL
Remissio	n (ITT) (follow	v-up mean 9) weeks; assesse	d with: Number	r of people sco	ring <=4 on Patie	nt Health Questionnai	re (PHQ-9))	•			

1 (Mantani 2017)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	reporting bias ²	25/81 (30.9%)	15/83 (18.1%)	RR 1.71 (0.97 to 3)	128 more per 1000 (from 5 fewer to 361 more)	VERY LOW	CRITICAL		
Response	Response (ITT) (follow-up mean 9 weeks; assessed with: Number of people showing at least 50% improvement on Patient Health Questionnaire (PHQ-9))													
1 (Mantani 2017)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	reporting bias ²	34/81 (42%)	18/83 (21.7%)	RR 1.94 (1.19 to 3.14)	204 more per 1000 (from 41 more to 464 more)	VERY LOW	CRITICAL		
Discontin	uation due to	any reaso	n (follow-up mea	n 9 weeks; asse	essed with: Nur	nber of participar	nts who dropped out fo	or any reason)						
1 (Mantani 2017)	randomised trials		no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ²	1/81 (1.2%)	0/83 (0%)	RR 3.07 (0.13 to 74.35)	-	VERY LOW	CRITICAL		

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SSRI: selective serotonin reuptake inhibitor

¹ Risk of bias is high or unclear across multiple domains

² Study partially funded by pharmaceutical companies
 ³ 95% CI crosses thresholds for both clinically important benefit and no effect
 ⁴ 95% CI crosses thresholds for no effect and both clinically important benefit and harm

No.of Risk of Other Augmenting with Attention - Re						Effect		Quality	Importance			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision			Attention- placebo	Relative (95% Cl)	Absolute		
Depressi	on symptom	atology er	ndpoint (follow-up	o mean 6 weeks;	measured with	: Beck Depressio	n Inventory (BDI-I	I); Better indi	cated by lov	ver values)		
1 (Nan 2017)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	52	48	-	SMD 0.56 lower (0.96 to 0.16 lower)		CRITICAL
Depressi values)	on symptom	atology cł	nange score (follo	w-up mean 6 we	eeks; measured	with: Beck Depre	ession Inventory (I	BDI-II) chang	e from basel	ine to endpoint; Bet	ter indicated	by lower
1 (Nan 2017)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	52	48	-	SMD 1.22 lower (1.64 to 0.79 lower)	MODERATE	CRITICAL
Disconti	nuation due to	o any reas	son (follow-up me	an 6 weeks; ass	essed with: Nu	mber of participa	nts who dropped o	out for any re	ason)			
1 (Nan 2017)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	1/53 (1.9%)	5/53 (9.4%)	RR 0.2 (0.02 to 1.65)	75 fewer per 1000 (from 92 fewer to 61 more)	VERY LOW	CRITICAL

Table 78: Clinical evidence profile for comparison 9. Augmenting with art therapy versus attention-placebo

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference

¹ Risk of bias is high or unclear across multiple domains
 ² 95% CI crosses thresholds for both clinically important benefit and no effect
 ³ 95% CI crosses thresholds for no effect and both clinically important benefit and harm

Table 79: Clinical evidence profile for comparison 10. Augmenting with eye movement desensitization reprocessing (EMDR) versus augmenting with cognitive behavioural therapy

Quality as	ssessment						No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness		Other considerations	Augmenting with eye movement desensitization reprocessing (EMDR)	Augmenting with cognitive behavioural therapy	Relative (95% Cl)	Absolute	Quality	Importance
Depressio	on symptoma	atology en	dpoint (follow-u	p 13-26 weeks;	measured w	vith: Beck Depres	sion Inventory (BDI-II); B	etter indicated by lo	ower value	s)		
1 Ostacoli 2018)	randomised trials		no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	31	35	-	SMD 0.65 lower (1.14 to 0.15 lower)	VERY LOW	CRITICAL
Remissio	n (ITT) (follo	w-up 13-26	weeks; assess	ed with: Numb	er of people s	scoring <13 on B	eck Depression Inventory	y (BDI-II))				
1 Ostacoli 2018)	randomised trials		no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	22/40 (55%)	17/42 (40.5%)	RR 1.36 (0.86 to 2.16)	146 more per 1000 (from 57 fewer to 470 more)	VERY LOW	CRITICAL
Remissio	n (ITT) at 6-n	nonth follo	w-up (follow-up	mean 6 month	s; assessed	with: Number of	people scoring <13 on Be	eck Depression Inve	entory (BD	I-II))		
1 Ostacoli 2018)	randomised trials		no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ³	17/40 (42.5%)	15/42 (35.7%)	RR 1.19 (0.69 to 2.05)	68 more per 1000 (from 111 fewer to 375 more)	VERY LOW	CRITICAL
Discontin	uation due to	o any reas	on (follow-up 13	-26 weeks; ass	sessed with:	Number of partic	ipants who dropped out f	for any reason)				
1 Ostacoli 2018)	randomised trials		no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ³	9/40 (22.5%)	7/42 (16.7%)	RR 1.35 (0.56 to 3.28)	58 more per 1000 (from 73 fewer to 380 more)	VERY LOW	CRITICAL
Global fu	nctioning at	endpoint (f	follow-up 13-26	weeks; measu	red with: Glo	bal Assessment	of Function (GAF); Better	indicated by highe	r values)			
1 Ostacoli 2018)	randomised trials		no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	31	35	-	SMD 0.22 higher (0.27 lower to 0.7 higher)	VERY LOW	IMPORTAN

	randomised			serious ²	reporting bias ³	31	35	-	SMD 0.24		IMPORTANT
(Ostacoli 2018)	trials	inconsistency	indirectness						higher (0.24 lower to 0.73	LOW	
									higher)		

¹ Risk of bias high or unclear across multiple domains
 ² 95% CI crosses thresholds for both clinically important benefit and no effect
 ³ Potential conflict of interest as study funded by the EMDR Research Foundation
 ⁴ 95% CI crosses thresholds for no effect and both clinically important benefit and harm

Table 80: Clinical evidence profile for comparison 11. Increasing the dose of SSRI versus continuing SSRI at the same dose

			-									
Quality assessment						No of patient	S	Effect		Quality	Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Increasing the dose of SSRI	Continuing SSRI at the same dose	Relative (95% Cl)	Absolute		
Depression symptom	natology end	point (follo	ow-up mean 6 w	eeks; measure	d with: Hamil	ton Rating Scale	for Depressio	on (HAM-D); Bet	ter indicate	ed by lower valu	ues)	
1 (Ruhe 2009)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	30	27	-	SMD 0.63 higher (0.1 to 1.17 higher)	MODERATE	CRITICAL
Depression symptom (MADRS) change fror				· · · · · · · · · · · · · · · · · · ·		ton Rating Scale	for Depression	on (HAM-D) or N	lontgomer	y Asberg Depre	ession Rating	g Scale
2 (Dornseif 1989, Kim 2019)	randomised trials	serious ²	serious ³	no serious indirectness	serious ⁴	reporting bias⁵	205	211	-	SMD 0.33 lower (0.73 lower to 0.07 higher)	VERY LOW	CRITICAL
Remission (ITT) (folic Rating Scale (MADRS		eks; asse	ssed with: Numl	ber of people s	coring <=7/<=	8 on Hamilton Ra	ating Scale for	r Depression (H	AM-D) or <	=10 on Montgo	mery Asberg	J Depressio
5 (Dornseif 1989, Kim 2019, Licht 2002, Ruhe 2009, Schweizer 2001)	trials	serious ²	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias⁵	116/372 (31.2%)	112/381 (29.4%)	RR 1.1 (0.84 to 1.45)	29 more per 1000 (from 47 fewer to 132 more)	VERY LOW	CRITICAL
Response (ITT) (follo Depression Rating So		· · · · · · · · · · · · · · · · · · ·			•			•	for Depres	ssion (HAM-D)/I	Montgomery	Asberg
6 (Dornseif 1989, Kim 2019, Licht 2002, Ruhe 2009, Schweizer	trials	serious ²	serious ³	no serious indirectness	serious ⁴	reporting bias⁵	195/408 (47.8%)	195/422 (46.2%)	RR 1.1 (0.86 to 1.39)	46 more per 1000 (from 65	VERY LOW	CRITICAL

									fewer to 180 more)		
o any reaso	n (follow-u	up 5-6 weeks; as	sessed with: N	lumber of part	ticipants who dro	pped out for a	iny reason (incl	uding adv	erse events))		
randomised trials	no serious risk of bias	serious ³	no serious indirectness	very serious ⁶	reporting bias⁵	66/372 (17.7%)	77/381 (20.2%)	RR 0.77 (0.4 to 1.48)	46 fewer per 1000 (from 121 fewer to 97 more)	VERY LOW	CRITICAL
o side effect	ts (follow-	up 5-6 weeks; as	ssessed with:	Number of par	ticipants who dro	opped out due	to adverse eve	nts)			
randomised trials	no serious risk of bias	serious ³	no serious indirectness	very serious ⁶	reporting bias⁵	27/272 (9.9%)	16/286 (5.6%)	RR 1.59 (0.42 to 6.03)	33 more per 1000 (from 32 fewer to 281 more)	VERY LOW	CRITICAL
Il componen	it score (P	CS) endpoint (fo	ollow-up mean	6 weeks; mea	sured with: 36-ite	m Short-Form	Survey (SF-36): Physical	l component sc	ore; Better i	ndicated by
randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	30	27	-	SMD 0.6 lower (1.13 to 0.06 lower)	MODERATE	IMPORTAN
component	score (MC	S) endpoint (fol	ow-up mean 6	weeks; meas	ured with: 36-iten	n Short-Form	Survey (SF-36):	Mental co	mponent score	; Better indic	cated by
randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	27	-	SMD 1.55 higher (0.95 to 2.14 higher)	HIGH	IMPORTAN
	randomised trials o side effec: randomised trials Il component randomised trials	randomised no trials serious risk of bias o side effects (follow- randomised no trials serious risk of bias Il component score (P randomised no trials serious risk of bias Component score (MC randomised no trials serious	randomised no serious ³ trials serious risk of bias o side effects (follow-up 5-6 weeks; as randomised no serious ³ trials serious risk of bias Il component score (PCS) endpoint (for randomised no no serious trials serious inconsistency risk of bias component score (MCS) endpoint (follow) randomised no no serious trials serious inconsistency trials serious inconsistency	randomised no trials serious serious risk of bias serious ³ no serious indirectness o side effects (follow-up 5-6 weeks; assessed with: I randomised no trials no serious serious risk of bias no serious indirectness Il component score (PCS) endpoint (follow-up mean trials no serious indirectness randomised no trials no serious risk of bias no serious indirectness Il component score (PCS) endpoint (follow-up mean trials no serious inconsistency no serious indirectness component score (MCS) endpoint (follow-up mean trials no serious inconsistency no serious indirectness	randomised trialsno serious risk of biasserious ³ no serious indirectnessvery serious ⁶ o side effects (follow-up 5-6 weeks; assessed with: Number of par randomised trialsno serious risk of biasno serious indirectnessvery serious ⁶ andomised trialsno serious risk of biasserious ³ no serious indirectnessvery serious ⁶ andomised trialsno serious risk of biasno serious indirectnessvery serious ⁶ andomised trialsno serious risk of biasno serious inconsistencyno serious indirectnessserious ¹ component score (MCS) endpoint (follow-up mean 6 weeks; meas randomised trialsno serious serious inconsistencyno serious indirectnessno serious indirectnessrandomised trialsno serious inconsistencyno serious indirectnessno serious indirectness	randomised trialsno serious risk of biasserious ³ no serious indirectnessvery serious ereporting bias ⁵ o side effects (follow-up 5-6 weeks; assessed with: Number of participants who drop randomised trialsno serious reporting bias ⁵ reporting bias ⁵ o side effects (follow-up 5-6 weeks; assessed with: Number of participants who drop randomised trialsno serious reporting bias ⁵ reporting bias ⁵ o side effects (follow-up 5-6 weeks; assessed with: Number of participants who drop randomised trialsno serious reporting bias ⁵ reporting bias ⁵ o side effects (follow-up 5-6 weeks; assessed with: Number of participants who drop serious risk of biasserious ³ no serious indirectnessvery serious ⁶ reporting bias ⁵ of component score (PCS) endpoint (follow-up mean 6 weeks; measured with: 36-item randomised biasno serious inconsistencyserious indirectnessnonecomponent score (MCS) endpoint (follow-up mean 6 weeks; measured with: 36-item randomised inconsistencyno serious indirectnessno serious indirectnessrandomised trialsno serious inconsistencyno serious indirectnessno serious imprecisionnone	randomised trialsno serious nisk of biasserious ³ no serious indirectnessvery serious ⁶ reporting bias ⁵ 66/372 (17.7%)o side effects (follow-up 5-6 weeks; assessed with: Number of participants who dropped out due randomised trialsserious serious risk of biasno serious indirectnessvery serious ⁶ reporting bias ⁵ 27/272 (9.9%)andomised trialsno serious risk of biasserious ³ no serious indirectnessvery serious ⁶ reporting bias ⁵ 27/272 (9.9%)andomised trialsno serious risk of biasno serious indirectnessvery serious ⁶ reporting bias ⁵ 27/272 (9.9%)andomised trialsno serious inconsistencyno serious indirectnessserious ¹ none30component score (MCS) endpoint (follow-up mean 6 weeks; measured with: 36-item Short-Form 3030component score (MCS) endpoint (follow-up mean 6 weeks; measured with: 36-item Short-Form 3030randomised trialsno serious inconsistencyno serious indirectnessno serious ingrectness30	randomised trialsno serious risk of biasserious^3no serious indirectnessvery serious^6 reporting bias^5reporting bias^566/372 (17.7%)77/381 (20.2%)o side effects(follow-up 5-6 weeks; assessed with: Number of participants who dropped out due to adverse ever randomised no serious risk of biasserious^3no serious indirectnessvery serious^6 reporting bias^577/381 (17.7%)(20.2%)andomised randomised biasno serious risk of biasserious^3no serious indirectnessvery serious^6 reporting bias^527/272 (9.9%)16/286 (5.6%)andomised randomised randomised rialsno serious inconsistencyno serious indirectnessvery serious^6 reporting bias^527/272 (9.9%)16/286 (5.6%)randomised randomised rialsno serious inconsistencyno serious indirectnessserious^1 nonenone3027randomised randomised randomised rialsno serious inconsistencyno serious indirectnessserious^1 indirectnessnone3027randomised randomised biasno serious inconsistencyno serious indirectnessno serious imprecisionnone3027	randomised trialsno serious risk of biasserious serious indirectnessvery serious ereporting biasreporting bias (17.7%)66/372 (17.7%)77/381 (20.2%)RR 0.77 (0.4 to 1.48)o side effects trialsfollow-up 5-6 weeks; assessed with: Number of participants who dropped out due to adverse events)randomised trialsno serious risk of biasserious ³ no serious indirectnessvery serious reporting bias27/272 (9.9%)16/286 (5.6%)RR 1.59 (0.42 to 6.03)Il component score (PCS) endpoint (follow-up mean 6 weeks; measured with: 36-item Short-Form Survey (SF-36): Physical inconsistency biasno serious indirectnessserious ¹ none3027-randomised trialsno serious risk of biasno serious inconsistencyno serious indirectnessserious ¹ none3027-	o any reason (follow-up 5-6 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events)) randomised no serious risk of bias no serious indirectness very serious ⁶ reporting bias ⁵ 66/372 (17.7%) 77/381 (20.2%) (R. 0.77 (20.2%)) 46 fewer per 14.48 (20.2%) o side effects (follow-up 5-6 weeks; assessed with: Number of participants who dropped out due to adverse events) 1.48) 46 fewer per 16.48 (20.2%) randomised no serious risk of bias no serious indirectness very serious ⁶ reporting bias ⁵ 27/272 (9.9%) 16/286 (5.6%) RR 1.59 (0.42 to 1000 (from 32 fewer to 281 more)) randomised no serious risk of bias serious indirectness very serious ⁶ reporting bias ⁵ 27/272 (9.9%) 16/286 (5.6%) RR 1.59 (0.42 to 1000 (from 32 fewer to 281 more)) of component score (PCS) endpoint (follow-up mean 6 weeks; measured with: 36-item Short-Form Survey (SF-36): Physical component score (1.13 to 0.06 lower) no serious indirectness no serious indirectness none 30 27 - SMD 0.6 lower (1.13 to 0.06 lower) randomised no inconsistency risk of bias no serious indirectness no serious indirectness none 30 27 - SMD 0.6 lower (1.13 to 0.06 lower) randomised no inconsistency indirectness no serious indirectness no serious indirectness <td>o any reason (follow-up 5-6 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events)) randomised no serious risk of bias serious³ no serious indirectness very serious⁶ reporting bias⁵ 66/372 (17.7%) 77/381 (20.2%) RR 0.77 (0.4 to 1.48) 46 fewer per 1000 (from 121 fewer to 97 more) VERY LOW o side effects (follow-up 5-6 weeks; assessed with: Number of participants who dropped out due to adverse events) reporting bias⁵ 27/272 (9.9%) 16/286 (5.6%) RR 1.59 (0.4 to 1.48) 33 more per 1000 (from 32 fewer to 281 more) randomised no serious risk of bias no serious indirectness very serious⁶ reporting bias⁵ 27/272 (9.9%) 16/286 (5.6%) RR 1.59 (0.4 to 1.48) 33 more per 1000 (from 32 fewer to 281 more) u component score (PCS) endpoint (follow-up mean 6 weeks; measured with: 36-item Short-Form Survey (SF-36): Physical component score; Better in a inconsistency risk of bias no serious indirectness serious serious indirectness serious inconsistency indirectness none 30 27 - SMD 0.6 lower MODERATE randomised no bias no serious inconsistency indirectness serious indirectness s</td>	o any reason (follow-up 5-6 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events)) randomised no serious risk of bias serious ³ no serious indirectness very serious ⁶ reporting bias ⁵ 66/372 (17.7%) 77/381 (20.2%) RR 0.77 (0.4 to 1.48) 46 fewer per 1000 (from 121 fewer to 97 more) VERY LOW o side effects (follow-up 5-6 weeks; assessed with: Number of participants who dropped out due to adverse events) reporting bias ⁵ 27/272 (9.9%) 16/286 (5.6%) RR 1.59 (0.4 to 1.48) 33 more per 1000 (from 32 fewer to 281 more) randomised no serious risk of bias no serious indirectness very serious ⁶ reporting bias ⁵ 27/272 (9.9%) 16/286 (5.6%) RR 1.59 (0.4 to 1.48) 33 more per 1000 (from 32 fewer to 281 more) u component score (PCS) endpoint (follow-up mean 6 weeks; measured with: 36-item Short-Form Survey (SF-36): Physical component score; Better in a inconsistency risk of bias no serious indirectness serious serious indirectness serious inconsistency indirectness none 30 27 - SMD 0.6 lower MODERATE randomised no bias no serious inconsistency indirectness serious indirectness s

³ Substantial heterogeneity
 ⁴ 95% Cl crosses thresholds for both clinically important benefit and no effect
 ⁵ Funding from pharmaceutical companies
 ⁶ 95% Cl crosses thresholds for no effect and both clinically important benefit and harm

Table 81: Clinical evidence profile for comparison 12. Increasing the dose of SSRI versus switching to SNRI

Quality a	ssessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Increasing the dose of SSRI		Relative (95% Cl)	Absolute	-	
Depressi	on symptoma	atology endp	ooint (follow-up m	ean 8 weeks; m	easured with: Q	Quick Inventory of	f Depressive Syn	nptomatology	(QIDS); Bet	ter indicated by lowe	r values)	

1 (Bose 2012)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ²	229	243	-	SMD 0.21 lower (0.39 to 0.03 lower)	LOW	CRITICAL
	ion symptoma I by lower val		nge score (follow	-up mean 8 wee	ks; measured w	vith: Quick Invento	ory of Depressive	Symptomate	ology (QIDS)	change from baseline	e to end	point; Better
1 (Bose 2012)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ²	229	243	-	SMD 0.16 lower (0.35 lower to 0.02 higher)	LOW	CRITICAL
Remissio	on (ITT) (follo	w-up mean 8	8 weeks; assesse	d with: Number	of people scori	ng <=10 on Montg	omery Asberg D	epression Ra	ating Scale (N	IADRS))		
1 (Bose 2012)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	reporting bias ²	124/238 (52.1%)	102/246 (41.5%)	RR 1.26 (1.04 to 1.52)	108 more per 1000 (from 17 more to 216 more)	VERY LOW	CRITICAL
Respons	e (ITT) (follov	v-up mean 8	weeks; assessed	d with: Number o	of people showi	ing at least 50% in	nprovement on M	lontgomery /	Asberg Depre	ssion Rating Scale (M)
1 (Bose 2012)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ²	167/238 (70.2%)	170/246 (69.1%)	RR 1.02 (0.9 to 1.14)	14 more per 1000 (from 69 fewer to 97 more)	LOW	CRITICAL
Disconti	nuation due t	o any reasor	n (follow-up mear	n 8 weeks; asses	ssed with: Num	ber of participants	who dropped ou	ut for any rea	ison (includin	ig adverse events))		
1 (Bose 2012)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ²	56/238 (23.5%)	53/246 (21.5%)	RR 1.09 (0.78 to 1.52)	19 more per 1000 (from 47 fewer to 112 more)	VERY LOW	CRITICAL
Disconti	nuation due t	o side effect	s (follow-up mea	n 8 weeks; asse	ssed with: Num	ber of participants	s who dropped o	ut due to adv	verse events)			
1 (Bose 2012)	randomised trials			no serious indirectness	very serious ⁴	reporting bias ²	13/238 (5.5%)	13/246 (5.3%)	RR 1.03 (0.49 to 2.18)	2 more per 1000 (from 27 fewer to 62 more)	VERY LOW	CRITICAL
Quality o	of life endpoin	t (follow-up	mean 8 weeks; m	neasured with: C	Quality of Life E	njoyment and Sati	sfaction Questio	nnaire-short	form (Q-LES	-Q-SF); Better indicat	ed by hi	gher values
1 (Bose 2012)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ²	229	243	-	SMD 0.11 higher (0.08 lower to 0.29 higher)	LOW	IMPORTAN

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

¹ Risk of bias is high or unclear across multiple domains ² Funding from pharmaceutical company

³ 95% CI crosses thresholds for both clinically important benefit and no effect
 ⁴ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 82: Clinical evidence profile for comparison 13. Increasing the dose of SSRI versus augmenting with TCA

Quality assessment	No of patients	Effect	Quality	Importance	
--------------------	----------------	--------	---------	------------	--

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Increasing the dose of SSRI	Augmenting with TCA	Relative (95% Cl)	Absolute		
Depression s	symptomatol	ogy endpoir	nt (follow-up mea	n 4 weeks; mea	sured with: H	lamilton Rating S	cale for Depress	sion (HAM-D); B	etter indicat	ed by lower values)		
2 (Fava 1994a, Fava 2002)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	48	46	-	SMD 0.67 lower (1.28 to 0.05 lower)	LOW	CRITICAL
Depression s indicated by			score (follow-up	mean 4 weeks;	measured w	ith: Hamilton Rat	ing Scale for De	pression (HAM-	D) change fr	om baseline to endpo	int; Bet	ter
2 (Fava 1994a, Fava 2002)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	48	46	-	SMD 0.44 lower (0.9 lower to 0.01 higher)	LOW	CRITICAL
Remission (I	TT) (follow-u	p mean 4 w	eeks; assessed w	/ith: Number of	people scori	ng <=7 on Hamilte	on Rating Scale	for Depression	(HAM-D))			
2 (Fava 1994a, Fava 2002)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	22/48 (45.8%)	13/46 (28.3%)	RR 1.6 (0.91 to 2.81)	170 more per 1000 (from 25 fewer to 512 more)	LOW	CRITICAL
Discontinuat	ion due to ar	ny reason (fe	ollow-up mean 4	weeks; assesse	d with: Numb	per of participants	s who dropped o	out for any reaso	on (including	g adverse events))		
2 (Fava 1994a, Fava 2002)	randomised trials		no serious inconsistency	no serious indirectness	very serious ³	none	5/48 (10.4%)	8/46 (17.4%)	RR 0.58 (0.21 to 1.64)	73 fewer per 1000 (from 137 fewer to 111 more)	LOW	CRITICAL
Discontinuat	ion due to si	de effects (f	ollow-up mean 4	weeks; assesse	d with: Num	ber of participant	s who dropped	out due to adve	rse events)			
`	randomised trials	risk of bias	no serious inconsistency		serious ³	reporting bias ⁴	0/15 (0%)	2/12 (16.7%)	RR 0.16 (0.01 to 3.09)	140 fewer per 1000 (from 165 fewer to 348 more)	LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant ¹ Risk of bias is high or unclear across multiple domains
 ² 95% CI crosses thresholds for both clinically important benefit and no effect

³ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

⁴ Study partially funded by pharmaceutical company

Table 83: Clinical evidence profile for comparison 14. Increasing the dose of SSRI versus augmenting with antipsychotic

Quality a	ssessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Increasing the dose of SSRI	Augmenting with antipsychotic	Relative (95% Cl)	Absolute		
Depressi	on symptoma	atology end	lpoint (follow-up	mean 13 weeks	; measured v	with: Hamilton Ra	ating Scale for D	Depression (HAM-D); Better ind	licated by lower va	lues)	

(Rocca 2002b)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	28	32	-	SMD 0.1 higher (0.41 lower to 0.6 higher)	MODERATE	CRITICAL
	on symptoma by lower val		nge score (follo	ow-up mean 13 v	weeks; meas	ured with: Hamilto	on Rating Scale	for Depression (H	AM-D) chang	ge from baseline to	endpoint; B	etter
(Rocca 002b)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	28	32	-	SMD 0.07 higher (0.43 lower to 0.58 higher)	MODERATE	CRITICAL
emissio	n (ITT) (follo	w-up mean	13 weeks; asse	ssed with: Num	ber of people	e scoring <=7 on ⊦	lamilton Rating	Scale for Depress	ion (HAM-D))		
(Rocca 2002b)	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	9/28 (32.1%)	14/32 (43.8%)	RR 0.73 (0.38 to 1.43)	118 fewer per 1000 (from 271 fewer to 188 more)	LOW	CRITICAL
espons	e (ITT) (follov	v-up mean 1	I3 weeks; asses	ssed with: Numl	ber of people	showing at least	50% improveme	ent on Hamilton Ra	ting Scale fo	or Depression (HAI	M-D))	
(Rocca 2002b)	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	15/28 (53.6%)	18/32 (56.3%)	RR 0.95 (0.6 to 1.51)	28 fewer per 1000 (from 225 fewer to 287 more)	LOW	CRITICAL
)iscontir	uation due to	o any reaso	n (follow-up me	ean 13 weeks; a	ssessed with	: Number of partic	cipants who dro	pped out for any r	eason (inclu	ding adverse even	ts))	
(Rocca 2002b)	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	4/28 (14.3%)	5/32 (15.6%)	RR 0.91 (0.27 to 3.08)	14 fewer per 1000 (from 114 fewer to 325 more)	LOW	CRITICAL
iscontin	uation due to	o side effec	ts (follow-up m	ean 13 weeks; a	ssessed witl	h: Number of parti	cipants who dro	opped out due to a	dverse even	ts)		
(Rocca 2002b)	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	2/28 (7.1%)	2/32 (6.3%)	RR 1.14 (0.17 to 7.59)	9 more per 1000 (from 52 fewer to 412 more)	LOW	CRITICAL
unction	al remission	(follow-up r	nean 13 weeks;	assessed with:	Number of p	people scoring =>7	71 on Global As	sessment of Func	tion (GAF))			
(Rocca 002b)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	11/28 (39.3%)	22/32 (68.8%)	RR 0.57 (0.34 to 0.96)	296 fewer per 1000 (from 28 fewer to 454 fewer)	MODERATE	IMPORTAN
Blobal fu	nctioning en	dpoint (follo	ow-up mean 13	weeks; measure	ed with: Glob	al Assessment of	Function (GAF); Better indicated	by higher va	alues)		
(Rocca	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	28	32	-	SMD 0.67 lower (1.19 to 0.15 lower)		IMPORTAN

² 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 84: Clinical evidence profile for comparison 15. Increasing the dose of SSRI versus augmenting with lithium

Quality assessment	No of patients	Effect	Quality	Importance	
--------------------	----------------	--------	---------	------------	--

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Increasing the dose of SSRI	Augmenting with lithium	Relative (95% Cl)	Absolute		
Depression s	symptomatol	ogy endpoir	nt (follow-up mea	n 4 weeks; mea	sured with: H	Hamilton Rating S	cale for Depress	sion (HAM-D); Be	etter indicate	ed by lower values)		
2 (Fava 1994a, Fava 2002)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	48	48	-	SMD 0.34 lower (0.75 lower to 0.06 higher)	LOW	CRITICAL
Depression s indicated by			score (follow-up	mean 4 weeks;	measured w	ith: Hamilton Rat	ing Scale for De	pression (HAM-E	D) change fro	om baseline to endpo	oint; Bet	ter
2 (Fava 1994a, Fava 2002)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	48	48	-	SMD 0.31 lower (0.72 lower to 0.09 higher)	LOW	CRITICAL
Remission (I	TT) (follow-u	p mean 4 w	eeks; assessed w	ith: Number of	people scori	ng <=7 on Hamilte	on Rating Scale	for Depression (HAM-D))			
2 (Fava 1994a, Fava 2002)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	22/48 (45.8%)	12/48 (25%)	RR 1.83 (1.03 to 3.25)	208 more per 1000 (from 7 more to 562 more)	LOW	CRITICAL
Discontinuat	ion due to ar	ny reason (fo	ollow-up mean 4	weeks; assesse	d with: Num	ber of participant	s who dropped o	out for any reaso	on (including	adverse events))		
2 (Fava 1994a, Fava 2002)	randomised trials		no serious inconsistency	no serious indirectness	very serious ³	none	5/48 (10.4%)	7/48 (14.6%)	RR 0.72 (0.24 to 2.11)	41 fewer per 1000 (from 111 fewer to 162 more)	LOW	CRITICAL
Discontinuat	ion due to si	de effects (f	ollow-up mean 4	weeks; assesse	d with: Num	ber of participant	s who dropped	out due to adver	se events)			
`	randomised trials		no serious inconsistency	no serious indirectness	very serious ³	reporting bias ⁴	0/15 (0%)	1/14 (7.1%)	RR 0.31 (0.01 to 7.09)	49 fewer per 1000 (from 71 fewer to 435 more)	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SSRI: selective serotonin reuptake inhibitor

¹ Risk of bias was high or unclear across multiple domains

² 95% CI crosses thresholds for both clinically important benefit and no effect

³ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

⁴ Study partially funded by pharmaceutical company

Table 85: Clinical evidence profile for comparison 16. Switching to SSRI versus continuing with antidepressant

Quality asse	essment						No of patier	nts	Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching to SSRI	Continuing with antidepressant	Relative (95% Cl)	Absolute		
Depression indicated by			score (follow-up	8-12 weeks; m	easured with:	Montgomery Asb	erg Depressi	ion Rating Scale (MA	ADRS) chang	ge from baseline to	endpoin	t; Better

2 (Corya 2006, Shelton 2005)	randomised trials	serious ¹	serious ²	no serious indirectness	no serious imprecision	reporting bias ³	198	126	-	SMD 0.03 higher (0.31 lower to 0.38 higher)	VERY LOW	CRITICAL
Remission ((ITT) (follow-u	p 8-12 week	s; assessed wit	h: Number of pe	ople scoring <	=8 on Montgomer	y Asberg De	pression Rating Sca	le (MADRS))		
2 (Corya 2006, Shelton 2005)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	29/202 (14.4%)	25/127 (19.7%)	RR 0.76 (0.46 to 1.24)	47 fewer per 1000 (from 106 fewer to 47 more)	VERY LOW	CRITICAL
Response (ITT) (follow-uj	o 8-12 week	s; assessed with	: Number of pe	ople showing a	it least 50% impro	vement on M	ontgomery Asberg	Depression	Rating Scale (MAD	RS))	
2 (Corya 2006, Shelton 2005)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	60/202 (29.7%)	50/127 (39.4%)	RR 0.78 (0.54 to 1.12)	87 fewer per 1000 (from 181 fewer to 47 more)	VERY LOW	CRITICAL
Discontinua	ation due to a	ny reason (f	ollow-up 8-12 we	eeks; assessed	with: Number o	of participants whe	o dropped ou	It for any reason (in	cluding adv	erse events))		
2 (Corya 2006, Shelton 2005)	randomised trials	no serious risk of bias	serious ²	no serious indirectness	very serious⁵	reporting bias ³	40/202 (19.8%)	23/127 (18.1%)	RR 1.13 (0.54 to 2.38)	24 more per 1000 (from 83 fewer to 250 more)	VERY LOW	CRITICAL
Discontinua	ation due to si	de effects (follow-up 8-12 w	eeks; assessed	with: Number	of participants wh	o dropped o	ut due to adverse ev	vents)			
2 (Corya 2006, Shelton 2005)	randomised trials		no serious inconsistency	no serious indirectness	very serious⁵	reporting bias ³	7/202 (3.5%)	3/127 (2.4%)	RR 1.43 (0.38 to 5.47)	10 more per 1000 (from 15 fewer to 106 more)	VERY LOW	CRITICAL

¹ Risk of bias is high or unclear across multiple domains

² Substantial heterogeneity
 ³ Funding from pharmaceutical companies
 ⁴ 95% CI crosses thresholds for both clinically important harm and no effect
 ⁵ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 86: Clinical evidence profile for comparison 17. Switching to a different SSRI versus continuing same SSRI

Quality ass	Quality assessment						No of patients		Effect		Quality	Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching to a different SSRI	Continuing same SSRI	Relative (95% Cl)	Absolute			
Remission	emission (ITT) (follow-up mean 6 weeks; assessed with: Number of people scoring <=10 on Montgomery Asberg Depression Rating Scale (MADRS))												

1 (Nakajima 2011)	randomised trials	very serious¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ²	12/20 (60%)	3/21 (14.3%)	RR 4.2 (1.39 to 12.71)	457 more per 1000 (from 56 more to 1000 more)	VERY LOW	CRITICAL		
Response (ITT) (follow-up mean 6 weeks; assessed with: Number of people showing at least 50% improvement on Montgomery Asberg Depression Rating Scale (MADRS))														
1 (Nakajima 2011)	randomised trials	very serious¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ²	15/20 (75%)	4/21 (19%)	RR 3.94 (1.57 to 9.85)	560 more per 1000 (from 109 more to 1000 more)	VERY LOW	CRITICAL		
Discontinua	iscontinuation due to any reason (follow-up mean 6 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))													
1 (Nakajima 2011)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	reporting bias ²	2/20 (10%)	5/21 (23.8%)	RR 0.42 (0.09 to 1.92)	138 fewer per 1000 (from 217 fewer to 219 more)	VERY LOW	CRITICAL		
Discontinua	ation due to s	ide effect	s (follow-up mea	n 6 weeks; asse	ssed with: Num	ber of participant	s who dropped o	out due to adv	erse events)					
1 (Nakajima	randomised	serious ¹	no serious	no serious	no serious	reporting bias ²	0/20	0/21	not pooled	not pooled	LOW	CRITICAL		

CI: confidence interval; ITT: intention to treat; RR: relative risk; SSRI: selective serotonin reuptake inhibitor

¹ Risk of bias is high or unclear across multiple domains and abrupt tapering of failed drug in switch arm
 ² Study partially funded by pharmaceutical company
 ³ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 87: Clinical evidence profile for comparison 18. Switching to SSRI versus antipsychotic

Quality assess	sment						No of patient	s	Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		Switching to SSRI	Antipsychotic	Relative (95% Cl)	Absolute		
Depression sy indicated by lo		gy change so	core (follow-up 8-	12 weeks; meas	ured with: M	ontgomery Asber	g Depression	Rating Scale (MADRS) cha	nge from baseline to	endpoin	t; Better
2 (Corya 2006, Shelton 2005)				no serious indirectness	serious ²	reporting bias ³	198	203	-	SMD 0.27 lower (0.5 to 0.03 lower)	VERY LOW	CRITICAL
Remission (IT	T) (follow-up	8-12 weeks;	assessed with: N	umber of people	scoring <=8	on Montgomery	Asberg Depre	ession Rating	Scale (MADR	S))		
2 (Corya 2006, Shelton 2005)					very serious ⁴	reporting bias ³	29/202 (14.4%)	27/206 (13.1%)	RR 1.1 (0.67 to 1.79)	13 more per 1000 (from 43 fewer to 104 more)		CRITICAL
Response (ITT) (follow-up	8-12 weeks; a	assessed with: Nu	umber of people	showing at	least 50% improve	ement on Mor	tgomery Asbe	erg Depressio	on Rating Scale (MAD	RS))	
2 (Corya 2006, Shelton 2005)				no serious indirectness	serious ²	reporting bias ³	60/202 (29.7%)	43/206 (20.9%)	RR 1.42 (1.01 to 2)	88 more per 1000 (from 2 more to 209 more)	VERY LOW	CRITICAL
Discontinuatio	on due to any	reason (follo	ow-up 8-12 weeks	; assessed with	: Number of	participants who	dropped out f	or any reason	(including a	dverse events))		

2 (Corya 2006, Shelton 2005)			no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	40/202 (19.8%)	50/206 (24.3%)	RR 0.82 (0.56 to 1.18)	44 fewer per 1000 (from 107 fewer to 44 more)		CRITICAL
Discontinuatio	on due to sid	e effects (fol	low-up 8-12 week	s; assessed with	h: Number of	f participants who	dropped out	due to adverse	events)			
2 (Corya 2006, Shelton 2005)			no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	7/202 (3.5%)	19/206 (9.2%)	RR 0.39 (0.16 to 0.91)	56 fewer per 1000 (from 8 fewer to 77 fewer)	LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SSRI: selective serotonin reuptake inhibitor

¹ Risk of bias is high or unclear across multiple domains ² 95% CI crosses thresholds for both clinically important benefit and no effect

³ Funding from pharmaceutical companies

⁴ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 88: Clinical evidence profile for comparison 19. Switching to combined SSRI + antipsychotic versus switching to antipsychoticonly

sessment						No of patients		Effect		Quality	Importance
Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching to combined SSRI + antipsychotic	Switching to antipsychotic- only	Relative (95% Cl)	Absolute		
		ge score (follow-	up 8-12 weeks;	measured w	ith: Montgomery	Asberg Depression	Rating Scale (MAD	RS) change	from baseline to	endpoin	t; Better
randomised trials	serious ¹	very serious ²	no serious indirectness	serious ³	reporting bias ⁴	376	203	-	SMD 0.44 lower (0.91 lower to 0.03 higher)	VERY LOW	CRITICAL
(ITT) (follow-	up 8-12 we	eks; assessed w	ith: Number of	people scori	ng <=8 on Montg	omery Asberg Depre	ssion Rating Scale	(MADRS))			
randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	reporting bias⁴	94/389 (24.2%)	27/206 (13.1%)	RR 1.63 (0.97 to 2.73)	83 more per 1000 (from 4 fewer to 227 more)	VERY LOW	CRITICAL
(ITT) (follow-u	ıp 8-12 wee	ks; assessed wi	th: Number of p	eople showi	ing at least 50% i	mprovement on Mon	tgomery Asberg De	pression R	ating Scale (MAD	RS))	
randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	reporting bias ⁴	140/389 (36%)	43/206 (20.9%)	RR 1.53 (1.12 to 2.1)	111 more per 1000 (from 25 more to 230 more)	VERY LOW	CRITICAL
	Design symptomato y lower value randomised trials (ITT) (follow- randomised trials	DesignRisk of biassymptomatology change y lower values)randomised trialsserious1(ITT) (follow-up 8-12 were randomised trials(ITT) (follow-up 8-12 were randomised trials	DesignRisk of biasInconsistencysymptomatology change score (follow- y lower values)serious ¹ very serious ² randomised serious ¹ very serious ² (ITT) (follow-up 8-12 weeks; assessed weight inconsistency(ITT) (follow-up 8-12 weeks; assessed weight inconsistencyno serious inconsistency(ITT) (follow-up 8-12 weeks; assessed weight inconsistencyno serious inconsistency(ITT) (follow-up 8-12 weeks; assessed weight inconsistencyno serious inconsistency	Design Risk of bias Inconsistency Indirectness symptomatology change score (follow-up 8-12 weeks; y lower values) serious ¹ very serious ² no serious indirectness randomised trials serious ¹ very serious ² no serious indirectness (ITT) (follow-up 8-12 weeks; assessed with: Number of randomised serious ¹ no serious indirectness indirectness (ITT) (follow-up 8-12 weeks; assessed with: Number of prandomised serious ¹ no serious no serious indirectness no serious indirectness	DesignRisk of biasInconsistencyIndirectnessImprecisionsymptomatology change score (follow-up 8-12 weeks; measured w y lower values)serious1very serious2no serious indirectnessserious3randomised trialsserious1very serious2no serious indirectnessserious3(ITT) (follow-up 8-12 weeks; assessed with: Number of people scori inconsistencyno serious indirectnessserious3(ITT) (follow-up 8-12 weeks; assessed with: Number of people scori inconsistencyno serious indirectnessserious3(ITT) (follow-up 8-12 weeks; assessed with: Number of people showi randomisedserious1no serious no seriousserious3	Design Risk of bias Inconsistency Indirectness Imprecision Other considerations symptomatology change score (follow-up 8-12 weeks; measured with: Montgomery lower values) serious ¹ very serious ² no serious indirectness serious ³ reporting bias ⁴ randomised trials serious ¹ very serious ² no serious indirectness serious ³ reporting bias ⁴ (ITT) (follow-up 8-12 weeks; assessed with: Number of people scoring <=8 on Montg inconsistency	Design Risk of bias Inconsistency Indirectness Imprecision Other considerations Switching to combined SSRI + antipsychotic r symptomatology change score (follow-up 8-12 weeks; measured with: Montgomery Asberg Depression I y lower values) serious ¹ very serious ² no serious serious ³ reporting bias ⁴ 376 randomised trials serious ¹ very serious ² no serious serious ³ reporting bias ⁴ 376 (ITT) (follow-up 8-12 weeks; assessed with: Number of people scoring <=8 on Montgomery Asberg Depresion indirectness	Design Risk of bias Inconsistency Indirectness Imprecision Other considerations Switching to combined SSRI + antipsychotic only Switching to antipsychotic only e symptomatology change score (follow-up 8-12 weeks; measured with: Montgomery Asberg Depression Rating Scale (MAD) y lower values no serious no serious serious ³ reporting bias ⁴ 376 203 (ITT) (follow-up 8-12 weeks; assessed with: Number of people scoring <=8 on Montgomery Asberg Depression Rating Scale	Design Risk of bias Inconsistency Indirectness Imprecision Other considerations Switching to combined SSRI + antipsychotic- only Switching to antipsychotic- only Relative (95% Cl) esymptomato/gy change score (follow-up 8-12 weeks; measured with: Montgomery Asberg Depression Rating Scale (MADRS) change rating scale (MADRS) no serious and indirectness serious ³ reporting bias ⁴ 376 203 - (ITT) (follow-up 8-12 weeks; assessed with: Number of people scorup serious ³ reporting bias ⁴ 376 203 - - randomised trials serious ¹ no serious indirectness serious ³ reporting bias ⁴ 376 203 - (ITT) (follow-up 8-12 weeks; assessed with: Number of people scorup serious ³ reporting bias ⁴ 94/389 27/206 RR 1.63 (0.97 to 2.73) (ITT) (follow-up 8-12 weeks; assessed with: Number of people show/up and inconsistency no serious indirectness serious ³ reporting bias ⁴ 94/389 27/206 RR 1.63 (0.97 to 2.73) (ITT) (follow-up 8-12 weeks; assessed with: Number of people show/up and inconsistency no serious indirectness serious ³ reporting bias ⁴ 94/389 23/206 RR 1.53 (0.97 to 2.73) 2.73)	Design Risk of bias Inconsistency Indirectness Imprecision Other considerations Switching to combined SSRI + antipsychotic - only Switching to antipsychotic - only Relative (95% CI) Absolute e symptomatology change score (follow-up 8-12 weeks; measured with: Montgomery Asberg Depression Rating Scale (MADRS) change from baseline to y lower values) no serious serious ³ reporting bias ⁴ 376 203 - SMD 0.44 lower (0.91 lower to 0.03 higher) (ITT) (follow-up 8-12 weeks; assessed with: Number of people scores no serious serious ³ reporting bias ⁴ 376 203 - SMD 0.44 lower (0.91 lower to 0.03 higher) (ITT) (follow-up 8-12 weeks; assessed with: Number of people scores serious ³ reporting bias ⁴ 94/389 27/206 (RR 1.63) 83 more per 1000 (ITT) (follow-up 8-12 weeks; assessed with: Number of people scores serious ³ reporting bias ⁴ 94/389 27/206 (RR 1.63) 83 more per 1000 (ITT) (follow-up 8-12 weeks; assessed with: Number of people scores serious ³ reporting bias ⁴ 94/389 27/206 (RR 1.63) 83 more per to 2.73) 27 more) (ITT) (follow-up 8-12 weeks; assessed with: Number of people scores serious ³ reporting bias ⁴ 94/389 <td>Jesign Risk of has Inconsistency Indirectness Imprecision Other considerations Switching to combined SSRI + antipsychotic-only Switching to antipsychotic-only Relative (95% CI) Absolute Absolute Imprecision Other considerations Switching to combined SSRI + antipsychotic-only Switching to antipsychotic-only Relative (95% CI) Absolute Imprecision Other considerations Switching to combined SSRI + antipsychotic-only Switching to antipsychotic-only Relative (95% CI) Absolute Imprecision Other considerations Switching to antipsychotic-only Relative (95% CI) Absolute Imprecision Other considerations Switching to antipsychotic-only Relative (95% CI) Absolute Imprecision Other considerations Switching to antipsychotic-only Relative (95% CI) Absolute Imprecision Other considerations Switching to antipsychotic-only Relative (95% CI) Absolute Imprecision Imprecision Switching to antipsychotic-only Relative (95% CI) Absolute Imprecision Imprecision</td>	Jesign Risk of has Inconsistency Indirectness Imprecision Other considerations Switching to combined SSRI + antipsychotic-only Switching to antipsychotic-only Relative (95% CI) Absolute Absolute Imprecision Other considerations Switching to combined SSRI + antipsychotic-only Switching to antipsychotic-only Relative (95% CI) Absolute Imprecision Other considerations Switching to combined SSRI + antipsychotic-only Switching to antipsychotic-only Relative (95% CI) Absolute Imprecision Other considerations Switching to antipsychotic-only Relative (95% CI) Absolute Imprecision Other considerations Switching to antipsychotic-only Relative (95% CI) Absolute Imprecision Other considerations Switching to antipsychotic-only Relative (95% CI) Absolute Imprecision Other considerations Switching to antipsychotic-only Relative (95% CI) Absolute Imprecision Imprecision Switching to antipsychotic-only Relative (95% CI) Absolute Imprecision Imprecision

2 (Corya 2006, Shelton 2005)	randomised trials		no serious inconsistency	no serious indirectness	serious ³	reporting bias ⁴	90/389 (23.1%)	50/206 (24.3%)	RR 0.89 (0.65 to 1.21)	27 fewer per 1000 (from 85 fewer to 51 more)	LOW	CRITICAL
Discontinua	ation due to s	ide effects	(follow-up 8-12	weeks; assess	ed with: Num	ber of participant	ts who dropped out d	ue to adverse ever	its)			
2 (Corya 2006, Shelton 2005)	randomised trials		no serious inconsistency	no serious indirectness	very serious⁵	reporting bias ⁴	39/389 (10%)	19/206 (9.2%)	RR 0.98 (0.48 to 2.03)	2 fewer per 1000 (from 48 fewer to 95 more)		CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SSRI: selective serotonin reuptake inhibitor

¹ Risk of bias is high or unclear across multiple domains

² Considerable heterogeneity

³ 95% CI crosses thresholds for both clinically important benefit and no effect

⁴ Funding from pharmaceutical companies

⁵ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 89: Clinical evidence profile for comparison 20. Augmenting with SSRI versus augmenting with lithium

Quality ass	sessment						No of patients		Effect		Quality	Importanc
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Augmenting with lithium	Relative (95% Cl)	Absolute		
	epression symptomatology change score (follow-up mean 10 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoin ndicated by lower values)											
1 (Navarro 2019b)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	52	52	-	SMD 0.56 lower (0.95 to 0.16 lower)	LOW	CRITICAL
Remission	(ITT) (follow-	up mean ⁻	10 weeks; assess	ed with: Number	of people s	coring <=7 on Han	nilton Rating Sca	ale for Depression	n (HAM-D))			
1 (Navarro 2019b)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	21/52 (40.4%)	11/52 (21.2%)	RR 1.91 (1.03 to	193 more per 1000 (from 6 more to 539	LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SSRI: selective serotonin reuptake inhibitor

¹ Risk of bias is high or unclear across multiple domains

² 95% CI crosses thresholds for both clinically important benefit and no effect

Table 90: Clinical evidence profile for comparison 21. Switching to TCA versus SSRI

Quality assessment	No of patients	Effect	Quality	Importance	,
--------------------	----------------	--------	---------	------------	---

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching to TCA	SSRI	Relative (95% Cl)	Absolute		
Depression	n symptomato	logy endpoin	t (follow-up mean 4	4 weeks; measure	ed with: Ham	ilton Rating Scale	for Depressio	on (HAM	-D); Better ind	licated by lower values)		
1 (Souery 2011a)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	67	85	-	SMD 0.2 lower (0.52 lower to 0.12 higher)	VERY LOW	CRITICAL
Remission (ITT) (follow-up mean 4 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Souery 2011a)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	21/84 (25%)	16/105 (15.2%)	•	98 more per 1000 (from 12 fewer to 296 more)	VERY LOW	CRITICAL
Response	(ITT) (follow-u	ip mean 4 wee	ks; assessed with	: Number of peop	ole showing	at least 50% impro	vement on Ha	milton	Rating Scale for	or Depression (HAM-D))		
1 (Souery 2011a)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ³	37/84 (44%)	46/105 (43.8%)	``	4 more per 1000 (from 118 fewer to 171 more)	VERY LOW	CRITICAL
Discontinu	ation due to a	iny reason (fo	llow-up mean 4 we	eks; assessed w	ith: Number	of participants wh	o dropped ou	t for any	reason (inclu	ding adverse events))		
1 (Souery 2011a)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ³	17/84 (20.2%)	20/105 (19%)	RR 1.06 (0.6 to 1.9)	11 more per 1000 (from 76 fewer to 171 more)	VERY LOW	CRITICAL
CI: confide	ence interval;	ITT: intention	to treat; RR: rela	tive risk; SMD: s	standardised	l mean difference	; SSRI: selec	tive ser	otonin reupta	ke inhibitor; TCA: tricyc	lic antide	epressant

¹ Risk of bias is high or unclear across multiple domains
 ² 95% Cl crosses thresholds for both clinically important benefit and no effect
 ³ Study partially funded by pharmaceutical company
 ⁴ 95% Cl crosses thresholds for no effect, and both clinically important benefit and harm

Table 91: Clinical evidence profile for comparison 22. Switching to TCA versus augmenting with mirtazapine

Quality ass	ality assessment							ts	Effect		Quality	Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Improcision		Switching to TCA	Augmenting with mirtazapine	Relative (95% Cl)	Absolute			
Depressio	Depression symptomatology endpoint (follow-up mean 10 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												
1 (Navarro 2019a)		· · ·		no serious indirectness	no serious imprecision	none	56	56	-	SMD 1.13 lower (1.53 to 0.73 lower)	LOW	CRITICAL	
	Depression symptomatology change score (follow-up mean 10 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
1 (Navarro 2019a)		very serious¹			no serious imprecision	none	56	56	-	SMD 1.47 lower (1.88 to 1.05 lower)	LOW	CRITICAL	
Remission	(ITT) (follow-	up mean	10 weeks: assess	ed with: Numbe	r of people sco	ring <=7 on Hamil	ton Rating S	cale for Depressio	n (HAM-D))				

1 (Navarro 2019a)	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	40/56 (71.4%)	22/56 (39.3%)	RR 1.82 (1.26 to 2.62)	322 more per 1000 (from 102 more to 636 more)	LOW	CRITICAL
Discontinu	ation due to a	any reaso	on (follow-up mea	n 10 weeks; ass	essed with: Nu	mber of participan	ts who dropp	ed out for any rea	son (includi	ng adverse events))		
1 (Navarro 2019a)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	5/56 (8.9%)	2/56 (3.6%)	· · ·	54 more per 1000 (from 18 fewer to 405 more)		CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; TCA: tricyclic antidepressant

¹ Risk of bias is high or unclear across multiple domains and rapid tapering of failed drug in switch arm

² 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 92: Clinical evidence profile for comparison 23. Switching to mianserin versus continuing with antidepressant

Quality as	f Risk of Constant Other							i -	Effect		Quality	Importanc
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching to mianserin	Continuing with antidepressant	Relative (95% Cl)	Absolute		
	epression symptomatology change score (follow-up mean 6 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from ba dicated by lower values)											ter
1 (Ferreri 2001)	randomised trials	very serious¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	33	38	-	SMD 0.24 lower (0.71 lower to 0.23 higher)	VERY LOW	CRITICAL
Remission (ITT) (follow-up mean 6 weeks; assessed with: Number of people scoring <=8 on Hamilton Rating Scale for Depression (HAM-D))												
•	randomised trials	very serious¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	12/34 (35.3%)	7/38 (18.4%)	RR 1.92 (0.85 to 4.3)	169 more per 1000 (from 28 fewer to 608 more)	VERY LOW	CRITICAL
Response	e (ITT) (follow	-up mean	6 weeks; assess	ed with: Numbe	r of people s	howing at least 5	0% improveme	ent on Hamilton Ratir	ng Scale for De	epression (HAM-D))		
1 (Ferreri 2001)	randomised trials	very serious¹	no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ³	16/34 (47.1%)	14/38 (36.8%)	RR 1.28 (0.74 to 2.21)	103 more per 1000 (from 96 fewer to 446 more)	VERY LOW	CRITICAL
Discontin	uation due to	o any reas	on (follow-up me	an 6 weeks; ass	essed with:	Number of partici	pants who dro	pped out for any rea	son (including	adverse events))		
1 (Ferreri 2001)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious⁵	reporting bias ³	12/34 (35.3%)	7/38 (18.4%)	RR 1.92 (0.85 to 4.3)	169 more per 1000 (from 28 fewer to 608 more)	VERY LOW	CRITICAL
Discontin	uation due to	side effe	ects (follow-up me	an 6 weeks; as	sessed with:	Number of partic	ipants who dro	pped out due to adv	erse events)			
•	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	reporting bias ³	8/34 (23.5%)	0/38 (0%)	RR 18.94 (1.13 to 316.35)	-	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference

¹ Risk of bias is high or unclear across multiple domains and abrupt tapering for the switch arm

² 95% CI crosses thresholds for both clinically important benefit and no effect

³ Study funded by pharmaceutical company

⁴ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
 ⁵ 95% CI crosses thresholds for both clinically important harm and no effect

Table 93: Clinical evidence profile for comparison 24. Augmenting with mianserin versus continuing with antidepressant (+/- placebo)

Quality ass	ality assessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Improcision	Other considerations	Augmenting with mianserin	Continuing with antidepressant (+/- placebo)	Relative (95% Cl)	Absolute		
	n symptomato y lower value		ge score (follow-	up mean 6 wee	ks; measure	d with: Hamilton	Rating Scale for	Depression (HAM-D)	change from	baseline to endpo	oint; Bet	ter
1 (Ferreri 2001)	randomised trials		no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	32	38	-	SMD 0.66 lower (1.14 to 0.17 lower)	VERY LOW	CRITICAL
Remission	(ITT) (follow-	up 5-6 weel	ks; assessed wit	h: Number of p	eople scorin	g <=7/<=8 on Hai	milton Rating Sc	ale for Depression (HA	AM-D))			
2 (Ferreri 2001, Licht 2002)	randomised trials	serious ¹	serious ⁴	no serious indirectness	very serious⁵	reporting bias ³	57/130 (43.8%)	44/137 (32.1%)	RR 1.53 (0.78 to 2.99)	170 more per 1000 (from 71 fewer to 639 more)	VERY LOW	CRITICAL
Response ((ITT) (follow-u	up 5-6 week	s; assessed witl	n: Number of p	eople showin	ig at least 50% in	nprovement on H	lamilton Rating Scale	for Depressi	on (HAM-D))		
2 (Ferreri 2001, Licht 2002)	randomised trials	serious ¹	serious ⁴	no serious indirectness	very serious⁵	reporting bias ³	86/130 (66.2%)	83/137 (60.6%)	RR 1.22 (0.7 to 2.13)	133 more per 1000 (from 182 fewer to 685 more)	VERY LOW	CRITICAL
Discontinu	ation due to a	any reason	(follow-up 5-6 w	eeks; assessed	with: Numb	er of participants	who dropped o	ut for any reason (incl	uding advers	se events))		
2 (Ferreri 2001, Licht 2002)	randomised trials		no serious inconsistency	no serious indirectness	very serious ⁵	reporting bias ³	23/130 (17.7%)	17/137 (12.4%)	RR 1.43 (0.79 to 2.56)	53 more per 1000 (from 26 fewer to 194 more)	VERY LOW	CRITICAL
Discontinu	ation due to	side effects	(follow-up mean	n 6 weeks; asse	ssed with: N	umber of particip	pants who dropp	ed out due to adverse	events)			
1 (Ferreri 2001)	randomised trials		no serious inconsistency	no serious indirectness	very serious⁵	reporting bias ³	2/32 (6.3%)	0/38 (0%)	RR 5.91 (0.29 to 118.78)	-	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference

¹ Risk of bias is high or unclear across multiple domains

² 95% CI crosses thresholds for both clinically important benefit and harm

³ Funding from pharmaceutical company

⁴ Substantial heterogeneity

⁵ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 94: Clinical evidence profile for comparison 25. Augmenting with mianserin versus increasing dose of antidepressant

Quality a	ality assessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with mianserin	Increasing dose of antidepressant	Relative (95% Cl)	Absolute		
Remissio	on (ITT) (follo	w-up mean	5 weeks; assess	ed with: Numbe	r of people s	coring <=7 on Ha	milton Rating Sc	ale for Depression (H	IAM-D))			
•	randomised trials		no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	43/98 (43.9%)	28/98 (28.6%)	RR 1.54 (1.05 to 2.26)	154 more per 1000 (from 14 more to 360 more)	VERY LOW	CRITICAL
Respons	e (ITT) (follov	w-up mean {	5 weeks; assesse	d with: Number	of people sl	nowing at least 50	0% improvement	on Hamilton Rating	Scale for Dep	pression (HAM-D))		
•	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	66/98 (67.3%)	54/98 (55.1%)	RR 1.22 (0.98 to 1.53)	121 more per 1000 (from 11 fewer to 292 more)	VERY LOW	CRITICAL
Discontir	nuation due t	o any reaso	n (follow-up mea	n 5 weeks; asse	essed with: N	lumber of partici	pants who dropp	ed out for any reasor	n (including a	adverse events))		
•	randomised trials	no serious risk of bias	no serious inconsistency		very serious ⁴	reporting bias ³	17/98 (17.3%)	15/98 (15.3%)	RR 1.13 (0.6 to 2.14)	20 more per 1000 (from 61 fewer to 174 more)	VERY LOW	CRITICAL
CI: confid	dence interv	al; ITT: inte	ntion to treat; RI	R: relative risk								

¹ Risk of bias is high or unclear across multiple domains

² 95% CI crosses thresholds for both clinically important benefit and no effect

³ Study funded by pharmaceutical company

⁴ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 95: Clinical evidence profile for comparison 26. Augmenting with mianserin versus switch to mianserin

			Quality	Importance
Design inconsistency indirectness imprecision	Augmenting with Switch to mianserin mianserin	Relative (95% CI) Absolute		

Depression symptomatology change score (follow-up mean 6 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)

1 (Ferreri 2001)	randomised trials	very serious¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	32	33	-	SMD 0.41 lower (0.91 lower to 0.08 higher)	VERY LOW	CRITICAL
Remissio	n (ITT) (follov	v-up mean 6	weeks; assessed	l with: Number o	f people sco	ring <=8 on Hamil	ton Rating Scale for	or Depression	(HAM-D))			
1 (Ferreri 2001)	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ³	14/32 (43.8%)	12/34 (35.3%)	RR 1.24 (0.68 to 2.26)	85 more per 1000 (from 113 fewer to 445 more)	VERY LOW	CRITICAL
Response	e (ITT) (follow	-up mean 6	weeks; assessed	with: Number of	people show	wing at least 50%	improvement on H	lamilton Ratin	g Scale for I	Depression (HAM-D))		
1 (Ferreri 2001)	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	20/32 (62.5%)	16/34 (47.1%)	RR 1.33 (0.85 to 2.08)	155 more per 1000 (from 71 fewer to 508 more)	VERY LOW	CRITICAL
Discontin	uation due to	any reason	(follow-up mean	6 weeks; assess	ed with: Nur	nber of participan	ts who dropped ou	ut for any reas	on (includin	g adverse events))		
1 (Ferreri 2001)	randomised trials		no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ³	6/32 (18.8%)	12/34 (35.3%)	RR 0.53 (0.23 to 1.25)	166 fewer per 1000 (from 272 fewer to 88 more)	VERY LOW	CRITICAL
Discontin	uation due to	side effects	(follow-up mean	6 weeks; asses	sed with: Nu	mber of participar	nts who dropped o	ut due to adve	erse events)			
1 (Ferreri 2001)	randomised trials		no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	2/32 (6.3%)	8/34 (23.5%)	RR 0.27 (0.06 to 1.16)	172 fewer per 1000 (from 221 fewer to 38 more)	LOW	CRITICAL

¹ Risk of bias is high or unclear across multiple domains and abrupt tapering for the switch arm
 ² 95% CI crosses thresholds for both clinically important benefit and no effect
 ³ Study funded by pharmaceutical company
 ⁴ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 96: Clinical evidence profile for comparison 27. Increasing the dose of SNRI versus continuing SNRI at the same dose

Quality asse	ality assessment								Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Improcision		Increasing the dose of SNRI	Continuing SNRI at the same dose		Absolute		
	symptomato / lower value		nge score (follow	-up mean 8 wee	ks; measured v	with: Hamilton Ra	ting Scale for D	epression (HAM-D)) change fro	m baseline to endpo	oint; Bett	er
1 (Kornstein 2008)	randomised trials	very serious¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ²	118	130	-	SMD 0.01 higher (0.24 lower to 0.26 higher)		CRITICAL
Remission (ITT) (follow-i	up mean 8	8 weeks; assesse	d with: Number	of people scor	ing <=7 on Hamil	ton Rating Scale	e for Depression (H	IAM-D))			
·	randomised trials	J .	no serious inconsistency	no serious indirectness	very serious ³	reporting bias ²	36/124 (29%)	39/131 (29.8%)	RR 0.98 (0.67 to 1.43)	6 fewer per 1000 (from 98 fewer to 128 more)	VERY LOW	CRITICAL

Depression in adults: Evidence review D FINAL (June 2022)

Response ((ITT) (follow-u	ip mean 8	weeks; assesse	d with: Number	of people show	ving at least 50% i	improvement on	Hamilton Rating S	cale for Dep	pression (HAM-D))		
1 (Kornstein 2008)	n randomised trials	J .	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ²	48/124 (38.7%)	58/131 (44.3%)	RR 0.87 (0.65 to 1.17)	58 fewer per 1000 (from 155 fewer to 75 more)	VERY LOW	CRITICAL
Discontinua	ation due to a	iny reaso	n (follow-up mea	n 8 weeks; asse	ssed with: Nun	nber of participan	ts who dropped	out for any reason	(including	adverse events))		
1 (Kornstein 2008)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ²	34/124 (27.4%)	26/131 (19.8%)	RR 1.38 (0.88 to 2.16)	75 more per 1000 (from 24 fewer to 230 more)	VERY LOW	CRITICAL
Discontinua	ation due to s	ide effect	ts (follow-up mea	n 8 weeks; asse	essed with: Nur	nber of participan	its who dropped	out due to adverse	e events)			
1 (Kornstein 2008)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	reporting bias ²	7/124 (5.6%)	6/131 (4.6%)	RR 1.23 (0.43 to 3.57)	11 more per 1000 (from 26 fewer to 118 more)	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SNRI: serotonin-norepinephrine reuptake inhibitor

¹ Risk of bias is high or unclear across multiple domains
 ² Study funded by pharmaceutical company
 ³ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
 ⁴ 95% CI crosses thresholds for both clinically important harm and no effect

Table 97: Clinical evidence profile f	or comparison 28.	Switching to SNRI versu	s continuing with antidepressant
		J	· · · · · · · · · · · · · · · · · · ·

Quality a	uality assessment						No of patients Effect				Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		Switching to SNRI	Continuing with antidepressant	Relative (95% Cl)	Absolute		
Remissio	n (ITT) (follo	w-up mea	n 8 weeks; asses	sed with: Numb	er of people sc	oring <=7 on Ham	ilton Rating	Scale for Depressior	(HAM-D))			
· · ·	randomised trials	· ·	no serious inconsistency	no serious indirectness	very serious ²	none	21/50 (42%)	21/45 (46.7%)	RR 0.9 (0.57 to 1.41)	47 fewer per 1000 (from 201 fewer to 191 more)	VERY LOW	CRITICAL
Response	e (ITT) (follov	v-up mear	n 8 weeks; assess	ed with: Numbe	er of people sho	owing at least 50%	improveme	nt on Hamilton Ratin	g Scale for D	epression (HAM-D))		
· · ·	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	32/50 (64%)	30/45 (66.7%)	RR 0.96 (0.72 to 1.29)	27 fewer per 1000 (from 187 fewer to 193 more)	VERY LOW	CRITICAL
Discontir	uation due to	o any reas	son (follow-up me	an 8 weeks; as	sessed with: Nu	mber of participa	nts who drop	oped out for any reas	on (includin	g adverse events))		
	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	9/50 (18%)	8/45 (17.8%)	RR 1.01 (0.43 to 2.4)	2 more per 1000 (from 101 fewer to 249 more)	VERY LOW	CRITICAL
Discontir	continuation due to side effects (follow-up mean 8 weeks; assessed with: Number of participants who dropped out due to adverse events)											

1 (Fang 2010)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	0/50 (0%)	1/45 (2.2%)	RR 0.3 (0.01 to 7.2)	16 fewer per 1000 (from 22 fewer to 138 more)	VERY LOW	CRITICAL
	of life physica r values)	l compor	nent score (PCS)	change score (f	ollow-up mean	8 weeks; measure	d with: 36-ite	m Short-Form Surve	y (SF-36): Ph	iysical component s	core; Be	tter indicated
1 (Fang 2010)	randomised trials	very serious¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	45	-	SMD 0.02 higher (0.38 lower to 0.42 higher)	LOW	IMPORTANT
Quality of higher values		compone	nt score (MCS) c	hange score (fo	llow-up mean 8	weeks; measured	with: 36-iten	n Short-Form Survey	(SF-36): Mer	ntal component scor	e; Better	indicated by
1 (Fang 2010)	randomised trials	very serious¹	no serious inconsistency	no serious indirectness	serious ³	none	50	45	-	SMD 0.14 higher (0.26 lower to 0.54 higher)	VERY LOW	IMPORTANT

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SNRI: serotonin-norepinephrine reuptake inhibitor ¹ Risk of bias is high or unclear across multiple domains

² 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
 ³ 95% CI crosses thresholds for both clinically important benefit and no effect

Table 98: Clinical evidence profile for comparison 29. Switching to SNRI versus switching to another antidepressant from same class

Quality assess	ality assessment							nts	Effect		Quality	Importanc
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching to SNRI	Switching to another antidepressant from same class	Relative (95% Cl)	Absolute		
		•••	score (follow-u point; Better indi			: Hamilton Rating	g Scale for D	Depression (HAM-D) or	Quick Inve	ntory of Depres	sive Symptor	matology
2 (Poirier 1999, Rush 2006)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	302	293	-	SMD 0.05 higher (0.11 lower to 0.21 higher)	MODERATE	CRITICAL
Remission (IT Symptomatolo		4-14 week	s; assessed wit	h: Number of p	eople scoring	<=4/<10 on Hami	ilton Rating	Scale for Depression (HAM-D) or	<=5 on Quick Inv	ventory of De	epressive
3 (Lenox-Smith 2008, Poirier 1999, Rush 2006)	randomised trials	serious ¹	very serious ²	no serious indirectness	serious ³	reporting bias ⁴	145/511 (28.4%)	107/506 (21.1%)	RR 1.48 (0.86 to 2.56)	102 more per 1000 (from 30 fewer to 330 more)	VERY LOW	CRITICAL

improved on CGI-I (score 1-2) or at least 50% improvement on Quick Inventory of Depressive Symptomatology (QIDS))

2 (Poirier 1999, Rush 2006)	randomised trials		no serious inconsistency	no serious indirectness	serious ³	none	97/311 (31.2%)	81/300 (27%)	RR 1.21 (0.85 to 1.7)	57 more per 1000 (from 40 fewer to 189 more)	LOW	CRITICAL
Discontinuatio	on due to any	/ reason (f	ollow-up 4-12 w	eeks; assessed	l with: Number	r of participants v	vho dropped	l out for any reason (in	cluding ad	verse events))		
2 (Lenox-Smith 2008, Poirier 1999)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious⁵	reporting bias ⁴	58/261 (22.2%)	50/268 (18.7%)	RR 1.19 (0.85 to 1.67)	35 more per 1000 (from 28 fewer to 125 more)	LOW	CRITICAL
Discontinuatio	on due to sid	e effects (f	follow-up 4-14 w	veeks; assessed	d with: Numbe	r of participants	who dropped	d out due to adverse ev	vents)			
3 (Lenox-Smith 2008, Poirier 1999, Rush 2006)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ⁶	none	69/511 (13.5%)	64/506 (12.6%)	RR 1.04 (0.76 to 1.41)	5 more per 1000 (from 30 fewer to 52 more)	LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SNRI: serotonin-norepinephrine reuptake inhibitor

- ¹ Risk of bias is high or unclear across multiple domains
- ² Considerable heterogeneity
- ³ 95% CI crosses thresholds for both clinically important benefit and no effect
- ⁴ Funding from pharmaceutical companies
 ⁵ 95% CI crosses thresholds for both clinically important harm and no effect
- ⁶ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 99: Clinical evidence profile for comparison 30. Switching to SNRI versus switching to bupropion

Quality a	ssessment						No of patient	s	Effect		Quality	Importance
No of studies	Docian	Risk of bias	Inconsistency	Indirectness	Improcision		Switching to SNRI	Switching to bupropion	Relative (95% Cl)	Absolute		
	epression symptomatology change score (follow-up mean 14 weeks; measured with: Quick Inventory of Depressive Symptomatology (QIDS) change from baseline to etter indicated by lower values)											ooint;
1 (Rush 2006)					no serious imprecision	none	250	239	-	SMD 0.01 lower (0.19 lower to 0.17 higher)	LOW	CRITICAL
Remissio	n (ITT) (follow	/-up mean	14 weeks; asses	sed with: Numbe	er of people sco	ring <=5 on Quick	Inventory of	Depressive Syn	nptomatology	(QIDS))		
1 (Rush 2006)		,		no serious indirectness	very serious ²	none	62/250 (24.8%)	61/239 (25.5%)		8 fewer per 1000 (from 71 fewer to 82 more)	VERY LOW	CRITICAL
Response	esponse (ITT) (follow-up mean 14 weeks; assessed with: Number of people showing at least 50% improvement on Quick Inventory of Depressive Symptomatology (QIDS)										y (QIDS))	

1 (Rush 2006)	randomised trials		no serious inconsistency	no serious indirectness	serious ³	none	70/250 (28%)	62/239 (25.9%)	RR 1.08 (0.81 to 1.45)	21 more per 1000 (from 49 fewer to 117 more)	VERY LOW	CRITICAL	
Discontir	Discontinuation due to side effects (follow-up mean 14 weeks; assessed with: Number of participants who dropped out due to adverse events)												
1 (Rush 2006)	randomised trials		no serious inconsistency	no serious indirectness	serious ³	none	53/250 (21.2%)	65/239 (27.2%)	RR 0.78 (0.57 to 1.07)	60 fewer per 1000 (from 117 fewer to 19 more)	LOW	CRITICAL	

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SNRI: serotonin-norepinephrine reuptake inhibitor

¹ Risk of bias is high or unclear across multiple domains and abrupt tapering of failed drug
 ² 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
 ³ 95% CI crosses thresholds for both clinically important benefit and no effect

Table 100: Clinical evidence profile for comparison 31. Switching to SNRI versus switching to mirtazapine

Quality assessment								No of patients			Quality	Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching to SNRI	Switching to mirtazapine	Relative (95% Cl)	Absolute			
Remissio	Remission (ITT) (follow-up mean 8 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Fang 2010)	randomised trials	· - · J	no serious inconsistency	no serious indirectness	very serious ²	none	21/50 (42%)	20/55 (36.4%)	RR 1.15 (0.72 to 1.86)	55 more per 1000 (from 102 fewer to 313 more)	VERY LOW	CRITICAL	
Respons	Response (ITT) (follow-up mean 8 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												
1 (Fang 2010)	randomised trials	very serious¹	no serious inconsistency	no serious indirectness	serious ³	none	32/50 (64%)	32/55 (58.2%)	RR 1.1 (0.81 to 1.49)	58 more per 1000 (from 111 fewer to 285 more)	VERY LOW	CRITICAL	
Discontii	nuation due to	o any reas	son (follow-up me	ean 8 weeks; as	sessed with: Nu	umber of participa	nts who drop	oped out for any	reason (inclu	uding adverse events	5))		
1 (Fang 2010)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	9/50 (18%)	10/55 (18.2%)	RR 0.99 (0.44 to 2.24)	2 fewer per 1000 (from 102 fewer to 225 more)	VERY LOW	CRITICAL	
Discontii	nuation due to	o side effe	ects (follow-up m	ean 8 weeks; as	sessed with: N	umber of participa	nts who dro	pped out due to	adverse ever	nts)			
1 (Fang 2010)	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	0/50 (0%)	0/55 (0%)	not pooled	not pooled	MODERATE	CRITICAL	
Quality o by highe		l compon	ent score (PCS) c	hange score (fo	ellow-up mean 8	3 weeks; measure	d with: 36-ite	m Short-Form S	urvey (SF-36)	: Physical compone	nt score; Bet	tter indicated	
1 (Fang 2010)	randomised trials	very serious¹	no serious inconsistency	no serious indirectness	serious ³	none	50	55	-	SMD 0.29 higher (0.09 lower to 0.68 higher)	VERY LOW	IMPORTANT	

Quality of life mental component score (MCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (SF-36): Mental component score; Better indicated by higher values)

1 (Fang 2010)	randomised trials	no serious inconsistency	no serious indirectness	serious ³	none	50	55	-	SMD 0.3 higher (0.08 lower to 0.69	VERY LOW IMPORTANT
_0.0)		 							higher)	

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SNRI: serotonin-norepinephrine reuptake inhibitor

¹ Risk of bias is high or unclear across multiple domains
 ² 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

³ 95% CI crosses thresholds for both clinically important benefit and no effect

Table 101: Clinical evidence profile for comparison 32. Switching to bupropion versus placebo

Quality assessment								No of patients			Quality	Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		Switching to bupropion	Placebo	Relative (95% Cl)	Absolute			
Depression symptomatology change score (follow-up mean 12 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better ndicated by lower values)													
1 (GlaxoSmithKline 2009)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ²	165	157	-	SMD 0.02 higher (0.19 lower to 0.24 higher)	LOW	CRITICAL	
Remission (ITT) (fo	Remission (ITT) (follow-up mean 12 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (GlaxoSmithKline 2009)	randomised trials		no serious inconsistency	no serious indirectness	very serious ³	reporting bias ²	40/166 (24.1%)	39/159 (24.5%)	RR 0.98 (0.67 to 1.44)	5 fewer per 1000 (from 81 fewer to 108 more)		CRITICAL	
Response (ITT) (fo	llow-up mear	n 12 week	s; assessed with:	Number of peo	ple showing at	east 50% improve	ment on Hamil	ton Ratin	ig Scale for I	Depression (HAM-D))			
1 (GlaxoSmithKline 2009)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	reporting bias ²	63/166 (38%)	58/159 (36.5%)	RR 1.04 (0.78 to 1.38)	15 more per 1000 (from 80 fewer to 139 more)		CRITICAL	
Discontinuation du	ue to any reas	son (follow	w-up mean 12 wee	eks; assessed w	ith: Number of	participants who	dropped out fo	r any rea	son (includir	ng adverse events))			
1 (GlaxoSmithKline 2009)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ²	67/166 (40.4%)	47/159 (29.6%)	RR 1.37 (1.01 to 1.85)	109 more per 1000 (from 3 more to 251 more)	VERY LOW	CRITICAL	
Discontinuation du	ue to side effe	ects (follo	w-up mean 12 we	eks; assessed v	vith: Number of	participants who	dropped out du	ue to adv	erse events)				
1 (GlaxoSmithKline 2009)	randomised trials		no serious inconsistency	no serious indirectness	very serious ³	reporting bias ²	39/166 (23.5%)	31/159 (19.5%)	RR 1.21 (0.79 to 1.83)	41 more per 1000 (from 41 fewer to 162 more)		CRITICAL	

Depression in adults: Evidence review D FINAL (June 2022)

¹ Rapid tapering of previous treatment

² Study run and funded by pharmaceutical company
 ³ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

⁴ 95% CI crosses thresholds for both clinically important harm and no effect

Table 102: Clinical evidence profile for comparison 33. Switching to bupropion versus switching to another antidepressant from same class

Quality assessment								3	Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching to bupropion	Switching to another antidepressant from same class	Relative (95% Cl)	Absolute		
Depression symptomatology change score (follow-up mean 14 weeks; measured with: Quick Inventory of Depressive Symptomatology (QIDS) change from baseline to endpoint; Better indicated by lower values)												
1 (Rush 2006)	randomised trials	J .	no serious inconsistency	no serious indirectness	no serious imprecision	none	239	238	-	SMD 0.12 higher (0.06 lower to 0.3 higher)	LOW	CRITICAL
Remissio	on (ITT) (follo	w-up mea	n 14 weeks; ass	essed with: Nu	mber of people	scoring <=5 on (Quick Inventor	y of Depressive Symptom	atology (QI	DS))		
1 (Rush 2006)	randomised trials	very serious¹	no serious inconsistency	no serious indirectness	very serious ²	none	61/239 (25.5%)	63/238 (26.5%)	RR 0.96 (0.71 to 1.31)	11 fewer per 1000 (from 77 fewer to 82 more)		CRITICAL
Respons	e (ITT) (follo	w-up mea	n 14 weeks; asse	essed with: Nun	nber of people	showing at least	50% improven	nent on Quick Inventory o	f Depressiv	e Symptomatology	(QIDS))	
1 (Rush 2006)	randomised trials	very serious¹	no serious inconsistency	no serious indirectness	very serious ²	none	62/239 (25.9%)	63/238 (26.5%)	RR 0.98 (0.73 to 1.32)	5 fewer per 1000 (from 71 fewer to 85 more)	VERY LOW	CRITICAL
Disconti	nuation due t	o side eff	ects (follow-up n	nean 14 weeks;	assessed with	: Number of parti	icipants who d	ropped out due to advers	e events)			
1 (Rush 2006)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	65/239 (27.2%)	50/238 (21%)	RR 1.29 (0.94 to 1.79)	61 more per 1000 (from 13 fewer to 166 more)	LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference

¹ Risk of bias is high or unclear across multiple domains and abrupt tapering of failed drug

² 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

³ 95% CI crosses thresholds for both clinically important harm and no effect

Table 103: Clinical evidence profile for comparison 34. Augmenting with bupropion versus placebo

Quality as	ssessment						No of patients		Effect		Quality	Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with bupropion	Placebo					
Remissio	Remission (ITT) (follow-up mean 4 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))												
1 (Gulrez 2012)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/30 (60%)	7/30 (23.3%)	RR 2.57 (1.26 to 5.24)	366 more per 1000 (from 61 more to 989 more)		CRITICAL	

CI: confidence interval; ITT: intention to treat; RR: relative risk

¹ Risk of bias is high or unclear across multiple domains

Table 104: Clinical evidence profile for comparison 35. Augmenting with bupropion versus switching to bupropion

Quality asse	ssment						No of patients		Effect		Quality	Importance		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with bupropion	Switching to bupropion	Relative (95% Cl)	Absolute				
Remission (I	TT) (follow-u	up mean 12	weeks; assesse	d with: Number	of people sco	ring <=5 on Quick	Inventory of De	pressive Symp	otomatology	(QIDS))				
1 (Mohamed 2017)			no serious inconsistency	no serious indirectness	serious ¹	none	136/506 (26.9%)	114/511 (22.3%)	RR 1.2 (0.97 to 1.5)	45 more per 1000 (from 7 fewer to 112 more)	MODERATE	CRITICAL		
Response (l ⁻	esponse (ITT) (follow-up mean 12 weeks; assessed with: Number of people showing at least 50% improvement on Quick Inventory of Depressive Symptomatology (QIDS))													
1 (Mohamed 2017)			no serious inconsistency	no serious indirectness	no serious imprecision	none	332/506 (65.6%)	319/511 (62.4%)	RR 1.05 (0.96 to 1.15)	31 more per 1000 (from 25 fewer to 94 more)	HIGH	CRITICAL		
Discontinuat	tion due to a	ny reason (follow-up mean	12 weeks; asse	ssed with: Nun	nber of participar	its who dropped	out for any rea	ason (includi	ng adverse events	5))			
1 (Mohamed 2017)			no serious inconsistency	no serious indirectness	serious ¹	none	128/506 (25.3%)	158/511 (30.9%)	RR 0.82 (0.67 to 1)	56 fewer per 1000 (from 102 fewer to 0 more)		CRITICAL		
Discontinuat	tion due to s	ide effects	(follow-up mean	12 weeks; asse	ssed with: Nu	mber of participa	nts who dropped	out due to adv	verse events)				
1 (Mohamed 2017)			no serious inconsistency	no serious indirectness	serious ¹	none	37/506 (7.3%)	51/511 (10%)	RR 0.73 (0.49 to 1.1)	27 fewer per 1000 (from 51 fewer to 10 more)	MODERATE	CRITICAL		

CI: confidence interval; ITT: intention to treat; RR: relative risk

¹ 95% CI crosses thresholds for both clinically important benefit and no effect

Table 105: Clinical evidence profile for comparison 36. Switching to mirtazapine versus continuing with antidepressant

Quality asse	ssment						No of patients	i	Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching to mirtazapine	Continuing with antidepressant	Relative (95% CI)	Absolute		
Depression s indicated by			int (follow-up m	ean 6 weeks; m	neasured with:	Patient Health Q	uestionnaire (I	PHQ-9) or Hamilton	Rating Sca	le for Depressio	n (HAM-D); B	etter
2 (Kato 2018, Xiao 2020)	randomised trials	no serious risk of bias		no serious indirectness	serious ²	none	618	605	-	SMD 0.21 lower (0.58 lower to 0.17 higher)	LOW	CRITICAL
Depression s indicated by			e score (follow-	up mean 6 weel	ks; measured	with: Hamilton Ra	ating Scale for	Depression (HAM-	D) change f	rom baseline to e	endpoint; Be	tter
1 (Xiao 2020)	randomised trials		no serious inconsistency	no serious indirectness	serious ²	reporting bias ⁴	68	68	-	SMD 0.19 lower (0.53 lower to 0.15 higher)	VERY LOW	CRITICAL
Depression s	symptomato	ogy at 4-m	onth follow-up (follow-up mean	4 months; m	easured with: Pat	ient Health Qu	estionnaire (PHQ-9); Better ind	dicated by lower	values)	
1 (Kato 2018)	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	540	538	-	SMD 0.01 higher (0.11 lower to 0.13 higher)	HIGH	CRITICAL
Remission (I	TT) (follow-u	p 6-8 week	s; assessed wit	h: Number of p	eople scoring	<=7 on Hamilton	Rating Scale f	or Depression (HAM	I-D) or <=4	on Patient Health	n Questionna	aire (PHQ-9)
3 (Fang 2010, Kato 2018, Xiao 2020)	randomised trials	no serious risk of bias		no serious indirectness	serious ²	none	232/681 (34.1%)	185/664 (27.9%)	RR 1.22 (1.04 to 1.43)	61 more per 1000 (from 11 more to 120 more)	LOW	CRITICAL
Remission (I	TT) at 4-mon	th follow-u	p (follow-up me	an 4 months; as	ssessed with:	Number of peopl	e scoring <=4	on Patient Health Q	uestionnai	re (PHQ-9))		
1 (Kato 2018)	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	262/558 (47%)	245/551 (44.5%)	RR 1.06 (0.93 to 1.2)	27 more per 1000 (from 31 fewer to 89 more)	HIGH	CRITICAL
Response (I1 Questionnaii		o 6-8 weeks	; assessed with	: Number of pe	ople showing	at least 50% imp	rovement on H	lamilton Rating Sca	le for Depr	ession (HAM-D) o	or Patient He	alth
3 (Fang 2010, Kato 2018, Xiao 2020)	randomised trials		no serious inconsistency	no serious indirectness	serious ²	none	357/681 (52.4%)	306/664 (46.1%)	RR 1.1 (0.95 to 1.28)	46 more per 1000 (from 23 fewer to 129 more)	MODERATE	CRITICAL

8 (Fang 2010, Kato 2018, Xiao 2020)	randomised trials	serious⁵	no serious inconsistency	no serious indirectness	very serious ⁶	reporting bias ⁷	30/681 (4.4%)	34/664 (5.1%)	RR 0.85 (0.54 to 1.36)	8 fewer per 1000 (from 24 fewer to 18 more)	VERY LOW	CRITICAL
Discontinua	tion due to si	ide effects	(follow-up 6-8 w	eeks; assesse	d with: Numbe	r of participants v	who dropped ou	ut due to adverse e	vents)			
2 (Fang 2010, Xiao 2020)	randomised trials	serious⁵	no serious inconsistency	no serious indirectness	very serious ⁶	reporting bias ⁷	3/123 (2.4%)	2/113 (1.8%)	RR 1.19 (0.12 to 11.73)	3 more per 1000 (from 16 fewer to 190 more)	VERY LOW	CRITICAL
Quality of life by higher va		omponent	score (PCS) cha	nge score (follo	ow-up mean 8	weeks; measured	with: 36-item S	Short-Form Survey	(SF-36): Pł	nysical componer	nt score; Bet	ter indicated
l (Fang 2010)	randomised trials	very serious ⁸	no serious inconsistency	no serious indirectness	serious ⁹	none	55	45	-	SMD 0.28 lower (0.67 lower to 0.12 higher)	VERY LOW	IMPORTAN ⁻
Quality of lif		nponent so	core (MCS) chan	ge score (follov	w-up mean 8 w	eeks; measured v	with: 36-item SI	hort-Form Survey (SF-36): Mei	ntal component s	core; Better	indicated by
1 (Fang 2010)	randomised trials	very serious ⁸	no serious inconsistency	no serious indirectness	serious ⁹	none	55	45	-	SMD 0.17 lower (0.56 lower to 0.22 higher)	VERY LOW	IMPORTAN ⁻
Substantia 95% CI cm Risk of bia Study part Statisticall 95% CI cm Funding fr	al heterogene osses thresh is is high acr tially funded ly significant osses thresh om pharmac	eity olds for b ross multip by pharma difference olds for n reutical co	oth clinically imp ole domains aceutical compa between group o effect, and bo	portant benefit ny s at baseline th clinically im _l	and no effect		rence					

⁸ Risk of bias is high or unclear across multiple domains
 ⁹ 95% CI crosses thresholds for both clinically important harm and no effect

Table 106: Clinical evidence profile for comparison 37. Augmenting with mirtazapine versus continuing with antidepressant (+/placebo)

Quality assessmen	t						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness		Other	Augmenting with mirtazapine	antidoproceant (1)	Relative (95% Cl)	Absolute		
Depression symptomatology endpoint (follow-up 4-12 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) or Patient Health Questionnaire (PHQ-9) or Beck Depression Inventory (BDI-II); Better indicated by lower values)												

Cato 2018, Kessler U0832018, Xiao 0000 Indirectness indirectness indirectness indirectness imprecision imprecision Impr													
voice values) Very endows very serious ¹ no serious indirectness reporting blas ⁵ 79 83 - SMD 0.52, VERY LOW CRITICAL isolated to prove to 0.43 migher) Depression symptomatology at 4-month follow-up (follow-up mean 4 months; measured with: Patient Health Questionnaire (PHQ-9); Better indicated by lower values) - SMD 0.77, IoN 0	4 (Carpenter 2002, Kato 2018, Kessler 2018a/2018b, Xiao 2020)		serious ¹	serious ²			none	820	837	-	lower (0.44 to	LOW	CRITICAL
Giao 2020) trials serious ¹ indirectness indirectness indirectness indirectness iower 10.43 iower 10.44	Depression sympto ower values)	omatology cl	nange sco	ore (follow-up 4-	6 weeks; meas	sured with: Ha	amilton Rating S	cale for Depres	sion (HAM-D) chang	ge from ba	seline to endp	oint; Better i	ndicated b
(Kato 2018) randomised no trials serious inconsistency indirectness indirectness indirectness inconsistency indirectness indidirectness indirectness indirectness indirectness indirectness in	2 (Carpenter 2002, Xiao 2020)		,	very serious ³		serious ⁴	reporting bias⁵	79	83	-	lower (1.53 lower to 0.48	VERY LOW	CRITICAL
trials serious risk of bias inconsistency insk of bias indirectness inconsistency indirectness inconsistency indirectness indirectness indirectness indif indi	Depression sympto	omatology at	t 4-month	follow-up (follo	w-up mean 4 n	nonths; meas	ured with: Patier	nt Health Questi	ionnaire (PHQ-9); B	etter indic	ated by lower	values)	
vr <10 on Beck Depression Inventory (BDI-III)	1 (Kato 2018)		serious risk of				none	520	538	-	lower (0.19 lower to 0.05	HIGH	CRITICAL
Cato 2018, Kessler 0008a/2018b, Xiao 0020)inconsistency inconsistencyindirectness(33.8%)(25.1%)(1.04 to 1.01)1000 (from 10 more to 153 more)Remission (ITT) at 4-mont follow-up (cato 2018), Kasole 0020)raidomised for biasno serious inconsistencyno serious indirectnessserious* serious*no no serious more)263/537 (49%)245/551 (44.5%)RR 1.1 (1.097)44 more pr 1000 (from 10 more)MODERATE MODERATE CRITICAL fewer to 111 more)CRITICAL fewer to 111 more)44 more pr 1000 (from 10 more)MODERATE MODERATE CRITICAL fewer to 111 more)CRITICAL fewer to 111 more)44 more pr fewer to 111 more)MODERATE fewer to 111 more)CRITICAL fewer to 111 more)CRITICAL fewer to 111 more)44 more pr fewer to 111 more)MODERATE fewer to 111 more)CRITICAL fewer to 111 more)CRITICAL fewer to 111 more)44 more pr fewer to 111 more)MODERATE fewer to 111 more)CRITICAL fewer to 111 more)44 more pr fewer to 111 more)MODERATE fewer to 111 more)CRITICAL fewer to 111 more)CRITICAL 					lumber of peo	ple scoring <=	=7 on Hamilton R	ating Scale for	Depression (HAM-D)) or <=4 o	n Patient Heal	th Questionr	naire (PHQ-
(Kato 2018)randomised trialsno serious niconsistency niconsistency tick of blasno serious no serious niconsistencyno serious nicinectnessserious ⁴ none263/537 (49%)245/551 (44.5%)RR 1.1 (0.97 to 1.25)44 more per 1000 (from 13 fewer to 111 more)MODERATECRITICALResponse (ITT) (follow-up 4-12 weeks; cuestionnaire (PHQ-9) or Beck Depression Inventory (BD-III)None263/537 (49.%)245/551 (49.%)RR 1.1 (0.97 to 1.25)44 more per 1000 (from 13 fewer to 111 more)Vol Patient Health LOWQuestionnaire (PHQ-9) or Beck Depression Inventory (BD-III)no serious inconsistencyno serious indirectnessserious ⁴ indirectnessnone422/857 (49.2%)357/873 (40.9%)RR 1.9 (1.06 to 1.06 to 1.06 to 1.00 (from 25 more)LOW LOWCRITICAL (0.07 fmore 25 indirectness(Carpenter 2002, (Carpenter 2002, (Carpenter 2002, (18a/2018) Kiao (2018)reserves indirectnessserious ⁴ indirectnessnone47/857 (5.5%)50/873 (5.7%)RR 9.95 (3.6%)3 fewer per 1000 (from 20 1.4)VERY LOW fewer to 23 more(Carpenter 2002, (18a/2018) Kiao (2018)reserves indirectnessno serious indirectnessno serious indirectnessno serious indirectnessno serious indirectnessno serious indirectnessserious ⁴ indirectnessnone47/857 (5.5%)50/873 (5.7%)RR 9.50 (5.7%)3 fewer per 1.4)VERY LOW indirectness(Carpenter 2002, <td></td> <td></td> <td>serious¹</td> <td></td> <td></td> <td>serious⁴</td> <td>none</td> <td></td> <td></td> <td>(1.04 to</td> <td>1000 (from 10 more to 153</td> <td>LOW</td> <td>CRITICAL</td>			serious ¹			serious ⁴	none			(1.04 to	1000 (from 10 more to 153	LOW	CRITICAL
trials serious risk of bas inconsistency indirectness indirectness (49%) (44.5%) (0.97 to 1.25) 1000 (from 13 fewer to 111) Response (ITT) (follow-up 4-12 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D) OP Patient Health Or Patient Health Questionnaire (PHQ-9) or Beck Depression Inventory (BDI-II)) no serious inconsistency	Remission (ITT) at	4-month foll	ow-up (fo	llow-up mean 4	months; asses	ssed with: Nu	mber of people s	coring <=4 on F	Patient Health Ques	tionnaire (PHQ-9))		
Questionnaire (PHQ-9) or Beck Depression Inventory (BDI-III) Restionation of the person of the p	1 (Kato 2018)		serious risk of			serious ⁴	none			(0.97 to	1000 (from 13 fewer to 111	MODERATE	CRITICAL
Kato 2018, Kessler (2018a/2018b, Xiao (200)trialsinconsistency indirectnessindirectnessindirectness(49.2%)(40.9%)(1.06 to 1.34)1000 (from 25 more to 139 more)IndirectnessIndirectnessIndirectness(49.2%)(40.9%)(1.06 to 1.34)1000 (from 25 more to 139 more)IndirectnessIndirectnessIndirectnessIndirectnessIndirectness(49.2%)(40.9%)(1.06 to 1.34)1000 (from 25 more to 139 more)Indirectness <th< td=""><td></td><td></td><td></td><td></td><td></td><td>ble showing at</td><td>t least 50% impro</td><td>ovement on Han</td><td>nilton Rating Scale</td><td>for Depres</td><td>sion (HAM-D)</td><td>or Patient H</td><td>ealth</td></th<>						ble showing at	t least 50% impro	ovement on Han	nilton Rating Scale	for Depres	sion (HAM-D)	or Patient H	ealth
(Carpenter 2002, Kato 2018, Kessler $(2018a/2018b, Xiao)$ randomised trialsserious1no serious inconsistencyno serious indirectnessvery serious6none $47/857$ $(5.5%)$ $50/873$ $(5.5%)$ RR 0.95 $(0.65 to)$ $3 fewer per$ $1000 (from 20)fewer to 23more)$ VERY LOW CRITICAL VERY LOW CRITICAL fewer to 23 more)Discontinuation due to side effects (follow-up 4-6 weeks; assessed with: Number of participants who dropped out due to adverse events)RR 1.69 $(2.4%)$ RR 1.69 $(0.29 to)$ To more per $1000 (from 20)fewer to 23more)$ VERY LOW CRITICAL VERY LOW CRITICAL (Siao 2020) (2020) randomised trialsserious1 mo serious inconsistencyno serious indirectnessvery serious6 reporting bias5 $3/79$ $(3.8%)$ $2/83$ $(2.4%)$ RR 1.69 $(0.29 to)$ 17 more per 1000 (from 17) fewer to 215VERY LOW CRITICAL VERY LOW CRITICAL fewer to 215			serious ¹			serious ⁴	none			(1.06 to	1000 (from 25 more to 139	LOW	CRITICAL
Kato 2018, Kessler 2018a/2018b, Xiaotrialsinconsistency indirectnessindirectness(5.5%)(5.7%)(0.65 to 1.4)1000 (from 20 fewer to 23 more)Discontinuation due to side effects (follow-up 4-6 weeks; assessed with: Carpenter 2002, Kiao 2020)randomised trialsserious1no serious inconsistencyno serious indirectnessvery serious6 reporting bias53/79 (3.8%)2/83 (2.4%)RR 1.69 (0.29 to 1000 (from 17 9.93)VERY LOW Fewer to 215CRITICAL CRITICAL	Discontinuation du	e to any reas	son (follo	w-up 4-12 week	s; assessed wi	ith: Number o	f participants wh	o dropped out	for any reason (incl	uding adv	erse events))		
2 (Carpenter 2002, randomised serious ¹ trials no serious inconsistency no serious indirectness very serious ⁶ reporting bias ⁵ 3/79 (3.8%) 2/83 (2.4%) RR 1.69 17 more per VERY LOW CRITICAL Viao 2020) very serious ¹ inconsistency indirectness very serious ⁶ reporting bias ⁵ 3/79 (3.8%) (2.4%) 1000 (from 17 9.93) 1000 (from 17 9.93)	4 (Carpenter 2002, Kato 2018, Kessler 2018a/2018b, Xiao		serious ¹			very serious ⁶	none			(0.65 to	1000 (from 20 fewer to 23	VERY LOW	CRITICAL
Kiao 2020)trialsinconsistencyindirectness(3.8%)(2.4%)(0.29 to1000 (from 17 9.93)fewer to 215	2020)										/		
	,	e to side eff	ects (follo	w-up 4-6 weeks	; assessed wit	th: Number of	participants wh	o dropped out d	lue to adverse even	ts)	,		

							040	040				
I (Kessler 2018a/2018b)	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	213	216	-	SMD 0.04 lower (0.23 lower to 0.15 higher)	LOW	IMPORTANT
	ical compon	ent score	(PCS) endpoint	t (follow-up me	ean 12 weeks;	measured with:	12-item Short-F	orm Survey (SF-12)	: Physical	component s	core; Better	indicated by
nigher values)												
l (Kessler 2018a/2018b)	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	208	210	-	SMD 0.14 lower (0.33 lower to 0.05 higher)	LOW	IMPORTANT
Quality of life men nigher values)	tal compone	nt score (MCS) endpoint (follow-up mea	an 12 weeks; i	measured with: 1	2-item Short-Fo	orm Survey (SF-12):	Mental co	mponent scor	e; Better ind	icated by
l (Kessler 2018a/2018b)	randomised trials	very serious¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	208	210	-	SMD 0.29 higher (0.1 to 0.48 higher)	LOW	IMPORTANT
Global functioning	endpoint (fo	llow-up n	nean 4 weeks; n	neasured with	Global Asse	ssment of Function	on (GAF); Bette	r indicated by highe	er values)			
(Carpenter 2002)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias⁵	11	15	-	SMD 0.92 higher (0.1 to	VERY LOW	IMPORTANT

¹ Risk of bias is high or unclear across multiple domains
 ² Substantial heterogeneity
 ³ Considerable heterogeneity
 ⁴ 95% CI crosses thresholds for both clinically important benefit and no effect
 ⁵ Funding from pharmaceutical companies
 ⁶ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 107: Clinical evidence profile for comparison 38. Augmenting with mirtazapine versus switching to mirtazapine

Quality ass	sessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with mirtazapine	Switching to mirtazapine	Relative (95% Cl)	Absolute		
Depression symptomatology endpoint (follow-up mean 6 weeks; measured with: Patient Health Questionnaire (PHQ-9) or Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)												

2 (Kato 2018, Xiao 2020)	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	595	618	-	SMD 0.01 lower (0.12 lower to 0.1 higher)	HIGH	CRITICAL
	n symptomato v lower value		ge score (follow-	up mean 6 wee	ks; measured	with: Hamilton Ra	ting Scale for Dep	pression (HAM-	D) change f	from baseline to er	ndpoint; Bet	ter
	randomised trials	very	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ²	68	68	-	SMD 0.12 higher (0.22 lower to 0.45 higher)		CRITICAL
Depressior	n symptomate	ology at 4-n	nonth follow-up	(follow-up meai	n 4 months; me	easured with: Pati	ent Health Questi	ionnaire (PHQ-9); Better in	dicated by lower va	alues)	
1 (Kato 2018)	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	520	540	-	SMD 0.08 lower (0.2 lower to 0.04 higher)	HIGH	CRITICAL
Remission (HAM-D))	(ITT) (follow-	up mean 6	weeks; assesse	d with: Number	of people sco	ring <=4 on Patier	nt Health Question	nnaire (PHQ-9)	or <=7 on H	amilton Rating Sca	ale for Depre	ession
2 (Kato 2018, Xiao 2020)	randomised trials		no serious inconsistency	no serious indirectness	serious ³	none	222/605 (36.7%)	212/626 (33.9%)	RR 1.04 (0.85 to 1.29)	14 more per 1000 (from 51 fewer to 98 more)	MODERATE	CRITICAL
Remission	(ITT) at 4-mo	nth follow-	up (follow-up me	an 4 months; a	ssessed with:	Number of people	e scoring <=4 on I	Patient Health C	Questionnai	ire (PHQ-9))		
1 (Kato 2018)	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	263/537 (49%)	262/558 (47%)	RR 1.04 (0.92 to 1.18)	19 more per 1000 (from 38 fewer to 85 more)	HIGH	CRITICAL
Response (Depression		up mean 6 v	weeks; assessed	l with: Number	of people shov	ving at least 50%	improvement on I	Patient Health C	Questionnai	ire (PHQ-9) or Ham	ilton Rating	Scale for
2 (Kato	randomised		no serious inconsistency	no serious indirectness	no serious imprecision	none	321/605 (53.1%)	325/626 (51.9%)	RR 1.01 (0.91 to 1.12)	5 more per 1000 (from 47 fewer to 62 more)	HIGH	CRITICAL
Discontinu	ation due to a	any reason	(follow-up mean	6 weeks; asse	ssed with: Nun	nber of participan	ts who dropped o	out for any reas	on (includir	ng adverse events))	
2 (Kato 2018, Xiao 2020)	randomised trials		no serious inconsistency	no serious indirectness	very serious ⁴	none	19/605 (3.1%)	20/626 (3.2%)	RR 0.95 (0.52 to 1.73)	2 fewer per 1000 (from 15 fewer to 23 more)	LOW	CRITICAL
			(fallow we were	A Gwaakay aaaa	seed with: Nu	mber of participar	nts who dropped o	out due to adve	rse events)			
Discontinu	ation due to s	side effects	(tollow-up meal	i o weeks, asse	SSeu with. Nul	inder of participal						

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
 ¹ Risk of bias is high across multiple domains
 ² Study partially funded by pharmaceutical company
 ³ 95% CI crosses threshold for both clinically important benefit and no effect
 ⁴ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 108:	Clinical evidence profile for comparison 39. Augmenting with trazodone versus continuing with antidepressa	nt

Quality a	issessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Improcision	Other considerations	Augmenting with trazodone	Continuing with antidepressant	Relative (95% Cl)	Absolute		
Remissio	on (ITT) (follo	w-up mea	an 8 weeks; asse	ssed with: Numl	ber of people	scoring <=7 on	Hamilton Rating S	Scale for Depression	(HAM-D))			
1 (Fang 2011)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious²	none	20/47 (42.6%)	21/45 (46.7%)	RR 0.91 (0.58 to 1.44)	42 fewer per 1000 (from 196 fewer to 205 more)	VERY LOW	CRITICAL
Respons	e (ITT) (follo	w-up mea	n 8 weeks; asses	sed with: Numb	er of people	showing at least	50% improvement	nt on Hamilton Rating	g Scale for D	epression (HAM-D))		
1 (Fang 2011)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious²	none	29/47 (61.7%)	30/45 (66.7%)	RR 0.93 (0.68 to 1.26)	47 fewer per 1000 (from 213 fewer to 173 more)	VERY LOW	CRITICAL
	of life physica r values)	I compor	ent score (PCS)	change score (f	ollow-up mea	an 8 weeks; meas	sured with: 36-ite	m Short-Form Survey	/ (SF-36): Ph	nysical component s	core; Be	tter indicate
1 (Fang 2011)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	47	45	-	SMD 0.26 lower (0.67 lower to 0.15 higher)	LOW	IMPORTAN [®]
Quality o higher va		compone	nt score (MCS) c	hange score (fo	llow-up mear	n 8 weeks; meası	ured with: 36-item	Short-Form Survey	(SF-36): Mer	ntal component scor	e; Better	indicated by
1 (Fang 2011)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	none	47	45	-	SMD 0.2 higher (0.21 lower to 0.61 higher)	LOW	IMPORTAN ⁻

¹ Risk of bias was high or unclear across multiple domains
 ² 95% CI crosses thresholds of no effect, and both clinically important benefit and harm
 ³ 95% CI crosses thresholds for both clinically important harm and no effect

⁴ 95% CI crosses thresholds for both clinically important benefit and no effect

Clinical evidence profile for comparison 40. Augmenting with anticonvulsant versus continuing with antidepressant (+/-Table 109: placebo)

Quality assessment							No of patients	Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness		Other considerations	Augmenting with	Relative (95% Cl)	Absolute		

: (Barbee 2011, Li 2009, Li 2015, Mowla 2011, Santos 2008, Wang 2012a, Yang 2016, Zhang 2016)	randomised trials	serious ¹	very serious ²	no serious indirectness	serious ³	none	301	298	-	SMD 1.39 lower (2.33 to 0.46 lower)	VERY LOW	CRITICAL
epression sympto MADRS) change fro						lamilton Rating S	cale for Depressio	n (HAM-D) or Mor	tgomery As	berg Depressio	on Ratin	g Scale
8 (Barbee 2011, Li 2009, Li 2015, Mowla 2011, Santos 2008, Wang 2012a, Yang 2016, Zhang 2016)	randomised trials	serious ¹	very serious ²	no serious indirectness	no serious imprecision	none	301	298	-	SMD 1.97 lower (3.07 to 0.87 lower)	VERY LOW	CRITICAL
Remission (ITT) (fol	low-up mean	8 weeks	s; assessed wit	h: Number of p	people scoring	<=7 on Hamiltor	Rating Scale for I	Depression (HAM-	D))			
(Fang 2011)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	19/39 (48.7%)	21/45 (46.7%)	RR 1.04 (0.67 to 1.63)	19 more per 1000 (from 154 fewer to 294 more)	VERY LOW	CRITICAL
Response (ITT) (foll Depression Rating S			ssessed with: N	umber of peop	ple showing at	least 50% impro	vement on Hamilto	on Rating Scale fo	r Depressio	n (HAM-D) or M	ontgom	ery Asber
8 (Barbee 2011, Fang 2011, Li 2009, Li 2015, Santos 2008, Wang 2012a, (ang 2016, Zhang 2016)	randomised trials	serious ¹	serious⁵	no serious indirectness	serious ³	none	149/320 (46.6%)	105/321 (32.7%)	RR 1.44 (0.93 to 2.24)	144 more per 1000 (from 23 fewer to 406 more)	VERY LOW	CRITICAL
Discontinuation due	to any reas	on (follo	w-up 8-10 week	s; assessed w	ith: Number of	f participants wh	o dropped out for a	any reason (includ	ing adverse	e events))		
(Barbee 2011, Iowla 2011, Santos 008)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ⁶	23/91 (25.3%)	26/92 (28.3%)	RR 0.89 (0.55 to 1.43)	31 fewer per 1000 (from 127 fewer to 122 more)	VERY LOW	CRITICAL
Discontinuation due	to side effe	cts (follo	w-up 8-10 weel	s; assessed v	vith: Number o	f participants wh	o dropped out due	to adverse event	s)			
! (Barbee 2011, Santos 2008)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias ⁶	9/65 (13.8%)	10/65 (15.4%)	RR 1.12 (0.21 to 5.94)	18 more per 1000 (from 122 fewer to 760 more)	VERY LOW	CRITICAL

1 (Fang 2011)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁷	none	39	45	-	SMD 0.21 lower (0.64 lower to 0.22 higher)	LOW	IMPORTANT
Quality of life men higher values)	tal componen	t score (MCS) change so	core (follow-up	mean 8 weel	s; measured witl	n: 36-item Short-Fe	orm Survey (SF-36):	Mental co	mponent score	; Better	indicated by
1 (Fang 2011)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	39	45	-	SMD 0.19 higher (0.24 lower to 0.62 higher)	LOW	IMPORTANT
CI: confidence inte	erval; ITT: int	ention to	o treat; RR: rela	ative risk; SML	D: standardis	ed mean differer	nce					

¹ Risk of bias is high or unclear across multiple domains
 ² Considerable heterogeneity
 ³ 95% CI crosses thresholds for both clinically important benefit and no effect
 ⁴ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

⁵ Substantial heterogeneity

⁶ Funding from pharmaceutical companies
 ⁷ 95% CI crosses thresholds for both clinically important harm and no effect

Clinical evidence profile for comparison 41. Augmenting with anticonvulsant versus lithium **Table 110:**

Quality asse	essment						No of patients Effect Augmenting with				Quality	Importanc	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		Augmenting with anticonvulsant	Lithium	Relative (95% Cl)	Absolute			
Depression symptomatology endpoint (follow-up mean 8 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)													
1 (Schindler 2007)	randomised trials		no serious inconsistency	no serious indirectness	serious ²	none	17	17	-	SMD 0.31 lower (0.99 lower to 0.36 higher)	LOW	CRITICAL	
	Depression symptomatology change score (follow-up mean 8 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better ndicated by lower values)												
1 (Schindler 2007)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	17	17	-	SMD 0.81 lower (1.51 to 0.11 lower)	LOW	CRITICAL	
Remission (ITT) (follow-u	ıp mean 8 w	eeks; assessed v	vith: Number of	people scoring	<=7 on Hamilton	Rating Scale for Dep	ression	(HAM-D))				
1 (Schindler 2007)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	4/17 (23.5%)	3/17 (17.6%)	RR 1.33 (0.35 to 5.08)	58 more per 1000 (from 115 fewer to 720 more)	VERY LOW	CRITICAL	
Response (I	Response (ITT) (follow-up mean 8 weeks; assessed with: Number of people showing at least 50% improvement on Hamilton Rating Scale for Depression (HAM-D))												

Depression in adults: Evidence review D FINAL (June 2022)

1 (Schindler 2007)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	9/17 (52.9%)	7/17 (41.2%)	RR 1.29 (0.62 to 2.65)	119 more per 1000 (from 156 fewer to 679 more)	VERY LOW	CRITICAL	
Discontinua	ation due to a	iny reason (f	follow-up mean 8	weeks; assesse	d with: Numbe	er of participants w	ho dropped out for a	any reaso	on (including	g adverse events))			
1 (Schindler 2007)		no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ³	none	2/17 (11.8%)	2/17 (11.8%)	RR 1 (0.16 to 6.3)	0 fewer per 1000 (from 99 fewer to 624 more)	LOW	CRITICAL	
Discontinuation due to side effects (follow-up mean 8 weeks; assessed with: Number of participants who dropped out due to adverse events)													
1 (Schindler 2007)			no serious inconsistency	no serious indirectness	no serious imprecision	none	0/17 (0%)	0/17 (0%)	not pooled	not pooled	HIGH	CRITICAL	

¹ Risk of bias is high or unclear across multiple domains
 ² 95% CI crosses thresholds for both clinically important benefit and no effect
 ³ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Clinical evidence profile for comparison 42. Switching to antipsychotic versus continuing with antidepressant Table 111:

Quality assessment No of patients Effect No of Risk of Risk of Relative												Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching to antipsychotic	• • •	Relative (95% Cl)	Absolute		
Depression s indicated by I	· ·		e score (follow-ı	up 8-12 weeks;	measured wit	h: Montgomery A	Asberg Depressi	on Rating Scale (M	ADRS) cha	nge from baseli	ne to endpoi	nt; Better
3 (Corya 2006, Shelton 2005, Thase 2007)	randomised trials	serious ¹	serious ²	no serious indirectness	serious ³	reporting bias ⁴	400	329	-	SMD 0.22 higher (0.12 lower to 0.56 higher)	VERY LOW	CRITICAL
Remission (I1	TT) (follow-u	p 8-12 wee	ks; assessed wi	th: Number of	people scoring	g <=8/<=10 on Mo	ontgomery Asbe	rg Depression Rati	ng Scale (N	(ADRS))		
3 (Corya 2006, Shelton 2005, Thase 2007)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	reporting bias ⁴	56/405 (13.8%)	59/333 (17.7%)	RR 0.79 (0.56 to 1.1)	37 fewer per 1000 (from 78 fewer to 18 more)	VERY LOW	CRITICAL
Response (IT	T) (follow-up	8-12 weel	ks; assessed wit	h: Number of p	eople showin	g at least 50% im	provement on N	Iontgomery Asberg	g Depressio	on Rating Scale	MADRS))	
3 (Corya 2006, Shelton 2005, Thase 2007)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	reporting bias ⁴	94/405 (23.2%)	110/333 (33%)	RR 0.68 (0.48 to 0.96)	106 fewer per 1000 (from 13 fewer to 172 fewer)	VERY LOW	CRITICAL
Discontinuati	on due to an	ny reason (follow-up 8-12 w	veeks; assesse	d with: Numbe	er of participants	who dropped or	ut for any reason (i	ncluding ad	dverse events))		

3 (Corya 2006, Shelton 2005, Thase 2007)	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ⁴	122/405 (30.1%)	63/333 (18.9%)	RR 1.67 (1.26 to 2.23)	127 more per 1000 (from 49 more to 233 more)	MODERATE	CRITICAL			
Discontinuati	on due to si	de effects (follow-up 8-12 v	weeks; assess	ed with: Numb	er of participants	who dropped o	ut due to adverse e	vents)						
· · ·	006, Shelton trials risk of bias inconsistency indirectness imprecision (12.6%) (2.4%) (2.57 to 1000 (from 38 11.09) 007) 007) 000 000 000 000 000														
	ality of life physical component score (PCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (SF-36): Physical component score; Better indicate higher values)														
`	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ⁴	197	203	-	SMD 0.15 lower (0.35 lower to 0.04 higher)	LOW	IMPORTANT			
Quality of life mental component score (MCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (SF-36): Mental component score; Better indicated by higher values)															
												-			

¹ Risk of bias is high or unclear across multiple domains

² Substantial heterogeneity
 ³ 95% CI crosses thresholds for both clinically important harm and no effect
 ⁴ Funding from pharmaceutical companies

Table 112: Clinical evidence profile for comparison 43. Switching to combined antipsychotic + SSRI versus continuing with antidepressant

Quality as	sessment						No of patients		Effect				
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Switching to combined antipsychotic + SSRI		Relative (95% Cl)	Absolute	Quality	Importance	
Depression symptomatology change score (follow-up 8-12 weeks; measured with: Montgomery Asberg Depression Rating Scale (MADRS) change from baseline to endpoint; Better indicated by lower values)													
2 (Corya 2006, Shelton 2005)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ²	376	126	-	SMD 0.09 lower (0.3 lower to 0.11 higher)	LOW	CRITICAL	

Remission	Remission (ITT) (follow-up 8-12 weeks; assessed with: Number of people scoring <=8 on Montgomery Asberg Depression Rating Scale (MADRS))														
2 (Corya 2006, Shelton 2005)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	reporting bias ²	94/389 (24.2%)	25/127 (19.7%)	RR 1.15 (0.77 to 1.71)	30 more per 1000 (from 45 fewer to 140 more)	VERY LOW	CRITICAL			
Response	(ITT) (follow-u	up 8-12 wee	eks; assessed w	ith: Number of	people showing	ng at least 50% im	provement on Mont	gomery Asberg De	oression Ra	ting Scale (MAD	RS))				
2 (Corya 2006, Shelton 2005)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ²	140/389 (36%)	50/127 (39.4%)	RR 0.85 (0.67 to 1.09)	59 fewer per 1000 (from 130 fewer to 35 more)	VERY LOW	CRITICAL			
Discontinu	ation due to a	any reason	(follow-up 8-12	weeks; assess	ed with: Numb	er of participants	who dropped out fo	r any reason (inclu	ding advers	e events))					
2 (Corya 2006, Shelton 2005)	randomised trials		no serious inconsistency	no serious indirectness	very serious ³	reporting bias ²	90/389 (23.1%)	23/127 (18.1%)	RR 1.22 (0.69 to 2.16)	40 more per 1000 (from 56 fewer to 210 more)	VERY LOW	CRITICAL			
Discontinu	ation due to	side effects	(follow-up 8-12	weeks; assess	sed with: Numb	per of participants	s who dropped out d	ue to adverse even	ts)						
2 (Corya 2006, Shelton 2005)	randomised trials		no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ²	39/389 (10%)	3/127 (2.4%)	RR 3.48 (1.06 to 11.44)	59 more per 1000 (from 1 more to 247 more)	LOW	CRITICAL			

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; SSRI: selective serotonin reuptake inhibitor ¹ Risk of bias is high or unclear across multiple domains ² Funding from pharmaceutical companies ³ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm ⁴ 95% CI crosses thresholds for both clinically important harm and no effect

Table 113: Clinical evidence profile for comparison 44. Switching to combined antipsychotic + SSRI versus switch to SS
--

Quality asse	essment				No of patients		Effect		Quality	Importance		
No of studies	Design Risk of Inconsistency Indirectness Imprecision Other considerations Switching to combined antipsychotic + SSRI SSRI-only (95% CI) Absolute Absolute											
Depression symptomatology change score (follow-up 8-12 weeks; measured with: Montgomery Asberg Depression Rating Scale (MADRS) change from baseline to endpoint; Better indicated by lower values)												
												CRITICAL
Remission (ITT) (follow-up 8-12 weeks; assessed with: Number of people scoring <=8 on Montgomery Asberg Depression Rating Scale (MADRS))												

randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	reporting bias ²	94/389 (24.2%)	29/202 (14.4%)	RR 1.46 (0.97 to 2.19)	66 more per 1000 (from 4 fewer to 171 more)	VERY LOW	CRITICAL			
ITT) (follow-uj	p 8-12 week	s; assessed with	n: Number of pe	ople showing a	at least 50% impro	ovement on Montgome	ry Asberg	Depression	Rating Scale (MAD	RS))				
(Corya randomised serious ¹ no serious no serious no serious and trials no serious no serious indirectness serious ³ reporting bias ² 140/389 (36%) 60/202 (29.7%) RR 1.1 (0.81 to 1.5) 30 more per 1000 VERY CRITICAL (19.7%) 0.06, trials inconsistency indirectness indirectness serious ³ reporting bias ² 140/389 (36%) 60/202 (29.7%) (0.81 to 1.5) (from 56 fewer to 149 more) LOW 0.05) iscontinuation due to any reason (follow-up 8-12 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events)) serious adverse events)														
randomised trials			no serious indirectness	very serious ⁴	reporting bias ²	90/389 (23.1%)	40/202 (19.8%)	RR 1.12 (0.78 to 1.59)	24 more per 1000 (from 44 fewer to 117 more)	VERY LOW	CRITICAL			
tion due to si	ide effects (follow-up 8-12 w	eeks; assessed	with: Number	of participants wh	no dropped out due to	adverse ev	vents)						
randomised trials			no serious indirectness	serious⁵	reporting bias ²	39/389 (10%)	7/202 (3.5%)	RR 2.41 (1.07 to 5.42)	49 more per 1000 (from 2 more to 153 more)	LOW	CRITICAL			
	trials TT) (follow-up randomised trials tion due to an randomised trials	trials TT) (follow-up 8-12 week randomised serious ¹ trials tion due to any reason (f randomised no serious trials risk of bias tion due to side effects (randomised no serious	trials inconsistency TT) (follow-up 8-12 weeks; assessed with randomised serious ¹ trials no serious inconsistency ttion due to any reason (follow-up 8-12 weights) randomised no serious randomised no serious randomised no serious no serious no serious trials risk of bias inconsistency inconsistency ttion due to side effects (follow-up 8-12 weight) randomised no serious no serious no serious	trialsinconsistencyindirectnessTT) (follow-up 8-12 weeks; assessed with: Number of per randomised serious1no serious inconsistencyno serious indirectnesstrialsserious1no serious inconsistencyno serious indirectnesstion due to any reason (follow-up 8-12 weeks; assessed randomised trialsno serious inconsistencyno serious indirectnesstion due to side effects (follow-up 8-12 weeks; assessed randomised no seriousno serious indirectnessno serious indirectness	trials inconsistency indirectness TT) (follow-up 8-12 weeks; assessed with: Number of people showing a randomised serious ¹ no serious indirectness serious ³ trials serious ¹ no serious inconsistency no serious indirectness serious ³ tion due to any reason (follow-up 8-12 weeks; assessed with: Number randomised no serious inconsistency no serious indirectness very serious ⁴ trials no serious inconsistency no serious indirectness very serious ⁴ trials no serious inconsistency no serious indirectness very serious ⁴ trials no serious inconsistency no serious indirectness very serious ⁴ trials no serious inconsistency no serious indirectness very serious ⁴ trials no serious inconsistency no serious indirectness serious ⁴ tion due to side effects (follow-up 8-12 weeks; assessed with: Number randomised no serious no serious no serious serious indirectnes serious ⁵	trials inconsistency indirectness TT) (follow-up 8-12 weeks; assessed with: Number of people showing at least 50% improvements of trials no serious randomised serious ¹ no serious no serious inconsistency no serious serious ³ reporting bias ² ition due to any reason (follow-up 8-12 weeks; assessed with: Number of participants where the periods of the periods	trialsinconsistencyindirectness(24.2%)TT) (follow-up 8-12 weeks; assessed with: Number of people showing at least 50% improvement on Montgome randomised trialsno serious inconsistencyserious indirectnessreporting bias2140/389 (36%)tion due to any reason (follow-up 8-12 weeks; assessed with: Number of participants who dropped out for any randomised trialsno serious inconsistencyvery serious4reporting bias290/389 (23.1%)tion due to side effects(follow-up 8-12 weeks; assessed with: Number of participants who dropped out due to indirectnessvery serious4reporting bias290/389 (23.1%)tion due to side effects(follow-up 8-12 weeks; assessed with: Number of participants who dropped out due to no serious no seriousno serious no seriousvery serious4 reporting bias2reporting bias2 (23.1%)90/389 (23.1%)	trialsinconsistencyindirectness(24.2%)(14.4%)TT) (follow-up 8-12 weeks; assessed with: Number of people showing at least 50% improvement on Montgomery Asberg randomised trialsno serious inconsistencyno serious indirectnessserious ³ reporting bias ² 140/389 (36%)60/202 (29.7%)tion due to any reason (follow-up 8-12 weeks; assessed with: Number of participants who dropped out for any reason (in randomised trialsno serious inconsistencyno serious indirectnessvery serious ⁴ reporting bias ² 90/389 (23.1%)40/202 (19.8%)tion due to side effects (follow-up 8-12 weeks; assessed with: Number of participants who dropped out due to adverse ev randomised no serious no seriousno serious indirectnessvery serious ⁴ reporting bias ² 90/389 (23.1%)40/202 (19.8%)tion due to side effects (follow-up 8-12 weeks; assessed with: Number of participants who dropped out due to adverse ev randomised no serious no serious no serious no serious no serious serious ⁵ reporting bias ² 39/3897/202	trialsinconsistencyindirectnessindirectness(24.2%)(14.4%)(0.97 to 2.19)TT) (follow-up 8-12 weeks; assessed with: Number of people showing at least 50% improvement on Montgomery Asberg Depression I randomised serious1no serious inconsistencyno serious indirectnessserious3reporting bias2140/389 (36%)60/202 (29.7%)RR 1.1 (0.81 to 1.5)ttion due to any reason (follow-up 8-12 weeks; assessed with: Number of participants who dropped out for any reason (including advecting bias290/389 (23.1%)40/202 (19.8%)RR 1.12 (0.78 to 1.59)ttion due to side effects (follow-up 8-12 weeks; assessed with: Number of participants who dropped out due to adverse events)RR 1.12 (0.78 to 1.59)ttion due to side effects (follow-up 8-12 weeks; assessed with: Number of participants who dropped out due to adverse events)RR 1.12 (0.78 to 1.59)ttion due to side effects (follow-up 8-12 weeks; assessed with: Number of participants who dropped out due to adverse events)RR 1.12 (0.78 to 1.59)ttion due to side effects (follow-up 8-12 weeks; assessed with: Number of participants who dropped out due to adverse events)RR 2.41 (1.07 to	trialsinconsistencyindirectnessindirectness(24.2%)(14.4%)(0.97 to 2.19)(from 4 fewer to 171 more)TT) (follow-up 8-12 weeks; assessed with: Number of people showing at least 50% improvement on Montgomery Asberg Depression Rating Scale (MAD randomised trialsno serious inconsistencyno serious indirectnessserious³reporting bias²140/389 (36%)60/202 (29.7%)(RR 1.1 (0.81 to 1.5)30 more per 1000 (from 56 fewer to 149 more)tion due to any reason (follow-up 8-12 weeks; assessed with: Number of participants who dropped out for any reason (including adverse trialso serious inconsistencyno serious indirectnessvery serious4 reporting bias²90/389 (23.1%)40/202 (19.8%)RR 1.12 (0.78 to 1.59)24 more per 1000 (from 44 fewer to 117 more)tion due to side effects (follow-up 8-12 weeks; assessed with: Number of participants who dropped out due to adverse events)RR 1.12 (0.78 to 1.59)RR 1.12 (0.78 to (117 more)24 more per 1000 (from 44 fewer to 117 more)tion due to side effects (follow-up 8-12 weeks; assessed with: Number of participants who dropped out due to adverse events)RR 2.41 (1.07 to (from 2 more to49 more per 1000 (from 2 more to	trialsinconsistencyindirectnessindirectness(24.2%)(14.4%)(0.97 to 2.19)(from 4 fewer to 171 more)LOWTT) (follow-up 8-12 weeks; assessed with: Number of people showing at least 50% improvement on Montgomery Asberg DepressionRating Scale (MADRS))randomised trialsserious1 inconsistencyno serious indirectnessserious3 indirectnessreporting bias2140/389 (36%)60/202 (29.7%)RR 1.1 (0.81 to 1.5)30 more per 1000 (from 56 fewer to 149 more)VERY LOWtion due to any reason (follow-up 8-12 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))RR 1.12 (0.78 to 1.59)24 more per 1000 (from 44 fewer to 117 more)VERY LOWrandomised trialsno serious no serious inconsistencyno serious indirectnessvery serious4 serious4reporting bias2 (23.1%)90/389 (23.1%)40/202 (19.8%)RR 1.12 (0.78 to (1.59)24 more per 1000 (from 44 fewer to 117 more)VERY LOWtoo due to site effects (follow-up 8-12 weeks; assessed with: Number of participants who dropped out due to atverse events)RR 1.12 (0.78 to (1.59)RR 1.12 (1.59)24 more per 1000 (from 44 fewer to 117 more)VERY LOWtion due to site effects (follow-up 8-12 weeks; assessed with: Number of participants who dropped out due to atverse events)RR 1.12 (0.78 to (1.59)40 more per 1000 (from 44 fewer to 117 more)VERY LOWtrialsno serious risk of bias inconsistencyno serious indirectnessser			

¹ Risk of bias is high or unclear across multiple domains

² Funding from pharmaceutical companies

³ 95% CI crosses thresholds for both clinically important benefit and no effect
 ⁴ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
 ⁵ 95% CI crosses thresholds for both clinically important harm and no effect

Clinical evidence profile for comparison 45. Augmenting with antipsychotic versus antidepressant-only or Table 114: antidepressant + placebo

Quality assessment							No of patients		Effect		Quellite		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Improcision	Other	Augmenting with antinsychotic	Antidepressant- only or antidepressant + placebo	Relative (95% Cl)	Absolute		Importance	
Depression symptomatology endpoint (follow-up 4-8 weeks; measured with: Montgomery Asberg Depression Rating Scale (MADRS) or Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)													
5 (Fava 2012/ Mischoulon 2012, Li 2013, Mahmoud 2007, Moica 2018, Song 2007)		serious ¹		no serious indirectness	serious ³	none	295	411	-	SMD 0.78 lower (1.24 to	VERY LOW	CRITICAL	

										0.32 lower)		
Depression symptomatology ((HAM-D) change from baseline					ith: Montgon	nery Asberg Dep	ression Rating	Scale (MADRS) o	r Hamilto	,	cale for Dep	ression
20 (Berman 2009, Dunner 2007, Durgam 2016, Earley 2018, Fava 2012/ Mischoulon 2012, Fava 2018, Fava 2019, Hobart 2018a, Hobart 2018b, Kamijima 2013, Kamijima 2018, Li 2013, Moica 2018, Otsuka Pharmaceutical 2015, Otsuka Pharmaceutical 2016, Papakostas 2015, Reeves 2008, Thase 2007, Thase 2015a, Thase 2015b)	randomised trials	serious ¹	serious ⁴	no serious indirectness	no serious imprecision	reporting bias⁵	3784	2932	-	SMD 0.33 lower (0.44 to 0.23 lower)	VERY LOW	CRITICAL
Remission (ITT) (follow-up 4-2 Depression (HAM-D))	4 weeks; as	sessed \	with: Number o	of people sco	ring <=10 on	Montgomery As	berg Depressio	on Rating Scale (N	IADRS) oi	r <=7 on Ha	milton Ratir	ig Scale for
28 (Bauer 2009, Bauer 2019, Berman 2007, Berman 2009, Dunner 2007, Durgam 2016, Earley 2018, El-Khalili 2010, Fang 2011, Fava 2012/ Mischoulon 2012, Fava 2018, Fava 2019, Hobart 2018a, Hobart 2018b, Kamijima 2013, Kamijima 2018, Keitner 2009, Li 2013, Lenze 2015, Mahmoud 2007, Marcus 2008, McIntyre 2007, Otsuka Pharmaceutical 2016, Papakostas 2015, Thase 2007, Thase 2015a, Thase 2015b)	randomised trials	serious ¹		no serious indirectness	serious ³	reporting bias⁵	1494/5653 (26.4%)	839/4425 (19%)	RR 1.37 (1.23 to 1.52)		VERY LOW	CRITICAL
Response (ITT) (follow-up 4-8 Rating Scale for Depression (H		essed wi	th: Number of	people showi	ing at least 50)% improvement	t on Montgome	ry Asberg Depres	sion Ratii	ng Scale (N	IADRS) or H	amilton
28 (Bauer 2009, Berman 2007, Berman 2009, Dunner 2007, Durgam 2016, Earley 2018, El- Khalili 2010, Fang 2011, Fava 2012/ Mischoulon 2012, Fava 2018, Fava 2019, Hobart 2018a, Hobart 2018b, Kamijima 2013, Kamijima 2018, Keitner 2009, Li 2013, Mahmoud 2007, Marcus 2008, McIntyre 2007, Otsuka Pharmaceutical 2015,	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ⁵	1912/5190 (36.8%)	1025/3964 (25.9%)	RR 1.37 (1.27 to 1.49)	96 more per 1000 (from 70 more to 127 more)	LOW	CRITICAL

Depression in adults: Evidence review D FINAL (June 2022)

Papakostas 2015, Reeves 2008, Song 2007, Thase 2007, Thase 2015a, Thase 2015b)												
iscontinuation due to any rea	ason (follow	-up 4-24	weeks; assess	ed with: Nun	ber of partic	ipants who drop	ped out for any	/ reason (includii	ng advers	e events))		
8 (Bauer 2009, Bauer 2019, Berman 2007, Berman 2009, Dunner 2007, Durgam 2016, Earley 2018, El-Khalili 2010, Fava 2012/ Mischoulon 2012, Fava 2018, Fava 2019, Hobart 018a, Hobart 2018b, Kamijima 013, Kamijima 2018, Keitner 009, Lenze 2015, Li 2013, Mahmoud 2007, Marcus 2008, McIntyre 2007, Otsuka Pharmaceutical 2015, Otsuka Pharmaceutical 2016, Papakostas 2015, Reeves 008, Thase 2007, Thase 015a, Thase 2015b)	randomised trials		no serious inconsistency	no serious indirectness	serious ⁶	reporting bias⁵	825/5620 (14.7%)	525/4392 (12%)		31 more per 1000 (from 16 more to 48 more)		CRITICAL
iscontinuation due to side ef	fects (follow	v-up 4-24	weeks; asses	sed with: Nur	nber of parti	cipants who drop	ped out due to	adverse events))			
7 (Bauer 2009, Bauer 2019, erman 2007, Berman 2009, punner 2007, Durgam 2016, arley 2018, El-Khalili 2010, ava 2012/ Mischoulon 2012, ava 2018, Fava 2019, Hobart 018a, Hobart 2018b, Kamijima 013, Kamijima 2018, Keitner 009, Li 2013, Mahmoud 2007, farcus 2008, McIntyre 2007, tosuka Pharmaceutical 2015, tosuka Pharmaceutical 2016, apakostas 2015, Reeves 008, Thase 2007, Thase 015a, Thase 2015b)	randomised trials	serious risk of bias	no serious inconsistency	no serious indirectness		reporting bias⁵	346/5608 (6.2%)	70/4381 (1.6%)	3.99)	per 1000 (from 22 more to 48 more)		
Quality of life endpoint (follow	up mean 6	weeks; r	measured with	Quality of Li	fe Enjoymen	t and Satisfaction	n Questionnair	e-short form (Q-I	ES-Q-SF	; Better inc	licated by high	gher value
(Mahmoud 2007)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	reporting bias⁵	101	101	-	SMD 0.47 higher (0.19 to 0.75 higher)	VERY LOW	IMPORTA

2 (Berman 2009, Otsuka Pharmaceutical 2016)			no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias⁵	446	281	-	SMD 0.17 higher (0 to 0.34 higher)	MODERATE	IMPORTANT
Quality of life physical compo by higher values)	nent score (PCS) ch	ange score (fol	llow-up mean	8 weeks; me	asured with: 36	item Short-For	m Survey (SF-36)	: Physica	l componei	nt score; Bet	ter indicated
2 (Fang 2011, Thase 2007)	randomised trials	serious ¹	serious ⁴	no serious indirectness	no serious imprecision	reporting bias⁵	243	248	-	SMD 0.04 higher (0.33 lower to 0.41 higher)	VERY LOW	IMPORTANT
Quality of life mental compone higher values)	ent score (M	CS) cha	nge score (follo	ow-up mean 8	8 weeks; mea	sured with: 36-if	tem Short-Form	Survey (SF-36):	Mental co	omponent s	core; Better	indicated by
2 (Fang 2011, Thase 2007)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias⁵	243	248	-	SMD 0.05 higher (0.19 lower to 0.3 higher)	LOW	IMPORTANT
Global functioning change sco higher values)	ore (follow-u	p mean	6 weeks; meas	ured with: So	ocial Adaptati	on Self-evaluati	on Scale (SASS	6) change from ba	seline to	endpoint; I	Better indica	ted by
1 (Kamijima 2018)			no serious inconsistency	no serious indirectness	serious ³	reporting bias⁵	164	149	-	SMD 0.58 higher (0.36 to 0.81 higher)	LOW	IMPORTANT
Functional remission (follow-u	up mean 24 v	weeks; a	ssessed with:	Number of pe	ople scoring	<=6 total score	on Sheehan Di	sability Scale (SD	S) and al	I SDS doma	ain scores <	=2)
1 (Bauer 2019)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁷	reporting bias⁵	68/444 (15.3%)	73/442 (16.5%)	RR 0.93 (0.68 to 1.26)		VERY LOW	IMPORTANT
Functional impairment endpoi	int (follow-up	o mean 6	6 weeks; measi	ured with: Sh	eehan Disabi	lity Scale (SDS);	Better indicate	d by lower values	s)			
1 (Mahmoud 2007)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	reporting bias⁵	100	101	-	SMD 0.62 lower (0.9 to 0.34 lower)	VERY LOW	IMPORTANT
Functional impairment change	e score (follo	w-up 5-	8 weeks; meas	ured with: Sh	eehan Disabi	ility Scale (SDS)	change from b	aseline to endpoi	nt; Better	indicated	by lower val	ues)
10 (Berman 2009, Durgam 2016, Fava 2019, Hobart 2018a, Hobart 2018b, Kamijima 2013, Otsuka Pharmaceutical 2015, Otsuka Pharmaceutical	randomised trials	serious ¹	no serious inconsistency	no serious indirectness		reporting bias⁵	2710	1844	-	SMD 0.17 lower (0.24 to 0.11 lower)	LOW	IMPORTANT

2016, Thase 2015a, Thase 2015b)

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference

¹ Risk of bias is high or unclear across multiple domains

² Considerable heterogeneity
 ³ 95% CI crosses thresholds for both clinically important benefit and no effect

⁴ Substantial heterogeneity

⁵ Funding from pharmaceutical companies

⁶ 95% CI crosses thresholds for both clinically important harm and no effect
 ⁷ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 115: Clinical evidence profile for comparison 46. Augmenting with antipsychotic versus bupropion

Quality assess	ment						No of patients		Effect		Quality	Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with antipsychotic	Bunronion	Relative (95% Cl)	Absolute			
Depression sy indicated by lo		ly change s	core (follow-up n	nean 6 weeks; n	neasured wit	th: Montgomery A	Asberg Depression	Rating Sca	le (MADRS)	change from base	line to endp	oint; Better	
1 (Cheon 2017)	randomised trials		no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	56	47	-	SMD 0.48 lower (0.87 to 0.08 lower)	VERY LOW	CRITICAL	
Remission (IT) Depressive Sy		· · · · · · · · · · · · · · · · · · ·	assessed with:	Number of peop	le scoring <	=10 on Montgom	ery Asberg Depres	sion Rating	Scale (MAI	DRS) or <=5 on Qui	ick Inventory	/ of	
2 (Cheon 2017, Mohamed 2017)	randomised trials	no serious risk of bias	serious ⁴	no serious indirectness	serious ²	none	177/561 (31.6%)	152/553 (27.5%)	RR 1.25 (0.85 to 1.85)	69 more per 1000 (from 41 fewer to 234 more)	LOW	CRITICAL	
Response (ITT Inventory of De	, ,			lumber of peop	le showing a	t least 50% impro	ovement on Montgo	omery Asbe	erg Depress	ion Rating Scale (M	MADRS) or Q	uick	
2 (Cheon 2017, Mohamed 2017)	randomised trials			no serious indirectness	serious ²	none	409/561 (72.9%)	352/553 (63.7%)	RR 1.17 (1 to 1.38)	108 more per 1000 (from 0 more to 242 more)	MODERATE	CRITICAL	
Discontinuatio	n due to any	reason (foll	ow-up 6-12 week	s; assessed wit	th: Number c	of participants wh	o dropped out for	any reason	(including a	adverse events))			
2 (Cheon 2017, Mohamed 2017)	randomised trials		no serious inconsistency	no serious indirectness	serious ²	none	113/561 (20.1%)	139/553 (25.1%)	RR 0.8 (0.64 to 1)	50 fewer per 1000 (from 90 fewer to 0 more)		CRITICAL	
Discontinuatio	n due to side	effects (fol	low-up 6-12 weel	ks; assessed wi	th: Number	of participants wi	ho dropped out due	e to adverse	e events)				

2 (Cheon 2017	, randomised	no serious	no serious	no serious	serious ²	none	27/561	37/553	RR 0.73	18 fewer per 1000	MODERATE C	CRITICAL
Mohamed	trials	risk of bias	inconsistency	indirectness			(4.8%)	(6.7%)	(0.45 to	(from 37 fewer to		
2017)									1.18)	12 more)		

¹ Risk of bias is high or unclear across multiple domains

² 95% CI crosses thresholds for both clinically important benefit and no effect

³ Funding from pharmaceutical companies

⁴ Substantial heterogeneity

Table 116: Clinical evidence profile for comparison 47. Augmenting with antipsychotic versus lithium

Quality assessme	- Risk of								Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with antipsychotic	I Ithuim	Relative (95% Cl)	Absolute		
Remission (ITT) (fe for Depression (H/		veeks; asse	ssed with: Numb	er of people sco	oring <=8/<= [,]	I0 on Montgomer	y Asberg Depressio	on Rating	g Scale (MA	DRS) or <=7 on Han	nilton Ra	ting Scale
3 (Bauer 2013, Doree 2007, Yoshimura 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	reporting bias ²	84/261 (32.2%)	65/249 (26.1%)	RR 1.35 (0.82 to 2.22)	91 more per 1000 (from 47 fewer to 318 more)	LOW	CRITICAL
Response (ITT) (follow-up 4-8 weeks; assessed with: Number of people showing at least 50% improvement on Montgomery Asberg Depression Rating Scale (MADRS) or Hamilton Rating Scale for Depression (HAM-D))												milton
3 (Bauer 2013, Doree 2007, Yoshimura 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	reporting bias ²	135/261 (51.7%)	111/249 (44.6%)		80 more per 1000 (from 9 fewer to 183 more)	LOW	CRITICAL
Discontinuation d	ue to any reas	on (follow-	up 4-8 weeks; as	sessed with: Nu	mber of part	icipants who dro	pped out for any rea	ason (ind	luding adve	erse events))		
3 (Bauer 2013, Doree 2007, Yoshimura 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	reporting bias ²	36/261 (13.8%)	51/249 (20.5%)	RR 0.71 (0.48 to 1.05)	59 fewer per 1000 (from 107 fewer to 10 more)	LOW	CRITICAL
Discontinuation d	Discontinuation due to side effects (follow-up 4-8 weeks; assessed with: Number of participants who dropped out due to adverse events)											
3 (Bauer 2013, Doree 2007, Yoshimura 2014)	trials		no serious inconsistency	no serious indirectness	very serious ³	reporting bias ²	24/261 (9.2%)	20/249 (8%)	RR 1.16 (0.66 to 2.04)	13 more per 1000 (from 27 fewer to 84 more)	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk

¹ 95% CI crosses thresholds for both clinically important benefit and no effect

² Funding from pharmaceutical companies
 ³ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 117:	Clinical evidence profile for comp	parison 48. Augmenting with	n antipsvchotic versus swi	itch to antipsychotic

Quality ass	sessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with antipsychotic	Switch to antipsychotic	Relative (95% Cl)	Absolute		
	n symptomato by lower value		e score (follow-	up mean 8 week	ks; measured v	vith: Montgomery	Asberg Depressio	on Rating Scale (MADRS) ch	ange from baselin	e to end	point; Bette
1 (Thase 2007)	randomised trials		no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	198	197	-	SMD 0.38 lower (0.58 to 0.18 lower)	VERY LOW	CRITICAL
Remission	(ITT) (follow-	up 6-8 week	s; assessed wit	h: Number of pe	ople scoring	<=10 on Montgom	ery Asberg Depres	ssion Rating Sca	le (MADRS))		
2 (Bauer 2013, Thase 2007)	randomised e trials		no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	127/431 (29.5%)	82/427 (19.2%)	RR 1.54 (1.14 to 2.07)	104 more per 1000 (from 27 more to 205 more)	LOW	CRITICAL
Response	(ITT) (follow-u	ip 6-8 weeks	s; assessed with	n: Number of pe	ople showing	at least 50% impr	ovement on Montg	omery Asberg D	epression F	Rating Scale (MAD	RS))	
2 (Bauer 2013, Thase 2007)		no serious risk of bias	very serious ⁴	no serious indirectness	serious ²	reporting bias ³	200/431 (46.4%)	165/427 (38.6%)	RR 1.25 (0.84 to 1.88)	97 more per 1000 (from 62 fewer to 340 more)	VERY LOW	CRITICAL
Discontinu	ation due to a	iny reason (follow-up 6-8 w	eeks; assessed	with: Number	of participants wl	ho dropped out for	any reason (inc	luding adve	rse events))		
2 (Bauer 2013, Thase 2007)	randomised e trials		no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	87/431 (20.2%)	121/427 (28.3%)	RR 0.71 (0.56 to 0.9)	82 fewer per 1000 (from 28 fewer to 125 fewer)	LOW	CRITICAL
Discontinu	ation due to s	ide effects	(follow-up 6-8 w	eeks; assessed	with: Number	of participants w	ho dropped out du	e to adverse eve	ents)			
2 (Bauer 2013, Thase 2007)	randomised e trials		no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	50/431 (11.6%)	60/427 (14.1%)	RR 0.83 (0.58 to 1.17)	24 fewer per 1000 (from 59 fewer to 24 more)	LOW	CRITICAL
Quality of I by higher v		omponent s	score (PCS) cha	nge score (follo	w-up mean 8 v	veeks; measured	with: 36-item Shor	t-Form Survey (S	6F-36): Phys	sical component so	core; Be	tter indicate
1 (Thase 2007)	randomised trials		no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	198	197	-	SMD 0.33 higher (0.13 to 0.53 higher)	VERY LOW	IMPORTAN
Quality of I higher valu		nponent sc	ore (MCS) chan	ge score (follow	-up mean 8 we	eks; measured w	vith: 36-item Short-	Form Survey (SI	-36): Menta	l component score	e; Better	indicated b
1 (Thase 2007)	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ³	198	197	-	SMD 0.18 higher (0.01 lower to 0.38 higher)	LOW	IMPORTAN

¹ Risk of bias is high or unclear across multiple domains
 ² 95% CI crosses thresholds for both clinically important benefit and no effect

³ Funding from pharmaceutical companies

⁴ Considerable heterogeneity

Clinical evidence profile for comparison 49. Augmenting with antipsychotic versus switch to bupropion **Table 118:**

Quality as	sessment						No of patients		Effect		Quality	Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with antipsychotic	Switch to bupropion	Relative (95% Cl)	Absolute			
Remission	n (ITT) (follow	/-up mean [/]	12 weeks; asses	sed with: Numb	er of people so	oring <=5 on Qui	ck Inventory of De	pressive Sym	ptomatology	y (QIDS))			
1 (Mohamed 2017)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	146/505 (28.9%)	114/511 (22.3%)	RR 1.3 (1.05 to 1.6)	67 more per 1000 (from 11 more to 134 more)	MODERATE	CRITICAL	
Response	(ITT) (follow	-up mean 1	2 weeks; assess	ed with: Numbe	er of people sh	owing at least 50 [°]	% improvement on	Quick Invent	ory of Depre	ssive Symptomato	logy (QIDS))		
1 (Mohamed 2017)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	375/505 (74.3%)	319/511 (62.4%)	RR 1.19 (1.09 to 1.29)	119 more per 1000 (from 56 more to 181 more)	MODERATE	CRITICAL	
Discontinu	uation due to	any reaso	n (follow-up mea	n 12 weeks; as	sessed with: N	umber of particip	ants who dropped	out for any re	ason (inclue	ding adverse events	5))		
1 (Mohamed 2017)	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	99/505 (19.6%)	158/511 (30.9%)	RR 0.63 (0.51 to 0.79)	114 fewer per 1000 (from 65 fewer to 152 fewer)	HIGH	CRITICAL	
Discontinu	uation due to	side effect	ts (follow-up mea	an 12 weeks; as	sessed with: N	lumber of particip	ants who dropped	out due to ad	lverse event	s)			
1 (Mohamed 2017)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	27/505 (5.3%)	51/511 (10%)	RR 0.54 (0.34 to 0.84)	46 fewer per 1000 (from 16 fewer to 66 fewer)	MODERATE	CRITICAL	

CI: confidence interval; ITT: intention to treat; RR: relative risk

¹ 95% CI crosses thresholds for both clinically important benefit and no effect

Table 119: Clinical evidence profile for comparison 50. Augmenting with buspirone versus continuing with antidepressant (+/placebo)

Quality assessment	No of patients	Effect	Quality	Importance	
--------------------	----------------	--------	---------	------------	--

Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Continuing with antidepressant (+/- placebo)	Relative (95% Cl)	Absolute		
T) (follow-up	o mean 8	weeks; assesse	d with: Numbe	or of people sc	oring <=7 on Har	nilton Rating Sc	ale for Depression (H	IAM-D))			
randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	15/46 (32.6%)	21/45 (46.7%)	RR 0.7 (0.42 to 1.18)	140 fewer per 1000 (from 271 fewer to 84 more)	LOW	CRITICAL
				people rated as	s much or very m	uch improved o	on Clinical Global Imp	pressions	scale (CGI-I) or s	howing at le	ast 50%
randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	43/97 (44.3%)	46/96 (47.9%)	RR 0.9 (0.68 to 1.19)	48 fewer per 1000 (from 153 fewer to 91 more)	LOW	CRITICAL
physical cor les)	mponent	score (PCS) cha	ange score (fol	low-up mean 8	weeks; measure	ed with: 36-item	Short-Form Survey (SF-36): Ph	ysical compone	nt score; Bet	ter indicate
randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	46	45	-	SMD 0.06 lower (0.48 lower to 0.35 higher)	MODERATE	IMPORTAN
mental com	ponent s	core (MCS) char	nge score (follo	ow-up mean 8	weeks; measured	d with: 36-item S	Short-Form Survey (S	F-36): Men	ital component s	core; Better	indicated by
randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	46	45	-	SMD 0.08 higher (0.34 lower to 0.49 higher)	MODERATE	IMPORTAN
	T) (follow-up randomised trials T) (follow-up on Hamilton randomised trials physical con es) randomised mental com randomised	Design bias I) (follow-up mean 8 randomised randomised serious ¹ (follow-up 6-8 weel on Hamilton Rating S randomised serious ¹ physical component es) randomised serious ¹	Design bias Inconsistency (follow-up mean 8 weeks; assessed randomised serious ¹ no serious inconsistency no serious inconsistency (follow-up 6-8 weeks; assessed with on Hamilton Rating Scale for Depress randomised serious ¹ no serious inconsistency physical component score (PCS) char es) randomised serious ¹ no serious inconsistency mental component score (MCS) char randomised serious ¹ no serious	Design bias Inconsistency Indirectness T) (follow-up mean 8 weeks; assessed with: Number randomised serious ¹ no serious inconsistency no serious indirectness T) (follow-up 6-8 weeks; assessed with: Number of pon Don Hamilton Rating Scale for Depression (HAM-D)) no serious inconsistency no serious indirectness T) (follow-up 6-8 weeks; assessed with: Number of pon Don Hamilton Rating Scale for Depression (HAM-D)) no serious inconsistency no serious indirectness randomised trials serious ¹ no serious inconsistency no serious indirectness no serious indirectness physical component score (PCS) change score (follow trials serious ¹ no serious inconsistency no serious indirectness mental component score (MCS) change score (follow randomised serious ¹ no serious no serious no serious	DesignbiasInconsistencyIndirectnessImprecisionT) (follow-up mean 8 weeks; assessed with: Number of people sc randomisedno serious inconsistencyno serious indirectnessserious²T) (follow-up 6-8 weeks; assessed with: Number of people rated as on Hamilton Rating Scale for Depression (HAM-D)) randomisedserious¹ no serious inconsistencyno serious no serious indirectnessserious²T) (follow-up 6-8 weeks; assessed with: Number of people rated as on Hamilton Rating Scale for Depression (HAM-D)) randomised serious¹no serious inconsistencyno serious indirectnessserious²physical component score (PCS) change score (follow-up mean 8 inconsistencyno serious indirectnessno serious imprecisionrandomised trialsserious¹ no serious inconsistencyno serious indirectnessno serious imprecisionmental component score (MCS) change score (follow-up mean 8 imprecisionno serious imprecisionno serious imprecision	DesignbiasInconsistencyIndirectnessImprecisionconsiderations(follow-up mean 8 weeks; assessed with: Number of people scoring <=7 on Har no serious inconsistencyno serious no serious indirectnessserious²none(follow-up 6-8 weeks; assessed with: Number of people rated as on Hamilton Rating Scale for Depression (HAM-D)) randomised trialsserious¹no serious no serious inconsistencyserious²none(follow-up 6-8 weeks; assessed with: Number of people rated as on Hamilton Rating Scale for Depression (HAM-D)) randomised trialsno serious inconsistencyno serious indirectnessserious²none(physical component score (PCS) change score (follow-up mean 8 weeks; measure es)no serious indirectnessno serious imprecisionnonemental component score (MCS) change score (follow-up mean 8 weeks; measured randomised serious¹no serious no serious no serious indirectnessno serious imprecisionnonemental component score (MCS) change score (follow-up mean 8 weeks; measured randomised serious¹no serious no serious no seriousnone	DesignbiasInconsistencyIndirectnessImprecisionconsiderationswith buspironeI) (follow-up mean 8 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Sc inconsistencyno serious indirectnessserious²none15/46 (32.6%)randomisedserious¹no serious inconsistencyno serious indirectnessserious²none15/46 (32.6%)r) (follow-up 6-8 weeks; assessed with: Number of people rated as much or very much improved or on Hamilton Rating Scale for Depression (HAM-D))none43/97 (44.3%)randomisedserious¹no serious inconsistencyno serious indirectnessserious²none43/97 (44.3%)physical component score (PCS) change score (follow-up mean 8 weeks; measured with: 36-item es)no serious indirectnessno serious imprecisionnone46mental component score (MCS) change score (follow-up mean 8 weeks; measured with: 36-item 5 indirectnessno serious imprecisionnone46	DesignNisk of biasInconsistencyIndirectnessImprecisionOther considerationsAugmenting with buspioneantidepressant (+/- placebo)T) (follow-up mean 8 weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (F randomised serious)no serious inconsistencyno serious indirectnessserious2none15/46 (32.6%)21/45 (46.7%)T) (follow-up 6-8 weeks; assessed with: Number of people rated as much or very much improved on Clinical Global Improved on Hamilton Rating Scale for Depression (HAM-D))none43/97 (44.3%)46/96 (47.9%)Trialsserious1no serious inconsistencyno serious indirectnessserious2none43/97 (44.3%)46/96 (47.9%)physical component score (PCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (es)no serious indirectnessno serious indirectnessnone4645mental component score (MCS) change score (follow-up mean 8 weeks; measured with: 36-item Short-Form Survey (S randomised serious1 no serious inconsistencyno serious indirectnessno serious imprecisionnone4645	DesignRisk of biasInconsistencyIndirectnessImprecisionOther considerationsAugmenting with buspironeAugmenting placebol	DesignKisk of hasInconsistencyIndirectnessImprecisionOther considerationsAugmenting with buspironantidepressant (+/- placebo)Relative (95% CI)AbsoluteIf) (follow-up mean 8weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D))	DesignNisk of bas basInconsistencyIndirectnessImprecisionOther considerationsAugmenting with buspinoeantidepressant (+/- placebo)Relative (95% CI)Absolute(follow-up mean 8weeks; assessed with: Number of people scoring <=7 on Hamilton Rating Scale for Depression (HAM-D)To serious indirectnessno serious indirectnessno serious serious ² no serious indirectnessno serious serious ² none15/46 (32.6%)21/45 (46.7%)RR 0.7 (0.42 to 1.18)140 fewer per 1000 (from 271 fewer to 84 more)LOW(follow-up 6-8 weeks; assessed with: Number of people rated as much or very much improved on Clinical Global ImpressionsRR 0.9 (44.3%)48 fewer per (44.3%)140 fewer to 84 more)1000 (from 271 fewer to 84 more)(follow-up 6-8 weeks; assessed with: Number of people rated as much or very much improved on Clinical Global ImpressionsRR 0.9 (14.3%)48 fewer per (47.9%)LOW(follow-up fraidsserious ¹ inconsistencyno serious indirectnessserious ² none43/97 (44.3%)46/96 (47.9%)RR 0.9 (0.68 to 1.19)48 fewer per fewer to 91 more)LOWphysical component score (PCS) charge score (follow-up mean 8 weeks; measured with: 36-itemShort-Form Survey (SF-36): Physical component score; Bet (0.48 lower to 0.35 higher)no serious indirectnessno serious imprecisionnone4645-SMD 0.06 lower MODERATE (0.48 lower to 0.35 higher)randomisedserious ¹ no serious indirectnessno serious in

¹ Risk of bias is high or unclear across multiple domains
 ² 95% CI crosses thresholds for both clinically important harm and no effect

Table 120: Clinical evidence profile for comparison 51. Augmenting with buspirone versus bupropion

Quality a	ssessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		Augmenting with buspirone	Bunronion	Relative (95% Cl)	Absolute		
Depressi	on symptoma	tology endp	oint (follow-up m	ean 6 weeks; m	easured with: (Quick Inventory o	f Depressive Sym	ptomatolog	y (QIDS); Be	tter indicated by lov	ver values)	
1 (Trivedi 2006)	randomised trials	serious ¹			no serious imprecision	none	286	279	-	SMD 0.2 higher (0.04 to 0.37 higher)	MODERATE	CRITICAL
	Depression symptomatology change score (follow-up mean 6 weeks; measured with: Quick Inventory of Depressive Symptomatology (QIDS) change from baseline to endpoint; Better indicated by lower values)											

1 (Trivedi 2006)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	286	279	-	SMD 0.17 higher (0.01 to 0.34 higher)		CRITICAL		
Remissio	n (ITT) (follow	w-up mean 6	weeks; assesse	d with: Number	of people scori	ing <=7 on Hamilto	on Rating Scale fo	r Depressi	on (HAM-D))					
1 (Trivedi 2006)			no serious inconsistency	no serious indirectness	very serious ²	none	86/286 (30.1%)	83/279 (29.7%)	RR 1.01 (0.79 to 1.3)	3 more per 1000 (from 62 fewer to 89 more)		CRITICAL		
Response	esponse (ITT) (follow-up mean 6 weeks; assessed with: Number of people showing at least 50% improvement on Quick Inventory of Depressive Symptomatology (QIDS))													
1 (Trivedi 2006)	randomised trials		no serious inconsistency	no serious indirectness	serious ³	none	77/286 (26.9%)	88/279 (31.5%)	RR 0.85 (0.66 to 1.1)	47 fewer per 1000 (from 107 fewer to 32 more)	MODERATE	CRITICAL		
Discontin	uation due to	side effect	s (follow-up mea	n 6 weeks; asse	ssed with: Num	ber of participant	s who dropped ou	it due to ad	lverse events	5)				
1 (Trivedi 2006)	randomised trials			no serious indirectness	serious ³	none	59/286 (20.6%)	35/279 (12.5%)	RR 1.64 (1.12 to 2.41)	80 more per 1000 (from 15 more to 177 more)	MODERATE	CRITICAL		

Risk of bias is high or unclear across multiple domains
 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
 95% CI crosses thresholds for both clinically important harm and no effect

Clinical evidence profile for comparison 52. Augmenting with methylphenidate versus placebo Table 121:

Quality assess	nent						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with methylphenidate	Placebo	Relative (95% Cl)	Absolute		
Depression syn indicated by lov		y change so	core (follow-up m	ean 5 weeks; m	neasured with:	Montgomery Ast	perg Depression Ratin	g Scale (MADRS) ch	ange from baseline	to endp	oint; Better
1 (Ravindran 2008a)	randomised trials	very serious ¹	no serious inconsistency		no serious imprecision	reporting bias ²	72	72	-	SMD 0.06 higher (0.27 lower to 0.38 higher)		CRITICAL
Remission (ITT)) (follow-up n	nean 4 wee	ks; assessed witl	n: Number of pe	ople showing	at least 50% impr	ovement on Hamilton	Rating S	Scale for Dep	pression (HAM-D))		
1 (Patkar 2006)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	reporting bias ²	4/30 (13.3%)	1/30 (3.3%)	RR 4 (0.47 to 33.73)	100 more per 1000 (from 18 fewer to 1000 more)	VERY LOW	CRITICAL
Response (ITT) Depression Rat			ssessed with: Nu	mber of people	showing at lea	ast 50% improven	nent on Hamilton Rati	ng Scale	for Depress	ion (HAM-D) or Mo	ntgomer	y Asberg
2 (Patkar 2006, Ravindran 2008a)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ²	46/103 (44.7%)	37/102 (36.3%)	RR 1.21 (0.87 to 1.68)	76 more per 1000 (from 47 fewer to 247 more)	VERY LOW	CRITICAL

Discontinuation	n due to any i	eason (foll	ow-up mean 5 we	eks; assessed	with: Number	of participants wh	no dropped out for any	/ reason	(including a	idverse events))				
1 (Ravindran 2008a)	randomised trials		no serious inconsistency	no serious indirectness	serious ⁶	reporting bias ²	11/73 (15.1%)	4/72 (5.6%)	RR 2.71 (0.91 to 8.12)	95 more per 1000 (from 5 fewer to 396 more)	VERY LOW	CRITICAL		
Discontinuation	iscontinuation due to side effects (follow-up 4-5 weeks; assessed with: Number of participants who dropped out due to adverse events)													
2 (Patkar 2006, Ravindran 2008a)		no serious risk of bias		no serious indirectness	very serious ³	reporting bias ²	8/103 (7.8%)	2/102 (2%)	RR 2.92 (0.21 to 40.65)	38 more per 1000 (from 15 fewer to 777 more)	VERY LOW	CRITICAL		

¹ Risk of bias is high or unclear across multiple domains

² Funding from pharmaceutical companies

³ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

⁴ 95% CI crosses thresholds for both clinically important benefit and no effect

⁵ Statistically significant group difference at baseline
 ⁶ 95% CI crosses thresholds for both clinically important harm and no effect

⁷ Substantial heterogeneity

Table 122: Clinical evidence profile for comparison 53. Augmenting with lithium versus continuing with antidepressant (+/placebo)

Quality assessmen	nt						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with lithium	Continuing with antidepressant (+/- placebo)	Relative (95% Cl)	Absolute		
Depression sympt Better indicated by			ollow-up 2-3 wee	ks; measured v	with: Hamilto	on Rating Scale fo	or Depression ((HAM-D) or Montgom	ery Asberg	Depression Rati	ng Scal	e (MADRS);
2 (Joffe 1993, Stein 1993)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	33	34	-	SMD 0.23 lower (0.71 lower to 0.25 higher)	LOW	CRITICAL
								ssion (HAM-D) or Mor Ited by lower values)	ntgomery A	sberg Depressio	n Rating	g Scale
3 (Girlanda 2014, Joffe 1993, Stein 1993)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	60	56	-	SMD 0.26 lower (0.76 lower to 0.23 higher)	LOW	CRITICAL
Remission (ITT) (fo on HAM-D))	ollow-up mea	n 3 weeks	; assessed with:	Number of pe	ople scoring	<=7 on Hamilton	Rating Scale f	or Depression (HAM	D) AND res	sponding (at leas	t 50% in	nprovement
1 (Joffe 1993)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ³	none	6/18 (33.3%)	2/16 (12.5%)	RR 2.67 (0.62 to 11.39)	209 more per 1000 (from 47	LOW	CRITICAL

										fewer to 1000 more)				
Response (ITT) (fo	llow-up 1-6 v	veeks; ass	essed with: Nun	ber of people	showing at l	east 50% improve	ment on Hami	ton Rating Scale for	Depressior	(HAM-D))				
2 (Baumann 1996, Nierenberg 2003a)		serious ¹	serious ⁴	no serious indirectness	very serious ³	reporting bias⁵	8/28 (28.6%)	5/31 (16.1%)	RR 1.72 (0.27 to 11.05)	116 more per 1000 (from 118 fewer to 1000 more)	VERY LOW	CRITICAL		
Discontinuation du	scontinuation due to any reason (follow-up 2-52 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))													
4 (Girlanda 2014, Joffe 1993, Nierenberg 2003a, Stein 1993)	randomised trials		no serious inconsistency	no serious indirectness	very serious ³	none	5/81 (6.2%)	7/78 (9%)	RR 0.67 (0.22 to 2.03)	30 fewer per 1000 (from 70 fewer to 92 more)	LOW	CRITICAL		
Discontinuation du	le to side eff	ects (follov	v-up 2-3 weeks;	assessed with	: Number of	participants who	dropped out d	ue to adverse events)						
2 (Joffe 1993, Stein 1993)	randomised trials		no serious inconsistency	no serious indirectness	very serious ³	none	1/34 (2.9%)	0/34 (0%)	RR 2.68 (0.12 to 61.58)	-	LOW	CRITICAL		

¹ Risk of bias was high or unclear across multiple domains

² 95% CI crosses thresholds for both clinically important benefit and no effect
 ³ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

⁴ Substantial heterogeneity

⁵ Funding from pharmaceutical companies

Clinical evidence profile for comparison 54. Augmenting with lithium versus switch to antipsychotic Table 123:

Quality as	ssessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Improcision	Other considerations	Augmenting with lithium		Relative (95% Cl)	Absolute		
Remissio	n (ITT) (follov	w-up meai	n 6 weeks; assess	ed with: Numbe	r of people s	coring <=10 on M	ontgomery Asbe	rg Depression Ra	ting Scale (M	IADRS))		
1 (Bauer 2013)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	60/229 (26.2%)	53/228 (23.2%)	RR 1.13 (0.82 to 1.55)	30 more per 1000 (from 42 fewer to 128 more)		CRITICAL
Response	e (ITT) (follow	/-up mean	6 weeks; assess	ed with: Number	of people sl	nowing at least 50	% improvement	on Montgomery A	sberg Depre	ssion Rating Scale (N	IADRS))	
1 (Bauer 2013)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	reporting bias ³	102/229 (44.5%)	114/228 (50%)	RR 0.89 (0.73 to 1.08)	55 fewer per 1000 (from 135 fewer to 40 more)		CRITICAL
Discontir	nuation due to	o any reas	on (follow-up mea	an 6 weeks; ass	essed with: N	lumber of particip	ants who droppe	ed out for any reas	son (includin	g adverse events))		

1 (Bauer 2013)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious⁵	reporting bias ³	47/229 (20.5%)	49/228 (21.5%)	RR 0.95 (0.67 to 1.36)	11 fewer per 1000 (from 71 fewer to 77 more)	VERY LOW	CRITICAL
Discontin	nuation due to	side effe	ects (follow-up me	an 6 weeks; ass	essed with:	Number of particip	ants who droppe	ed out due to adve	erse events)			
1 (Bauer 2013)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	reporting bias ³	18/229 (7.9%)	28/228 (12.3%)	RR 0.64 (0.36 to 1.12)	44 fewer per 1000 (from 79 fewer to 15 more)	VERY LOW	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk

¹ Rapid switch from failed drug for quetiapine monotherapy arm ² 95% CI crosses thresholds for both clinically important benefit and no effect

³ Study funded by pharmaceutical company

⁴ 95% CI crosses thresholds for both clinically important harm and no effect
 ⁵ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 124: Clinical evidence profile for comparison 55. Augmenting with lithium versus augmenting with a psychological intervention

Quality as	sessment						No of patients		Effect		Quality	Importanc
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Improcision	Other considerations	Augmenting with lithium	Augmenting with a psychological intervention	Relative (95% Cl)	Absolute		
Depressio	on symptomat	ology end	point (follow-up	mean 8 weeks;	measured w	ith: Hamilton Ra	ting Scale for D	epression (HAM-D); B	etter indica	ted by lower value	es)	
1 (Kennedy 2003)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	19	20	-	SMD 0.41 lower (1.05 lower to 0.22 higher)	MODERATE	CRITICAL
	on symptomat by lower valu		nge score (follov	v-up mean 8 we	eks; measur	ed with: Hamilto	n Rating Scale	for Depression (HAM-	D) change f	rom baseline to e	ndpoint; Bett	er
1 (Kennedy 2003)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	19	20	-	SMD 0.42 lower (1.06 lower to 0.21 higher)	MODERATE	CRITICAL
Depressio	on symptomat	tology at 1	-month follow-up	o (follow-up me	an 1 months	; measured with:	Hamilton Ratin	g Scale for Depressio	n (HAM-D);	Better indicated b	oy lower valu	es)
1	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	19	20	-	SMD 0.65 lower (1.29 lower to 0	MODERATE	CRITICAL

1 (Kennedy 2003)	randomised trials		no serious inconsistency	no serious indirectness	very serious²	none	8/21 (38.1%)	6/23 (26.1%)	RR 1.46 (0.61 to 3.51)	120 more per 1000 (from 102 fewer to 655 more)	LOW	CRITICAL
Discontinu	uation due to	any reaso	n (follow-up mea	an 8 weeks; ass	essed with:	Number of partic	ipants who dro	pped out for any reaso	on (includin	g adverse events))		
1 (Kennedy 2003)	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	3/21 (14.3%)	3/23 (13%)	RR 1.1 (0.25 to 4.84)	13 more per 1000 (from 98 fewer to 501 more)	LOW	CRITICAL
Discontinu	uation due to	side effect	ts (follow-up me	an 8 weeks; as	sessed with:	Number of partic	ipants who dro	pped out due to adver	se events)			
1 (Kennedy 2003)	randomised trials		no serious inconsistency	no serious indirectness	very serious ²	none	1/21 (4.8%)	0/23 (0%)	RR 3.27 (0.14 to 76.21)	-	LOW	CRITICAL

¹ 95% CI crosses thresholds for both clinically important benefit and no effect ² 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Clinical evidence profile for comparison 56. Augmenting with lithium versus augmenting with TCA Table 125:

Quality asse	ssment						No of patients		Effect		Quality	Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		Augmenting with lithium		Relative (95% Cl)	Absolute			
Depression s	symptomatol	ogy endpoir	nt (follow-up mea	n 4 weeks; meas	sured with: H	lamilton Rating S	cale for Depress	ion (HAM-D); Be	etter indicate	ed by lower values)			
2 (Fava 1994a, Fava 2002)	randomised trials			no serious indirectness	serious ²	none	48	46	-	SMD 0.32 lower (0.73 lower to 0.09 higher)	LOW	CRITICAL	
	pression symptomatology change score (follow-up mean 4 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; licated by lower values)												
2 (Fava 1994a, Fava 2002)	randomised trials		no serious inconsistency	no serious indirectness	serious ³	none	46	48	-	SMD 0.1 higher (0.31 lower to 0.51 higher)	LOW	CRITICAL	
Remission (I	TT) (follow-u	p mean 4 we	eks; assessed w	ith: Number of p	people scori	ng <=7 on Hamilto	on Rating Scale f	for Depression (HAM-D))				
2 (Fava 1994a, Fava 2002)	randomised trials			no serious indirectness	very serious ⁴	none	12/48 (25%)	13/46 (28.3%)	RR 0.88 (0.45 to 1.74)	34 fewer per 1000 (from 155 fewer to 209 more)	VERY LOW	CRITICAL	
Discontinuat	tion due to ar	ny reason (fo	ollow-up mean 4 v	weeks; assesse	d with: Numl	per of participants	who dropped o	ut for any reaso	n (including	adverse events))			
2 (Fava 1994a, Fava 2002)	randomised trials			no serious indirectness	very serious ⁴	none	7/48 (14.6%)	8/46 (17.4%)	RR 0.83 (0.33 to 2.11)	30 fewer per 1000 (from 117 fewer to 193 more)	LOW	CRITICAL	

Discontinua	tion due to si	de effects (f	follow-up mean 4	weeks; assess	ed with: Num	ber of participant	s who dropped o	ut due to adver	se events)		
1 (Fava 1994a)	randomised trials		no serious inconsistency	no serious indirectness	very serious ⁴	reporting bias⁵	1/14 (7.1%)	2/12 (16.7%)	RR 0.43 (0.04 to 4.16)	95 fewer per 1000 (from 160 fewer to 527 more)	CRITICAL

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; TCA: tricyclic antidepressant

¹ Risk of bias high or unclear across multiple domains
 ² 95% CI crosses thresholds for both clinically important benefit and no effect

³ 95% CI crosses thresholds for both clinically important harm and no effect
 ⁴ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

⁵ Study partially funded by pharmaceutical company

Table 126: Clinical evidence profile for comparison 57. Augmenting with omega-3 fatty acids versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with omega-3 fatty acids	Placebo	Relative (95% Cl)	Absolute		
Depression symptoma	tology endpo	oint (follow	-up 4-12 weeks; I	measured with:	Hamilton Rat	ing Scale for Dep	ression (HAM-D);	Better in	dicated by	lower values)		
3 (Jahanggard 2018, Mozaffari-Khosravi 2013, Nemets 2002)	randomised trials	serious ¹	very serious ²	no serious indirectness	serious ³	none	76	56	-	SMD 1.73 lower (3.59 lower to 0.12 higher)	VERY LOW	CRITICAL
Depression symptoma by lower values)	tology chang	e score (fo	ollow-up 4-12 wee	eks; measured	with: Hamiltor	Rating Scale for	Depression (HAM	I-D) char	ige from ba	seline to endpoir	it; Better	indicated
3 (Jahanggard 2018, Mozaffari-Khosravi 2013, Nemets 2002)	randomised trials	serious ¹	very serious ²	no serious indirectness	serious ³	none	76	56	-	SMD 1.65 lower (3.02 to 0.27 lower)	VERY LOW	CRITICAL
Remission (ITT) (follow	/-up mean 12	weeks; as	sessed with: Nu	nber of people	scoring <=7 o	n Hamilton Ratin	g Scale for Depres	sion (HA	AM-D))			
1 (Mozaffari-Khosravi 2013)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	5/54 (9.3%)	0/27 (0%)	RR 5.6 (0.32 to 97.69)	-	VERY LOW	CRITICAL
Response (ITT) (follow or 50% improvement o					wing at least 5	0% improvement	on Montgomery A	sberg D	epression F	Rating Scale (MAI	ORS) or a	at least 30%
3 (Mozaffari-Khosravi 2013, Nemets 2002, Peet 2002)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	28/116 (24.1%)	5/54 (9.3%)	RR 2.49 (0.77 to 8.06)	138 more per 1000 (from 21 fewer to 654 more)	VERY LOW	CRITICAL
Discontinuation due to	any reason	(follow-up	4-12 weeks; asse	essed with: Nur	nber of partici	pants who dropp	ed out for any reas	son (incl	uding adve	rse events))		

4 (Jahangard 2018, Mozaffari-Khosravi 2013, Nemets 2002, Peet 2002)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ⁴	none	19/141 (13.5%)	11/80 (13.8%)	RR 0.8 (0.41 to 1.56)	27 fewer per 1000 (from 81 fewer to 77 more)	LOW	CRITICAL
Discontinuation due to	side effects	(follow-up	4-12 weeks; ass	essed with: Nu	mber of partic	ipants who dropp	oed out due to adv	erse evei	nts)			
4 (Jahangard 2018, Mozaffari-Khosravi 2013, Nemets 2002, Peet 2002)	randomised trials		no serious inconsistency	no serious indirectness	very serious ⁴	none	6/141 (4.3%)	5/80 (6.3%)	RR 0.57 (0.18 to 1.73)	27 fewer per 1000 (from 51 fewer to 46 more)	LOW	CRITICAL
Sleeping difficulties er	ndpoint (follo	w-up mean	12 weeks; meas	sured with: Inso	omnia Severity	Index (ISI); Bette	er indicated by low	ver values	;)			
1 (Jahangard 2018)	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	25	25	-	SMD 3.36 lower (4.24 to 2.47 lower)	HIGH	IMPORTANT

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference
 ¹ Risk of bias is high or unclear across multiple domains
 ² Considerable heterogeneity
 ³ 95% CI crosses thresholds for both clinically important benefit and no effect
 ⁴ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 127: Clinical evidence profile for comparison 58. Augmenting with thyroid hormone versus continuing with antidepressant (+/- placebo)

Quality as	sessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with thyroid hormone	Continuing with antidepressant (+/- placebo)	Relative (95% Cl)	Absolute		
Depressio	on symptoms	endpoint (follow-up mean	2 weeks; meas	sured with: Ha	milton Rating Sc	ale for Depression	on (HAM-D); Better in	dicated by	lower values)		
1 (Joffe 1993)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	17	16	-	SMD 0.53 lower (1.22 lower to 0.17 higher)	MODERATE	CRITICAL
Depressio lower valu		change sc	ore (follow-up r	nean 2 weeks;	measured wit	n: Hamilton Ratin	ng Scale for Depr	ression (HAM-D) char	ige from ba	seline to endpoi	nt; Better ind	dicated by
1 (Joffe 1993)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	17	16	-	SMD 0.78 lower (1.5 to 0.07 lower)	MODERATE	CRITICAL
Remissio	n (ITT) (follow	v-up 2-8 we	eks; assessed v	with: Number o	f people scori	ng <=7 on Hamil	ton Rating Scale	for Depression (HAM	I-D))			

2 (Fang 2011, Joffe 1993)	randomised trials	serious ²	serious ³	no serious indirectness	very serious ⁴	none	25/65 (38.5%)	23/61 (37.7%)	RR 1.39 (0.35 to 5.53)	147 more per 1000 (from 245 fewer to 1000 more)	VERY LOW	CRITICAL
Response	(ITT) (follow	-up mean	8 weeks; assess	ed with: Numb	er of people s	howing at least 5	0% improvement	on Hamilton Rating	Scale for D	epression (HAM	-D))	
· 5	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious⁵	none	28/48 (58.3%)	30/45 (66.7%)	RR 0.88 (0.64 to 1.2)	80 fewer per 1000 (from 240 fewer to 133 more)	LOW	CRITICAL
Discontinu	ation due to	any reaso	on (follow-up me	an 2 weeks; as	sessed with:	Number of partici	pants who dropp	ed out for any reaso	n (including	g adverse events	;))	
1 (Joffe 1993)		no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/17 (0%)	0/16 (0%)	not pooled	not pooled	HIGH	CRITICAL
Discontinu	ation due to	side effec	ts (follow-up m	ean 2 weeks; as	ssessed with:	Number of partic	ipants who dropp	ed out due to adver	se events)			
\ -		no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/17 (0%)	0/16 (0%)	not pooled	not pooled	HIGH	CRITICAL
Quality of by higher		componei	nt score (PCS) c	hange score (f	ollow-up mear	n 8 weeks; measu	ired with: 36-item	Short-Form Survey	(SF-36): Ph	ysical compone	nt score; Bet	ter indicate
(Fang 2011)	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious⁵	none	48	45	-	SMD 0.12 lower (0.53 lower to 0.28 higher)	LOW	IMPORTAN
Quality of higher valu		omponent	score (MCS) ch	ange score (fol	llow-up mean	8 weeks; measur	ed with: 36-item S	Short-Form Survey (S	SF-36): Men	ital component s	core; Better	indicated by
l (Fang 2011)	randomised trials	serious ²	no serious inconsistency	no serious indirectness	no serious imprecision	none	48	45	-	SMD 0.02 lower (0.42 lower to 0.39 higher)	MODERATE	IMPORTAN
95% CI c	crosses thre	sholds for	ention to treat; F both clinically across multiple	important bene		dardised mean c ect	lifference					

³ Substantial heterogeneity

⁴ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
 ⁵ 95% CI crosses thresholds for both clinically important harm and no effect

Clinical evidence profile for comparison 59. Augmenting with thyroid hormone versus augmenting with lithium **Table 128:**

Quality assessn	nent						No of patients		Effect		Quality	Importance	
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with thyroid hormone	Augmenting with lithium	Relative (95% Cl)	Absolute			

(QIDS); Better				weeks, measur		ton Nating Scale			inventory o	f Depressive Sym	Jiomato	logy
2 (Joffe 1993, Nierenberg 2006)	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	90	86	-	SMD 0.33 lower (0.63 to 0.03 lower)	VERY LOW	CRITICAL
			core (follow-up 2 int; Better indica			amilton Rating S	cale for Depressio	n (HAM-D) or Q	uick Invent	ory of Depressive	Sympto	matology
2 (Joffe 1993, Nierenberg 2006)	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	90	86	-	SMD 0.15 lower (0.45 lower to 0.14 higher)	LOW	CRITICAL
Remission (ITT Symptomatolo	· · ·	2-14 weeks;	assessed with:	Number of peo	ple scoring <=	7 on Hamilton Ra	ting Scale for Dep	ression (HAM-D)) or <=5 on	Quick Inventory o	of Depre	ssive
2 (Joffe 1993, Nierenberg 2006)	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	25/90 (27.8%)	15/87 (17.2%)	RR 1.58 (0.91 to 2.77)	100 more per 1000 (from 16 fewer to 305 more)	VERY LOW	CRITICAL
Response (ITT) (follow-up m	nean 14 we	eks; assessed w	ith: Number of	people showin	g at least 50% im	provement on Qu	ick Inventory of	Depressive	Symptomatology	(QIDS))	
1 (Nierenberg 2006)	randomised trials	· · · ·	no serious inconsistency	no serious indirectness	very serious ³	none	17/73 (23.3%)	11/69 (15.9%)	RR 1.46 (0.74 to 2.89)	73 more per 1000 (from 41 fewer to 301 more)	VERY LOW	CRITICAL
Discontinuatio	n due to any	reason (fol	low-up mean 2 w	eeks; assesse	d with: Numbe	r of participants v	vho dropped out f	or any reason (i	ncluding ad	lverse events))		
1 (Joffe 1993)	randomised trials		no serious inconsistency	no serious indirectness	very serious ³	none	0/17 (0%)	1/18 (5.6%)	RR 0.35 (0.02 to 8.09)	36 fewer per 1000 (from 54 fewer to 394 more)	LOW	CRITICAL
Discontinuatio	n due to side	effects (fol	llow-up 2-14 wee	ks; assessed v	vith: Number o	f participants wh	o dropped out due	to adverse eve	nts)			
2 (Joffe 1993, Nierenberg 2006)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	7/90 (7.8%)	17/87 (19.5%)	RR 0.41 (0.18 to 0.91)	115 fewer per 1000 (from 18 fewer to 160 fewer)	LOW	CRITICAL

¹ Risk of bias is high or unclear across multiple domains

² 95% CI crosses thresholds for both clinically important benefit and no effect
 ³ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Clinical evidence profile for comparison 60. Switching to ECT versus switching to paroxetine Table 129:

Quality a	ssessment						No of patier	nts	Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switching to ECT		Relative (95% Cl)	Absolute		

Depressio	n symptomat	ology endpo	oint (follow-up 2-4	weeks; measur	ed with: Hamilt	on Rating Scale fo	r Depression	(HAM-D); Bett	er indicated I	oy lower values)		
1 (Folkerts 1997)	randomised trials	very serious¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	21	18	-	SMD 1.35 lower (2.06 to 0.65 lower)	LOW	CRITICAL
Depressio lower valu		ology chang	je score (follow-u	p 2-4 weeks; me	asured with: Ha	amilton Rating Sca	le for Depres	sion (HAM-D)	change from	baseline to endpoint;	Better i	ndicated by
1 (Folkerts 1997)	randomised trials	very serious¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	21	18	-	SMD 1.61 lower (2.34 to 0.87 lower)	LOW	CRITICAL
Response	(ITT) (follow-	up 2-4 week	s; assessed with:	Number of peo	ple showing at l	east 50% improve	ment on Ham	ilton Rating So	cale for Depre	ession (HAM-D))		
1 (Folkerts 1997)	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	15/21 (71.4%)	5/19 (26.3%)	RR 2.71 (1.22 to 6.04)	450 more per 1000 (from 58 more to 1000 more)	VERY LOW	CRITICAL
Discontinu	ation due to	any reason ((follow-up 2-4 we	eks; assessed w	ith: Number of	participants who d	dropped out f	or any reason	(including ad	verse events))		
1 (Folkerts 1997)	randomised trials		no serious inconsistency	no serious indirectness	very serious ³	none	0/21 (0%)	1/19 (5.3%)	RR 0.3 (0.01 to 7.02)	37 fewer per 1000 (from 52 fewer to 317 more)	LOW	CRITICAL
Discontinu	ation due to	side effects	(follow-up 2-4 we	eks; assessed v	vith: Number of	participants who	dropped out	due to adverse	events)			
1 (Folkerts 1997)	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	0/21 (0%)	0/19 (0%)	not pooled	not pooled	HIGH	CRITICAL

CI: confidence interval; ECT: electroconvulsive therapy; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference

¹ Risk of bias is high or unclear across multiple domains and rapid tapering of prior antidepressant treatment

² 95% CI crosses thresholds for both clinically important benefit and no effect

³ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 130: Clinical evidence profile for comparison 61. Augmenting with ECT versus continuing with antidepressant

Quality asso	essment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Continuing with antidepressant	Relative (95% Cl)	Absolute		
Depression	symptomato	logy endp	ooint (follow-up m	ean 4 weeks; me	easured with	: Hamilton Rating	Scale for Depre	ssion (HAM-D); Bette	r indicate	ed by lower values)		
1 (Haghighi 2013)	randomised trials	serious ¹	no serious inconsistency		very serious ²	none	20	20	-	SMD 0.08 higher (0.54 lower to 0.7 higher)	VERY LOW	CRITICAL
Depression symptomatology change score (follow-up mean 4 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D) change from baseline to endpoint; Better indicated by lower values)												
1 (Haghighi 2013)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	20	20		SMD 0.6 lower (1.23 lower to 0.04 higher)		CRITICAL

CI: confidence interval; ECT: electroconvulsive therapy; SMD: standardised mean difference

¹ Risk of bias is high or unclear across multiple domains

² 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

³ 95% CI crosses thresholds for both clinically important benefit and no effect

Table 131: Clinical evidence profile for comparison 62. Augmenting with ECT versus augmenting with exercise

Quality as	ssessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with ECT	Augmenting with exercise	Relative (95% Cl)	Absolute		
Depressi	on symptoma	atology end	point (follow-up n	nean 4 weeks; n	neasured wit	h: Hamilton Ratin	g Scale for Dep	ression (HAM-D);	Better indic	ated by lower value	es)	
1 (Salehi 2016)	randomised trials		no serious inconsistency	no serious indirectness	very serious ¹	none	20	20	-	SMD 0.12 higher (0.5 lower to 0.74 higher)	LOW	CRITICAL
	on symptoma by lower val		nge score (follow	-up mean 4 wee	ks; measure	d with: Hamilton I	Rating Scale for	Depression (HAM	A-D) change	from baseline to e	ndpoint; Bett	ter
1 (Salehi 2016)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²	none	20	20	-	SMD 0.18 lower (0.81 lower to 0.44 higher)	MODERATE	CRITICAL
Remissio	n (ITT) (follo	w-up mean 4	4 weeks; assesse	d with: Number	of people so	oring <=7 on Han	nilton Rating Sc	ale for Depressio	n (HAM-D))			
1 (Salehi 2016)	randomised trials		no serious inconsistency	no serious indirectness	very serious ¹	none	2/20 (10%)	2/20 (10%)	RR 1 (0.16 to 6.42)	0 fewer per 1000 (from 84 fewer to 542 more)	LOW	CRITICAL

CI: confidence interval; ECT: electroconvulsive therapy; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference

¹ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

² 95% CI crosses thresholds for both clinically important benefit and no effect

Table 132: Clinical evidence profile for comparison 63. Augmenting with ECT + exercise versus augmenting with exercise

Quality a	ssessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with ECT + exercise	Augmenting with exercise	Relative (95% Cl)	Absolute		
Depressi	on symptom	atology en	dpoint (follow-up	mean 4 weeks	; measured wit	h: Hamilton Ratir	ng Scale for Depre	ssion (HAM-D);	Better indic	ated by lower value	es)	

1 (Salehi 2016)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	20	20	-	SMD 0.99 lower (1.65 to 0.33 lower)	MODERATE	CRITICAL
	on symptom I by lower va		ange score (follo	w-up mean 4 w	eeks; measure	d with: Hamilton I	Rating Scale for D	epression (HAM	-D) change	from baseline to er	ndpoint; Bet	ter
1 (Salehi 2016)	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	20	20	-	SMD 1.84 lower (2.59 to 1.09 lower)	HIGH	CRITICAL
Remissio	on (ITT) (follo	w-up mean	4 weeks; asses	sed with: Numb	er of people so	oring <=7 on Han	nilton Rating Scale	ofor Depression	(HAM-D))			
1 (Salehi 2016)	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	13/20 (65%)	2/20 (10%)	RR 6.5 (1.68 to 25.16)	550 more per 1000 (from 68 more to 1000 more)	HIGH	CRITICAL

CI: confidence interval; ECT: electroconvulsive therapy; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference ¹ 95% *CI crosses thresholds for both clinically important benefit and no effect*

Table 133: Clinical evidence profile for comparison 64. Augmenting with exercise versus TAU

Quality assessm	nent						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with exercise		Relative (95% Cl)	Absolute		
Depression sym	ptomatology	endpoint (f	ollow-up mean 3	weeks; measure	ed with: Mon	tgomery Asberg	Depression Ratin	g Scale	(MADRS); B	etter indicated by lo	wer values)	
1 (Ho 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	26	26	-	SMD 0.59 lower (1.15 to 0.04 lower)	MODERATE	CRITICAL
Depression sym indicated by low		change sco	ore (follow-up 3-1	0 weeks; meası	ired with: Mo	ontgomery Asberg	J Depression Rat	ing Scal	e (MADRS) o	change from baselin	e to endpoint	t; Better
2 (Danielsson 2014, Ho 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	48	46	-	SMD 0.68 lower (1.1 to 0.26 lower)	MODERATE	CRITICAL
Remission (ITT)	(follow-up 3-	10 weeks; a	ssessed with: Nu	mber of people	scoring <=1	0 on Montgomery	Asberg Depress	ion Rati	ng Scale (M/	ADRS))		
2 (Danielsson 2014, Ho 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ¹	none	21/48 (43.8%)	10/46 (21.7%)	RR 2.03 (1.09 to 3.79)	224 more per 1000 (from 20 more to 607 more)	MODERATE	CRITICAL
Response (ITT)	(follow-up me	ean 10 week	s; assessed with	: Number of peo	ople showing	at least 50% imp	rovement on Mor	ntgomer	y Asberg De	pression Rating Sca	ale (MADRS))	
1 (Danielsson 2014)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious²	none	9/22 (40.9%)	5/20 (25%)	RR 1.64 (0.66 to 4.07)	160 more per 1000 (from 85 fewer to 768 more)	LOW	CRITICAL

Depression in adults: Evidence review D FINAL (June 2022)

Discontinuation	Discontinuation due to any reason (follow-up 3-10 weeks; assessed with: Number of participants who dropped out for any reason (including adverse events))													
2 (Danielsson 2014, Ho 2014)					very serious²	none	11/48 (22.9%)		RR 1.18 (0.54 to 2.59)	35 more per 1000 (from 90 fewer to 311 more)	LOW	CRITICAL		

CI: confidence interval; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference; TAU: treatment as usual

¹ 95% CI crosses thresholds for both clinically important benefit and no effect

² 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 134: Clinical evidence profile for comparison 65. Augmenting with exercise versus attention-placebo

Quality assessment				No of patients		Effect		Quality	Importance				
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with exercise		Relative (95% CI)	Absolute	-		
epression symptomatology endpoint (follow-up mean 10 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)													
1 (Lavretsky 2011)			no serious inconsistency	no serious indirectness	serious ¹	none	33	35	-	SMD 0.4 lower (0.88 lower to 0.08 higher)	MODERATE	CRITICAL	
Depression symption indicated by lower		change sco	re (follow-up me	ean 12 weeks; r	neasured with	: Hamilton Rating	Scale for Depr	ession (HAN	I-D) change	e from baseline to	endpoint; B	etter	
1 (Mota-Pereira 2011)	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ³	19	10	-	SMD 5.47 lower (7.17 to 3.77 lower)	LOW	CRITICAL	
Remission (ITT) (f	ollow-up 10-	12 weeks; a	assessed with: I	Number of peop	ole scoring <=	7 or <7 on Hamilte	on Rating Scale	for Depress	ion (HAM-I))			
2 (Lavretsky 2011, Mota-Pereira 2011)			no serious inconsistency	no serious indirectness	very serious ⁴	none	26/58 (44.8%)	18/48 (37.5%)	RR 1.5 (0.47 to 4.77)	188 more per 1000 (from 199 fewer to 1000 more)	LOW	CRITICAL	
Response (ITT) (fo	bllow-up 10-1	l2 weeks; a	ssessed with: N	umber of peop	le showing at	least 30% or 50%	improvement o	n Hamilton I	Rating Sca	le for Depression	(HAM-D))		
2 (Mather 2002, Mota-Pereira 2011)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	27/65 (41.5%)	14/54 (25.9%)	RR 1.7 (1.03 to 2.81)	181 more per 1000 (from 8 more to 469 more)	LOW	CRITICAL	
Discontinuation d	ue to any rea	ason (follov	v-up 10-12 week	s; assessed wi	th: Number of	participants who	dropped out fo	r any reason	(including	j adverse events)))		
3 (Lavretsky 2011, Mather 2002, Mota-Pereira 2011)	randomised trials		no serious inconsistency	no serious indirectness	very serious ⁴	none	6/101 (5.9%)	3/91 (3.3%)	RR 1.53 (0.4 to 5.86)	17 more per 1000 (from 20 fewer to 160 more)		CRITICAL	
Global functioning	g change sco	ore (follow-	up mean 12 wee	ks; measured	with: Global As	ssessment of Fur	nction (GAF); Be	etter indicate	d by highe	r values)			

1 (Mota-Pereira 2011)	randomised trials				no serious imprecision	reporting bias ³	19	10	-	SMD 6.15 higher (4.28 to 8.02 higher)	LOW	IMPORTANT
Sleeping difficulti	ies endpoint	(follow-up	mean 10 weeks;	measured with	: Pittsburgh S	leep Quality Index	(PSQI); Better	indicated by	lower valu	ies)		
1 (Lavretsky 2011)				no serious indirectness	serious ¹	none	33	35	-	SMD 0.25 lower (0.72 lower to 0.23 higher)	MODERATE	IMPORTANT

¹ 95% CI crosses thresholds for both clinically important benefit and no effect

² Risk of bias is high or unclear across multiple domains

³ Study partially funded by pharmaceutical company

⁴ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm

Table 135: Clinical evidence profile for comparison 66. Augmenting with exercise + ECT versus augmenting with ECT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision		Augmenting with exercise + ECT	• •	Relative (95% Cl)	Absolute		
Depressi	epression symptomatology endpoint (follow-up mean 4 weeks; measured with: Hamilton Rating Scale for Depression (HAM-D); Better indicated by lower values)											
1 (Salehi 2016)	randomised trials		no serious inconsistency	no serious indirectness	serious ¹	none	20	20	-	SMD 1.13 lower (1.81 to 0.46 lower)		CRITICAL
	on symptom I by lower val		inge score (follo	w-up mean 4 we	eks; measure	d with: Hamilton I	Rating Scale for De	epression (HAN	I-D) change	from baseline to er	ndpoint; Bett	er
1 (Salehi 2016)	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	20	20	-	SMD 1.45 lower (2.15 to 0.74 lower)	HIGH	CRITICAL
Remissio	on (ITT) (follo	w-up mean	4 weeks; assess	sed with: Numb	er of people sc	oring <=7 on Han	nilton Rating Scale	e for Depression	n (HAM-D))			
1 (Salehi 2016)	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	13/20 (65%)	2/20 (10%)	RR 6.5 (1.68 to 25.16)	550 more per 1000 (from 68 more to 1000 more)	HIGH	CRITICAL

CI: confidence interval; ECT: electroconvulsive therapy; ITT: intention to treat; RR: relative risk; SMD: standardised mean difference ¹ 95% CI crosses thresholds for both clinically important benefit and no effect

Table 136: Clinical evidence profile for comparison 67. Augmenting with yoga versus continuing with antidepressant (+/- waitlist or attention-placebo)

Quality assessment No of patients Effect Quality Importa	Importance
--	------------

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmenting with yoga	Continuing with antidepressant (+/- waitlist or attention- placebo)	Relative (95% Cl)	Absolute		
Depression sy indicated by lo		gy change	score (follow-up	o mean 8 weeks	s; measured w	vith: Hamilton Ra	ting Scale for	Depression (HAM-D) cha	nge from b	aseline to endpo	int; Bet	ter
1 (Sharma 2017)	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	13	12	-	SMD 1.49 lower (2.39 to 0.58 lower)	HIGH	CRITICAL
Remission (ITT Symptomatolo		8-10 weeks	s; assessed with	n: Number of p	eople scoring	<=7 on Hamilton	Rating Scale	for Depression (HAM-D)	or <=5 on C	uick Inventory o	f Depre	ssive
2 (Sharma 2017, Uebelacker 2017)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	21/76 (27.6%)	12/71 (16.9%)	RR 1.58 (0.84 to 3)	98 more per 1000 (from 27 fewer to 338 more)	LOW	CRITICAL
Remission (IT1	() at 3-month	follow-up	(follow-up mean	n 3 months; as	sessed with: N	umber of people	e scoring <=5 o	on Quick Inventory of De	pressive Sy	mptomatology (QIDS))	
1 (Uebelacker 2017)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	19/63 (30.2%)	11/59 (18.6%)	RR 1.62 (0.84 to 3.11)	116 more per 1000 (from 30 fewer to 393 more)	LOW	CRITICAL
Remission (ITT	() at 6-month	follow-up	(follow-up mean	n 6 months; as	sessed with: N	umber of people	e scoring <=5 o	on Quick Inventory of De	pressive Sy	mptomatology (QIDS))	
1 (Uebelacker 2017)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	19/63 (30.2%)	14/59 (23.7%)	RR 1.27 (0.7 to 2.3)	64 more per 1000 (from 71 fewer to 308 more)	VERY LOW	CRITICAL
Response (ITT Depressive Sy			; assessed with	: Number of pe	eople showing	at least 50% imp	provement on I	Hamilton Rating Scale fo	r Depressio	on (HAM-D) or Qu	lick Invo	entory of
2 (Sharma 2017, Uebelacker 2017)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	27/76 (35.5%)	14/71 (19.7%)	RR 2.06 (0.68 to 6.19)	209 more per 1000 (from 63 fewer to 1000 more)	VERY LOW	CRITICAL
Response (ITT Symptomatolo		follow-up ((follow-up mean	3 months; ass	essed with: N	umber of people	showing at lea	ast 50% improvement on	Quick Inve	ntory of Depress	sive	
1 (Uebelacker 2017)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	22/63 (34.9%)	13/59 (22%)	RR 1.58 (0.88 to 2.85)	128 more per 1000 (from 26 fewer to 408 more)	LOW	CRITICAL
Response (ITT Symptomatolo		follow-up ((follow-up mean	6 months; ass	sessed with: N	umber of people	showing at lea	ast 50% improvement on	Quick Inve	ntory of Depress	sive	
1 (Uebelacker 2017)	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	23/63 (36.5%)	14/59 (23.7%)	RR 1.54 (0.88 to 2.7)	128 more per 1000 (from 28	LOW	CRITICAL

										fewer to 403 more)	
Discontinuatio	on due to any	reason (fo	llow-up 8-10 we	eks; assessed	with: Number	of participants v	who dropped ou	ut for any reason (includi	ing advers	e events))	
2 (Sharma 2017, Uebelacker 2017)	randomised trials	no serious risk of bias		no serious indirectness	very serious ³	none	7/76 (9.2%)	13/71 (18.3%)	RR 0.88 (0.08 to 9.88)	22 fewer per 1000 (from 168 fewer to 1000 more)	CRITICAL
CI: confidence	e interval; IT	T: intentior	n to treat; RR: r	elative risk; Sl	MD: standard	ised mean differ	ence				

¹ Risk of bias is high or unclear across multiple domains
 ² 95% CI crosses thresholds for both clinically important benefit and no effect
 ³ 95% CI crosses thresholds for no effect, and both clinically important benefit and harm
 ⁴ Substantial heterogeneity

Click here to enter text.