# **National Institute for Health and Care Excellence**

Consultation draft

# Depression in adults: treatment and management

Appendix U2.14: Text from CG90 Appendix 19d that has been deleted

**NICE** Guideline

**Appendices** 

May 2018

#### Disclaimer

Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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# Appendix 19d: Clinical evidence forest plots for the management of subthreshold depressive symptoms

#### Contents

Pharmacological interventions	2
Pharm subthreshold 01 Efficacy: active treatment versus placebo	
Pharm subthreshold 02 Acceptability and tolerability: active treatment versus placeboplacebo	
Pharm subthreshold 03 Efficacy: active treatment versus active treatment	10
Pharm subthreshold 04 Acceptability versus tolerability: active treatment versus active treatment	17
Pharm subthreshold 05 Relapse prevention: active treatment versus placebo	23
Psychological interventions	24
Psych sub-thresh 01 Psychological therapies versus control	
Psych sub-thresh 02 Psychological therapies versus antidepressants	26
Psych sub-thresh 03 Psychological therapies + antidepressants versus antidepressants	
Psych sub-thresh 04 Psychological therapies + antidepressants versus psychological therapies	
Psych sub-thresh 05 Short psychodynamic verbal therapy versus short psychodynamic art therapy	33
Psych sub-thresh 06 Partial responders: psychological therapy + SSRI versus SSRI	35

# **Pharmacological interventions**

## Pharm subthreshold 01 Efficacy: active treatment versus placebo

#### 1.1 Non-response at endpoint

Review: Depression Update Subthreshold: Pharm

Comparison: 01 Overall efficacy (versus placebo)

Outcome: 01 Number of people not achieving at least 50% reduction in depression score

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 SSRIs: dysthymia only						
BARRETT99DPx(Pst)*C	51/111	66/112		28.36	0.78 [0.60, 1.01]	0
HELLERSTEIN93 Flx*C	9/19	13/16	-	6.09	0.58 [0.34, 0.99]	0
RAVINDRAN2000 Stl	76/158	101/152	-	44.43	0.72 [0.59, 0.88]	0
RAVINDRAN99St(cbt)*C	10/22	18/26	<del></del>	7.12	0.66 [0.39, 1.11]	0
VANELLE1997 Flx	30/72	25/39	<del></del>	14.00	0.65 [0.45, 0.93]	0
Subtotal (95% CI)	382	345	<b>•</b>	100.00	0.72 [0.63, 0.82]	
Total events: 176 (Treatment), 2 Test for heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Z = 4.90 (	.40, df = 4 (P = 0.84), I <sup>2</sup>	= 0%				
02 SSRIs: minor depression or						
BARRETT99M Px(Pst)*C	55/106	57/109		100.00	0.99 [0.77, 1.28]	0
Subtotal (95% CI)	106	109	<b>*</b>	100.00	0.99 [0.77, 1.28]	
Total events: 55 (Treatment), 57 Test for heterogeneity: not appli Test for overall effect: Z = 0.06 (	icable					
03 TCAs: dysthymia only			_ 1			
VERSIANI97Imp(McI)*C	25/68	54/76	<del></del>	100.00	0.52 [0.37, 0.73]	0
Subtotal (95% CI) Total events: 25 (Treatment), 5- Test for heterogeneity: not appli Test for overall effect: Z = 3.76 (	icable	76	•	100.00	0.52 [0.37, 0.73]	
04 MAOIs: dysthymia only						
VERSIANI97Mcl(Imp)*C	25/70	54/76	<del>-</del>	100.00	0.50 [0.36, 0.71]	0
Subtotal (95% CI)	70	76	<b>◆</b>	100.00	0.50 [0.36, 0.71]	
Total events: 25 (Treatment), 54 Test for heterogeneity: not appli Test for overall effect: Z = 3.90 (	icable					
			.1 0.2 0.5 1 2	5 10		-
			Favours treatment Favours c	ontrol		

# 1.2 Non-remission at endpoint

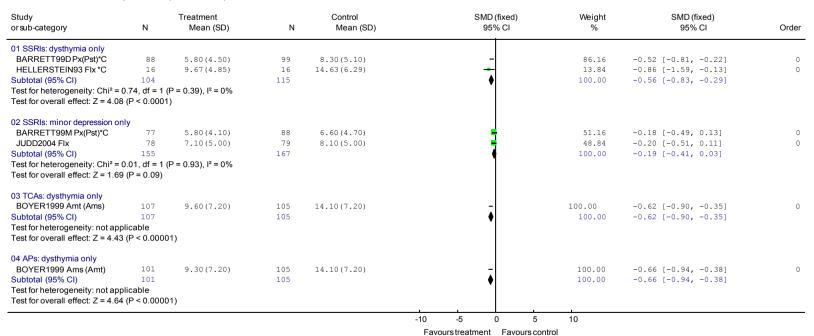
Review: Depression Update Subthreshold: Pharm Comparison: 01 Overall efficacy (versus placebo)

Outcome: 02 Number of people not achieving remission

Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Order
01 SSRIs: dysthymia only						
BARRETT99D Px(Pst)*C	56/111	70/112		33.25	0.81 [0.64, 1.02]	0
THASE1996A Stl (Imp)	71/134	95/140		39.29	0.78 [0.64, 0.95]	0
VANELLE1997 Flx	40/72	29/39	<del>-</del> -	27.46	0.75 [0.57, 0.99]	0
Subtotal (95% CI)	317	291	◆	100.00	0.78 [0.68, 0.89]	
Total events: 167 (Treatment), 1 Test for heterogeneity: $Chi^2 = 0$ . Test for overall effect: $Z = 3.66$ (	18, df = 2 (P = 0.92), l <sup>2</sup>	= 0%				
02 SSRIs: minor depression or	*					
BARRETT99MPx(Pst)*C	62/106	60/109		100.00	1.06 [0.84, 1.34]	0
Subtotal (95% CI)	106	109	◆	100.00	1.06 [0.84, 1.34]	
Total events: 62 (Treatment), 60 Test for heterogeneity: not appli Test for overall effect: Z = 0.51 (	cable					
03 TCAs: dysthymia only			·			
THASE1996A Imp (Stl)	83/136	95/140	+	57.98	0.90 [0.75, 1.07]	0
VERSIANI97Imp(McI)*C	37/68	59/76		42.02	0.70 [0.55, 0.90]	0
Subtotal (95% CI)	204	216	<b>◆</b>	100.00	0.81 [0.63, 1.03]	
Total events: 120 (Treatment), 1 Test for heterogeneity: $Chi^2 = 2$ . Test for overall effect: $Z = 1.74$ (	57, df = 1 (P = 0.11), l <sup>2</sup>	= 61.1%				
04 MAOIs: dysthymia only		/	_			
VERSIANI97Mcl(Imp)*C	34/70	59/76		100.00	0.63 [0.48, 0.82]	0
Subtotal (95% CI)	70	76		100.00	0.63 [0.48, 0.82]	
Total events: 34 (Treatment), 59 Test for heterogeneity: not appli	'					
Test for overall effect: Z = 3.41 (	P = 0.0007)					
		0.	1 0.2 0.5 1 2	5 10		
		F	avours treatment Favours	control		

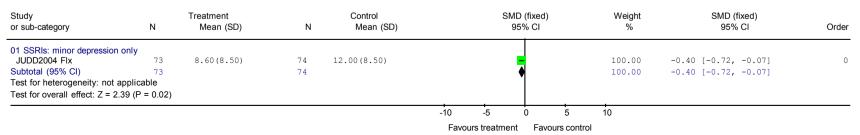
#### 1.3 Mean endpoint (clinician-rated)

Review: Depression Update Subthreshold: Pharm
Comparison: 01 Overall efficacy (versus placebo)
Outcome: 03 Mean endpoint scores (clinician rated)



#### 1.4 Mean endpoint (self-rated)

Review: Depression Update Subthreshold: Pharm Comparison: 01 Overall efficacy (versus placebo)
Outcome: 04 Mean endpoint scores (self rated)



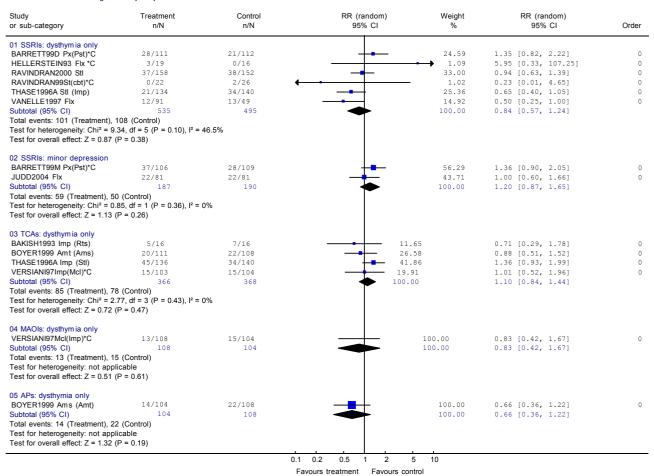
# 1.5 Mean change at endpoint (clinician-rated)

Review: Depression Update Subthreshold: Pharm Comparison: 01 Overall efficacy (versus placebo) Outcome: 05 Mean change (clinician rated)

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI	Order
01 SSRIs: dysthymia only THASE1996A Stl (Imp) VANELLE1997 Flx	134 72	-5.60(6.10) -10.20(7.30)	140 39	-3.90(5.10) -7.70(7.60)	-	58.76 41.24	-0.30 [-0.54, -0.06] -0.34 [-0.73, 0.06]	0
Subtotal (95% CI) Test for heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: Z = 2.99	206 0.02, df = 1	I (P = 0.89), I <sup>2</sup> = 0%	179	7176 (7166)	•	100.00	-0.31 [-0.51, -0.11]	, and the second
02 TCAs: dysthymia only	(1 - 0.000	5)						
BOYER1999 Amt (Ams)	107	-8.20 (7.24)	105	-3.80 (7.17)	-	34.31	-0.61 [-0.88, -0.33]	0
THASE1996A Imp (Stl)	136	-5.90 (5.80)	140	-3.90(5.10)	-	37.21	-0.37 [-0.60, -0.13]	0
VERSIANI97Imp(McI)*C	63	-11.10(5.60)	72	-5.60(6.30)	<u>-,</u>	28.48	-0.91 [-1.27, -0.56]	0
Subtotal (95% CI) Test for heterogeneity: Chi <sup>2</sup> = 6 Test for overall effect: Z = 3.99	,	, ,,	317		•	100.00	-0.61 [-0.90, -0.31]	
03 APs: dysthymia only BOYER1999 Ams (Amt) Subtotal (95% CI) Test for heterogeneity: not app Test for overall effect: Z = 4.70		-8.60(7.03) <b>001)</b>	105 105	-3.80(7.17)	•	100.00	-0.67 [-0.95, -0.39] -0.67 [-0.95, -0.39]	0
04 MAOIs: dysthymia only VERSIANI97Mc(Imp)*C Subtotal (95% CI) Test for heterogeneity: not app Test for overall effect: Z = 5.40		-11.80(6.40)	72 72	-5.60(6.30)	•	100.00	-0.97 [-1.32, -0.62] -0.97 [-1.32, -0.62]	0
					-10 -5 0 5	10		

# Pharm subthreshold 02 Acceptability and tolerability: active treatment versus placebo 02.01 Dropout at endpoint for any reason

Review: Depression Update Subthreshold: Pharm
Comparison: 02 Overall acceptability and tolerability (versus placebo)
Outcome: 01 Leaving the study early

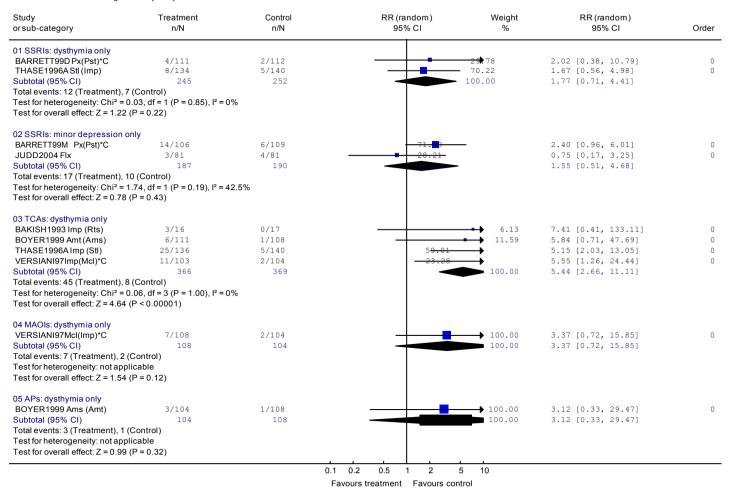


#### 02.02 Dropout at endpoint due to side effects

Review: Depression Update Subthreshold: Pharm

Comparison: 02 Overall acceptability and tolerability (versus placebo)

Outcom e: 02 Leaving the study early due to side effects

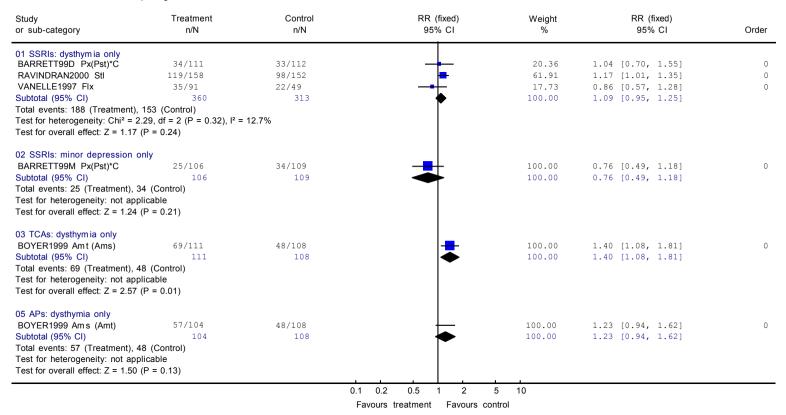


#### 02.03 Number reporting side effects at endpoint

Review: Depression Update Subthreshold: Pharm

Comparison: 02 Overall acceptability and tolerability (versus placebo)

Outcom e: 03 Patients reporting side effects



# Pharm subthreshold 03 Efficacy: active treatment versus active treatment 3.1 Non-response at endpoint: SSRI

Review: Depression Update Subthreshold: Pharm

Comparison: 03 Overall efficacy (head to head)

Outcom e: 01 Number of people not achieving at least 50% reduction in depression score: SSRI

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Dysthymia =/> 50% (v AD)						
DEJONGHE1991 Fvx/Mpt	18/24	18/24	<del></del>	100.00	1.00 [0.72, 1.39]	0
Subtotal (95% CI)	24	24	•	100.00	1.00 [0.72, 1.39]	
Total events: 18 (Treatment), 18	(Control)					
Test for heterogeneity: not applic	able					
Test for overall effect: Z = 0.00 (P	= 1.00)					
02 Dysthymia =/> 50% (v AP)						
AMORE2001 Srt/Ams	37/156	26/157	<del> </del>	40.18	1.43 [0.91, 2.25]	0
SMERALDI1996 Flx/Ams	52/139	39/142	<del>  ■ </del>	59.82	1.36 [0.97, 1.92]	0
Subtotal (95% CI)	295	299	•	100.00	1.39 [1.06, 1.83]	
Total events: 89 (Treatment), 65	(Control)		•			
Test for heterogeneity: Chi <sup>2</sup> = 0.0		0%				
Test for overall effect: Z = 2.36 (P						
03 Minor depression only						
SZEGEDI1997 Prx/Mpt	30/126	39/119		100.00	0.73 [0.48, 1.09]	0
Subtotal (95% CI)	126	119	<u> </u>	100.00	0.73 [0.48, 1.09]	
Total events: 30 (Treatment), 39	(Control)		$\mathbf{Y}$			
Test for heterogeneity: not applic						
Test for overall effect: Z = 1.55 (P						
1.00 (1	J,		_ , _ , _   _ ,			
		0.1	0.2 0.5 1 2	5 10		
		F	avours treatment Favours co	ontrol		

# 3.2 Non-response at endpoint: TCA

Review: Depression Update Subthreshold: Pharm Comparison: 03 Overall efficacy (head to head)

Outcom e: 02 Number of people not achieving at least 50% reduction in depression score: TCA

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Dysthymia only						
SALZMANN95 Imp/Mnp*C	21/34	18/33	<del>-</del>	42.58	1.13 [0.75, 1.70]	0
VERSIANI97Imp(McI)*C	25/68	25/70	<del></del>	57.42	1.03 [0.66, 1.60]	0
Subtotal (95% CI)	102	103	•	100.00	1.07 [0.79, 1.46]	
Total events: 46 (Treatment), 43	(Control)		ľ			
Test for heterogeneity: Chi <sup>2</sup> = 0. Test for overall effect: Z = 0.45 (F 02 Dysthymia =/> 50%		<del>-</del> 0%				
RAVIZZA1999 Amt/Ams	34/87	67/166		100.00	0.97 [0.70, 1.33]	Ω
Subtotal (95% CI)	87	166		100.00	0.97 [0.70, 1.33]	· ·
Total events: 34 (Treatment), 67 Test for heterogeneity: not applic Test for overall effect: Z = 0.20 (F	(Control)	100		100.00	0.57 [0.70, 1.00]	
•	·	0.1	0.2 0.5 1 2	5 10		
		F	avours treatment Favours co	entrol		

#### 3.3 Non-remission at endpoint: SSRI

Review: Depression Update Subthreshold: Pharm Comparison: 03 Overall efficacy (head to head)

Outcom e: 03 Number of people not achieving remission: SSRI

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Dysthymia only						
THASE1996A Stl (Imp)	71/134	83/136	<del></del>	100.00	0.87 [0.70, 1.07]	0
Subtotal (95% CI)	134	136	•	100.00	0.87 [0.70, 1.07]	
Total events: 71 (Treatment), 8						
Test for heterogeneity: not app	licable					
Test for overall effect: Z = 1.33	(P = 0.18)					
02 Dysthymia =/> 50%						
AMORE2001 Srt/Ams	54/156	42/157	+	100.00	1.29 [0.92, 1.81]	0
Subtotal (95% CI)	156	157	<b>—</b>	100.00	1.29 [0.92, 1.81]	
Total events: 54 (Treatment), 4	2 (Control)					
Test for heterogeneity: not app	licable					
Test for overall effect: Z = 1.50						
03 Minor depression and subs	syndromal depressive sy	mptomatology (49% v 51%)				
ROCCA2005 Stl/Ctp	42/72	31/66	<del> </del> -	100.00	1.24 [0.90, 1.71]	0
Subtotal (95% CI)	72	66	<b>—</b>	100.00	1.24 [0.90, 1.71]	
Total events: 42 (Treatment), 3	31 (Control)		1			
Test for heterogeneity: not app						
Test for overall effect: Z = 1.32						
	/					
		0.1	0.2 0.5 1 2	5 10		
		Fa	vours treatment Favours	s control		

#### 3.4 Non-remission at endpoint: TCA

Review: Depression Update Subthreshold: Pharm Comparison: 03 Overall efficacy (head to head)

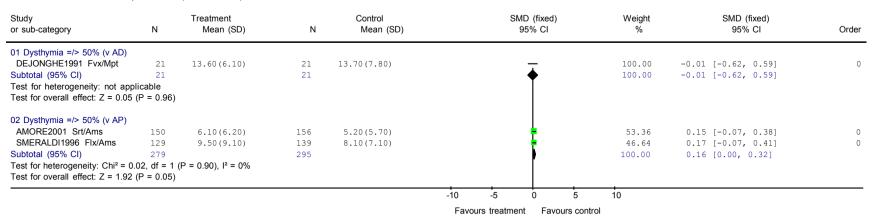
Outcome: 04 Number of people not achieving remssion: TCA

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Dysthymia only						
VERSIANI97Imp(McI)*C	37/68	34/70	+	100.00	1.12 [0.81, 1.55]	0
Subtotal (95% CI)	68	70	<b>*</b>	100.00	1.12 [0.81, 1.55]	
Total events: 37 (Treatment), 3	4 (Control)		Γ			
Test for heterogeneity: not appl						
Test for overall effect: Z = 0.69	(P = 0.49)					
-		(		5 10		
			Favours treatment Favours co	ntrol		

#### 3.5 Mean endpoint (clinician-rated): SSRI

Review: Depression Update Subthreshold: Pharm Comparison: 03 Overall efficacy (head to head)

Outcome: 05 Mean endpoint scores (clinician rated): SSRI



# 3.6 Mean endpoint (clinician-rated): TCA

Review: Depression Update Subthreshold: Pharm
Comparison: 03 Overall efficacy (head to head)
Outcome: 06 Mean endpoint scores (clinician rated): TCA

Study orsub-category	N	Treatment Mean (SD)	N	Control Mean (SD)		S	MD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI	Order
01 Dysthymia only (v AD)										
SALZMANN95 Imp/Mnp*C	24	14.50(7.15)	27	13.67(8.07)			<del>+</del>	63.06	0.11 [-0.44, 0.66]	0
VALLEJO87 Imp/Phz *C	16	10.44(5.10)	16	7.25(3.17)			-	36.94	0.73 [0.01, 1.45]	0
Subtotal (95% CI)	40		43				<b>♦</b>	100.00	0.34 [-0.10, 0.77]	
Test for heterogeneity: $Chi^2 = 1$ . Test for overall effect: $Z = 1.52$ (		(P = 0.18), I <sup>2</sup> = 45.5%								
02 Dysthymia only (v AP) BOYER1999 Ant (Ams) Subtotal (95% CI) Test for heterogeneity: not appli Test for overall effect: Z = 0.30 (		9.60(7.20)	101 101	9.30(7.20)			  ∳ 	100.00 100.00	0.04 [-0.23, 0.31] 0.04 [-0.23, 0.31]	0
04 Dysthymia =/> 50% (v AP) RAVIZZA1999 Amt/Ams Subtotal (95% CI) Test for heterogeneity: not appli Test for overall effect: Z = 0.09 (		10.10(8.50)	165 165	10.20(8.30)			•	100.00	-0.01 [-0.27, 0.25] -0.01 [-0.27, 0.25]	0
					-10	-5	0	5 10		_
					Favo	urs treatme	ent Favours	control		

#### 3.7 Mean endpoint (clinician-rated): antipsychotic

Review: Depression Update Subthreshold: Pharm
Comparison: 03 Overall efficacy (head to head)
Outcome: 07 Mean endpoint scores (clinician rated): AP

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)			(fixed) % CI	Weight %	SMD (fixed) 95% CI	Order
01 Dysthymia only GEISLER1992Flp/Rts Subtotal (95% CI) Test for heterogeneity: not app Test for overall effect: Z = 1.05		11.00(4.21)	31 31	12.10(4.21)			•	100.00	-0.26 [-0.74, 0.22] -0.26 [-0.74, 0.22]	0
					-10	-5	Ö	5 10		
					Favour	streatment	Favour	scontrol		

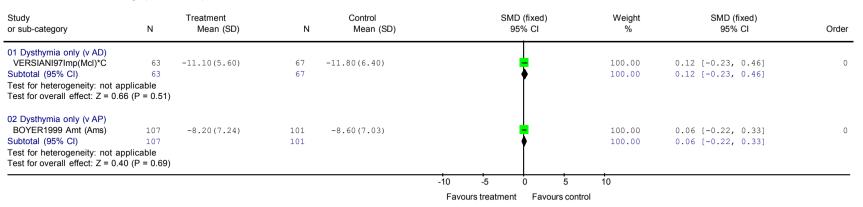
## 3.8 Mean change at endpoint (clinician-rated): SSRI

Review: Depression Update Subthreshold: Pharm Comparison: 03 Overall efficacy (head to head)
Outcome: 08 Mean change (clinician rated): SSRI

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)			O (fixed) 5% CI		Weight %	SMD (fixed) 95% CI	Order
01 Dysthymia only THASE1996A Stl (Imp) Subtotal (95% Cl) Test for heterogeneity: not applica Test for overall effect: Z = 0.41 (P :		-5.60(6.10)	136 136	-5.90(5.80)			•		100.00	0.05 [-0.19, 0.29] 0.05 [-0.19, 0.29]	0
					-10	-5	Ö _	5 irs control	10		

#### 3.9 Mean change at endpoint (clinician-rated): TCA

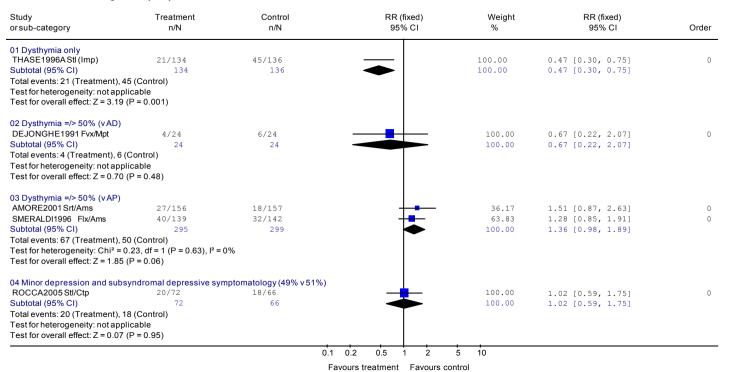
Review: Depression Update Subthreshold: Pharm Comparison: 03 Overall efficacy (head to head)
Outcome: 09 Mean change (clinician rated): TCA



# Pharm subthreshold 04 Acceptability versus tolerability: active treatment versus active treatment 4.1 Dropout at endpoint for any reason: SSRI

Review: Depression Update Subthreshold: Pharm
Comparison: 04 Overall acceptability and tolerability (head to head)

Outcom e: 01 Leaving the study early: SSRI



# 4.2 Dropout at endpoint for any reason: TCA

Review: Depression Update Subthreshold: Pharm

Comparison: 04 Overall acceptability and tolerability (head to head)

Outcom e: 02 Leaving the study early: TCA

Study orsub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Dysthymia only (vAD) VERSIANI97Imp(McI)*C Subtotal (95% CI) Total events: 15 (Treatment), 13 Test for heterogeneity: not appli Test for overall effect: Z = 0.54 (	icable	13/108 108		100.00	1.21 [0.61, 2.42] 1.21 [0.61, 2.42]	0
02 Dysthymia only (v AP) BOYER1999 Amt (Ams) Subtotal (95% CI) Total events: 20 (Treatment), 14 Test for heterogeneity: not appli Test for overall effect: Z = 0.91 (	icable	14/104 104		100.00	1.34 [0.71, 2.51] 1.34 [0.71, 2.51]	0
03 Dysthymia =/> 50% (AD) VALLEJO87 Imp/Phz*C Subtotal (95% CI) Total events: 5 (Treatment), 4 (C Test for heterogeneity: not appli Test for overall effect: Z = 0.31 (	icable	4/36 36		100.00	1.22 [0.35, 4.17] 1.22 [0.35, 4.17]	0
04 Dysthymia =/> 50% (vAP) RAVIZZA1999 Amt/Ams Subtotal (95% CI) Total events: 41 (Treatment), 73 Test for heterogeneity: not appli Test for overall effect: Z = 0.48 (	icable	73/166 166	<u> </u>	100.00	1.07 [0.81, 1.42] 1.07 [0.81, 1.42]	0
	<u> </u>	0.1 F	0.2 0.5 1 2 avours treatment Favours	5 10		

## 4.3 Dropout at endpoint for any reason: antipsychotic

Review: Depression Update Subthreshold: Pharm

Comparison: 04 Overall acceptability and tolerability (head to head)

Outcome: 03 Leaving the study early: AP

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Dysthymia only						
GEISLER1992 Flp/Rts	3/36	2/31		100.00	1.29 [0.23, 7.24]	0
Subtotal (95% CI)	36	31		100.00	1.29 [0.23, 7.24]	
Total events: 3 (Treatment), 2	(Control)					
Test for heterogeneity: not app	licable					
Test for overall effect: Z = 0.29	(P = 0.77)					
	<u> </u>		<del></del>			
		0.1	0.2 0.5 1 2 5	5 10		
		_				

## 4.4 Dropout at endpoint due to side effects: SSRI

Review: Depression Update Subthreshold: Pharm

Comparison: 04 Overall acceptability and tolerability (head to head)
Outcom e: 04 Leaving the study early due to side effects: SSRI

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Dysthymia only (v AD)						
THASE1996A Stl (Imp)	8/134	25/136		100.00	0.32 [0.15, 0.69]	0
Subtotal (95% CI)	134	136		100.00	0.32 [0.15, 0.69]	
Total events: 8 (Treatment), 25 ( Test for heterogeneity: not applic Test for overall effect: Z = 2.90 (F	cable					
02 Dysthymia =/> 50% (vAP)						
AMORE2001 Srt/Ams	12/156	10/157		43.66	1.21 [0.54, 2.71]	0
SMERALDI1996 Flx/Ams	10/139	13/142		56.34	0.79 [0.36, 1.73]	0
Subtotal (95% CI)	295	299		100.00	0.97 [0.55, 1.70]	
Total events: 22 (Treatment), 23		00/	T			
Test for heterogeneity: $Chi^2 = 0.5$ Test for overall effect: $Z = 0.11$ (F		= 0%				
03 Minor depression and subsy	ndromal depressive sy	mptomatology (49% v 51%) (	vAD)			
ROCCA2005 Stl/Ctp	8/72	10/66	· ·	100.00	0.73 [0.31, 1.75]	0
Subtotal (95% CI)	72	66		100.00	0.73 [0.31, 1.75]	
Total events: 8 (Treatment), 10 (	Control)					
Test for heterogeneity: not applic						
Test for overall effect: Z = 0.70 (F						
	,					
		0.1	1 0.2 0.5 1 2	5 10		
		F	avours treatment Favours	s control		

# 4.5 Dropout at endpoint due to side effects: TCA

Review: Depression Update Subthreshold: Pharm

Comparison: 04 Overall acceptability and tolerability (head to head)
Outcom e: 05 Leaving the study early due to side effects: TCA

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Dysthymia only (v AD)						
SALZMANN95 Imp/Mnp*C	4/34	3/33		30.82	1.29 [0.31, 5.34]	0
VERSIANI97Imp(McI)*C	11/103	7/108		<b>-</b> 69.18	1.65 [0.66, 4.09]	0
Subtotal (95% CI)	137	141		100.00	1.54 [0.72, 3.30]	
Total events: 15 (Treatment), 10 ( Test for heterogeneity: Chi² = 0.0 Test for overall effect: Z = 1.11 (P	8, df = 1 (P = 0.78), l <sup>2</sup> =	0%				
02 Dysthymia only (v AP)						
BOYER1999 Amt (Ams)	6/111	3/104		100.00	1.87 [0.48, 7.30]	0
Subtotal (95% CI)	111	104		100.00	1.87 [0.48, 7.30]	
Total events: 6 (Treatment), 3 (Co Test for heterogeneity: not applica Test for overall effect: Z = 0.91 (P	able					
	,					
03 Dysthymia =/> 50% (vAP) RAVIZZA1999 Amt/Ams	11/87	23/166		100.00	0.91 [0.47, 1.78]	0
Subtotal (95% CI)	87	166		100.00	0.91 [0.47, 1.78]	0
Total events: 11 (Treatment), 23 ( Test for heterogeneity: not applica Test for overall effect: Z = 0.27 (P	(Control) able	100		100.00	0.91 [0.47, 1.70]	
	,		1 02 05 1 2	5 10		
		0.				
		F	Favours treatment Favours	control		

## 4.6 Dropout at endpoint due to side effects: antipsychotic

Review: Depression Update Subthreshold: Pharm

Comparison: 04 Overall acceptability and tolerability (head to head)
Outcome: 06 Leaving the study early due to side effects: AP

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Dythsymia only						
GEISLER1992 Flp/Rts	2/36	2/33		<b>—</b> 100.00	0.92 [0.14, 6.14]	0
Subtotal (95% CI)	36	33		<del>-</del> 100.00	0.92 [0.14, 6.14]	
Total events: 2 (Treatment), 2	(Control)					
Test for heterogeneity: not app	,					
Test for overall effect: Z = 0.09						
		(	0.1 0.2 0.5 1 2	5 10		
			Favours treatment Favours con	trol		

## 4.7 Number reporting side effects at endpoint: SSRI

Review: Depression Update Subthreshold: Pharm

Comparison: 04 Overall acceptability and tolerability (head to head)

Outcom e: 07 Patients reporting side effects: SSRI

Study or sub-category	Treatment n/N	Control n/N		RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Dysthymia =/> 50% (v AP)							
AMORE2001 Srt/Ams	74/156	70/157		-	51.38	1.06 [0.84, 1.35]	0
SMERALDI1996 Flx/Ams	56/137	67/141		<del></del>	48.62	0.86 [0.66, 1.12]	0
Subtotal (95% CI)	293	298		•	100.00	0.96 [0.81, 1.15]	
Total events: 130 (Treatment), 1	137 (Control)			Ĭ			
Test for heterogeneity: Chi <sup>2</sup> = 1.	35, df = 1 (P = 0.24), l2 =	= 26.1%					
Test for overall effect: Z = 0.39 (	P = 0.69)						
<u> </u>	<u> </u>						
			0.1 0.2	0.5 1 2	5 10		
			Favours to	reatment Favours of	control		

# 4.8 Number reporting side effects at endpoint: TCA

Review: Depression Update Subthreshold: Pharm

Comparison: 04 Overall acceptability and tolerability (head to head)

Outcom e: 08 Patients reporting side effects: TCA

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Dysthymia only (v AD)						
SALZMANN95 Imp/Mnp*C	20/34	14/33	+=-	100.00	1.39 [0.85, 2.26]	0
Subtotal (95% CI)	34	33	<del></del>	100.00	1.39 [0.85, 2.26]	
Total events: 20 (Treatment), 14						
Test for heterogeneity: not applic Test for overall effect: Z = 1.32 (P						
02 Dysthymia only (v AP)						
BOYER1999 Amt (Ams)	69/111	57/104	+-	100.00	1.13 [0.90, 1.42]	0
Subtotal (95% CI)	111	104	<b>*</b>	100.00	1.13 [0.90, 1.42]	
Total events: 69 (Treatment), 57						
Test for heterogeneity: not applic						
Test for overall effect: $Z = 1.09$ (P	' = 0.28)					
03 Dysthymia =/> 50% (v AP)						
RAVIZZA1999 Amt/Ams	62/85	106/165	<del>                                     </del>	100.00	1.14 [0.96, 1.35]	0
Subtotal (95% CI)	85	165	₩	100.00	1.14 [0.96, 1.35]	
Total events: 62 (Treatment), 106						
Test for heterogeneity: not applic						
Test for overall effect: Z = 1.44 (P	= 0.15)					
		0.	1 0.2 0.5 1 2	5 10		
			Favours treatment Favours	control		

## 4.9 Number reporting side effects at endpoint: antipsychotic

Review: Depression Update Subthreshold: Pharm

Comparison: 04 Overall acceptability and tolerability (head to head)

Outcome: 09 Patients reporting side effects: AP

Study or sub-category	Treatment n/N	Control n/N		RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Dysthymia only							
GEISLER1992 Flp/Rts	16/36	15/33			100.00	0.98 [0.58, 1.65]	0
Subtotal (95% CI)	36	33			100.00	0.98 [0.58, 1.65]	
Total events: 16 (Treatment), 1	15 (Control)			Ţ			
Test for heterogeneity: not app	olicable						
Test for overall effect: Z = 0.08	(P = 0.93)						
			0.1 0.2	0.5 1 2	5 10		
			Favours tr	eatment Favou	rs control		

# Pharm subthreshold 05 Relapse prevention: active treatment versus placebo 05.01 Recurrence at endpoint

Review: Depression Update Subthreshold: Pharm Comparison: 05 Relapse prevention (versus placebo)

Outcome: 01 Recurrence

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
O1 TCAs MILLER2001ADsp/Plb Subtotal (95% CI) Total events: 0 (Treatment), 6 Test for heterogeneity: not app Test for overall effect: Z = 1.86	licable	6/13 13		100.00	0.07 [0.00, 1.16] 0.07 [0.00, 1.16]	0
			0.1 0.2 0.5 1 2  Favours treatment Favours	5 10		

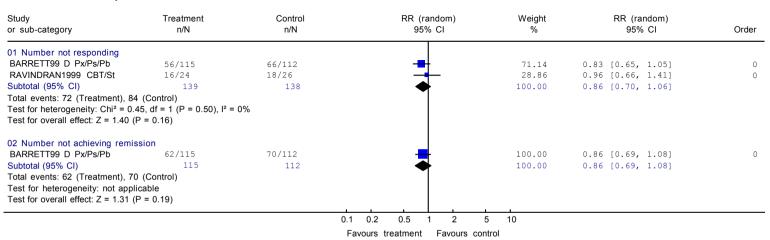
#### **Psychological interventions**

#### Psych sub-thresh 01 Psychological therapies versus control

#### 1.1 Dichotomous outcomes at endpoint and follow-up

Review: Depression Update Subthreshold: Psych Comparison: 01 Psychological therapies vs control

Outcom e: 01 Efficacy data



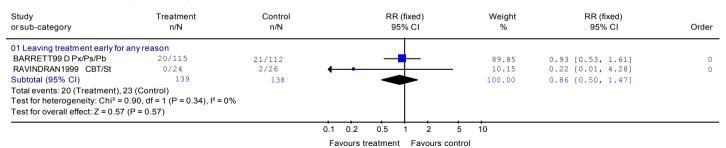
#### 1.2 Continuous outcomes at endpoint and follow-up

Review: Depression Update Subthreshold: Psych
Comparison: 01 Psychological therapies vs control
Outcome: 02 Efficacy data (continuous)

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)		SI	MD (random) 95% CI	)	Weight %	SMD (random) 95% CI	Order
01 Clinician-rated endpoint scores	3		,		-						
BARRETT99 D Px/Ps/Pb	97	6.90(5.10)	99	8.30(5.10)			_		100.00	-0.27 [-0.55, 0.01]	0
Subtotal (95% CI)	97		99						100.00	-0.27 [-0.55, 0.01]	
Test for heterogeneity: not applica	able						1				
Test for overall effect: Z = 1.90 (P	= 0.06)										
					-4	-2	0	2	4		
					Favo	ours treatm	ent Favo	urs control			

#### 1.3 Dropout at endpoint

Review: Depression Update Subthreshold: Psych
Comparison: 01 Psychological therapies vs control
Outcom e: 03 Acceptability and tolerablity data



# Psych sub-thresh 02 Psychological therapies versus antidepressants

#### 2.1 Dichotomous outcomes at endpoint

Review: Depression Update Subthreshold: Psych
Comparison: 02 Psychological therapies vs antidepressants

Outcom e: 01 Efficacy data

Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Order
01 Number not responding						
BARRETT99 D Px/Ps/Pb	56/115	51/111	<del></del>	38.57	1.06 [0.80, 1.40]	0
MARKOWITZ05 lp/St/BS	20/23	20/24	<del>-</del>	51.31	1.04 [0.82, 1.33]	0
RAVINDRAN1999 CBT/St	16/24	10/22	+-	10.11	1.47 [0.86, 2.51]	0
Subtotal (95% CI)	162	157	<b>.</b>	100.00	1.09 [0.92, 1.29]	
Total events: 92 (Treatment), 81	I (Control)					
Test for heterogeneity: Chi <sup>2</sup> = 1.3	38, df = 2 (P = 0.50), $I^2$ =	0%				
Test for overall effect: Z = 0.95 (	P = 0.34)					
02 Number not remitting						
BARRETT99 D Px/Ps/Pb	62/115	56/111	<del></del>	71.99	1.07 [0.83, 1.37]	0
MARKOWITZ05 lp/St/BS	18/23	14/24	+	28.01	1.34 [0.90, 2.00]	0
Subtotal (95% CI)	138	135	<b>.</b>	100.00	1.14 [0.92, 1.41]	
Total events: 80 (Treatment), 70	(Control)		ľ			
Test for heterogeneity: Chi <sup>2</sup> = 0.9	,	0%				
Test for overall effect: Z = 1.20 (						
		0.	1 0.2 0.5 1 2	5 10		
		F	Favours treatment Favours con	ntrol		

# 2.2 Continuous outcomes at endpoint and follow-up

Review: Depression Update Subthreshold: Psych
Comparison: 02 Psychological therapies vs antidepressants

Outcome: 02 Efficacy data (continuous)

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	SMD (fix 95% (	,	SMD (fixed) 95% CI	Order
01 Clinician-rated mean endpo	oint							_
BARRETT99 D Px/Ps/Pb	97	6.90(5.10)	88	5.80(4.50)	<b>)</b>	29.68	0.23 [-0.06, 0.52]	0
BROWNE02 IPT/Stl/Cmb	178	16.80(10.60)	196	14.30(9.80)	<b>.</b>	59.94	0.24 [0.04, 0.45]	0
DUNNER1996 CT/Flx	10	10.80(5.50)	12	6.90(5.50)	<del>  -</del>	3.30	0.68 [-0.19, 1.55]	0
MARKOWITZ05 lp/St/BS	23	12.50(5.90)	24	8.30(5.40)	-	7.09	0.73 [0.14, 1.32]	0
Subtotal (95% CI)	308		320		•	100.00	0.29 [0.13, 0.45]	
Test for heterogeneity: $Chi^2 = 3$ Test for overall effect: $Z = 3.59$								
02 Clinician-rated mean endpo	oint 6-mont	h follow-up						
BROWNE02 IPT/Stl/Cmb	167	15.30(10.60)	186	13.40(9.80)	<u>-</u>	100.00	0.19 [-0.02, 0.40]	0
Subtotal (95% CI)	167		186		•	100.00	0.19 [-0.02, 0.40]	
Test for heterogeneity: not app Test for overall effect: Z = 1.74								
03 Clinician-rated mean endpo	oint 18-mor	nth follow-up						
BROWNE02 IPT/Stl/Cmb	156	14.30(10.00)	179	11.70(9.70)	<del>.</del>	100.00	0.26 [0.05, 0.48]	0
Subtotal (95% CI)	156		179		•	100.00	0.26 [0.05, 0.48]	
Test for heterogeneity: not app Test for overall effect: Z = 2.40								
04 Self-rated mean endpoint								
DUNNER1996 CT/FIx	9	9.10(5.20)	11	9.10(9.70)	+	30.46	0.00 [-0.88, 0.88]	0
MARKOWITZ05 lp/St/BS	2.3	12.80(8.90)	24	8.30(7.60)	<b>⊢</b>	69.54	0.54 [-0.05, 1.12]	0
Subtotal (95% CI)	32		35		<b>♦</b>	100.00	0.37 [-0.11, 0.86]	
Test for heterogeneity: $Chi^2 = 0$ Test for overall effect: $Z = 1.50$								
					-10 -5 0	5 10		
					Favours treatment F	avours control		

# 2.3 Dropout at endpoint

Review: Depression Update Subthreshold: Psych
Comparison: 02 Psychological therapies vs antidepressants

Outcome: 03 Acceptability and tolerablity data

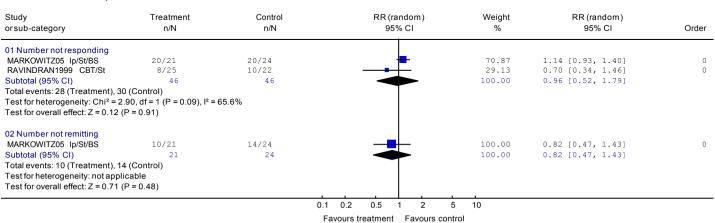
Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Order
01 Leaving treatment early for a	nyreason					
BARRETT99 D Px/Ps/Pb	20/115	28/111	<del></del>	79.86	0.69 [0.41, 1.15]	0
DUNNER1996 CT/FIx	1/13	6/18	<del>-</del>	5.25	0.23 [0.03, 1.69]	0
MARKOWITZ05 lp/St/BS	4/23	5/24		14.89	0.83 [0.26, 2.73]	0
RAVINDRAN1999 CBT/St	0/24	0/22			Not estimable	0
Subtotal (95% CI)	175	175		100.00	0.67 [0.42, 1.06]	
Test for heterogeneity: $Chi^2 = 1.7$ Test for overall effect: $Z = 1.72$ (Fig. 2) Leaving treatment early due to	P = 0.09)	0,10				
DUNNER1996 CT/FIx	0/13	1/18	<b>—</b>	100.00	0.45 [0.02, 10.30]	0
Subtotal (95% CI)	13	18		100.00	0.45 [0.02, 10.30]	
Total events: 0 (Treatment), 1 (C Test for heterogeneity: not applie Test for overall effect: Z = 0.50 (F	cable					
			0.1 0.2 0.5 1 2	5 10		
			Favours treatment Favours co	ntrol		

# Psych sub-thresh 03 Psychological therapies + antidepressants versus antidepressants 3.1 Dichotomous outcomes at endpoint

Review: Depression Update Subthreshold: Psych

Comparison: 03 Psychological therapies + antidepressants vs antidepressants

Outcom e: 01 Efficacy data

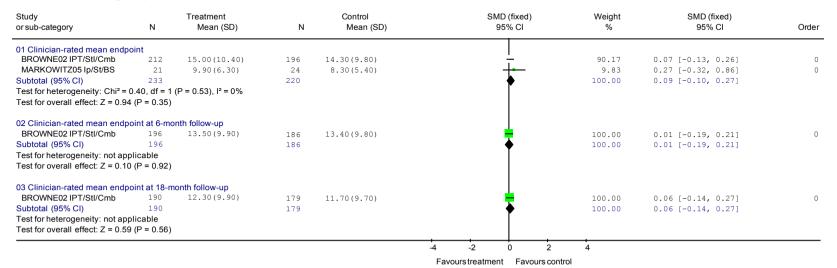


#### 3.2 Continuous outcomes at endpoint and follow-up

Review: Depression Update Subthreshold: Psvch

Comparison: 03 Psychological therapies + antidepressants vs antidepressants

Outcome: 02 Efficacy data (continuous)

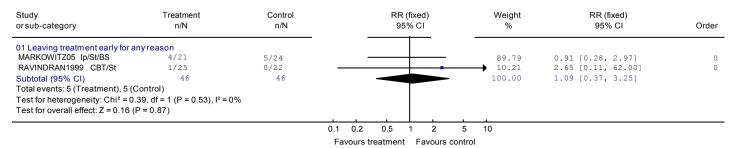


#### 3.3 Dropout at endpoint

Review: Depression Update Subthreshold: Psych

Comparison: 03 Psychological therapies + antidepressants vs antidepressants

Outcom e: 03 Acceptability and tolerablity data



# Psych sub-thresh 04 Psychological therapies + antidepressants versus psychological therapies 4.1 Dichotomous outcomes at endpoint

Review: Depression Update Subthreshold: Psych

Comparison: 04 Psychological therapies + antidepressants vs psychological therapies

Outcome: 01 Efficacy data

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Number not responding						
RAVINDRAN1999 CBT/St	8/25	16/24		100.00	0.48 [0.25, 0.91]	0
Subtotal (95% CI)	25	24		100.00	0.48 [0.25, 0.91]	
Total events: 8 (Treatment), 16 (	(Control)					
Test for heterogeneity: not appli	cable					
Test for overall effect: Z = 2.26 (I	P = 0.02)					
	,		0.1 0.2 0.5 1 2	5 10		
			Favours treatment Favours c	ontrol		

## 4.2 Continuous outcomes at endpoint and follow-up

Review: Depression Update Subthreshold: Psych

Comparison: 04 Psychological therapies + antidepressants vs psychological therapies

Outcome: 02 Efficacy data (continuous)

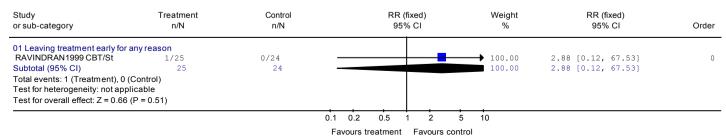
Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)			) (fixed) 5% Cl	Weight %	SMD (fixed) 95% CI	Order
01 Clinician-rated mean endpoin	it data									
BROWNE02 IPT/Stl/Cmb	212	15.00(10.40)	178	16.80(10.60)		-	4	100.00	-0.17 [-0.37, 0.03]	0
Subtotal (95% CI)	212		178			•		100.00	-0.17 [-0.37, 0.03]	
Test for heterogeneity: not applicate Test for overall effect: Z = 1.68 (Fig. 2)										
02 Clinician-rated mean endpoin	it data 6-n	nonth follow-up								
BROWNE02 IPT/StI/Cmb	196	13.50(9.90)	167	15.30(10.60)		-		100.00	-0.18 [-0.38, 0.03]	0
Subtotal (95% CI)	196		167			•	•	100.00	-0.18 [-0.38, 0.03]	
Test for heterogeneity: not applied Test for overall effect: Z = 1.66 (Fig. 2)										
03 Clinician-rated mean endpoin	it data 18-	month follow-up								
BROWNE02 IPT/Stl/Cmb	190	12.30(9.90)	156	14.30(10.00)				100.00	-0.20 [-0.41, 0.01]	0
Subtotal (95% CI)	190		156			•		100.00	-0.20 [-0.41, 0.01]	
Test for heterogeneity: not applie	cable									
Test for overall effect: Z = 1.85 (F	P = 0.06									
					-4	-2	0 2	4		
					Favou	ırs treatment	Favours cor	ntrol		

#### 4.3 Dropout at endpoint

Review: Depression Update Subthreshold: Psvch

Comparison: 04 Psychological therapies + antidepressants vs psychological therapies

Outcome: 03 Acceptability and tolerablity data



# Psych sub-thresh 05 Short psychodynamic verbal therapy versus short psychodynamic art therapy 5.1 Continuous outcomes at endpoint and follow-up

Review: Depression Update Subthreshold: Psych

Comparison: 05 Short Psychodynamic Verbal v Short Psychodynamic Art

Outcome: 01 Efficacy data

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)		SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI	Order
01 Self-rated mean endpoint									
THYME07 vrbl v art*C	21	13.38(11.03)	18	14.44(7.35)		<b>_</b>	100.0	-0.11 [-0.74, 0.52]	0
Subtotal (95% CI)	21		18			•	0	-0.11 [-0.74, 0.52]	
Test for heterogeneity: not appli	cable								
Test for overall effect: Z = 0.34	(P = 0.73)								
02 Self-rated mean endpoint at	3-month follo	w-up							
THYME07 vrbl v art*C	21	10.67(7.20)	18	12.89(9.40)			100.0	-0.26 [-0.90, 0.37]	0
Subtotal (95% CI)	21		18			<b>→</b>	0	-0.26 [-0.90, 0.37]	
Test for heterogeneity: not appli	cable					1			
Test for overall effect: Z = 0.81	(P = 0.42)								
					-10	-5 0 5	5 10		
					Favours tre	atment Favours	control		

# 5.2 Dropout at endpoint

Review: Depression Update Subthreshold: Psych

Comparison: 07 Short Psychodynamic Verbal v Short Psychodynamic Art

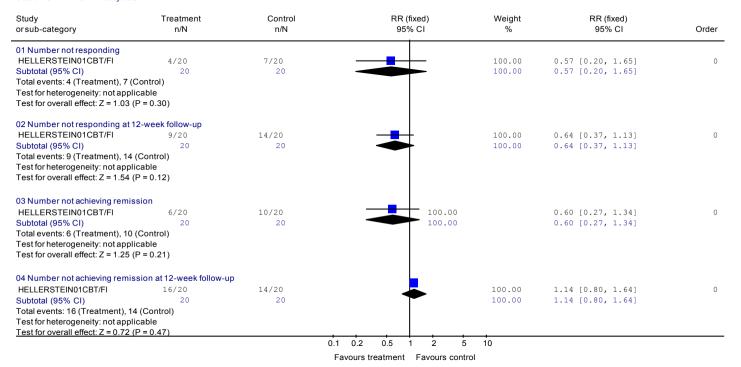
Outcome: 02 Acceptability and tolerablity data

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Leaving treatment early for	r any reason					
THYME07 vrbl v art*C	1/22	3/21	<b>←</b>	100.00	0.32 [0.04, 2.82]	0
Subtotal (95% CI)	22	21		100.00	0.32 [0.04, 2.82]	
Total events: 1 (Treatment), 3	(Control)					
Test for heterogeneity: not ap	plicable					
Test for overall effect: Z = 1.03	3 (P = 0.30)					
	<u> </u>		0.1 0.2 0.5 1 2	5 10		
			Favours treatment Favours cor	itrol		

# Psych sub-thresh 06 Partial responders: psychological therapy + SSRI versus SSRI 6.1 Dichotomous outcomes at endpoint

Review: Depression Update Subthreshold: Psych
Comparison: 08 Partial responders: Psych/SSRI combo v SSRI

Outcom e: 01 Efficacy data



# Dropout at endpoint

Depression Update Subthreshold: Psych Comparison: 08 Partial responders: Psych/SSRI combo v SSRI
Outcome: 02 Acceptability and tolerability data

Study or sub-category	Treatment n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
01 Leaving study early for any re	eason					
HELLERSTEIN01CBT/FI	2/20	3/20		100.00	0.67 [0.12, 3.57]	0
Subtotal (95% CI)	20	20		100.00	0.67 [0.12, 3.57]	
Total events: 2 (Treatment), 3 (0	Control)					
Test for heterogeneity: not appli						
Test for overall effect: Z = 0.47 (						
		0.1	0.2 0.5 1 2	5 10		
		F	avours treatment Favours cor	ntrol		