Table of Contents

Supplementary figure S1: Meta-analysis of tricyclic antidepressants versus placebo on HDRS-17	7
Supplementary figure S2: Meta-analysis of tricyclic antidepressants versus placebo on HDRS-17 (outlier removed	1)8
Supplementary figure S3: Funnel plot of tricyclic antidepressants versus placebo on HDRS-17	9
Supplementary figure S4: Trial Sequential Analysis of tricyclic antidepressants versus placebo on HDRS-17	10
Supplementary figure S5: Subgroup analysis of 'active' versus inert placebo on HDRS-17	11
Supplementary figure S6: Subgroup analysis of different tricyclic antidepressants on HDRS-17	12
Supplementary figure S7: Subgroup analysis of placebo washout on HDRS-17	13
Supplementary figure S8: Subgroup analysis of age on HDRS-17.	14
Supplementary figure S9: Trial Sequential Analysis of tricyclic antidepressants versus placebo on serious adverse	
events	
Supplementary figure S10: Subgroup analysis of risk of for-profit bias on serious adverse events	
Supplementary figure S11: Subgroup analysis of different tricyclic antidepressants on serious adverse events	
Supplementary figure S12: Subgroup analysis of age on serious adverse events	
Supplementary figure S13: Subgroup analysis of placebo washout on serious adverse events	19
Supplementary figure S14: Meta-analysis of tricyclic antidepressants versus placebo on hypotension	20
Supplementary figure S15: Meta-analysis of tricyclic antidepressants versus placebo on urinary retention	21
Supplementary figure S16: Meta-analysis of tricyclic antidepressants versus placebo on amblyopia	22
Supplementary figure S17: Meta-analysis of tricyclic antidepressants versus placebo on sexual dysfunction	23
Supplementary figure S18: Meta-analysis of tricyclic antidepressants versus placebo on taste alteration	24
Supplementary figure S19: Meta-analysis of tricyclic antidepressants versus placebo on amnesia	25
Supplementary figure S20: Meta-analysis of tricyclic antidepressants versus placebo on anorexia	26
Supplementary figure S21: Meta-analysis of tricyclic antidepressants versus placebo on anxiety	27
Supplementary figure S22: Meta-analysis of tricyclic antidepressants versus placebo on dyscoordination	28
Supplementary figure S23: Meta-analysis of tricyclic antidepressants versus placebo on hyperkinesia	29
Supplementary figure S24: Meta-analysis of tricyclic antidepressants versus placebo on hypertension	30
Supplementary figure S25: Meta-analysis of tricyclic antidepressants versus placebo on hypokinesia	31
Supplementary figure S26: Meta-analysis of tricyclic antidepressants versus placebo on mania	32
Supplementary figure S27: Meta-analysis of tricyclic antidepressants versus placebo on syncope	33
Supplementary figure S28: Meta-analysis of tricyclic antidepressants versus placebo on tinnitus	34
Supplementary figure S29: Meta-analysis of tricyclic antidepressants versus placebo on suicides or suicide attem	-
Supplementary figure S30: Trial Sequential Analysis of tricyclic antidepressants versus placebo on non-serious adverse events	
Supplementary figure S31: Subgroup analysis of drug co-interventions versus no drug co-intervention on non-ser	ious 37

Supplementary figure S32: Meta-analysis of tricyclic antidepressants versus placebo on dry mouth	38
Supplementary figure S33: Meta-analysis of tricyclic antidepressants versus placebo on anticholinergic sympton	ns. 39
Supplementary figure S34: Meta-analysis of tricyclic antidepressants versus placebo on somnolence	40
Supplementary figure S35: Meta-analysis of tricyclic antidepressants versus placebo on sedation	41
Supplementary figure S36: Meta-analysis of tricyclic antidepressants versus placebo on dizziness	42
Supplementary figure S37: Meta-analysis of tricyclic antidepressants versus placebo on constipation	43
Supplementary figure S38: Meta-analysis of tricyclic antidepressants versus placebo on sweating	44
Supplementary figure S39: Meta-analysis of tricyclic antidepressants versus placebo on tremor	45
Supplementary figure S40: Meta-analysis of tricyclic antidepressants versus placebo on blurred vision	46
Supplementary figure S41: Meta-analysis of tricyclic antidepressants versus placebo on flushing	47
Supplementary figure S42: Meta-analysis of tricyclic antidepressants versus placebo on diarrhoea	48
Supplementary figure S43: Meta-analysis of tricyclic antidepressants versus placebo on infection	49
Supplementary figure S44: Meta-analysis of tricyclic antidepressants versus placebo on agitation	50
Supplementary figure S45: Meta-analysis of tricyclic antidepressants versus placebo on decreased appetite	51
Supplementary figure S46: Meta-analysis of tricyclic antidepressants versus placebo on increased appetite	52
Supplementary figure S47: Meta-analysis of tricyclic antidepressants versus placebo on asthenia	53
Supplementary figure S48: Meta-analysis of tricyclic antidepressants versus placebo on CNS	54
Supplementary figure S49: Meta-analysis of tricyclic antidepressants versus placebo on confusion	55
Supplementary figure S50: Meta-analysis of tricyclic antidepressants versus placebo on abnormal dreams	56
Supplementary figure S51: Meta-analysis of tricyclic antidepressants versus placebo on dyspepsia	57
Supplementary figure S52: Meta-analysis of tricyclic antidepressants versus placebo on headache	58
Supplementary figure S53: Meta-analysis of tricyclic antidepressants versus placebo on impaired urination	59
Supplementary figure S54: Meta-analysis of tricyclic antidepressants versus placebo on insomnia	60
Supplementary figure S55: Meta-analysis of tricyclic antidepressants versus placebo on micturition disorder	61
Supplementary figure S56: Meta-analysis of tricyclic antidepressants versus placebo on nausea	62
Supplementary figure S57: Meta-analysis of tricyclic antidepressants versus placebo on nervousness	63
Supplementary figure S58: Meta-analysis of tricyclic antidepressants versus placebo on paraesthesia	64
Supplementary figure S59: Meta-analysis of tricyclic antidepressants versus placebo on pharyngitis	65
Supplementary figure S60: Meta-analysis of tricyclic antidepressants versus placebo on rash	66
Supplementary figure S61: Meta-analysis of tricyclic antidepressants versus placebo on rhinitis	67
Supplementary figure S62: Meta-analysis of tricyclic antidepressants versus placebo on tachycardia	68
Supplementary figure S63: Meta-analysis of tricyclic antidepressants versus placebo on upper respiratory tract	
infection.	
Supplementary figure S64: Meta-analysis of tricyclic antidepressants versus placebo on urinary hesitancy	
Supplementary figure S65: Meta-analysis of tricyclic antidepressants versus placebo on vasodilatation	
Supplementary figure S66: Meta-analysis of tricyclic antidepressants versus placebo on weight gain	
Supplementary figure S67: Meta-analysis of tricyclic antidepressants versus placebo on yawning	73

Supplementary figure S68: Meta-analysis of tricyclic antidepressants versus placebo on serious adverse events (as reported by trialists)74
Supplementary figure S69: Meta-analysis of tricyclic antidepressants versus placebo on MADRS, BDI, and HDRS-6. 75
Supplementary figure S70: Meta-analysis of tricyclic antidepressants versus placebo on suicidal ideation76
Supplementary figure S71: Meta-analysis of tricyclic antidepressants versus placebo on response77
Supplementary figure S72: Meta-analysis of tricyclic antidepressants versus placebo on remission78
Supplementary figure S73: Meta-analysis of tricyclic antidepressants versus placebo on HDRS-17 (sensitivity analysis)79
Supplementary figure S74: Meta-analysis of tricyclic antidepressants versus placebo on HDRS-17 (standardised mean difference)
Supplementary figure S75: Meta-analysis of tricyclic antidepressants versus placebo on serious adverse events (sensitivity analysis)81
Supplementary figure S76: Meta-analysis of tricyclic antidepressants versus placebo on urinary retention (sensitivity analysis).
Supplementary figure S77: Meta-analysis of tricyclic antidepressants versus placebo on hypotension (sensitivity analysis)83
Supplementary figure S78: Meta-analysis of tricyclic antidepressants versus placebo on amblyopia (sensitivity analysis)
Supplementary figure S79: Meta-analysis of tricyclic antidepressants versus placebo on sexual dysfunction (sensitivity analysis)85
Supplementary figure S80: Meta-analysis of tricyclic antidepressants versus placebo on taste alteration (sensitivity analysis)86
Supplementary figure S81: Meta-analysis of tricyclic antidepressants versus placebo on amnesia (sensitivity analysis)87
Supplementary figure S82: Meta-analysis of tricyclic antidepressants versus placebo on anorexia (sensitivity analysis)
Supplementary figure S83: Meta-analysis of tricyclic antidepressants versus placebo on anxiety (sensitivity analysis). 89
Supplementary figure S84: Meta-analysis of tricyclic antidepressants versus placebo on dyscoordination (sensitivity analysis)90
Supplementary figure S85: Meta-analysis of tricyclic antidepressants versus placebo on hyperkinesia (sensitivity analysis)
Supplementary figure S86: Meta-analysis of tricyclic antidepressants versus placebo on hypertension (sensitivity analysis)
Supplementary figure S87: Meta-analysis of tricyclic antidepressants versus placebo on hypokinesia (sensitivity analysis)
Supplementary figure S88: Meta-analysis of tricyclic antidepressants versus placebo on mania (sensitivity analysis). 94
Supplementary figure S89: Meta-analysis of tricyclic antidepressants versus placebo on syncope (sensitivity analysis)
Supplementary figure S90: Meta-analysis of tricyclic antidepressants versus placebo on tinnitus (sensitivity analysis). 96

Supplementary figure S91: Meta-analysis of tricyclic antidepressants versus placebo on suicides or suicide attemp (sensitivity analysis)	ots 97
Supplementary figure S92: Meta-analysis of tricyclic antidepressants versus placebo on non-serious adverse even (sensitivity analysis)	
Supplementary figure S93: Meta-analysis of tricyclic antidepressants versus placebo on dry mouth (sensitivity analysis).	99
Supplementary figure S94: Meta-analysis of tricyclic antidepressants versus placebo on anticholinergic symptoms (sensitivity analysis)	
Supplementary figure S95: Meta-analysis of tricyclic antidepressants versus placebo on somnolence (sensitivity analysis).	101
Supplementary figure S96: Meta-analysis of tricyclic antidepressants versus placebo on sedation (sensitivity analysis).	102
Supplementary figure S97: Meta-analysis of tricyclic antidepressants versus placebo on dizziness (sensitivity analysis).	103
Supplementary figure S98: Meta-analysis of tricyclic antidepressants versus placebo on constipation (sensitivity analysis).	104
Supplementary figure S99: Meta-analysis of tricyclic antidepressants versus placebo on sweating (sensitivity analysis).	105
Supplementary figure S100: Meta-analysis of tricyclic antidepressants versus placebo on tremor (sensitivity analysis).	106
Supplementary figure S101: Meta-analysis of tricyclic antidepressants versus placebo on blurred vision (sensitivit analysis).	-
Supplementary figure S102: Meta-analysis of tricyclic antidepressants versus placebo on flushing (sensitivity analysis).	108
Supplementary figure S103: Meta-analysis of tricyclic antidepressants versus placebo on diarrhoea (sensitivity analysis).	109
Supplementary figure S104: Meta-analysis of tricyclic antidepressants versus placebo on infection (sensitivity analysis).	110
Supplementary figure S105: Meta-analysis of tricyclic antidepressants versus placebo on agitation (sensitivity analysis).	111
Supplementary figure S106: Meta-analysis of tricyclic antidepressants versus placebo on decreased appetite (sensitivity analysis).	112
Supplementary figure S107: Meta-analysis of tricyclic antidepressants versus placebo on increased appetite (sensitivity analysis).	113
Supplementary figure S108: Meta-analysis of tricyclic antidepressants versus placebo on asthenia (sensitivity analysis).	114
Supplementary figure S109: Meta-analysis of tricyclic antidepressants versus placebo on CNS (sensitivity analysis	•
Supplementary figure S110: Meta-analysis of tricyclic antidepressants versus placebo on confusion (sensitivity analysis).	
Supplementary figure S111: Meta-analysis of tricyclic antidepressants versus placebo on abnormal dreams (sensitivity analysis).	
Supplementary figure S112: Meta-analysis of tricyclic antidepressants versus placebo on dyspepsia (sensitivity analysis).	

Supplementary figure S113: Meta-analysis of tricyclic antidepressants versus placebo on headache (sensitivity analysis).	. 119
Supplementary figure S114: Meta-analysis of tricyclic antidepressants versus placebo on impaired urination (sensitivity analysis).	. 120
Supplementary figure S115: Meta-analysis of tricyclic antidepressants versus placebo on insomnia (sensitivity analysis)	. 121
Supplementary figure S116: Meta-analysis of tricyclic antidepressants versus placebo on micturition disorder (sensitivity analysis)	. 122
Supplementary figure S117: Meta-analysis of tricyclic antidepressants versus placebo on nausea (sensitivity analysis)	. 123
Supplementary figure S118: Meta-analysis of tricyclic antidepressants versus placebo on nervousness (sensitivity analysis)	
Supplementary figure S119: Meta-analysis of tricyclic antidepressants versus placebo on paraesthesia (sensitivit analysis)	-
Supplementary figure S120: Meta-analysis of tricyclic antidepressants versus placebo on pharyngitis (sensitivity analysis)	
Supplementary figure S121: Meta-analysis of tricyclic antidepressants versus placebo on rash (sensitivity analysi	
Supplementary figure S122: Meta-analysis of tricyclic antidepressants versus placebo on rhinitis (sensitivity analysis)	. 128
Supplementary figure S123: Meta-analysis of tricyclic antidepressants versus placebo on tachycardia (sensitivity analysis)	
Supplementary figure S124: Meta-analysis of tricyclic antidepressants versus placebo on upper respiratory tract infection (sensitivity analysis)	
Supplementary figure S125: Meta-analysis of tricyclic antidepressants versus placebo on urinary hesitancy (sensitivity analysis)	. 131
Supplementary figure S126: Meta-analysis of tricyclic antidepressants versus placebo on vasodilatation (sensitiv analysis)	ity . 132
Supplementary figure S127: Meta-analysis of tricyclic antidepressants versus placebo on weight gain (sensitivity analysis)	
Supplementary figure S128: Meta-analysis of tricyclic antidepressants versus placebo on yawning (sensitivity analysis).	. 134
Supplementary figure S129: Meta-analysis of tricyclic antidepressants versus placebo on MADRS, BDI, and HDRS ((sensitivity analysis)	
Supplementary figure S130: Meta-analysis of tricyclic antidepressants versus placebo on suicidal ideation (sensit analysis)	•
Supplementary figure S131: Meta-analysis of tricyclic antidepressants versus placebo on response (sensitivity analysis).	. 137
Supplementary figure S132: Meta-analysis of tricyclic antidepressants versus placebo on remission (sensitivity analysis)	. 138
 Supplementary figure S133: Meta-analysis of tricyclic antidepressants versus placebo on quality of life (standard mean difference)	lised
Supplementary file 1: PRISMA 2020 Checklist	
Supplementary file 2: Search strategies	. 142

Supplementary file 3: Supplementary results	145
Supplementary file 4: List of non-serious adverse events combined for meta-analyses	152
Supplementary table S1: Characteristics of the included trials	153
Supplementary table S2: Serious adverse events in the included trials	160
Supplementary table S3: Number needed to harm for serious adverse events	162
Supplementary table S4: Number needed to treat for non-serious adverse events	163
Supplementary table S5: Number needed to harm for non-serious adverse events	164

Supplementary figure S1: Meta-analysis of tricyclic antidepressants versus placebo on HDRS-17.

Study	N	TCA Mean	SD	N	Placeb Mean	-					ean diff. h 95% C		Weight (%)
Akhondzadeh 2003	15	4.5	3.9	15	12	7.7				-7.50 [11 87	-3 13]	4.89
Barge-Schaapveld 2002	29	8.9	6.2	30	12.5	6.3				-3.60 [•	5.40
Emsley 2018	105	13.3		106	17.1	6.9		=		-3.80		•	5.85
Ferguson 1994 - dothiepin	184	12.2	7	93	15.9	7.9		=		-3.70 [5.87
Ferguson 1994 - doxepin	184	12.7	7.4	93	15.9	7.9				-3.20 [•	5.85
Jacobson 1990	48	9.5	5.4	48	13	7.5		-		-3.50 [5.62
Lydiard 1997	104	-12.8	6.8	115	-8.8	7.0		= =		-4.00 [5.87
McGrath 2000	53	5.8	4.8	52	10.3	6.3				-4.50 [•	5.78
Murphy 1984 - NT vs CT	11	8.23	7	24	7.75	6.5			_	•	-4.27,	5.231	4.71
Murphy 1984 - NT vs CT + placebo	11	8.23	7	17	5.76			J		2.47 [7.011	4.81
Mynors-Wallis 1995	27	8.1	7.1	26	11.8	7.3				-3.70 [. ,	0.18]	5.11
Niklson 1997	141	13.29	8.4	106		7.9				-2.79 [-0.73]	5.80
Organon 3-020	40	14.4	7.7	39	20.6	8.3		_		-6.20 [5.26
Organon 84062	15	10.3	12.1	15	8.4	9.6			_	1.90 [9.72]	3.38
Philipp 1999	105	-14.2	7.3	46	-12.1	7.4		_		-2.10 [0.441	5.64
Reimherr 1990		-12.64			-8.16					-4.48 [5.86
Roth 1990	24	18.4	9.3	29	20.5	9.4			_	-2.10 [,	2.96]	4.57
Shipley 1981	53	9.3	10.9	23	31.6	14.9	_			-22.30 [-		•	4.15
Silverstone 1994	66	13.5	7.9	69	13.8	7.7	_	-	ļ.	-0.30 [2.33]	5.61
	00	10.0	7.0	-	10.0			$ \lambda$ T		•		•	0.01
Overall	0/ 1.12	44.07								-3.77 [-5.91,	-1.63]	
Heterogeneity: $\tau^2 = 19.51$, $I^2 = 91.58$,	= 11.8/											
Test of $\theta_i = \theta_j$: Q(18) = 64.55, p = 0.0	U												
Test of $\theta = 0$: $z = -3.45$, $p = 0.00$,					
						-(30 -20 -	10 0	1	0			

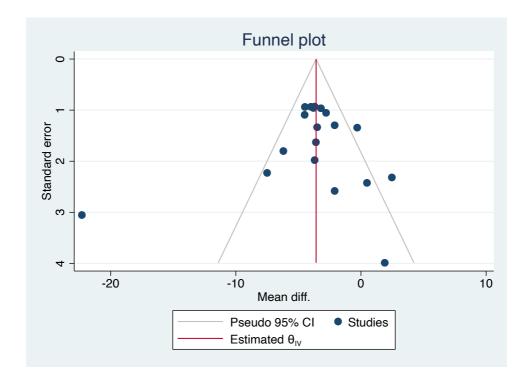


Supplementary figure S2: Meta-analysis of tricyclic antidepressants versus placebo on HDRS-17 (outlier removed).

		TCA				Mean diff.	Weight		
Study	N	Mean	SD	N	Mean	SD		with 95% CI	(%)
Akhondzadeh 2003	15	4.5	3.9	15	12	7.7		-7.50 [-11.87, -3.13]	3.85
Barge-Schaapveld 2002	29	8.9	6.2	30	12.5	6.3		-3.60 [-6.79, -0.41]	5.30
Emsley 2018	105	13.3	7	106	17.1	6.9	-	-3.80 [-5.68, -1.92]	7.36
Ferguson 1994 - dothiepin	184	12.2	7	93	15.9	7.9		-3.70 [-5.52, -1.88]	7.44
Ferguson 1994 - doxepin	184	12.7	7.4	93	15.9	7.9		-3.20 [-5.09, -1.31]	7.34
Jacobson 1990	48	9.5	5.4	48	13	7.5	-	-3.50 [-6.11, -0.89]	6.16
Lydiard 1997	104	-12.8	6.8	115	-8.8	7		-4.00 [-5.83, -2.17]	7.43
McGrath 2000	53	5.8	4.8	52	10.3	6.3	-	-4.50 [-6.64, -2.36]	6.93
Murphy 1984 - NT vs CT	11	8.23	7	24	7.75	6.5		0.48 [-4.27, 5.23]	3.48
Murphy 1984 - NT vs CT + placebo	11	8.23	7	17	5.76	5.26		2.47 [-2.07, 7.01]	3.68
Mynors-Wallis 1995	27	8.1	7.1	26	11.8	7.3	-	-3.70 [-7.58, 0.18]	4.40
Niklson 1997	141	13.29	8.4	106	16.08	7.9	-	-2.79 [-4.85, -0.73]	7.05
Organon 3-020	40	14.4	7.7	39	20.6	8.3	-	-6.20 [-9.73, -2.67]	4.83
Organon 84062	15	10.3	12.1	15	8.4	9.6		1.90 [-5.92, 9.72]	1.69
Philipp 1999	105	-14.2	7.3	46	-12.1	7.4		-2.10 [-4.64, 0.44]	6.28
Reimherr 1990	144	-12.64	7.97	141	-8.16	7.85	-	-4.48 [-6.32, -2.64]	7.42
Roth 1990	24	18.4	9.3	29	20.5	9.4		-2.10 [-7.16, 2.96]	3.21
Silverstone 1994	66	13.5	7.9	69	13.8	7.7	-	-0.30 [-2.93, 2.33]	6.14
Overall							•	-3.16 [-4.29, -2.04]	
Heterogeneity: $\tau^2 = 3.54$, $I^2 = 67.39\%$, H ² = 3	3.07							
Test of $\theta_i = \theta_j$: Q(17) = 26.59, p = 0.0	6								
Test of $\theta = 0$: $z = -5.52$, $p = 0.00$									
							-10 -5 0 5	10	

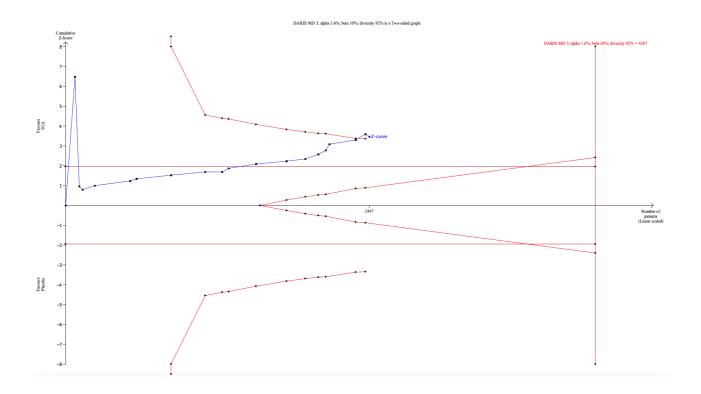


Supplementary figure S3: Funnel plot of tricyclic antidepressants versus placebo on HDRS-17.



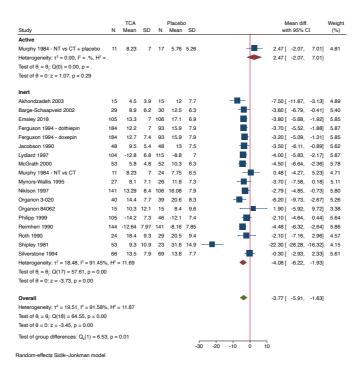


Supplementary figure S4: Trial Sequential Analysis of tricyclic antidepressants versus placebo on HDRS-17.



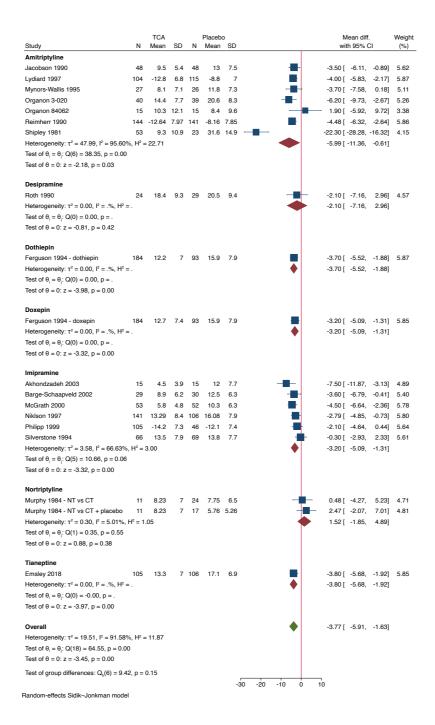
Supplementary figure S5: Subgroup analysis of 'active' versus inert placebo on HDRS-17.

Graph 22/05/2023, 11.03



Stata

Supplementary figure S6: Subgroup analysis of different tricyclic antidepressants on HDRS-17.





Supplementary figure S7: Subgroup analysis of placebo washout on HDRS-17.

Graph 22/05/2023, 10.59

Study	N	TCA Placebo Mean SD N Mean SD			Mean diff. with 95% CI							
No		moun			woun					***********	<u> </u>	(%)
Akhondzadeh 2003	15	4.5	3.9	15	12	7.7		-	-7.50) [-11.87,	-3.13]	4.89
Barge-Schaapveld 2002	29	8.9	6.2	30	12.5	6.3		-	-3.60	6.79,	-0.41]	5.40
Murphy 1984 - NT vs CT	11	8.23	7	24	7.75	6.5		-	- 0.48	3 [-4.27,	5.23]	4.71
Murphy 1984 - NT vs CT + placebo	11	8.23	7	17	5.76	5.26		-	2.47	[-2.07,	7.01]	4.81
Mynors-Wallis 1995	27	8.1	7.1	26	11.8	7.3		-	-3.70	7.58,	0.18]	5.11
Niklson 1997	141	13.29	8.4	106	16.08	7.9		-	-2.79	-4.85,	-0.73]	5.80
Organon 84062	15	10.3	12.1	15	8.4	9.6			1.90	[-5.92,	9.72]	3.38
Philipp 1999	105	-14.2	7.3	46	-12.1	7.4		-	-2.10	-4.64,	0.44]	5.64
Silverstone 1994	66	13.5	7.9	69	13.8	7.7		-	-0.30	[-2.93,	2.33]	5.61
Heterogeneity: $\tau^2 = 5.98$, $I^2 = 67.39\%$, H ² =	3.07						•	-1.98	g [-4.02,	0.05]	
Test of $\theta_i = \theta_j$: Q(8) = 15.62, p = 0.05												
Test of θ = 0: z = -1.91, p = 0.06												
Yes												
Emsley 2018	105	13.3	7	106	17.1	6.9			-3.80	-5.68,	-1.92]	5.85
Ferguson 1994 - dothiepin	184	12.2	7	93	15.9	7.9		-	-3.70	[-5.52,	-1.88]	5.87
Ferguson 1994 - doxepin	184	12.7	7.4	93	15.9	7.9			-3.20	-5.09,	-1.31]	5.85
Jacobson 1990	48	9.5	5.4	48	13	7.5		-	-3.50	6.11,	-0.89]	5.62
Lydiard 1997	104	-12.8	6.8	115	-8.8	7		-	-4.00	-5.83,	-2.17]	5.87
McGrath 2000	53	5.8	4.8	52	10.3	6.3		-	-4.50	6.64,	-2.36]	5.78
Organon 3-020	40	14.4	7.7	39	20.6	8.3		-	-6.20	9.73,	-2.67]	5.26
Reimherr 1990	144	-12.64	7.97	141	-8.16	7.85		-	-4.48	6.32,	-2.64]	5.86
Roth 1990	24	18.4	9.3	29	20.5	9.4		-	-2.10	7.16,	2.96]	4.57
Shipley 1981	53	9.3	10.9	23	31.6	14.9	-		-22.30	[-28.28,	-16.32]	4.15
Heterogeneity: τ^2 = 27.39, I^2 = 95.25	%, H² =	21.07						•	-5.45	6 [-8.83,	-2.06]	
Test of $\theta_i = \theta_j$: Q(9) = 39.07, p = 0.00												
Test of θ = 0: z = -3.16, p = 0.00												
Overall								•	-3.77	'[-5.91,	-1.63]	
Heterogeneity: $\tau^2 = 19.51$, $I^2 = 91.58$	%, H² =	11.87										
Test of $\theta_i = \theta_i$: Q(18) = 64.55, p = 0.0												
Test of $\theta = 0$: $z = -3.45$, $p = 0.00$												
Test of group differences: Q _b (1) = 2.9	96, p =	0.09							_			
Random-effects Sidik-Jonkman mode	d					-3	30 -20	-10 0	10			



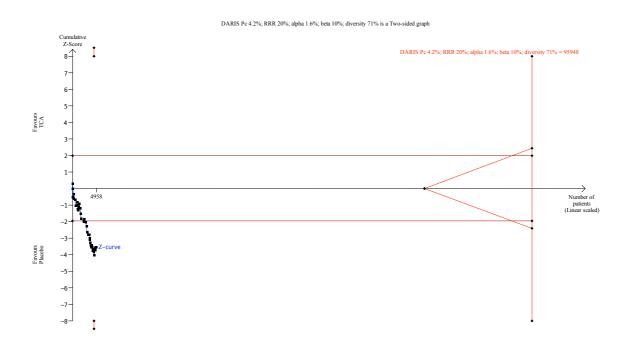
Supplementary figure S8: Subgroup analysis of age on HDRS-17.

Graph 22/05/2023, 11.02

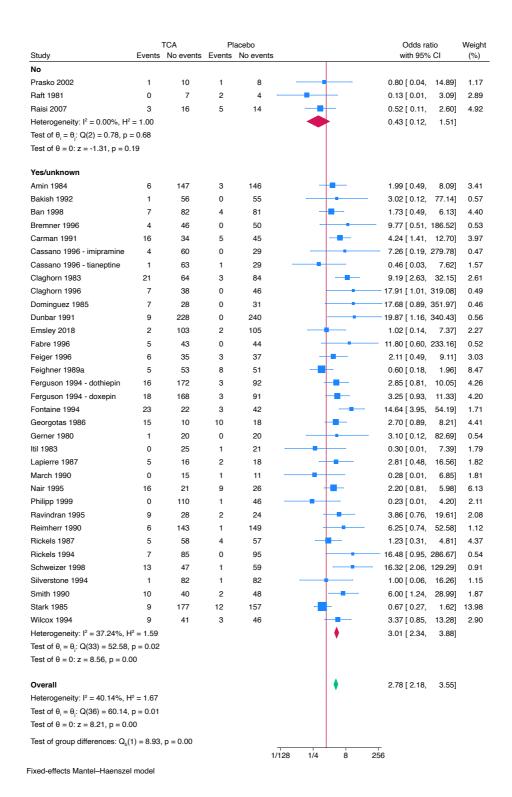
Study	N	TCA Mean	SD	N	Placeb Mean				N wi	Weight (%)			
50/older													
Emsley 2018	105	13.3	7	106	17.1	6.9			-	-3.80 [-5.68,	-1.92]	5.85
Heterogeneity: τ^2 = 0.00, I^2 = .%, H^2	= .							•		-3.80 [-5.68,	-1.92]	
Test of $\theta_i = \theta_j$: Q(0) = -0.00, p = .													
Test of θ = 0: z = -3.97, p = 0.00													
No specific age group													
Akhondzadeh 2003	15	4.5	3.9	15	12	7.7		-		-7.50 [-11.87,	-3.13]	4.89
Barge-Schaapveld 2002	29	8.9	6.2	30	12.5	6.3		-	Н	-3.60 [-6.79,	-0.41]	5.40
Ferguson 1994 - dothiepin	184	12.2	7	93	15.9	7.9			-	-3.70 [-5.52,	-1.88]	5.87
Ferguson 1994 - doxepin	184	12.7	7.4	93	15.9	7.9			ŀ	-3.20 [-5.09,	-1.31]	5.85
Jacobson 1990	48	9.5	5.4	48	13	7.5		-	H	-3.50 [-6.11,	-0.89]	5.62
Lydiard 1997	104	-12.8	6.8	115	-8.8	7			:	-4.00 [-5.83,	-2.17]	5.87
McGrath 2000	53	5.8	4.8	52	10.3	6.3				-4.50 [-6.64,	-2.36]	5.78
Murphy 1984 - NT vs CT	11	8.23	7	24	7.75	6.5		_	-	0.48 [-4.27,	5.23]	4.71
Murphy 1984 - NT vs CT + placebo	11	8.23	7	17	5.76	5.26				2.47 [-2.07,	7.01]	4.81
Mynors-Wallis 1995	27	8.1	7.1	26	11.8	7.3		-	+	-3.70 [-7.58,	0.18]	5.11
Niklson 1997	141	13.29	8.4	106	16.08	7.9			ŀ	-2.79 [-4.85,	-0.73]	5.80
Organon 3-020	40	14.4	7.7	39	20.6	8.3		-		-6.20 [-9.73,	-2.67]	5.26
Organon 84062	15	10.3	12.1	15	8.4	9.6		_		1.90 [-5.92,	9.72]	3.38
Philipp 1999	105	-14.2	7.3	46	-12.1	7.4		-	-	-2.10 [-4.64,	0.44]	5.64
Reimherr 1990	144	-12.64	7.97	141	-8.16	7.85				-4.48 [-6.32,	-2.64]	5.86
Roth 1990	24	18.4	9.3	29	20.5	9.4		-	-	-2.10 [-7.16,	2.96]	4.57
Shipley 1981	53	9.3	10.9	23	31.6	14.9	-			-22.30 [-28.28,	-16.32]	4.15
Silverstone 1994	66	13.5	7.9	69	13.8	7.7		-	-	-0.30 [-2.93,	2.33]	5.61
Heterogeneity: $\tau^2 = 20.94$, $I^2 = 91.70$	%, H² =	12.04						•		-3.77 [-6.05,	-1.49]	
Test of $\theta_i = \theta_i$: Q(17) = 64.49, p = 0.0	00												
Test of θ = 0: z = -3.24, p = 0.00													
Overall								•		-3.77 [-5.91,	-1.631	
Heterogeneity: $\tau^2 = 19.51$, $I^2 = 91.58$	%, H ² =	= 11.87											
Test of $\theta_i = \theta_i$: Q(18) = 64.55, p = 0.0													
Test of θ = 0: z = -3.45, p = 0.00													
Test of group differences: $Q_b(1) = 0.0$	00, p =	0.98							Щ,				
Random-effects Sidik-Jonkman mod	ol .					-3	30 -20	-10	0 1	0			
nancom Silbota Oluin-Johnillali IIIOU	-												



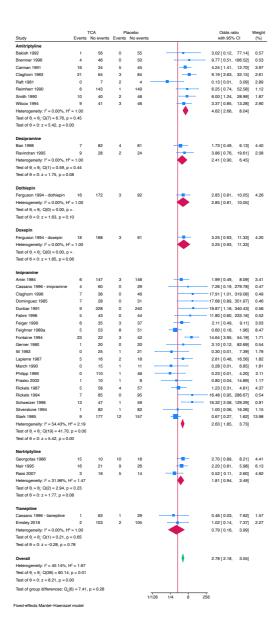
Supplementary figure S9: Trial Sequential Analysis of tricyclic antidepressants versus placebo on serious adverse events.



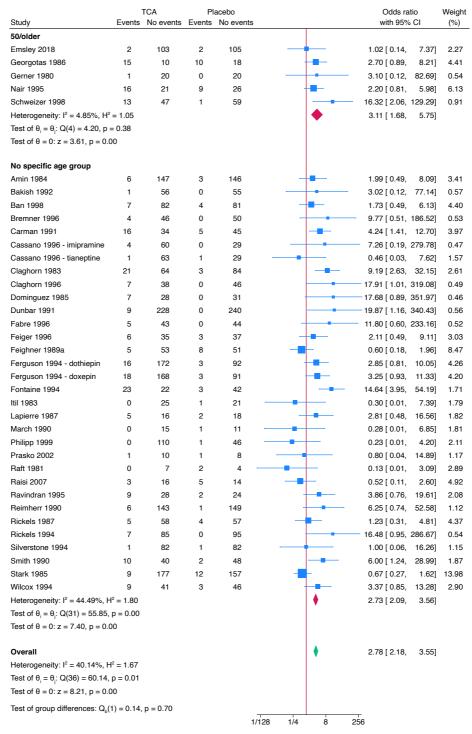
Supplementary figure S10: Subgroup analysis of risk of for-profit bias on serious adverse events.



Supplementary figure S11: Subgroup analysis of different tricyclic antidepressants on serious adverse events.



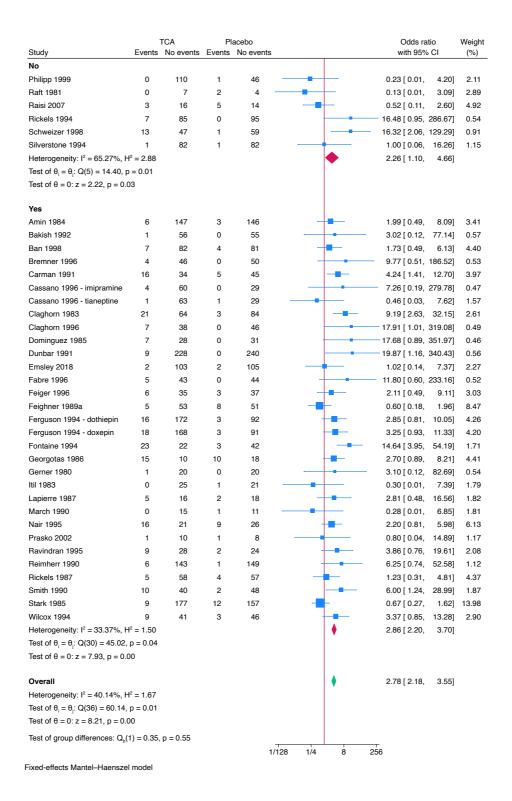
Supplementary figure S12: Subgroup analysis of age on serious adverse events.



Fixed-effects Mantel-Haenszel model

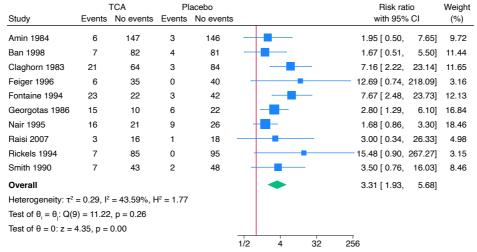


Supplementary figure S13: Subgroup analysis of placebo washout on serious adverse events.



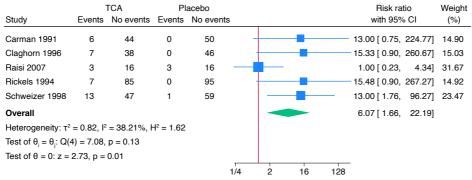


Supplementary figure S14: Meta-analysis of tricyclic antidepressants versus placebo on hypotension.



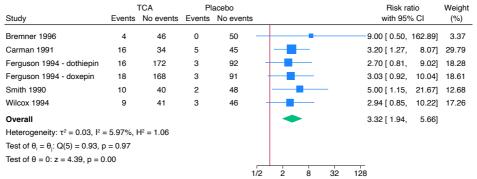


Supplementary figure S15: Meta-analysis of tricyclic antidepressants versus placebo on urinary retention.



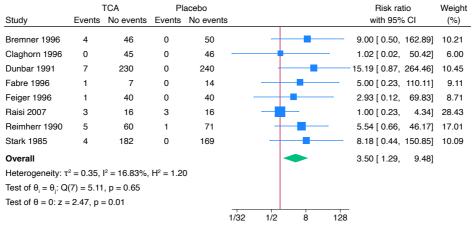


Supplementary figure S16: Meta-analysis of tricyclic antidepressants versus placebo on amblyopia.



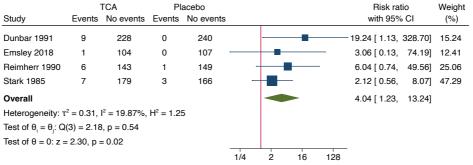


Supplementary figure S17: Meta-analysis of tricyclic antidepressants versus placebo on sexual dysfunction.



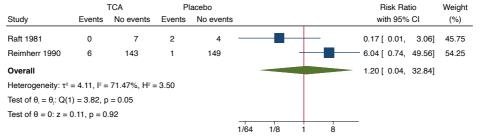


Supplementary figure S18: Meta-analysis of tricyclic antidepressants versus placebo on taste alteration.



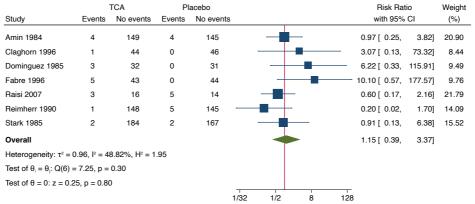


Supplementary figure S19: Meta-analysis of tricyclic antidepressants versus placebo on amnesia.



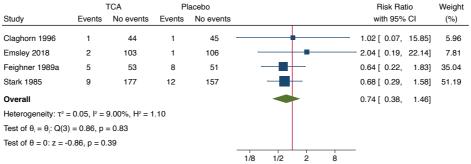


Supplementary figure S20: Meta-analysis of tricyclic antidepressants versus placebo on anorexia.



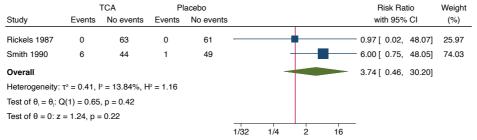


Supplementary figure S21: Meta-analysis of tricyclic antidepressants versus placebo on anxiety.



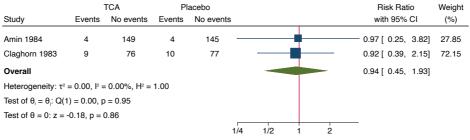


Supplementary figure S22: Meta-analysis of tricyclic antidepressants versus placebo on dyscoordination.



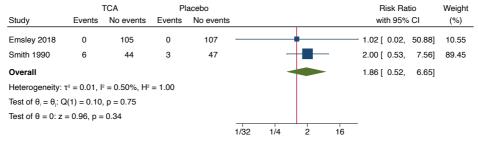


Supplementary figure S23: Meta-analysis of tricyclic antidepressants versus placebo on hyperkinesia.



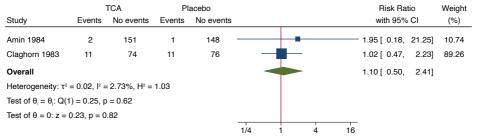


Supplementary figure S24: Meta-analysis of tricyclic antidepressants versus placebo on hypertension.



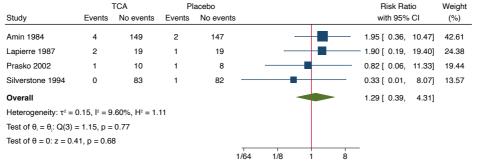


Supplementary figure S25: Meta-analysis of tricyclic antidepressants versus placebo on hypokinesia.



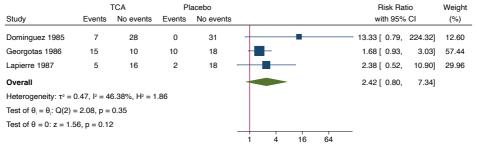


Supplementary figure S26: Meta-analysis of tricyclic antidepressants versus placebo on mania.



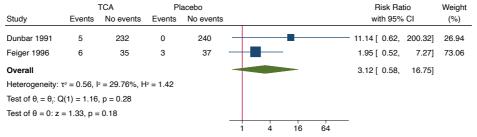


Supplementary figure S27: Meta-analysis of tricyclic antidepressants versus placebo on syncope.



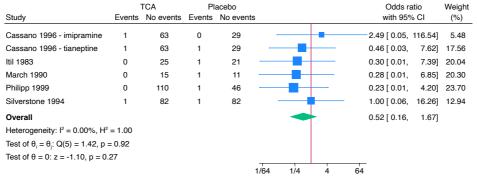


Supplementary figure S28: Meta-analysis of tricyclic antidepressants versus placebo on tinnitus.





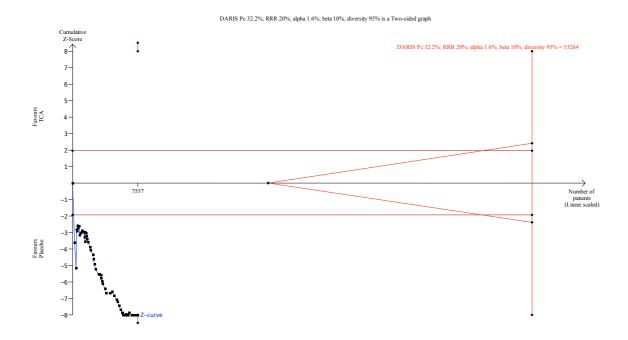
Supplementary figure S29: Meta-analysis of tricyclic antidepressants versus placebo on suicides or suicide attempts.



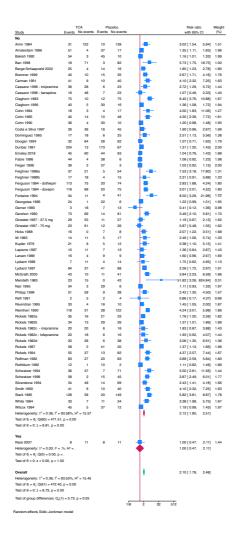
Fixed-effects Mantel-Haenszel model



Supplementary figure S30: Trial Sequential Analysis of tricyclic antidepressants versus placebo on non-serious adverse events.



Supplementary figure S31: Subgroup analysis of drug co-interventions versus no drug co-intervention on non-serious adverse events.



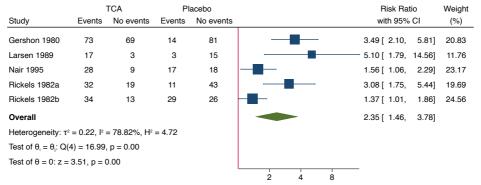
Supplementary figure S32: Meta-analysis of tricyclic antidepressants versus placebo on dry mouth.

Graph 11/08/2023, 21.06

Study		CA No events		acebo No events		Risk ratio with 95% CI	Weigh (%)
Amin 1984	31	122	10	139	-	3.02 [1.54, 5.	941 2.39
Bakish 1992	6	51	1	54		5.79 [0.72, 46.	
Ban 1998	18	71	3	82			751 1.40
Barge-Schaapveld 2002	25	4	14	16			781 3.04
Bremner 1996	40	10	15	35	-	2.67 [1.71. 4.	16] 2.95
Carman 1991	41	9	10	40	-		251 2.65
Claphorn 1983	75	10	12	75	-	6.40 [3.76, 10.	881 2.74
Claghorn 1996	29	16	5	41			95] 1.98
Cohn 1984	10	11	0	21		21.00 [1.31, 336	
Cohn 1985	40	14	10	48	-		72] 2.61
Cohn 1990	25	15	6	34	-	4.17 [1.92. 9.	05] 2.15
Costa e Silva 1997	6	56	2	59		2.95 [0.62, 14.	061 0.96
Dominguez 1985	17	18	6	25			56] 2.11
Doogan 1994	9	99	1	100		8.42 [1.09, 65.	
Dunbar 1991	164	73	38	202			921 3.27
Emsley 2018	2	103	4	103			721 0.87
Fabre 1996	32	16	6	38	-		561 2.17
Feiger 1996	2	39	0	40			601 0.32
Feighner 1989a	37	21	5	54			80] 1.97
Feighner 1989b	17	18	4	15	-		88] 1.82
Ferguson 1994 - dothiepin	113	75	20	75			291 3.05
Ferguson 1994 - doxepin	118	68	20	74			471 3.05
Fontaine 1994	34	11	4	41	T	8.50 [3.29. 21.	
Georgotas 1986	14	11	10	18		1.57 [0.86, 2.	881 2.56
Gershon 1980	63	79	8	87	-		491 2.36
Hicks 1988	16	0	7	8			511 2.75
Itil 1983	14	11	5	17	-		741 2.00
Lapierre 1987	10	11	7	13			871 2.22
Lydiard 1997	63	68	14	115	-		501 2.76
Merideth 1983	23	15	0	42		-51.82 [3.26, 824.	841 0.38
Philipp 1999	42	68	6	41	-		551 2.13
Raisi 2007	9	10	5	14	-	1.80 [0.74, 4.	38] 1.91
Reimherr 1990	118	31	28	122	_		981 3.19
Rickels 1982b	27	20	23	32		1.37 [0.92. 2.	041 3.07
Rickels 1982d	20	28	6	38		3.06 [1.35, 6.	911 2.07
Rickels 1987	47	16	17	44	- I -		11] 2.99
Rickels 1994	55	37	13	82	-		44] 2.74
Roffman 1982	83	27	20	83			841 3.04
Schweizer 1994	36	37	7	71	-		561 2.23
Schweizer 1998	58	2	15	45	- I		01] 2.97
Silverstone 1994	34	49	14	69	- I		18] 2.71
Smith 1990	41	9	10	40	-		25] 2.65
Stark 1985	128	58	20	149	- I -		871 3.01
White 1984	33	7	11	34	I = -		751 2.74
Wilcox 1994	38	12	10	39	1.		61] 2.63
Overall					T		10)
Heterogeneity: $\tau' = 0.23$. $l' =$	70.000	16 250			*	J.43 [2.07, 4.	101
Test of $\theta_i = \theta_i$: Q(44) = 97.66		n = 3.58					
Test of $\theta = 0$: $z = 13.50$, $p = 0$							

stata

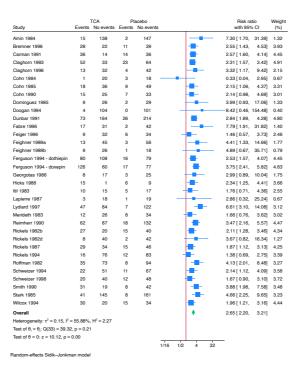
Supplementary figure S33: Meta-analysis of tricyclic antidepressants versus placebo on anticholinergic symptoms.





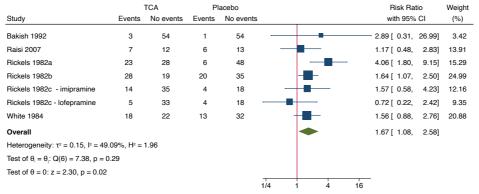
Supplementary figure S34: Meta-analysis of tricyclic antidepressants versus placebo on somnolence.

Graph 11/08/2023, 21.14



Stata

Supplementary figure S35: Meta-analysis of tricyclic antidepressants versus placebo on sedation.





Supplementary figure S36: Meta-analysis of tricyclic antidepressants versus placebo on dizziness.

Graph 11/08/2023, 21.39

		TCA	PI	acebo					Risk ra	tio	Weight
Study	Events	No events	Events	No events					with 959	6 CI	(%)
Amin 1984	15	138	4	145		-	-		3.65 [1.24,	10.75]	2.68
Bakish 1992	2	55	1	54		٠.			1.93 [0.18,	20.68]	0.86
Barge-Schaapveld 2002	21	8	14	16		-			1.55 [1.00,	2.42]	4.92
Carman 1991	28	22	10	40			-		2.80 [1.53,	5.13]	4.29
Claghorn 1983	20	65	8	79		-	-		2.56 [1.19,	5.49]	3.69
Claghorn 1996	7	38	0	46		\vdash	-		15.33 [0.90,	260.67]	0.63
Cohn 1984	2	19	1	20	_	-	_		2.00 [0.20,	20.41]	0.89
Cohn 1985	28	26	4	54		-	-		7.52 [2.82,	20.03]	2.96
Cohn 1990	8	32	3	37		-	_		2.67 [0.76,	9.33]	2.25
Doogan 1994	3	105	5	96	_	+			0.56 [0.14,	2.29]	1.94
Dunbar 1991	55	182	19	221		-	-		2.93 [1.80,	4.78]	4.74
Emsley 2018	3	102	10	97	-	+			0.31 [0.09,	1.08]	2.23
Fabre 1996	24	24	5	39		1	-		4.40 [1.84,	10.53]	3.31
Feighner 1989a	17	41	4	55			-		4.32 [1.55,	12.08]	2.82
Feighner 1989b	9	26	4	15	_	•			1.22 [0.43,	3.45]	2.80
Ferguson 1994 - dothiepin	34	154	8	87		-			2.15 [1.04,	4.45]	3.81
Ferguson 1994 - doxepin	44	142	9	85		-	-		2.47 [1.26,	4.84]	4.03
Fontaine 1994	7	38	2	43		-	_		3.50 [0.77,	15.94]	1.75
Hicks 1988	13	3	8	7		-			1.52 [0.90,	2.58]	4.59
Larsen 1989	9	11	3	15		-	_		2.70 [0.86,	8.45]	2.52
Lydiard 1997	12	119	6	123		╼	-		1.97 [0.76,	5.09]	3.06
Merideth 1983	9	29	3	39		-	_		3.32 [0.97,	11.35]	2.30
Philipp 1999	7	103	1	46	_	٠.	_		2.99 [0.38,	23.64]	1.09
Raft 1981	2	5	2	4	_	-	-		0.86 [0.17,	4.37]	1.57
Raisi 2007	4	15	4	15	_	•			1.00 [0.29,	3.43]	2.30
Reimherr 1990	47	102	15	135		-	-		3.15 [1.85,	5.39]	4.56
Rickels 1982d	3	45	0	44	_	-	•		6.43 [0.34,	121.05]	0.59
Rickels 1987	18	45	11	50		-			1.58 [0.82,	3.07]	4.07
Rickels 1994	12	80	7	88					1.77 [0.73,	4.30]	3.26
Roffman 1982	21	86	10	94		-			2.04 [1.01,	4.12]	3.91
Schweizer 1994	14	59	3	75		-	_		4.99 [1.49,	16.64]	2.36
Schweizer 1998	20	40	7	53		-	-		2.86 [1.31,	6.25]	3.62
Smith 1990	7	43	3	47	-	+•	_		2.33 [0.64,	8.51]	2.16
Stark 1985	43	143	8	161		4	-		4.88 [2.36,	10.09]	3.83
White 1984	16	24	7	38		-	-		2.57 [1.18,	5.61]	3.63
Overall						l •			2.37 [1.87,	3.01]	
Heterogeneity: $\tau^2 = 0.25$, $l^2 =$	56.58%	H ² = 2.30				T.			,		
Test of $\theta_1 = \theta_2$: Q(34) = 47.23	p = 0.07	7									
Test of $\theta = 0$: $z = 7.09$, $p = 0$						1					
					1/8	1	8	64			
Random-affacts Sidik- lonkm	an modal										

stata

Supplementary figure S37: Meta-analysis of tricyclic antidepressants versus placebo on constipation.

Graph 11/08/2023, 21.16

Amin 1984 11 142 5 144 15 142 15 144 15 15 144 15 15 144 15 15 144 15 15 144 15 15 144 15 15 144 15 15 144 15 15 144 15 15 144 15 15 144 15 15 144 15 15 144 15 15 144 15 15 144 15 15 144 15 15 144 15 15 144 15 14 144 15 15 144 15 14 14 14 14 14 15 15 14 14 14 14 14 15 15 14 14 14 14 14 15 15 14 14 14 14 15 15 14 14 14 14 15 15 14 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 14 15 15 15 14 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 14 15 15 15 14 14 14 14 15 15 15 14 14 14 14 15 15 15 14 14 14 14 15 15 15 14 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 15 15 15 14 14 14 14 15 15 15 14 14 14 14 15 15 15 14 14 14 14 15 15 15 14 14 14 14 15 15 15 14 14 14 14 14 15 15 15 14 14 14 14 14 14 15 15 15 14 14 14 14 14 14 14 15 15 14 14 14 14 14 14 14 14 14 14 14 14 14	Study		TCA No events		lacebo No events		Risk ra with 95%		Weight (%)
Bakeh 1982 2 55 1 54 54	Amin 1084	-11	140	-	144		2141076	6 021	
Ban 1989 16 73 1 84									
Bemone 1986 12 38 3 47									
Carman 1991							-	-	
Claybom 1988									
Clayborn 1996									
Cohn 1980 5 48 48 3 55	-								
Cahn 1990 14 28 6 34									
Costa e Shu 1987 10 S2 2 59 4.82 1.12 2.133 3.71 Choquinguar 1986 9 20 2 20 3 3 30 3 30 Choquinguar 1984 2 106 1 100 1.87 10.71 3 3 3 3 3 3 3 3 3									
Deminguez 1985 9 9 28 2 2 29 Deminguez 1986 1									
Deogan 1989a 2 1 100									
Durbast 1991		-		-					
Emeley 2018 0 105 2 105									
Fabre 1986 15 33 0 44									
Fager 1996 3 3 38 0 40 40									
Feginer 1989e 15 43 4 55				-					
Feghane 1980b 8 27 2 177 Feghane 1980b 182 162 10 85 1 131 10 88, 261 3 208 Ferguson 1984 - doshejan 28 148 10 84 132 1 20.0 3.68] 4.00 Fortiare 1984 21 24 6 8 39 1 3.00 1.50, 7.85] 3.35 Hotes 1988 10 6 5 10 1 1.88 10.83 2.20 Floss 1989 10 6 5 5 10 1 1.88 10.83 2.20 Floss 1980 10 15 10 0 1 1.88 10.83 2.20 Floss 1980 10 15 10 0 1 1.88 10.83 2.20 Floss 1980 1 0 10 6 5 10 1 1.88 10.83 2.20 Floss 1980 1 0 1 6 5 10 1 1.88 10.83 2.20 Floss 1980 1 0 1 6 5 10 1 1.88 10.83 2.20 Floss 1980 1 0 1 6 5 10 1 1.88 10.83 2.20 Floss 1980 1 0 1 6 5 10 1 1.88 10.83 2.20 Floss 1980 1 0 1 6 5 10 1 1.88 10.83 2.20 Floss 1980 1 1 1 6 2 127 Floss 1980 7 1 10 1 10 10 10 10 10 10 10 10 10 10 10		-		-					
Ferguson 1984 - dothespin 28 162 10 85 Ferguson 1984 - dothespin 38 148 10 84 Ferguson 1984 - dothespin 38 148 10 84 Ferguson 1984 - dothespin 38 148 10 84 Ferguson 1984 10 84 8 10 84 Ferguson 1984 11 12 12 8 12 12 12 12 12 12 12 12 12 12 12 12 12									
Ferguann 1984 - dosepin									
Fortisine 1994 21 24 6 6 39	-								
Georgicus 1986 13 12 3 25									
Hobs 1988 10 8 5 10 477 [0.24, 352] Lapiener 1987 2 19 0 20 477 [0.24, 352] Moridoh 1989 15 116 2 127 7 7 [0.24, 352] Moridoh 1989 5 33 4 8 7 [0.24, 352] Moridoh 1989 7 100 3 4 7 [0.24, 352] Maridoh 1989 7 100 3 4 7 [0.24, 352] Maridoh 1989 7 100 3 4 7 [0.24, 352] Maridoh 1989 7 100 3 4 7 [0.24, 352] Maridoh 1989 7 100 3 4 7 [0.24, 352] Maridoh 1989 1 100 [0.27, 369] Maridoh 1989 1 100 [0.27, 369] Maridoh 1989 2 117 10 140				-					
Lapiener 1987 2 19 0 20	-								
Lydand 1897 15 116 2 127						—			
Meriden 1988 5 33 4 38 - 1.38 [0.40, 4.77] 2.42 Philips 1989 7 103 3 44 - 1.00 [0.27, 3.68] 2.28 Philips 1989 7 103 3 44 - 1.00 [0.27, 3.68] 2.28 Philips 1989 7 103 3 44 - 1.00 [0.27, 3.68] 2.28 Philips 1980 3 22 117 10 140 - 2.22 [1.64, 6.31] 3.33 Philips 1982 2 46 0 44 - 2.20 [1.32, 3.69] 0.66 Philips 1987 2 1 42 7 54 - 2.20 [1.33, 6.33] 3.61 Philips 1982 2 1 86 15 89 - 2.20 [1.33, 6.28] 1.38 [0.74, 2.49] 4.13 Philips 1982 2 1 86 15 89 - 1.36 [0.74, 2.49] 4.13 Philips 1982 2 1 86 15 89 - 1.36 [0.74, 2.49] 4.13 Philips 1984 1 9 5 7 7 - 2.21 Philips 1984 1 3 70 6 77 - 2.21 Philips 1984 1 3 70 6 77 - 2.21 Philips 1984 1 3 70 6 77 - 2.21 Philips 1984 1 3 70 6 77 - 2.21 Philips 1984 1 2 8 3 42 - 4.50 [1.37, 14.81] 2.53 Philips 1984 1 2 28 3 42 - 4.50 [1.37, 14.81] 2.53 Philips 1984 1 2 28 3 42 - 4.50 [1.37, 14.81] 2.53 Philips 1984 4 7 1, pc = 0.10 Phi									
Philipp 1999 7 103 3 44 1 100 [0.27, 3.69] 2.28 Phalis 2007 8 11 8 11 1 100 [0.27, 3.69] 2.28 Phalis 2007 8 11 8 11 1 100 [0.27, 3.69] 2.28 Phalis 2007 8 11 1 8 11 1 100 [0.27, 3.69] 3.29 Phalis 200 [0.27, 3.6									
Raid 2007 8 11 8 11 1 1 100 [0.47, 2.11] 3.71 Reminder 1900 32 1177 10 140		-							
Reimberr 1990 32 117 10 140				-					
Richels 1982d 2 46 0 44 4 45 [0.23, 93.09] 0.86 Richels 1987 21 42 7 54 4 2 90 [1.33, 93.09] 0.86 Richels 1987 20 72 1 94 2 20 [1.33, 93.09] 1.31 Richels 1984 20 72 1 94 2 20 [1.33, 93.09] 1.31 Richels 1984 14 95 5 73 4 2 91 [1.37, 93.09] 1.37 Schweizer 1989 25 35 3 3 57 4 2 93 [1.37, 10.8] 3.67 Schweizer 1989 13 70 6 77 4 2.97 [1.37, 10.8] 5.43 Schweizer 1989 13 37 2 48 4 5 93.09 [1.37, 78.0] 3.62 Smith 1990 13 37 2 48 4 5 93.09 [1.37, 78.0] 3.62 White 1984 12 28 3 42 4 5 93.09 [1.37, 14.81] 2.53 Overall						T _			
Rickets 1887 21 42 7 54						-			
Richael 1994 20 72 1 94 Rolfman 1982 21 86 15 89									
Roffman 1982 21 86 15 88 13.6 [0.74, 2.49] 4.13 Schweizer 1984 14 59 5 72 1 2.17 [0.84, 5.43] 2.18 Schweizer 1989 25 35 3 57 1 1 2.17 [0.84, 5.43] 2.17 [0.						-			
Schweizer 1994 14 59 5 73 Schweizer 1994 25 35 3 57									
Schweizer 1998 25 35 3 57						-			
Silvenstone 1994 13 70 6 77						-			
Sombin 900 13 37 2 48									
Stark 1986 41 145 7 162						-	,		
White 1984 12 28 3 42				_					
Overall 1 1 Heterogeneity: 1° = 0.34, 1° = 58.58%, 1° = 2.41 Test of 0 = 0; C(38) = 49.71, p = 0.10 Test of 0 = 0: 2 = 774, p = 0.00						-			
Heterogeneily: $\tau^{i} = 0.34$, $\Gamma = 0.34$, $\Gamma = 0.589$ %, $H^{i} = 2.41$ Test of $\theta = 0.9$, $C(0.39) = 49.71$, $p = 0.10$	White 1984	12	28	3	42	-	4.50 [1.37,	14.81]	2.53
Test of θ, = θ; Q(38) = 49.71, p = 0.10 Test of θ = 0; z = 7.74, p = 0.00	Overall					•	2.81 [2.16,	3.65]	
Test of θ = 0: z = 7.74, p = 0.00	Heterogeneity: $\tau^2 = 0.34$, $I^2 =$	58.58%,	$H^2 = 2.41$						
	Test of $\theta_i = \theta_j$: Q(38) = 49.71	, p = 0.10)						
1/64 1/4 4 64	Test of $\theta = 0$: $z = 7.74$, $p = 0$.00							
						1/64 1/4 4 64	_		

stata

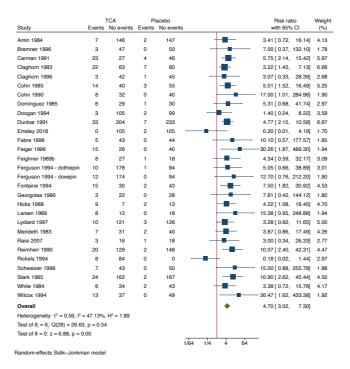
Supplementary figure S38: Meta-analysis of tricyclic antidepressants versus placebo on sweating.

		TCA	PI	acebo		Risk ra	tio	Weight
Study	Events	No events	Events	No events		with 95%	6 CI	(%)
Amin 1984	13	140	4	145		3.17 [1.06,	9.49]	6.59
Claghorn 1983	9	76	3	84		3.07 [0.86,	10.96]	5.68
Claghorn 1996	5	40	0	46	-	11.24 [0.64,	197.51]	1.77
Cohn 1984	1	20	0	21	-	3.00 [0.13,	69.70]	1.51
Cohn 1985	22	32	4	54	-	5.91 [2.18,	16.04]	7.17
Cohn 1990	11	29	0	40		— 23.00 [1.40,	377.52]	1.85
Dominguez 1985	6	29	1	30	-	5.31 [0.68,	41.74]	3.02
Dunbar 1991	45	192	7	233		6.51 [3.00,	14.14]	8.61
Emsley 2018	1	104	1	106		1.02 [0.06,	16.08]	1.89
Fabre 1996	10	38	1	43		9.17 [1.22,	68.72]	3.13
Feiger 1996	8	33	1	39		7.80 [1.02,	59.59]	3.09
Feighner 1989b	8	27	4	15	-	1.09 [0.38,	3.14]	6.79
Fontaine 1994	7	38	0	45	-	15.00 [0.88,	255.04]	1.81
Lapierre 1987	6	15	1	19	-	5.71 [0.75,	43.36]	3.10
Merideth 1983	9	29	4	38		2.49 [0.83,	7.42]	6.62
Raisi 2007	7	12	4	15	-	1.75 [0.61,	5.01]	6.86
Reimherr 1990	5	144	5	145	-	1.01 [0.30,	3.41]	5.95
Rickels 1987	13	50	2	59	■	6.29 [1.48,	26.74]	4.90
Schweizer 1998	12	48	3	57		4.00 [1.19,	13.46]	5.97
Silverstone 1994	11	72	6	77	-	1.83 [0.71,	4.73]	7.49
Stark 1985	30	156	3	166	-	9.09 [2.82,	29.23]	6.21
Overall					•	3.64 [2.41,	5.50]	
Heterogeneity: τ²	= 0.36, I ²	= 43.27%, H	² = 1.76					
Test of $\theta_i = \theta_j$: Q(2)	0) = 25.3	7, p = 0.19						
Test of $\theta = 0$: $z = 6$	6.15, p = 0	0.00						
					1/8 1 8 64	_		



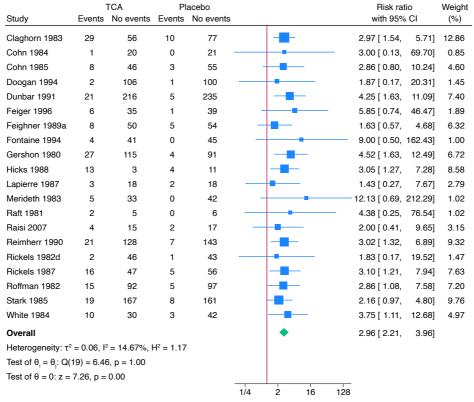
Supplementary figure S39: Meta-analysis of tricyclic antidepressants versus placebo on tremor.

Graph 22/05/2023, 12.59



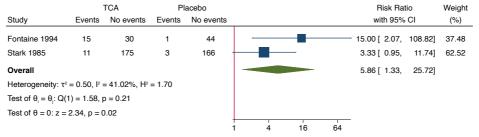
Stata

Supplementary figure S40: Meta-analysis of tricyclic antidepressants versus placebo on blurred vision.





Supplementary figure S41: Meta-analysis of tricyclic antidepressants versus placebo on flushing.



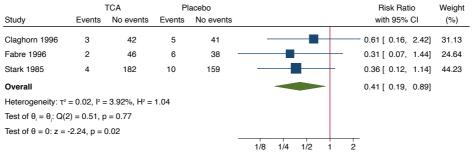


Supplementary figure S42: Meta-analysis of tricyclic antidepressants versus placebo on diarrhoea.

		TCA	PI	acebo		Risk Ratio	Weight
Study	Events	No events	Events	No events	3	with 95% CI	(%)
Claghorn 1983	3	82	9	78	-	0.34 [0.10, 1.22]	9.80
Claghorn 1996	1	44	1	45		- 1.02 [0.07, 15.85]	2.75
Cohn 1990	4	27	6	27		0.71 [0.22, 2.28]	11.03
Emsley 2018	0	105	3	104	-	0.15 [0.01, 2.78]	2.40
Fabre 1996	2	46	5	39		0.37 [0.07, 1.79]	7.03
Feiger 1996	3	38	6	34		0.49 [0.13, 1.82]	9.34
Georgotas 1986	2	23	4	24		0.56 [0.11, 2.80]	6.88
Merideth 1983	1	37	4	38		0.28 [0.03, 2.36]	4.26
Raisi 2007	1	18	3	16		0.33 [0.04, 2.93]	4.17
Reimherr 1990	8	141	15	135		0.54 [0.23, 1.23]	16.49
Rickels 1987	3	60	8	53		0.36 [0.10, 1.31]	9.72
Schweizer 1998	0	60	10	50		0.05 [0.00, 0.79]	2.62
Stark 1985	7	179	8	161	-	0.80 [0.29, 2.15]	13.52
Overall					•	0.46 [0.29, 0.74]	
Heterogeneity: τ² =	0.18, I ² = 2	24.78%, H² =	1.33				
Test of $\theta_i = \theta_j$: Q(12	2) = 5.97, p	= 0.92					
Test of $\theta = 0$: $z = -3$	3.22, p = 0.	00					
					1/256 1/32 1/4 2	_	

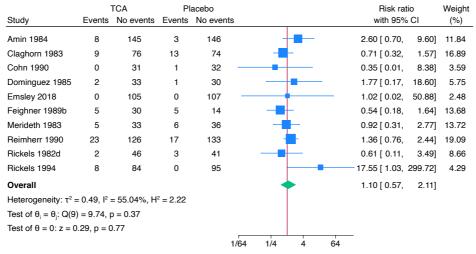


Supplementary figure S43: Meta-analysis of tricyclic antidepressants versus placebo on infection.



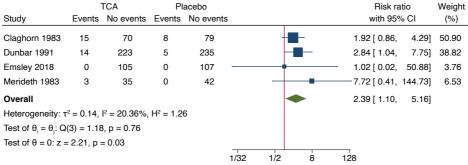


Supplementary figure S44: Meta-analysis of tricyclic antidepressants versus placebo on agitation.



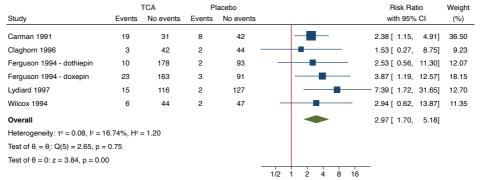


Supplementary figure S45: Meta-analysis of tricyclic antidepressants versus placebo on decreased appetite.





Supplementary figure S46: Meta-analysis of tricyclic antidepressants versus placebo on increased appetite.



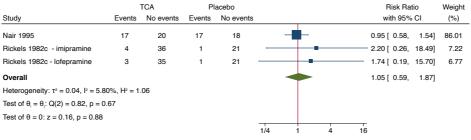


Supplementary figure S47: Meta-analysis of tricyclic antidepressants versus placebo on asthenia.

		TCA		acebo		Risk ra		Weight
Study	Events	No events	Events	No events		with 959	% CI	(%)
Bremner 1996	4	46	3	47		1.33 [0.31,	5.65]	2.80
Claghorn 1996	1	44	0	46	-	3.07 [0.13,	73.32]	0.65
Cohn 1985	5	49	3	55		1.79 [0.45,	7.13]	3.02
Cohn 1990	3	37	6	34	-	0.50 [0.13,	1.86]	3.29
Dominguez 1985	4	31	2	29		1.77 [0.35,	9.01]	2.27
Dunbar 1991	31	206	22	218	-	1.43 [0.85,	2.39]	11.46
Emsley 2018	4	101	1	106	-	4.08 [0.46,	35.87]	1.33
Fabre 1996	6	42	3	41	-	1.83 [0.49,	6.89]	3.25
Ferguson 1994 - dothiepin	19	169	5	90	-	1.92 [0.74,	4.98]	5.47
Ferguson 1994 - doxepin	23	163	5	89	-	2.32 [0.91,	5.92]	5.64
Lapierre 1987	3	18	0	20	-	- 6.68 [0.37,	121.71]	0.77
Lydiard 1997	9	122	5	124	-	1.77 [0.61,	5.15]	4.62
Raisi 2007	6	13	3	16	-	2.00 [0.58,	6.85]	3.67
Reimherr 1990	35	114	15	135		2.35 [1.34,	4.12]	10.60
Rickels 1982d	5	43	3	41		1.53 [0.39,	6.02]	3.06
Rickels 1987	7	56	3	58	-	2.26 [0.61,	8.34]	3.32
Rickels 1994	20	72	7	88		2.95 [1.31,	6.64]	6.87
Roffman 1982	15	92	3	99		4.77 [1.42,	15.98]	3.78
Schweizer 1994	15	58	10	68	-	1.60 [0.77,	3.34]	7.84
Schweizer 1998	20	40	13	47	-	1.54 [0.84,	2.80]	9.89
Stark 1985	17	169	7	162	-	2.21 [0.94,	5.19]	6.40
Overall					•	1.91 [1.47,	2.47]	
Heterogeneity: $\tau^2 = 0.08$, $I^2 = 0.08$	= 25.25%,	$H^2 = 1.34$						
Test of $\theta_i = \theta_j$: Q(20) = 11.73	, p = 0.93	3						
Test of $\theta = 0$: $z = 4.88$, $p = 0$.00							
					1/4 1 4 16 64	1		



Supplementary figure S48: Meta-analysis of tricyclic antidepressants versus placebo on CNS.



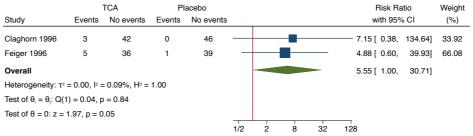


Supplementary figure S49: Meta-analysis of tricyclic antidepressants versus placebo on confusion.

		TCA	PI	acebo		Risk r	atio	Weight
Study	Events	No events	Events	No events		with 95	% CI	(%)
Claghorn 1983	16	69	5	82	-	3.28 [1.26	, 8.54]	30.73
Dominguez 1985	6	29	1	30	-	- 5.31 [0.68	, 41.74]	8.25
Dunbar 1991	5	232	0	240	-	11.14 [0.62	, 200.32]	4.34
Ferguson 1994 - dothiepin	7	181	1	94		3.54 [0.44	, 28.33]	8.10
Ferguson 1994 - doxepin	9	177	0	94	-	9.65 [0.57	, 164.07]	4.51
Hicks 1988	7	9	3	12		2.19 [0.69	, 6.94]	22.95
Raisi 2007	2	17	1	18	-	2.00 [0.20	, 20.24]	6.63
White 1984	7	33	2	43		3.94 [0.87	, 17.87]	14.49
Overall					•	3.44 [1.86	, 6.35]	
Heterogeneity: $\tau^2 = 0.08$, $I^2 =$	= 9.76%, I	$H^2 = 1.11$						
Test of $\theta_i = \theta_i$: Q(7) = 2.15, p	0.95							
Test of $\theta = 0$: $z = 3.95$, $p = 0$.00							
					1/4 2 16	128		

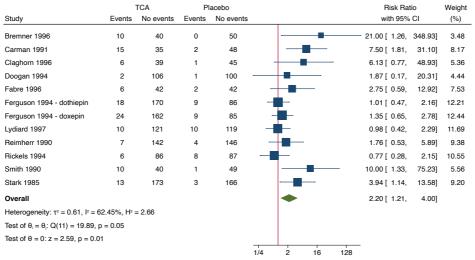


Supplementary figure S50: Meta-analysis of tricyclic antidepressants versus placebo on abnormal dreams.





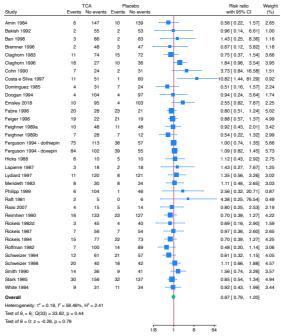
Supplementary figure S51: Meta-analysis of tricyclic antidepressants versus placebo on dyspepsia.





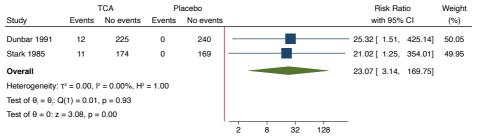
Supplementary figure S52: Meta-analysis of tricyclic antidepressants versus placebo on headache.

Graph 11/08/2023, 21.33





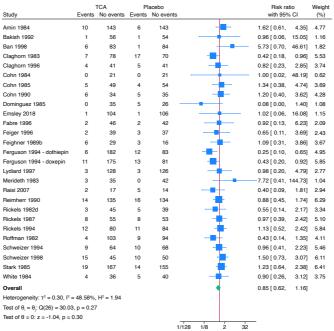
Supplementary figure S53: Meta-analysis of tricyclic antidepressants versus placebo on impaired urination.





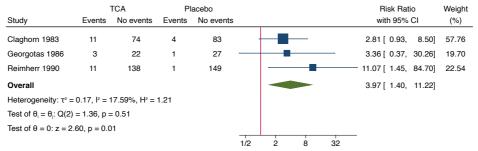
Supplementary figure S54: Meta-analysis of tricyclic antidepressants versus placebo on insomnia.

Graph 11/08/2023, 21.57





Supplementary figure S55: Meta-analysis of tricyclic antidepressants versus placebo on micturition disorder.





Supplementary figure S56: Meta-analysis of tricyclic antidepressants versus placebo on nausea.

Graph 11/08/2023, 21.26

Study	Events	TCA No events		lacebo No events		Risk rat with 95%		Weight (%)
Amin 1984	9	144	6	143		1.46 [0.53.	4.001	3.33
Barge-Schaapveld 2002	12	17	11	19		1.13 [0.60,	2.14]	4.49
Bremner 1996	3	47	1	49		3.00 [0.32,	27.87]	1.24
Claghorn 1983	5	80	7	80	_	0.73 [0.24,	2.21]	3.06
Claghorn 1996	4	41	4	42	_	1.02 [0.27,	3.84]	2.54
Cohn 1984	4	17	3	18	_	1.33 [0.34,	5.24]	2.44
Cohn 1985	12	42	3	55		4.30 [1.28,	14.40]	2.80
Cohn 1990	6	34	7	33	-	0.86 [0.32,	2.33]	3.36
Costa e Silva 1997	5	57	1	60		4.92 [0.59,	40.89]	1.35
Dominguez 1985	9	26	1	30		7.97 [1.07,	59.41]	1.46
Doogan 1994	1	107	3	98		0.31 [0.03,	2.95]	1.23
Dunbar 1991	45	192	29	211		1.57 [1.02,	2.42]	5.15
Emsley 2018	9	96	6	101	-	1.53 [0.56,	4.14]	3.36
Fabre 1996	6	42	8	36		0.69 [0.26,	1.82]	3.42
Feiger 1996	13	28	4	36	-	3.17 [1.13,	8.90]	3.26
Feighner 1989a	10	48	7	52	-	1.45 [0.59,	3.56]	3.66
Feighner 1989b	7	28	3	16	-	1.27 [0.37,	4.34]	2.75
Ferguson 1994 - dothiepin	20	168	15	80	-	0.67 [0.36,	1.26]	4.55
Ferguson 1994 - doxepin	14	172	14	80	-	0.51 [0.25,	1.02]	4.30
Hicks 1988	6	10	3	12	-	1.88 [0.57,	6.19]	2.84
Lapierre 1987	3	18	1	19		2.86 [0.32,	25.24]	1.29
Lydiard 1989	7	11	4	14	-	1.75 [0.62,	4.95]	3.24
Lydiard 1997	4	127	12	117		0.33 [0.11,	0.99]	3.06
Merideth 1983	8	30	6	36	-	1.47 [0.56,	3.86]	3.46
Philipp 1999	12	98	1	46	-	5.13 [0.69,	38.31]	1.46
Raisi 2007	1	18	2	17		0.50 [0.05,	5.06]	1.17
Reimherr 1990	16	133	13	137	-	1.24 [0.62,	2.48]	4.30
Rickels 1982d	6	42	0	44	-	11.94 [0.69,	205.95]	0.83
Rickels 1987	14	49	6	55	-	2.26 [0.93,	5.50]	3.68
Rickels 1994	15	77	12	83	-	1.29 [0.64,	2.61]	4.28
Schweizer 1994	6	67	11	67		0.58 [0.23,	1.50]	3.52
Schweizer 1998	17	43	10	50	-	1.70 [0.85,	3.40]	4.31
Stark 1985	28	158	20	149	-	1.27 [0.75,	2.17]	4.83
Overall					•	1.31 [0.99,	1.73]	
Heterogeneity: $\tau^2 = 0.35$, $I^2 =$	60.67%,	H ² = 2.54						
Test of $\theta_i = \theta_i$: Q(32) = 45.87	, p = 0.05	5						
Test of θ = 0: z = 1.88, p = 0.	.06							
					1/16 1/2 4 32	-		

STata

Supplementary figure S57: Meta-analysis of tricyclic antidepressants versus placebo on nervousness.

		TCA	PI	acebo		Risk Ra	tio	Weight
Study	Events	No events	Events	No event		with 95%	CI	(%)
Bremner 1996	5	45	1	49		5.00 [0.61,	41.28]	4.37
Claghorn 1996	4	41	1	45	-	4.09 [0.48,	35.19]	4.26
Cohn 1984	6	15	0	21	-	13.00 [0.78,	217.03]	2.91
Cohn 1985	9	45	5	53	- 	1.93 [0.69,	5.41]	8.56
Cohn 1990	4	27	1	32	-	4.26 [0.50,	36.04]	4.31
Fabre 1996	0	48	7	37		0.06 [0.00,	1.04]	2.89
Feighner 1989a	11	47	10	49	-	1.12 [0.52,	2.43]	9.83
Hicks 1988	10	6	2	13		4.69 [1.22,	17.99]	7.07
Lydiard 1997	6	125	4	125	-	1.48 [0.43,	5.11]	7.54
Rickels 1987	13	50	5	56	-	2.52 [0.95,	6.64]	8.86
Schweizer 1994	9	64	3	75		3.21 [0.90,	11.38]	7.42
Schweizer 1998	15	45	8	52	- <mark></mark>	1.88 [0.86,	4.09]	9.81
Stark 1985	24	162	14	155	-	1.56 [0.83,	2.91]	10.55
Wilcox 1994	37	13	22	27		1.65 [1.16,	2.34]	11.63
Overall					•	2.07 [1.19,	3.59]	
Heterogeneity: τ² =	0.65, I ² =	73.33%, H² =	3.75					
Test of $\theta_i = \theta_j$: Q(13	3) = 14.66,	p = 0.33						
Test of $\theta = 0$: $z = 2$.59, p = 0.0	01						
					/256 1/8 4 128	3		

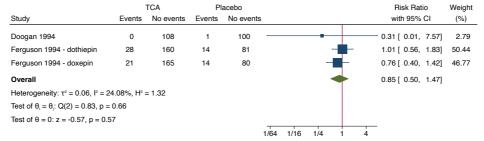


Supplementary figure S58: Meta-analysis of tricyclic antidepressants versus placebo on paraesthesia.

Study	Events	TCA No events		acebo No events	•				Risk ra		Weight
Study	Events	No events	Events	No event	5		1		willi 95	% CI	(%)
Cohn 1985	10	44	4	54					2.69 [0.89,	8.06]	20.95
Dominguez 1985	5	30	1	30		-		_	4.43 [0.55,	35.87]	10.01
Dunbar 1991	19	218	5	235			-		3.85 [1.46,	10.14]	23.09
Emsley 2018	0	105	1	106					0.34 [0.01,	8.24]	5.12
Fabre 1996	5	43	1	43		_		_	4.58 [0.56,	37.72]	9.90
Ferguson 1994 - dothiepin	1	187	1	94	_				0.51 [0.03,	7.99]	6.52
Ferguson 1994 - doxepin	7	179	0	94		_	-		7.62 [0.44,	132.01]	6.18
Raisi 2007	5	14	3	16		-			1.67 [0.46,	6.01]	18.21
Overall							•		2.55 [1.17,	5.56]	
Heterogeneity: $\tau^2 = 0.44$, $I^2 =$	38.63%,	$H^2 = 1.63$									
Test of $\theta_i = \theta_i$: Q(7) = 5.06, p	0.65										
Test of $\theta = 0$: $z = 2.35$, $p = 0$.02										
					1/64	1/4	4	64	-		

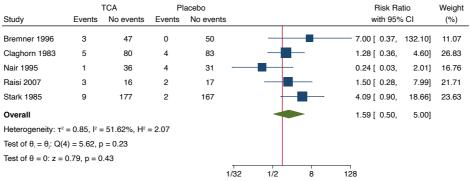


Supplementary figure S59: Meta-analysis of tricyclic antidepressants versus placebo on pharyngitis.



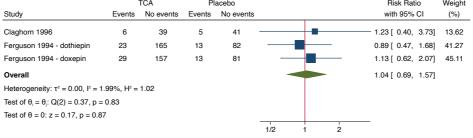


Supplementary figure S60: Meta-analysis of tricyclic antidepressants versus placebo on rash.





Supplementary figure S61: Meta-analysis of tricyclic antidepressants versus placebo on rhinitis.



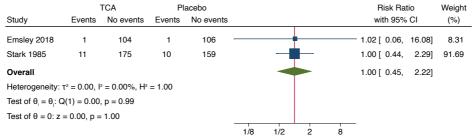


Supplementary figure S62: Meta-analysis of tricyclic antidepressants versus placebo on tachycardia.

		TCA	PI	acebo		Risk ratio	Weight
Study	Events	No events	Events	No events		with 95% CI	(%)
Bakish 1992	1	56	1	54		0.96 [0.06, 15.05]	3.77
Ban 1998	4	85	2	83		1.91 [0.36, 10.16]	8.26
Claghorn 1983	13	72	10	77	-	1.33 [0.62, 2.87]	18.45
Doogan 1994	1	107	0	101		2.81 [0.12, 68.13]	2.90
Dunbar 1991	9	228	1	239		9.11 [1.16, 71.38]	6.07
Feiger 1996	1	40	0	40	-	2.93 [0.12, 69.83]	2.93
Gerner 1980	5	16	0	20	-	10.50 [0.62, 178.40]	3.57
Hicks 1988	6	10	0	15	-	- 12.24 [0.75, 200.05 <u>]</u>	3.66
Philipp 1999	6	104	0	47		5.62 [0.32, 97.81]	3.52
Raisi 2007	3	16	3	16	_	1.00 [0.23, 4.34]	9.83
Reimherr 1990	9	140	3	147		3.02 [0.83, 10.94]	11.56
Rickels 1987	11	52	3	58		3.55 [1.04, 12.11]	12.20
Smith 1990	9	41	2	48		4.50 [1.02, 19.79]	9.72
Wilcox 1994	7	43	0	49	-	— 14.71 [0.86, 250.70]	3.57
Overall					•	2.89 [1.63, 5.13]	
Heterogeneity: τ	$r^2 = 0.31$,	$I^2 = 29.18\%$	$H^2 = 1.4$	1			
Test of $\theta_i = \theta_i$: Q	(13) = 11.	.21, p = 0.59					
Test of $\theta = 0$: z =	= 3.62, p =	= 0.00					
				1/	16 1/2 4 32	_	

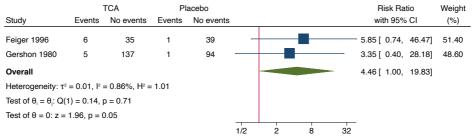


Supplementary figure S63: Meta-analysis of tricyclic antidepressants versus placebo on upper respiratory tract infection.



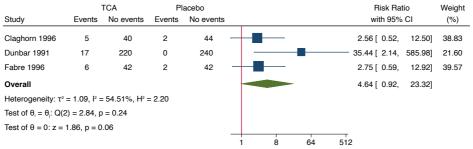


Supplementary figure S64: Meta-analysis of tricyclic antidepressants versus placebo on urinary hesitancy.



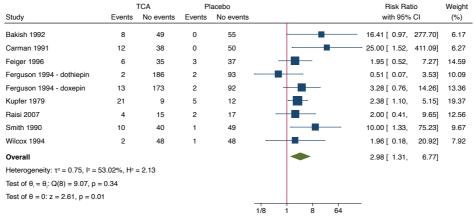


Supplementary figure S65: Meta-analysis of tricyclic antidepressants versus placebo on vasodilatation.



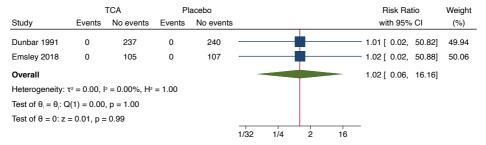


Supplementary figure S66: Meta-analysis of tricyclic antidepressants versus placebo on weight gain.





Supplementary figure S67: Meta-analysis of tricyclic antidepressants versus placebo on yawning.



Random-effects Sidik-Jonkman model



Supplementary figure S68: Meta-analysis of tricyclic antidepressants versus placebo on serious adverse events (as reported by trialists).

		TCA	PI	acebo				Odds ratio	Weight
Study	Events	No events	Events	No events				with 95% CI	(%)
Bakish 1992	1	56	1	54			•	- 0.96 [0.06, 15.81] 13.68
Emsley 2018	2	103	2	105		-	•	1.02 [0.14, 7.37] 26.58
Fabre 1996	0	48	2	42				0.18 [0.01, 3.75] 34.99
Philipp 1999	0	110	1	46	-			0.23 [0.01, 4.20] 24.75
Overall								0.52 [0.15, 1.77]
Heterogeneity	$I^2 = 0.00$	%, H ² = 1.00)						
Test of $\theta_i = \theta_i$:	Q(3) = 1.	40, p = 0.71							
Test of $\theta = 0$:	z = -1.04,	p = 0.30							
					1/64	1/8	1 8		



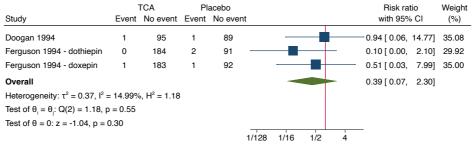
Supplementary figure S69: Meta-analysis of tricyclic antidepressants versus placebo on MADRS, BDI, and HDRS-6.

		TCA			Placeb	0		Hedges's g	Weight
Study	N	Mean	SD	N	Mean	SD		with 95% CI	(%)
Cassano 1996 - imipramine	47	14.3	8.2	18	16.1	6.4	-	-0.23 [-0.77, 0.31]	5.02
Cassano 1996 - tianeptine	46	11.8	8.1	18	16.1	6.4	-	-0.55 [-1.10, -0.01]	4.95
Costa e Silva 1997	62	16.3	11.5	61	22	13.8	-	-0.45 [-0.80, -0.09	6.57
Ferguson 1994 - dothiepin	184	14	9.7	93	19.2	10.8		-0.51 [-0.77, -0.26	7.46
Ferguson 1994 - doxepin	184	14.4	9.8	93	19.2	10.8	-	-0.47 [-0.72, -0.22]	7.47
Georgotas 1982	15	8.8	7	18	12.7	8.1	-	-0.50 [-1.18, 0.18]	4.02
Ginestet 1997 - 37.5 mg	58	11	8.4	23	9	5.3	-	0.26 [-0.22, 0.74]	5.49
Ginestet 1997 - 75 mg	67	11.4	9.8	23	9	5.3	-	0.27 [-0.20, 0.74]	5.56
Jacobson 1990	48	-6.21	3.88	48	-3.83	4.59	-	-0.56 [-0.96, -0.15	6.14
Lydiard 1997	128	-6.9	6.8	124	-4.7	6.8		-0.32 [-0.57, -0.07]	7.50
Murphy 1984 - NT vs CT	11	10.09	10.61	24	10.88	8.93	_	-0.08 [-0.78, 0.62	3.90
Murphy 1984 - NT vs CT + placebo	11	10.09	10.61	17	8.18	8.43		0.20 [-0.54, 0.94]	3.66
Mynors-Wallis 1995	27	11.9	10.5	26	16.8	12.4	-	-0.42 [-0.96, 0.12]	5.03
Niklson 1997	141	18.05	11.5	106	22.45	10.9		-0.39 [-0.64, -0.14	7.45
Organon 3-020	40	-4.5	3.78	39	-2.13	2.93	_	-0.69 [-1.14, -0.24	5.75
Prasko 2002	11	18.4	12	9	8.7	5.4		0.96 [0.07, 1.86	2.88
Roth 1990	24	18.2	9.6	29	21	10.4	-	-0.27 [-0.81, 0.26	5.04
Schweizer 1994	40	-17.7	7.9	57	-11.9	10	-	-0.63 [-1.04, -0.22]	6.09
Overall							•	-0.30 [-0.49, -0.12	
Heterogeneity: $\tau^2 = 0.10$, $I^2 = 71.67\%$, H ² =	3.53							
Test of $\theta_i = \theta_j$: Q(17) = 32.57, p = 0.0	1								
Test of $\theta = 0$: $z = -3.17$, $p = 0.00$									
							-1 0	1 2	

Random-effects Sidik-Jonkman model



Supplementary figure S70: Meta-analysis of tricyclic antidepressants versus placebo on suicidal ideation.



Random-effects Sidik-Jonkman model



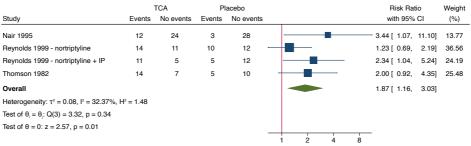
Supplementary figure S71: Meta-analysis of tricyclic antidepressants versus placebo on response.

Graph 22/05/2023, 11.41

		TCA		acebo		Risk ra		Weight
Study	Events	No events	Events	No events		with 959	% CI	(%)
Amin 1984	44	60	35	65	-	1.21 [0.85,	1.71]	3.34
Amsterdam 1986	28	14	8	13	-	1.75 [0.97,	3.14]	2.06
Bakish 1992	34	23	20	35		1.64 [1.09,	2.47]	2.96
Ban 1998	43	46	30	55	= -	1.37 [0.96,	1.96]	3.27
Bremner 1996	27	20	15	33		1.84 [1.13,	2.99]	2.53
Claghorn 1983	49	36	35	50	-	1.40 [1.02,	1.91]	3.58
Cohn 1985	22	30	12	45		2.01 [1.11,	3.64]	2.02
Cohn 1996	18	5	14	17		1.73 [1.11,	2.70]	2.76
Costa e Silva 1997	36	26	25	36	-	1.42 [0.98,	2.05]	3.21
Dominguez 1985	13	6	11	10	-	1.31 [0.78,	2.17]	2.41
Doogan 1994	46	50	40	50		1.08 [0.79,	1.47]	3.59
Edwards 1983	3	13	8	11		0.45 [0.14,	1.40]	0.77
Emsley 2018	49	56	36	70	-	1.37 [0.98,	1.92]	3.43
Escobar 1980	14	1	6	6		1.87 [1.04,	3.34]	2.08
Fabre 1996	22	21	15	31	-	1.57 [0.94,	2.61]	2.42
Feighner 1980	5	13	0	10	-	6.37 [0.39,	104.54]	0.15
Ferguson 1994 - dothiepin	95	89	32	61	-	1.50 [1.10,	2.05]	3.57
Ferguson 1994 - doxepin	88	96	32	61		1.39 [1.01,	1.91]	3.54
Fontaine 1994	22	23	14	31	-	1.57 [0.93,	2.66]	2.32
Gelenberg 1990a	6	2	6	8		1.75 [0.85,	3.61]	1.57
Gershon 1980	57	43	18	54	-8-	2.28 [1.48,	3.52]	2.81
Jacobson 1990	31	17	21	27	 -	1.48 [1.01,	2.17]	3.12
Katz 2004	16	10	6	14		2.05 [0.98,	4.28]	1.54
Lapierre 1987	3	2	1	5		3.60 [0.52,	24.73]	0.30
Lydiard 1997	55	49	43	72		1.41 [1.05,	1.91]	3.67
Mann 1981	2	7	1	8		2.00 [0.22,	18.33]	0.23
Merideth 1983	10	24	17	21		0.66 [0.35,	1.23]	1.89
Nair 1995	11	24	6	25		1.62 [0.68,	3.87]	1.20
Organon 3-020	14	26	5	34		2.73 [1.09,	6.86]	1.10
Organon 84062	13	2	13	2	•	1.00 [0.76,	1.32]	3.79
Philipp 1999	70	35	29	17	•	1.06 [0.82,	1.37]	3.93
Reimherr 1990	86	36	49	79		1.84 [1.44,	2.36]	4.01
Reynolds 1999 - nortriptyline	14	11	10	12	-	1.23 [0.69,	2.19]	2.11
Reynolds 1999 - nortriptyline + IP	11	5	5	12		2.34 [1.04,	5.24]	1.35
Rickels 1987	26	11	14	23		1.86 [1.17,	2.95]	2.65
Schweizer 1994	24	16	27	30	-	1.27 [0.87,	1.84]	3.18
Schweizer 1998	37	23	21	37		1.70 [1.15,	2.53]	3.04
Smith 1990	24	11	12	13	 -	1.43 [0.90,	2.28]	2.64
Stark 1985	85	46	39	63	-	1.70 [1.29,	2.24]	3.82
Wilcox 1994	20	9	8	11	-	1.64 [0.92,	2.93]	2.08
Overall						1.48 [1.33,	1.65]	
Heterogeneity: τ ² = 0.06, I ² = 57.13	%, H ² = 2.	33						
Test of θ _i = θ _i : Q(39) = 50.01, p = 0.								
Test of θ = 0: z = 7.04, p = 0.00								

stata

Supplementary figure S72: Meta-analysis of tricyclic antidepressants versus placebo on remission.



Random-effects Sidik-Jonkman model



Supplementary figure S73: Meta-analysis of tricyclic antidepressants versus placebo on HDRS-17 (sensitivity analysis).

		TCA			Placeb	0				N.	lean diff		Weight
Study	N	Mean	SD	N	Mean	SD				wi	th 95% (CI	(%)
Akhondzadeh 2003	15	4.5	3.9	15	12	7.7		-		-7.50 [-11.87,	-3.13]	1.85
Barge-Schaapveld 2002	29	8.9	6.2	30	12.5	6.3		-		-3.60 [-6.79,	-0.41]	3.47
Emsley 2018	105	13.3	7	106	17.1	6.9		-		-3.80 [-5.68,	-1.92]	10.04
Ferguson 1994 - dothiepin	184	12.2	7	93	15.9	7.9				-3.70 [-5.52,	-1.88]	10.61
Ferguson 1994 - doxepin	184	12.7	7.4	93	15.9	7.9		-		-3.20 [-5.09,	-1.31]	9.90
Jacobson 1990	48	9.5	5.4	48	13	7.5		-		-3.50 [-6.11,	-0.89]	5.16
Lydiard 1997	104	-12.8	6.8	115	-8.8	7				-4.00 [-5.83,	-2.17]	10.52
McGrath 2000	53	5.8	4.8	52	10.3	6.3		-		-4.50 [-6.64,	-2.36]	7.71
Murphy 1984 - NT vs CT	11	8.23	7	24	7.75	6.5		_	-	0.48 [-4.27,	5.23]	1.56
Murphy 1984 - NT vs CT + placebo	11	8.23	7	17	5.76	5.26		-	-	2.47 [-2.07,	7.01]	1.71
Mynors-Wallis 1995	27	8.1	7.1	26	11.8	7.3		-	-	-3.70 [-7.58,	0.18]	2.35
Niklson 1997	141	13.29	8.4	106	16.08	7.9		-		-2.79 [-4.85,	-0.73]	8.29
Organon 3-020	40	14.4	7.7	39	20.6	8.3		-		-6.20 [-9.73,	-2.67]	2.83
Organon 84062	15	10.3	12.1	15	8.4	9.6			-	1.90 [-5.92,	9.72]	0.58
Philipp 1999	105	-14.2	7.3	46	-12.1	7.4		-	+	-2.10 [-4.64,	0.44]	5.47
Reimherr 1990	144	-12.64	7.97	141	-8.16	7.85		-		-4.48 [-6.32,	-2.64]	10.46
Roth 1990	24	18.4	9.3	29	20.5	9.4		-	-	-2.10 [-7.16,	2.96]	1.38
Shipley 1981	53	9.3	10.9	23	31.6	14.9	_			-22.30 [-28.28,	-16.32]	0.99
Silverstone 1994	66	13.5	7.9	69	13.8	7.7		-	-	-0.30 [-2.93,	2.33]	5.10
Overall								•		-3.58 [-4.18,	-2.99]	
Heterogeneity: $I^2 = 72.11\%$, $H^2 = 3.59$	9												
Test of $\theta_i = \theta_i$: Q(18) = 64.55, p = 0.0	0												
Test of $\theta = 0$: $z = -11.82$, $p = 0.00$													
						-3	0 -20	-10 (0 10)			
Fixed-effects inverse-variance model													



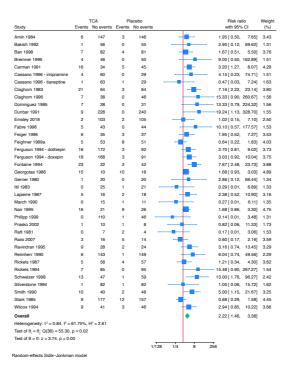
Supplementary figure S74: Meta-analysis of tricyclic antidepressants versus placebo on HDRS-17 (standardised mean difference).

		TCA			Placeb)			Cohen's d	Weight
Study	N	Mean	SD	N	Mean	SD			with 95% CI	(%)
Akhondzadeh 2003	15	4.5	3.9	15	12	7.7			-1.23 [-2.01, -0.45]	3.59
Barge-Schaapveld 2002	29	8.9	6.2	30	12.5	6.3	-		-0.58 [-1.10, -0.06]	4.90
Emsley 2018	105	13.3	7	106	17.1	6.9			-0.55 [-0.82, -0.27]	6.21
Ferguson 1994 - dothiepin	184	12.2	7	93	15.9	7.9			-0.51 [-0.76, -0.25]	6.31
Ferguson 1994 - doxepin	184	12.7	7.4	93	15.9	7.9	-		-0.42 [-0.67, -0.17]	6.32
Jacobson 1990	48	9.5	5.4	48	13	7.5	-		-0.54 [-0.94, -0.13]	5.53
Lydiard 1997	104	-12.8	6.8	115	-8.8	7	-		-0.58 [-0.85, -0.31]	6.23
McGrath 2000	53	5.8	4.8	52	10.3	6.3	-		-0.80 [-1.20, -0.41]	5.58
Murphy 1984 - NT vs CT	11	8.23	7	24	7.75	6.5	-	_	0.07 [-0.64, 0.79]	3.90
Murphy 1984 - NT vs CT + placebo	11	8.23	7	17	5.76	5.26			- 0.41 [-0.35, 1.18]	3.66
Mynors-Wallis 1995	27	8.1	7.1	26	11.8	7.3	-	-	-0.51 [-1.06, 0.03]	4.76
Niklson 1997	141	13.29	8.4	106	16.08	7.9	-		-0.34 [-0.59, -0.09]	6.31
Organon 3-020	40	14.4	7.7	39	20.6	8.3	-		-0.77 [-1.23, -0.32]	5.25
Organon 84062	15	10.3	12.1	15	8.4	9.6		_	0.17 [-0.54, 0.89]	3.89
Philipp 1999	105	-14.2	7.3	46	-12.1	7.4	-	-	-0.29 [-0.63, 0.06]	5.85
Reimherr 1990	144	-12.64	7.97	141	-8.16	7.85	-		-0.57 [-0.80, -0.33]	6.38
Roth 1990	24	18.4	9.3	29	20.5	9.4		_	-0.22 [-0.77, 0.32]	4.78
Shipley 1981	53	9.3	10.9	23	31.6	14.9	_		-1.82 [-2.39, -1.26]	4.64
Silverstone 1994	66	13.5	7.9	69	13.8	7.7	-	-	-0.04 [-0.38, 0.30]	5.90
Overall							•		-0.49 [-0.70, -0.27]	
Heterogeneity: $\tau^2 = 0.17$, $I^2 = 83.11\%$, H ² = \$	5.92								
Test of $\theta_i = \theta_i$: Q(18) = 51.31, p = 0.0	0									
Test of $\theta = 0$: $z = -4.49$, $p = 0.00$										
							-2 -1 () 1	_	
andom-effects Sidik-Jonkman mode	el									



Supplementary figure S75: Meta-analysis of tricyclic antidepressants versus placebo on serious adverse events (sensitivity analysis).

Graph 16/08/2023, 08.56



STata

Supplementary figure S76: Meta-analysis of tricyclic antidepressants versus placebo on urinary retention (sensitivity analysis).

		TCA	PI	acebo		Risk ratio	Weight
Study	Events	No events	Events	No events		with 95% CI	(%)
Carman 1991	6	44	0	50	-	— 13.00 [0.75, 224.77]	9.11
Claghorn 1996	7	38	0	46	-	15.33 [0.90, 260.67]	9.01
Raisi 2007	3	16	3	16	_	1.00 [0.23, 4.34]	54.68
Rickels 1994	7	85	0	95	-	15.48 [0.90, 267.27]	8.97
Schweizer 1998	13	47	1	59		13.00 [1.76, 96.27]	18.23
Overall					•	6.87 [2.86, 16.49]	
Heterogeneity: I ²	= 48.84%	, H ² = 1.95					
Test of $\theta_i = \theta_j$: Q(4) = 7.82,	p = 0.10					
Test of $\theta = 0$: $z =$	4.32, p =	0.00					
					/4 2 16 12	28	

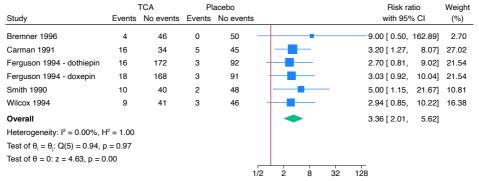


Supplementary figure S77: Meta-analysis of tricyclic antidepressants versus placebo on hypotension (sensitivity analysis).

Study	Events	TCA No events		acebo		Risk ratio with 95% CI	Weight
Olddy	LVCIIIO	140 CVCIII3	LVCIII	INO EVEIRS		WIGH 35 /0 OI	(%)
Amin 1984	6	147	3	146		1.95 [0.50, 7.65]	9.50
Ban 1998	7	82	4	81		1.67 [0.51, 5.50]	12.79
Claghorn 1983	21	64	3	84		7.16 [2.22, 23.14]	9.26
Feiger 1996	6	35	0	40	-	12.69 [0.74, 218.09]	1.58
Fontaine 1994	23	22	3	42		7.67 [2.48, 23.73]	9.37
Georgotas 1986	15	10	6	22	-	2.80 [1.29, 6.10]	17.69
Nair 1995	16	21	9	26	+	1.68 [0.86, 3.30]	28.90
Raisi 2007	3	16	1	18	-	3.00 [0.34, 26.33]	3.12
Rickels 1994	7	85	0	95	-	15.48 [0.90, 267.27]	1.54
Smith 1990	7	43	2	48	-	3.50 [0.76, 16.03]	6.25
Overall					•	3.51 [2.45, 5.04]	
Heterogeneity: I2	= 26.42%	, H ² = 1.36					
Test of $\theta_i = \theta_i$: Q(9)	9) = 12.23	3, p = 0.20					
Test of $\theta = 0$: $z =$	6.81, p =	0.00					
					1/2 4 32	256	

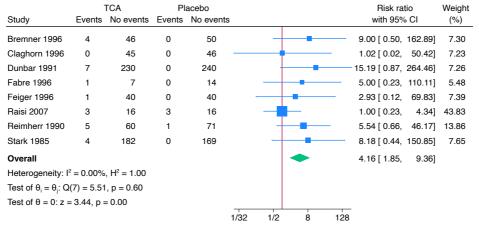


Supplementary figure S78: Meta-analysis of tricyclic antidepressants versus placebo on amblyopia (sensitivity analysis).



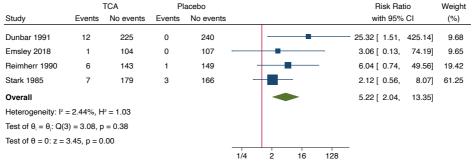


Supplementary figure S79: Meta-analysis of tricyclic antidepressants versus placebo on sexual dysfunction (sensitivity analysis).



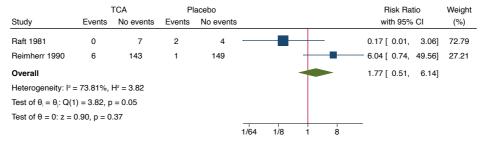


Supplementary figure S80: Meta-analysis of tricyclic antidepressants versus placebo on taste alteration (sensitivity analysis).



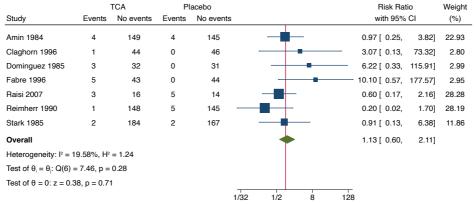


Supplementary figure S81: Meta-analysis of tricyclic antidepressants versus placebo on amnesia (sensitivity analysis).



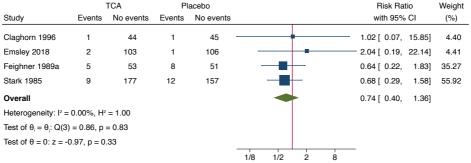


Supplementary figure S82: Meta-analysis of tricyclic antidepressants versus placebo on anorexia (sensitivity analysis).



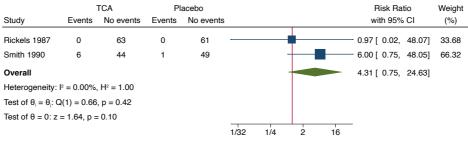


Supplementary figure S83: Meta-analysis of tricyclic antidepressants versus placebo on anxiety (sensitivity analysis).



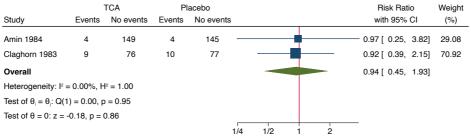


Supplementary figure S84: Meta-analysis of tricyclic antidepressants versus placebo on dyscoordination (sensitivity analysis).



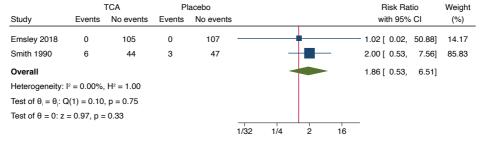


Supplementary figure S85: Meta-analysis of tricyclic antidepressants versus placebo on hyperkinesia (sensitivity analysis).



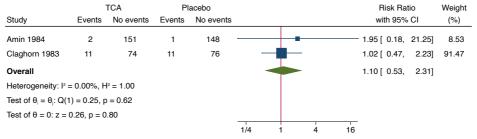


Supplementary figure S86: Meta-analysis of tricyclic antidepressants versus placebo on hypertension (sensitivity analysis).



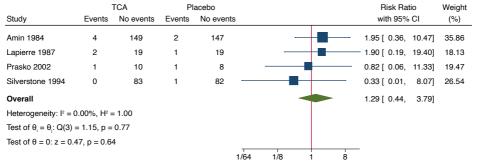


Supplementary figure S87: Meta-analysis of tricyclic antidepressants versus placebo on hypokinesia (sensitivity analysis).



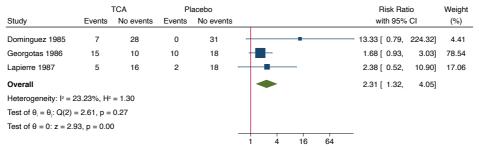


Supplementary figure S88: Meta-analysis of tricyclic antidepressants versus placebo on mania (sensitivity analysis).



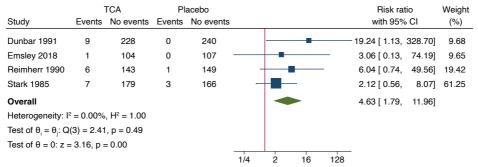


Supplementary figure S89: Meta-analysis of tricyclic antidepressants versus placebo on syncope (sensitivity analysis).



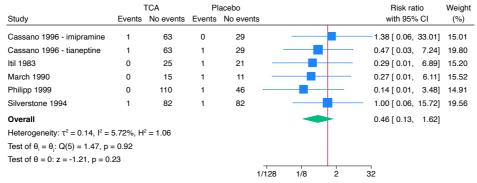


Supplementary figure S90: Meta-analysis of tricyclic antidepressants versus placebo on tinnitus (sensitivity analysis).





Supplementary figure S91: Meta-analysis of tricyclic antidepressants versus placebo on suicides or suicide attempts (sensitivity analysis).



Random-effects Sidik-Jonkman model



Supplementary figure S92: Meta-analysis of tricyclic antidepressants versus placebo on non-serious adverse events (sensitivity analysis).

Study		TCA No events		acebo No events		Risk ratio with 95% 0		Weig (%
Amin 1984	31	122	10	139		3.02 [1.54,	5.94]	0.8
Amsterdam 1986	51	4	37	17		1.35 [1.11,	1.651	3.1
Bakish 1992	54	3	45	10		1.16 [1.01,	1.331	3.8
Ban 1998	18	71	3	82			18.751	0.2
Barge-Schaapveld 2002	25	4	14	16		1.85 [1.23,	2.781	1.1
Bremner 1996	40	10	15	35		2.67 [1.71.	4.161	1.2
Carman 1991	41	9	10	40		4.10 [2.32,	7.25]	0.8
Cassano 1996 - imipramine	36	28	6	23		2.72 [1.29,	5.72	0.7
Cassano 1996 - tianeptine	16	48	7	23		1.07 [0.49,	2.33]	0.8
Claghorn 1983	75	10	12	75			10.881	1.0
Claghorn 1996	40	5	30	16		1.36 [1.08,	1.721	25
Cohn 1984	18	3	4	17			11.061	0.0
John 1985	40	14	10	48		4.30 [2.39,	7.721	0.0
Cohn 1990	36	4	30	10		1.20 [0.98,	1.481	2.5
Costa e Silva 1997		36					2.671	
	26		16	45	-	1.60 [0.96,		1.3
Dominguez 1985	17	18	6	25		2.51 [1.13,	5.56]	0.5
Doogan 1994	32	64	28	62	<u> </u>	1.07 [0.71,	1.63]	2.4
Ounbar 1991	224	13	173	67		1.31 [1.20,	1.43]	14.4
Emsley 2018	45	60	44	63	+	1.04 [0.76,	1.43]	3.6
abre 1996	44	4	38	6	•	1.06 [0.92,	1.23]	3.0
Feiger 1996	39	2	37	3	•	1.03 [0.92,	1.15]	3.
eighner 1989a	37	21	5	54		7.53 [3.18,	17.80]	0.4
eighner 1989b	17	18	4	15	-	2.31 [0.91,	5.88]	0.4
Ferguson 1994 - dothiepin	113	75	20	74	444	2.83 [1.88,	4.24]	2.
erguson 1994 - doxepin	118	68	20	75		3.01 [2.01,	4.52]	2.
Fontaine 1994	34	11	4	41		8.50 [3.29,	21.981	0.
Georgotas 1986	24	1	22	6		1.22 [0.99.	1.511	1.7
Gemer 1980	3	18	7	13		0.41 [0.12,	1.361	0.6
Gershon 1980	73	69	14	81		3.49 [2.10,	5.811	1.4
3inestet 1997 - 37.5 mg	29	55	11	27		1.19 [0.67,	2.131	1.1
Sinestet 1997 - 75 mg	23	61	12	26		0.87 [0.48,	1.55]	1.3
licks 1988	16	0	7	26 8	Т.	2.07 [1.22,	3.51]	0.6
11CKS 1988 til 1983	14	11	5	17	-		5.741	0.
					-	2.46 [1.06,		
Cupter 1979	21	9	5	12	-	2.38 [1.10,	5.15]	0.5
apierre 1987	10	11	7	13	-	1.36 [0.64,	2.87]	0.6
Larsen 1989	16	4	9	9	-	1.60 [0.96,	2.67]	0.8
Lydiard 1989	7	11	4	14	+	1.75 [0.62,	4.95]	0.3
Lydiard 1997	94	37	41	88	-	2.26 [1.72,	2.97]	3.4
McGrath 2000	43	10	11	41		3.84 [2.23,	6.59]	0.9
Merideth 1983	23	15	0	42		51.82 [3.26, 8	24.84]	0.0
Nair 1995	34	3	29	6	•	1.11 [0.93,	1.33]	2.5
Philipp 1999	51	59	9	38		2.42 [1.30,	4.50]	1.0
Raft 1981	2	5	2	4		0.86 [0.17,	4.37]	0.
Raisi 2007	8	11	8	11	-	1.00 [0.47,	2.111	0.6
Ravindran 1995	33	4	16	10	-	1.45 [1.05.	2.001	1.5
Reimherr 1990	118	31	28	122	_	4.24 [3.01,	5.98]	2:
Rickels 1982a	35	16	21	33		1.76 [1.20,	2.59]	1.
Rickels 1982h	34	13	29	26		1.37 [1.01,	1.86]	2
Rickels 1982c - imipramine	20	20	6	16	T.	1.83 [0.87,	3.881	0
			-		_		,	-
Rickels 1982c - Iofepramine	20	18	6	16		1.93 [0.92,	4.07]	0.
Rickels 1982d	20	28	6	38		3.06 [1.35,	6.91]	0.
Rickels 1987	58	5	41	20	•	1.37 [1.13,	1.66]	3.
Rickels 1994	55	37	13	82		4.37 [2.57,	7.44]	1.
Roffman 1982	83	27	20	83	-	3.89 [2.59,	5.84]	1.7
Rothblum 1982	12	1	10	2	+	1.11 [0.82,	1.49]	0.5
Schweizer 1994	36	37	7	71		5.50 [2.61,	11.56]	0.
Schweizer 1998	58	2	15	45	-8-	3.87 [2.49,	6.01]	1.3
Silverstone 1994	34	49	14	69		2.43 [1.41,	4.18]	1.
Smith 1990	41	9	10	40		4.10 [2.32,	7.25]	0.5
Stark 1985	128	58	20	149	1 +	5.82 [3.81,	8.871	1.
White 1984	33	7	11	34		3.38 [1.98,	5.75]	0.
White 1984 Vilcox 1994	33 45	5	37	12	L		1.431	3.
	45		31	12	Γ.	1.19 [0.99,		3.
Overall						2.05 [1.95,	2.16]	
Heterogeneity: I ² = 92.55%, H ²	= 13.43							
Test of θ _i = θ _i : Q(61) = 819.28,	p = 0.00							

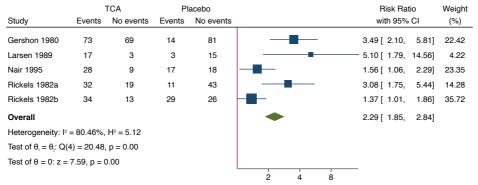
Supplementary figure S93: Meta-analysis of tricyclic antidepressants versus placebo on dry mouth (sensitivity analysis).

Graph 11/08/2023, 21.08

	т	CA	PI	acebo		Risk rat	in	Weight
Study				No events		with 95%		(%)
Amin 1984	31	122	10	139		3.02 [1.54,	5.94]	2.15
Bakish 1992	6	51	1	54		5.79 [0.72,	46.54]	0.22
Ban 1998	18	71	3	82		5.73 [1.75,	18.75]	0.65
Barge-Schaapveld 2002	25	4	14	16	-	1.85 [1.23,	2.78]	2.92
Bremner 1996	40	10	15	35	-	2.67 [1.71,	4.16]	3.18
Carman 1991	41	9	10	40		4.10 [2.32,	7.25]	2.12
Claghorn 1983	75	10	12	75	-	6.40 [3.76,	10.88]	2.51
Claghorn 1996	29	16	5	41		5.93 [2.52,	13.95]	1.05
Cohn 1984	10	11	0	21		21.00 [1.31,	336.75]	0.11
Cohn 1985	40	14	10	48		4.30 [2.39,	7.72]	2.04
Cohn 1990	25	15	6	34		4.17 [1.92,	9.05]	1.27
Costa e Silva 1997	6	56	2	59		2.95 [0.62,	14.06]	0.43
Dominguez 1985	17	18	6	25		2.51 [1.13,	5.56]	1.35
Doogan 1994	9	99	1	100		8.42 [1.09,	65.26]	0.22
Dunbar 1991	164	73	38	202		4.37 [3.23,	5.92]	8.01
Emsley 2018	2	103	4	103		0.51 [0.10,	2.72]	0.84
Fabre 1996	32	16	6	38		4.89 [2.26,	10.56]	1.33
Feiger 1996	2	39	0	40		4.88 [0.24,	98.60]	0.11
Feighner 1989a	37	21	5	54		7.53 [3.18,	17.80]	1.05
Feighner 1989b	17	18	4	15	-	2.31 [0.91,	5.88]	1.10
Ferguson 1994 - dothiepin	113	75	20	75	-	2.86 [1.90,	4.29]	5.63
Ferguson 1994 - doxepin	118	68	20	74	-	2.98 [1.99,	4.47]	5.63
Fontaine 1994	34	11	4	41		8.50 [3.29,	21.98]	0.85
Georgotas 1986	14	11	10	18	-	1.57 [0.86,	2.88]	2.00
Gershon 1980	63	79	8	87		5.27 [2.65,	10.49]	2.03
Hicks 1988	16	0	7	8	-=-	2.07 [1.22,	3.51]	1.64
Itil 1983	14	11	5	17		2.46 [1.06,	5.74]	1.13
Lapierre 1987	10	11	7	13		1.36 [0.64,	2.87]	1.52
Lydiard 1997	63	68	14	115	-	4.43 [2.62,	7.50]	2.99
Merideth 1983	23	15	0	42		51.82 [3.26,	824.84]	0.10
Philipp 1999	42	68	6	41		2.99 [1.37,	6.55]	1.78
Raisi 2007	9	10	5	14	-	1.80 [0.74,	4.38]	1.06
Reimherr 1990	118	31	28	122	-	4.24 [3.01,	5.98]	5.92
Rickels 1982b	27	20	23	32	-	1.37 [0.92,	2.04]	4.49
Rickels 1982d	20	28	6	38		3.06 [1.35,	6.91]	1.33
Rickels 1987	47	16	17	44	-	2.68 [1.74,	4.11]	3.66
Rickels 1994	55	37	13	82	-	4.37 [2.57,	7.44]	2.71
Roffman 1982	83	27	20	83	-	3.89 [2.59,	5.84]	4.38
Schweizer 1994	36	37	7	71		5.50 [2.61,	11.56]	1.44
Schweizer 1998	58	2	15	45	-	3.87 [2.49,	6.01]	3.18
Silverstone 1994	34	49	14	69		2.43 [1.41,	4.18]	2.97
Smith 1990	41	9	10	40	-	4.10 [2.32,	7.25]	2.12
Stark 1985	128	58	20	149	-	5.82 [3.81,	8.87]	4.44
White 1984	33	7	11	34	-	3.38 [1.98,	5.75]	2.20
Wilcox 1994	38	12	10	39		3.72 [2.10,	6.61]	2.14
Overall					+	3.71 [3.40,	4.05]	
Heterogeneity: $l^2 = 57.25\%$,	$H^2 = 2.34$							
Test of $\theta_i = \theta_j$: Q(44) = 102.5	33, p = 0.00)						
Test of θ = 0: z = 29.23, p =	0.00					_		
					1/8 2 32 5	12		
Circuit affects Mandal Manager								



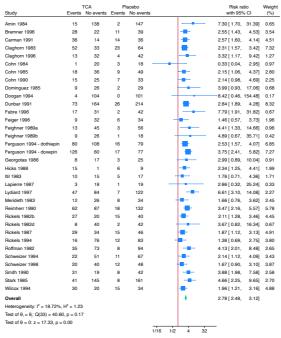
Supplementary figure S94: Meta-analysis of tricyclic antidepressants versus placebo on anticholinergic symptoms (sensitivity analysis).





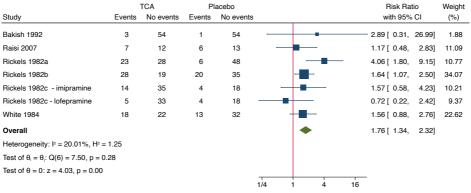
Supplementary figure S95: Meta-analysis of tricyclic antidepressants versus placebo on somnolence (sensitivity analysis).

Graph 11/08/2023, 21.15





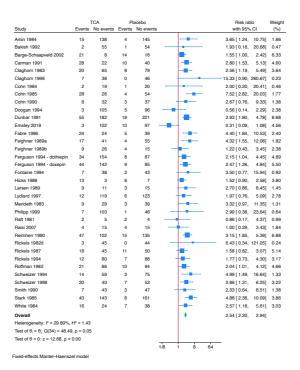
Supplementary figure S96: Meta-analysis of tricyclic antidepressants versus placebo on sedation (sensitivity analysis).





Supplementary figure S97: Meta-analysis of tricyclic antidepressants versus placebo on dizziness (sensitivity analysis).

Graph 11/08/2023, 21.43



Stata

Supplementary figure S98: Meta-analysis of tricyclic antidepressants versus placebo on constipation (sensitivity analysis).

Graph 11/08/2023, 21.20

Study	Events	TCA No events		lacebo No events			Risk ra with 95%		Weight (%)
Amin 1984	11	142	5	144			2.14 [0.76,	6.021	2.45
Bakish 1992	2	55	1	54			1.93 [0.18,		0.49
Ban 1998	16	73	1	84			15.28 [2.07,		0.49
Bremner 1996	12	38	3	47			4.00 [1.20,	13.321	1.45
Carman 1991	18	32	6	44		-	3.00 [1.20,	6.931	2.90
Claghorn 1983	32	53	15	72		-	2.18 [1.28,	3.731	7.17
Claghorn 1996	10	35	4	42		-	2.56 [0.86,	7.561	1.91
Cohn 1985	5	49	3	55	_	-	1.79 [0.45,	7.13]	1.40
Cohn 1990	14	26	6	34		-	2.33 [1.00,	5.46]	2.90
Costa e Silva 1997	10	52	2	59			4.92 [1.12,	21.53]	0.98
Dominguez 1985	9	26	2	29		-	3.99 [0.93,	17.06]	1.03
Doogan 1994	2	106	1	100	_	-	1.87 [0.17,	20.31]	0.50
Dunbar 1991	76	161	29	211			2.65 [1.80,	3.91]	13.94
Emsley 2018	0	105	2	105	_	_	0.20 [0.01,	4.19]	1.20
Fabre 1996	15	33	0	44			28.47 [1.75,	462.09]	0.25
Feiger 1996	3	38	0	40	_	-	6.83 [0.36,	128.20]	0.24
Feighner 1989a	15	43	4	55		-	3.81 [1.35,	10.81]	1.92
Feighner 1989b	8	27	2	17	-	-	2.17 [0.51,	9.21]	1.25
Ferguson 1994 - dothiepin	26	162	10	85	-	-	1.31 [0.66,	2.61]	6.43
Ferguson 1994 - doxepin	38	148	10	84		-	1.92 [1.00,	3.68]	6.43
Fontaine 1994	21	24	6	39			3.50 [1.56,	7.85]	2.90
Georgotas 1986	13	12	3	25			4.85 [1.56,	15.08]	1.37
Hicks 1988	10	6	5	10		-	1.88 [0.83,	4.22]	2.50
Lapierre 1987	2	19	0	20	_	-	4.77 [0.24,		0.25
Lydiard 1997	15	116	2	127		-	7.39 [1.72,	31.65]	0.97
Merideth 1983	5	33	4	38	_	-	1.38 [0.40,	4.77]	1.84
Philipp 1999	7	103	3	44	_		1.00 [0.27,	3.69]	2.03
Raisi 2007	8	11	8	11	-		1.00 [0.47,	2.11]	3.87
Reimherr 1990	32	117	10	140		-	3.22 [1.64,	6.31]	4.82
Rickels 1982d	2	46	0	44	_		4.59 [0.23,		0.25
Rickels 1987	21	42	7	54		-	2.90 [1.33,	6.33]	3.44
Rickels 1994 Roffman 1982	20 21	72 86	1 15	94 89			20.65 [2.83,	2,491	0.48 7.36
	14					-	1.36 [0.74,		
Schweizer 1994 Schweizer 1998	25	59 35	5	73 57			2.99 [1.13, 8.33 [2.66,	7.89]	2.34 1.45
Silverstone 1994	13	70	6	77			2.17 [0.86,	5.431	2.90
Smith 1990	13	37	2	48			6.50 [1.55.		0.97
Stark 1985	41	145	7	162			5.32 [2.45,	11.54]	3.55
White 1984	12	28	3	42			4.50 [1.37,	14.811	1.37
		20				1.7			1.01
Overall	10 407					1.1	2.86 [2.47,	3.32]	
Heterogeneity: I ² = 26.84%,									
Test of θ _i = θ _j : Q(38) = 51.94									
Test of θ = 0: z = 13.94, p =	0.00				1/64 1/4	4 64	_		
					1/04 1/4	4 64			
Fixed-effects Mantel-Haensz									

Stata

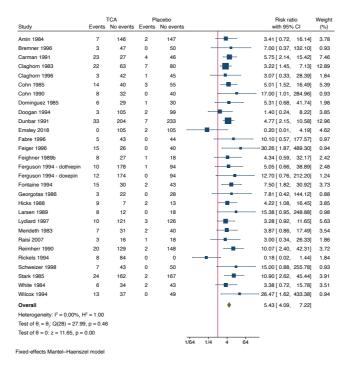
Supplementary figure S99: Meta-analysis of tricyclic antidepressants versus placebo on sweating (sensitivity analysis).

	-	TCA	Pl	acebo		Risk ra	tio	Weight
Study	Events	No events	Events	No events		with 95%	6 CI	(%)
Amin 1984	13	140	4	145	-	3.17 [1.06,	9.49]	7.10
Claghorn 1983	9	76	3	84	-	3.07 [0.86,	10.96]	5.19
Claghorn 1996	5	40	0	46	-	11.24 [0.64,	197.51]	0.87
Cohn 1984	1	20	0	21	-	3.00 [0.13,	69.70]	0.88
Cohn 1985	22	32	4	54	-	5.91 [2.18,	16.04]	6.75
Cohn 1990	11	29	0	40		- 23.00 [1.40,	377.52]	0.88
Dominguez 1985	6	29	1	30	-	5.31 [0.68,	41.74]	1.86
Dunbar 1991	45	192	7	233	-	6.51 [3.00,	14.14]	12.18
Emsley 2018	1	104	1	106		1.02 [0.06,	16.08]	1.73
Fabre 1996	10	38	1	43		9.17 [1.22,	68.72]	1.83
Feiger 1996	8	33	1	39	-	7.80 [1.02,	59.59]	1.77
Feighner 1989b	8	27	4	15	-	1.09 [0.38,	3.14]	9.08
Fontaine 1994	7	38	0	45	-	15.00 [0.88,	255.04]	0.88
Lapierre 1987	6	15	1	19	-	5.71 [0.75,	43.36]	1.79
Merideth 1983	9	29	4	38	-	2.49 [0.83,	7.42]	6.65
Raisi 2007	7	12	4	15	+	1.75 [0.61,	5.01]	7.01
Reimherr 1990	5	144	5	145	-	1.01 [0.30,	3.41]	8.73
Rickels 1987	13	50	2	59		6.29 [1.48,	26.74]	3.56
Schweizer 1998	12	48	3	57	-	4.00 [1.19,	13.46]	5.25
Silverstone 1994	11	72	6	77	+	1.83 [0.71,	4.73]	10.51
Stark 1985	30	156	3	166	-	9.09 [2.82,	29.23]	5.51
Overall					•	4.16 [3.15,	5.50]	
Heterogeneity: I ² =	25.25%,	$H^2 = 1.34$						
Test of $\theta_i = \theta_j$: Q(2)	0) = 26.76	6, p = 0.14						
Test of $\theta = 0$: $z = 1$	0.02, p =	0.00						
					1/8 1 8 64	_		



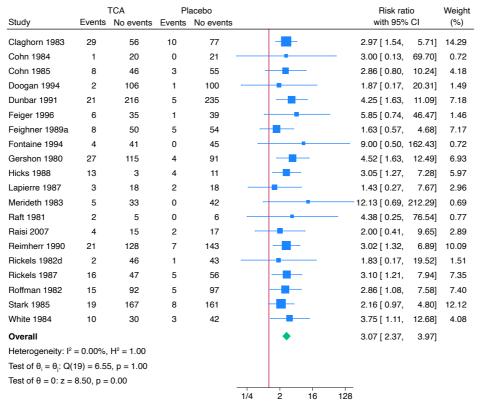
Supplementary figure S100: Meta-analysis of tricyclic antidepressants versus placebo on tremor (sensitivity analysis).

Graph 22/05/2023, 12.59



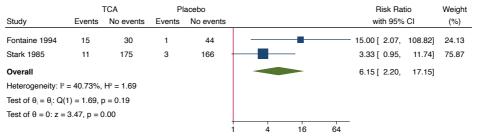


Supplementary figure S101: Meta-analysis of tricyclic antidepressants versus placebo on blurred vision (sensitivity analysis).





Supplementary figure S102: Meta-analysis of tricyclic antidepressants versus placebo on flushing (sensitivity analysis).



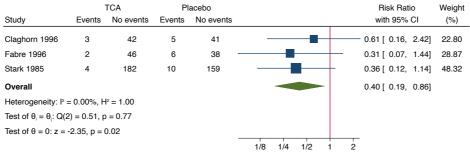


Supplementary figure S103: Meta-analysis of tricyclic antidepressants versus placebo on diarrhoea (sensitivity analysis).

		TCA	PI	acebo					Risk Ra	tio	Weight
Study	Events	No events	Events	No event	s				with 95%	CI	(%)
Claghorn 1983	3	82	9	78				_	0.34 [0.10,	1.22]	10.72
Claghorn 1996	1	44	1	45		_			- 1.02 [0.07,	15.85]	1.19
Cohn 1990	4	27	6	27			_	_	0.71 [0.22,	2.28]	7.00
Emsley 2018	0	105	3	104			-		0.15 [0.01,	2.78]	4.18
Fabre 1996	2	46	5	39		-	_	_	0.37 [0.07,	1.79]	6.29
Feiger 1996	3	38	6	34				_	0.49 [0.13,	1.82]	7.32
Georgotas 1986	2	23	4	24			_		0.56 [0.11,	2.80]	4.55
Merideth 1983	1	37	4	38			_		0.28 [0.03,	2.36]	4.58
Raisi 2007	1	18	3	16		_	_		0.33 [0.04,	2.93]	3.61
Reimherr 1990	8	141	15	135				-	0.54 [0.23,	1.23]	18.01
Rickels 1987	3	60	8	53				-	0.36 [0.10,	1.31]	9.80
Schweizer 1998	0	60	10	50	-				0.05 [0.00,	0.79]	12.65
Stark 1985	7	179	8	161			-	-	0.80 [0.29,	2.15]	10.10
Overall							•		0.43 [0.30,	0.63]	
Heterogeneity: I ² =	0.00%, H ²	= 1.00									
Test of $\theta_i = \theta_i$: Q(12	e) = 6.27, p	= 0.90									
Test of $\theta = 0$: $z = -4$	I.34, p = 0.	00									
					1/256	1/32	1/4	2	_		

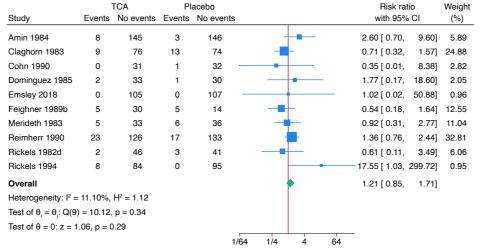


Supplementary figure S104: Meta-analysis of tricyclic antidepressants versus placebo on infection (sensitivity analysis).





Supplementary figure S105: Meta-analysis of tricyclic antidepressants versus placebo on agitation (sensitivity analysis).



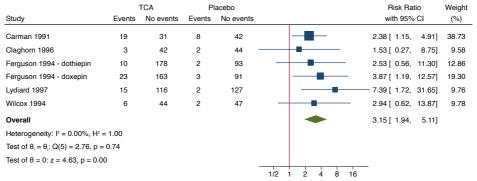


Supplementary figure S106: Meta-analysis of tricyclic antidepressants versus placebo on decreased appetite (sensitivity analysis).

		TCA	PI	acebo				Risk ratio	Weight
Study	Events	No events	Events	No events	\$			with 95% CI	(%)
Claghorn 1983	15	70	8	79		-	-	1.92 [0.86, 4.29]	57.10
Dunbar 1991	14	223	5	235		\vdash	_	2.84 [1.04, 7.75]	35.88
Emsley 2018	0	105	0	107		+		1.02 [0.02, 50.88]	3.58
Merideth 1983	3	35	0	42		-	-	7.72 [0.41, 144.73]	3.43
Overall						<	•	2.41 [1.32, 4.40]	
Heterogeneity: I	$^{2} = 0.00\%$	$H^2 = 1.00$							
Test of $\theta_i = \theta_i$: Q	(3) = 1.20), p = 0.75							
Test of $\theta = 0$: z =	= 2.88, p =	= 0.00							
					1/32	1/2	8	128	



Supplementary figure S107: Meta-analysis of tricyclic antidepressants versus placebo on increased appetite (sensitivity analysis).



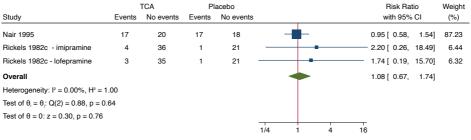


Supplementary figure S108: Meta-analysis of tricyclic antidepressants versus placebo on asthenia (sensitivity analysis).

		TCA		acebo		Risk ra		Weight
Study	Events	No events	Events	No events		with 959	% CI	(%)
Bremner 1996	4	46	3	47		1.33 [0.31,	5.65]	2.43
Claghorn 1996	1	44	0	46	-	3.07 [0.13,	73.32]	0.40
Cohn 1985	5	49	3	55		1.79 [0.45,	7.13]	2.34
Cohn 1990	3	37	6	34	-	0.50 [0.13,	1.86]	4.86
Dominguez 1985	4	31	2	29		1.77 [0.35,	9.01]	1.72
Dunbar 1991	31	206	22	218	-	1.43 [0.85,	2.39]	17.71
Emsley 2018	4	101	1	106		4.08 [0.46,	35.87]	0.80
Fabre 1996	6	42	3	41		1.83 [0.49,	6.89]	2.54
Ferguson 1994 - dothiepin	19	169	5	90	-	1.92 [0.74,	4.98]	5.38
Ferguson 1994 - doxepin	23	163	5	89	-	2.32 [0.91,	5.92]	5.38
Lapierre 1987	3	18	0	20	-	6.68 [0.37,	121.71]	0.41
Lydiard 1997	9	122	5	124	-	1.77 [0.61,	5.15]	4.08
Raisi 2007	6	13	3	16		2.00 [0.58,	6.85]	2.43
Reimherr 1990	35	114	15	135	-	2.35 [1.34,	4.12]	12.11
Rickels 1982d	5	43	3	41		1.53 [0.39,	6.02]	2.54
Rickels 1987	7	56	3	58		2.26 [0.61,	8.34]	2.47
Rickels 1994	20	72	7	88	-	2.95 [1.31,	6.64]	5.58
Roffman 1982	15	92	3	99		4.77 [1.42,	15.98]	2.49
Schweizer 1994	15	58	10	68	-	1.60 [0.77,	3.34]	7.83
Schweizer 1998	20	40	13	47	-	1.54 [0.84,	2.80]	10.53
Stark 1985	17	169	7	162	-	2.21 [0.94,	5.19]	5.94
Overall					•	1.93 [1.57,	2.37]	
Heterogeneity: I ² = 0.00%, F	$H^2 = 1.00$					•	·	
Test of $\theta_i = \theta_i$: Q(20) = 11.80), p = 0.92	<u>!</u>						
Test of $\theta = 0$: $z = 6.25$, $p = 0$	0.00							
					1/4 1 4 16 64	 \$		

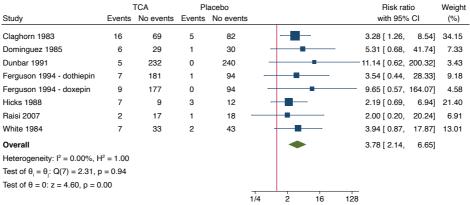


Supplementary figure S109: Meta-analysis of tricyclic antidepressants versus placebo on CNS (sensitivity analysis).



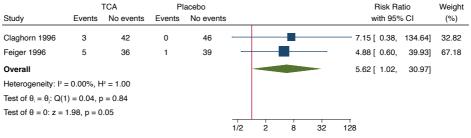


Supplementary figure S110: Meta-analysis of tricyclic antidepressants versus placebo on confusion (sensitivity analysis).



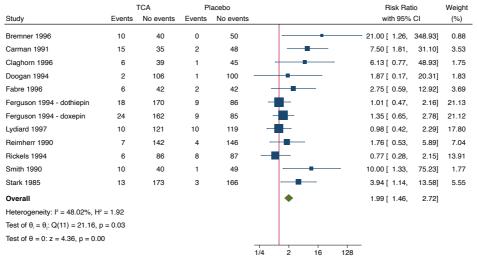


Supplementary figure S111: Meta-analysis of tricyclic antidepressants versus placebo on abnormal dreams (sensitivity analysis).





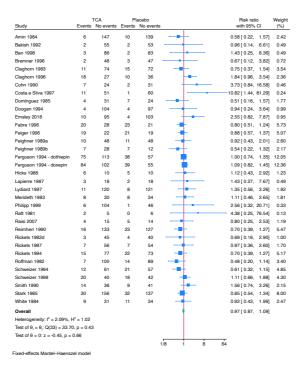
Supplementary figure S112: Meta-analysis of tricyclic antidepressants versus placebo on dyspepsia (sensitivity analysis).





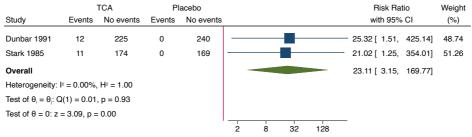
Supplementary figure S113: Meta-analysis of tricyclic antidepressants versus placebo on headache (sensitivity analysis).

Graph 11/08/2023, 21.34



Stata

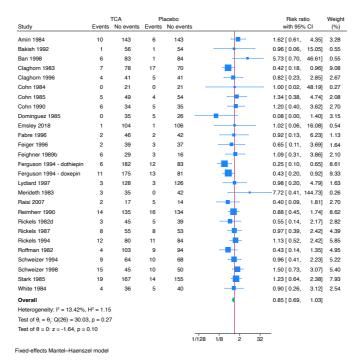
Supplementary figure S114: Meta-analysis of tricyclic antidepressants versus placebo on impaired urination (sensitivity analysis).





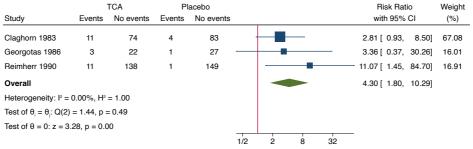
Supplementary figure S115: Meta-analysis of tricyclic antidepressants versus placebo on insomnia (sensitivity analysis).

Graph 11/08/2023, 21.58



stata

Supplementary figure S116: Meta-analysis of tricyclic antidepressants versus placebo on micturition disorder (sensitivity analysis).





Supplementary figure S117: Meta-analysis of tricyclic antidepressants versus placebo on nausea (sensitivity analysis).

Graph 11/08/2023, 21.29

Study	Events	TCA No events		acebo No events		Risk ratio with 95% CI	Weigh (%)
Amin 1984	9	144	6	143		1.46 [0.53, 4.00]	
Barge-Schaapveld 2002	12	17	11	19	-	1.13 [0.60, 2.14]	4.40
Bremner 1996	3	47	1	49		3.00 [0.32. 27.87	
Claghorn 1983	5	80	7	80		0.73 [0.24, 2.21]	2.82
Claghorn 1996	4	41	4	42		1.02 [0.27, 3.84]	1.61
Cohn 1984	4	17	3	18		1.33 [0.34, 5.24]	1.22
Cohn 1985	12	42	3	55		4.30 [1.28. 14.40]	1.18
Cohn 1990	6	34	7	33	_	0.86 [0.32, 2.33]	2.85
Costa e Silva 1997	5	57	1	60		4.92 [0.59, 40.89]	0.41
Dominguez 1985	9	26	1	30		7.97 [1.07, 59.41]	0.43
Doogan 1994	1	107	3	98		0.31 [0.03, 2.95]	1.26
Dunbar 1991	45	192	29	211		1.57 [1.02, 2.42]	11.73
Emsley 2018	9	96	6	101		1.53 [0.56, 4.14	2.42
Fabre 1996	6	42	8	36		0.69 [0.26, 1.82]	3.40
Feiger 1996	13	28	4	36		3.17 [1.13, 8.90]	1.65
Feighner 1989a	10	48	7	52		1.45 [0.59, 3.56]	2.83
Feighner 1989b	7	28	3	16		1.27 [0.37, 4.34]	1.58
Ferguson 1994 - dothiepin	20	168	15	80	-	0.67 [0.36, 1.26]	8.11
Ferguson 1994 - doxepin	14	172	14	80	-	0.51 [0.25, 1.02]	7.57
Hicks 1988	6	10	3	12		1.88 [0.57, 6.19]	1.26
Lapierre 1987	3	18	1	19		2.86 [0.32, 25.24]	0.42
Lydiard 1989	7	11	4	14		1.75 [0.62, 4.95]	1.63
Lydiard 1997	4	127	12	117	-	0.33 [0.11, 0.99]	4.92
Merideth 1983	8	30	6	36	-	1.47 [0.56, 3.86]	2.32
Philipp 1999	12	98	1	46	-	5.13 [0.69, 38.31]	0.57
Raisi 2007	1	18	2	17		0.50 [0.05, 5.06]	0.81
Reimherr 1990	16	133	13	137	-	1.24 [0.62, 2.48]	5.27
Rickels 1982d	6	42	0	44	-	11.94 [0.69, 205.95]	0.21
Rickels 1987	14	49	6	55	-	2.26 [0.93, 5.50]	2.48
Rickels 1994	15	77	12	83	-	1.29 [0.64, 2.61]	4.81
Schweizer 1994	6	67	11	67		0.58 [0.23, 1.50]	4.3
Schweizer 1998	17	43	10	50	-	1.70 [0.85, 3.40]	4.07
Stark 1985	28	158	20	149	+	1.27 [0.75, 2.17]	8.53
Overall					•	1.30 [1.11, 1.51]	
Heterogeneity: I ² = 30.57%, I	H ² = 1.44						
Test of $\theta_i = \theta_i$: Q(32) = 46.09,	p = 0.05						
Test of θ = 0: z = 3.29, p = 0.	00						
					1/16 1/2 4 32	-	

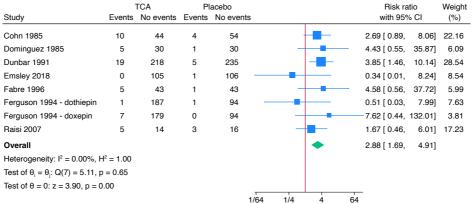
Stata

Supplementary figure S118: Meta-analysis of tricyclic antidepressants versus placebo on nervousness (sensitivity analysis).

		TCA	PI	acebo		Risk Ra	tio	Weight
Study	Events	No events	Events	No events		with 95%	CI	(%)
Bremner 1996	5	45	1	49	-	5.00 [0.61,	41.28]	1.18
Claghorn 1996	4	41	1	45		4.09 [0.48,	35.19]	1.16
Cohn 1984	6	15	0	21	-	13.00 [0.78,	217.03]	0.59
Cohn 1985	9	45	5	53	- -	1.93 [0.69,	5.41]	5.67
Cohn 1990	4	27	1	32		4.26 [0.50,	36.04]	1.14
Fabre 1996	0	48	7	37		0.06 [0.00,	1.04]	9.20
Feighner 1989a	11	47	10	49		1.12 [0.52,	2.43]	11.67
Hicks 1988	10	6	2	13		4.69 [1.22,	17.99]	2.43
Lydiard 1997	6	125	4	125	-	1.48 [0.43,	5.11]	4.74
Rickels 1987	13	50	5	56	-	2.52 [0.95,	6.64]	5.98
Schweizer 1994	9	64	3	75		3.21 [0.90,	11.38]	3.41
Schweizer 1998	15	45	8	52		1.88 [0.86,	4.09]	9.41
Stark 1985	24	162	14	155	-	1.56 [0.83,	2.91]	17.26
Wilcox 1994	37	13	22	27		1.65 [1.16,	2.34]	26.15
Overall					♦	1.80 [1.42,	2.27]	
Heterogeneity: I ² =	11.33%, H	² = 1.13						
Test of $\theta_i = \theta_i$: Q(13)	3) = 14.66,	p = 0.33						
Test of $\theta = 0$: $z = 4$.91, p = 0.0	00						
					256 1/8 4 128	}		

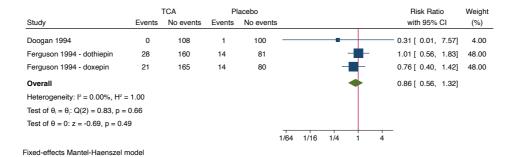


Supplementary figure S119: Meta-analysis of tricyclic antidepressants versus placebo on paraesthesia (sensitivity analysis).



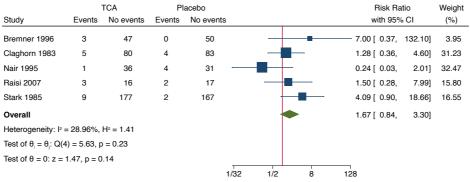


Supplementary figure S120: Meta-analysis of tricyclic antidepressants versus placebo on pharyngitis (sensitivity analysis).



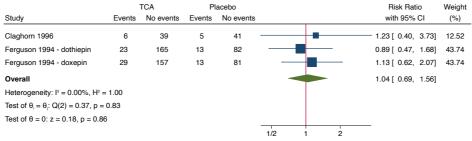


Supplementary figure S121: Meta-analysis of tricyclic antidepressants versus placebo on rash (sensitivity analysis).



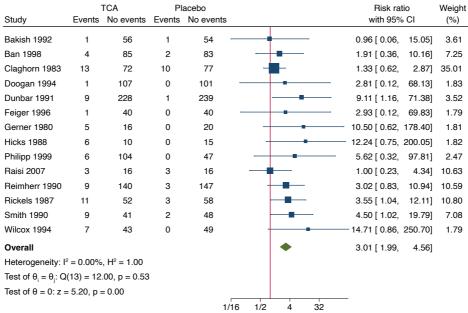


Supplementary figure S122: Meta-analysis of tricyclic antidepressants versus placebo on rhinitis (sensitivity analysis).



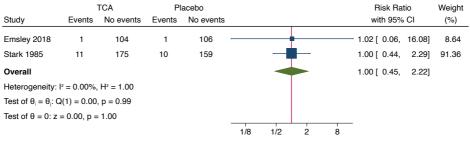


Supplementary figure S123: Meta-analysis of tricyclic antidepressants versus placebo on tachycardia (sensitivity analysis).



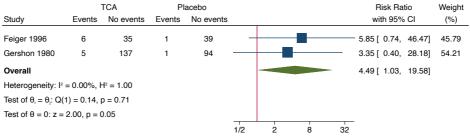


Supplementary figure S124: Meta-analysis of tricyclic antidepressants versus placebo on upper respiratory tract infection (sensitivity analysis).



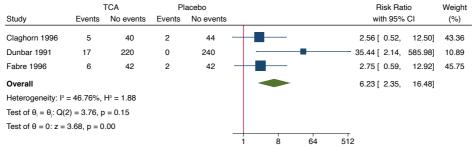


Supplementary figure S125: Meta-analysis of tricyclic antidepressants versus placebo on urinary hesitancy (sensitivity analysis).



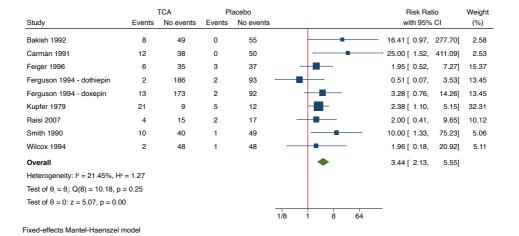


Supplementary figure S126: Meta-analysis of tricyclic antidepressants versus placebo on vasodilatation (sensitivity analysis).



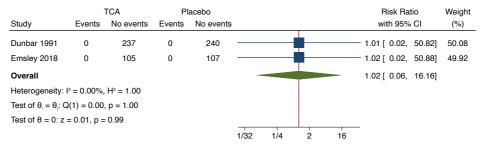


Supplementary figure S127: Meta-analysis of tricyclic antidepressants versus placebo on weight gain (sensitivity analysis).





Supplementary figure S128: Meta-analysis of tricyclic antidepressants versus placebo on yawning (sensitivity analysis).





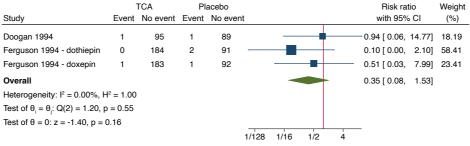
Supplementary figure S129: Meta-analysis of tricyclic antidepressants versus placebo on MADRS, BDI, and HDRS-6 (sensitivity analysis).

		TCA			Placeb	0		Hedges's g	Weight
Study	N	Mean	SD	N	Mean	SD		with 95% CI	(%)
Cassano 1996 - imipramine	47	14.3	8.2	18	16.1	6.4		-0.23 [-0.77, 0.31]	3.22
Cassano 1996 - tianeptine	46	11.8	8.1	18	16.1	6.4		-0.55 [-1.10, -0.01]	3.12
Costa e Silva 1997	62	16.3	11.5	61	22	13.8	-	-0.45 [-0.80, -0.09]	7.38
Ferguson 1994 - dothiepin	184	14	9.7	93	19.2	10.8		-0.51 [-0.77, -0.26]	14.67
Ferguson 1994 - doxepin	184	14.4	9.8	93	19.2	10.8		-0.47 [-0.72, -0.22]	14.74
Georgotas 1982	15	8.8	7	18	12.7	8.1		-0.50 [-1.18, 0.18]	2.02
Ginestet 1997 - 37.5 mg	58	11	8.4	23	9	5.3		0.26 [-0.22, 0.74]	4.05
Ginestet 1997 - 75 mg	67	11.4	9.8	23	9	5.3		0.27 [-0.20, 0.74]	4.21
Lydiard 1997	128	-6.9	6.8	124	-4.7	6.8	-	-0.32 [-0.57, -0.07]	15.21
Murphy 1984 - vs CT	11	10.09	10.61	24	10.88	8.93		-0.08 [-0.78, 0.62]	1.92
Murphy 1984 - vs CT + placebo	11	10.09	10.61	17	8.18	8.43		0.20 [-0.54, 0.94]	1.71
Mynors-Wallis 1995	27	11.9	10.5	26	16.8	12.4		-0.42 [-0.96, 0.12]	3.24
Niklson 1997	141	18.05	11.5	106	22.45	10.9		-0.39 [-0.64, -0.14]	14.53
Prasko 2002	11	18.4	12	9	8.7	5.4		— 0.96 [0.07, 1.86]	1.17
Roth 1990	24	18.2	9.6	29	21	10.4		-0.27 [-0.81, 0.26]	3.26
Schweizer 1994	40	-17.7	7.9	57	-11.9	10	-■ -	-0.63 [-1.04, -0.22]	5.54
Overall							•	-0.34 [-0.44, -0.24]	
Heterogeneity: I ² = 49.06%, H ² =	1.96							. , .	
Test of $\theta_i = \theta_i$: Q(15) = 29.45, p =	0.01								
Test of $\theta = 0$: $z = -6.91$, $p = 0.00$									
, p							-1 0 1		

Fixed-effects inverse-variance model



Supplementary figure S130: Meta-analysis of tricyclic antidepressants versus placebo on suicidal ideation (sensitivity analysis).





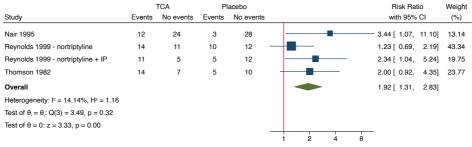
Supplementary figure S131: Meta-analysis of tricyclic antidepressants versus placebo on response (sensitivity analysis).

Graph 22/05/2023, 11.42

			_					
Study	Events	TCA No events		acebo No events		Risk ratio		Weight (%)
Amin 1984	44	60	35	65	<u> </u>	1.21 [0.85.	1.711	4.60
Amsterdam 1986	28	14	8	13		1.75 [0.97.	3.14]	1.37
Bakish 1992	34	23	20	35	<u>-</u>	1.64 [1.09,	2.471	2.62
Ban 1998	43	46	30	55	_	1.37 [0.96,	1.961	3.95
Bremner 1996	27	20	15	33		1.84 [1.13,	2.991	1.91
Claphorn 1983	49	36	35	50		1.40 [1.02,	1.911	4.51
Cohn 1985	22	30	12	45		2.01 [1.11,	3.641	1.47
Cohn 1996	18	5	14	17		1.73 [1.11,	2.701	1.54
Costa e Silva 1997	36	26	25	36	-	1.42 [0.98,	2.051	3.25
Dominguez 1985	13	6	11	10	-	1.31 [0.78,	2.17	1.35
Doogan 1994	46	50	40	50		1.08 [0.79,	1.47	5.32
Edwards 1983	3	13	8	11	 ∓	0.45 [0.14,	1.40]	0.94
Emsley 2018	49	56	36	70	-	1.37 [0.98,	1.92]	4.61
Escobar 1980	14	1	6	6		1.87 [1.04,	3.34]	0.86
Fabre 1996	22	21	15	31		1.57 [0.94,	2.61]	1.87
Feighner 1980	5	13	0	10		6.37 [0.39, 1	04.54]	0.08
Ferguson 1994 - dothiepin	95	89	32	61	-	1.50 [1.10,	2.05]	5.47
Ferguson 1994 - doxepin	88	96	32	61	-	1.39 [1.01,	1.91]	5.47
Fontaine 1994	22	23	14	31		1.57 [0.93,	2.66]	1.80
Gelenberg 1990a	6	2	6	8		1.75 [0.85,	3.61]	0.56
Gershon 1980	57	43	18	54	-8-	2.28 [1.48,	3.52]	2.70
Jacobson 1990	31	17	21	27	= -	1.48 [1.01,	2.17]	2.70
Katz 2004	16	10	6	14		2.05 [0.98,	4.28]	0.87
Lapierre 1987	3	2	1	5		3.60 [0.52,	24.73]	0.12
Lydiard 1997	55	49	43	72	=	1.41 [1.05,	1.91]	5.26
Mann 1981	2	7	1	8		2.00 [0.22,	18.33]	0.13
Merideth 1983	10	24	17	21		0.66 [0.35,	1.23]	2.07
Nair 1995	11	24	6	25	+	1.62 [0.68,	3.87]	0.82
Organon 3-020	14	26	5	34		2.73 [1.09,	6.86]	0.65
Organon 84062	13	2	13	2	+	1.00 [0.76,	1.32]	1.67
Philipp 1999	70	35	29	17		1.06 [0.82,	1.37]	5.19
Reimherr 1990	86	36	49	79		1.84 [1.44,	2.36]	6.16
Reynolds 1999 - nortriptyline	14	11	10	12	-	1.23 [0.69,	2.19]	1.37
Reynolds 1999 - nortriptyline + IP	11	5	5	12		2.34 [1.04,	5.24]	0.62
Rickels 1987	26	11	14	23		1.86 [1.17,	2.95]	1.80
Schweizer 1994	24	16	27	30	-	1.27 [0.87,	1.84]	2.87
Schweizer 1998	37	23	21	37		1.70 [1.15,	2.53]	2.75
Smith 1990	24	11	12	13	-	1.43 [0.90,	2.28]	1.80
Stark 1985	85	46	39	63		1.70 [1.29,	2.24]	5.65
Wilcox 1994	20	9	8	11	-	1.64 [0.92,	2.93]	1.24
Overall					+	1.49 [1.39,	1.59]	
Heterogeneity: $I^2 = 23.19\%$, $H^2 = 1.3$	30							
Test of $\theta_i = \theta_j$: Q(39) = 50.77, p = 0.	10							
Test of θ = 0: z = 11.46, p = 0.00						_		
					1/4 1 4 16	64		
Fixed-effects Mantel-Haenszel mode	el le							

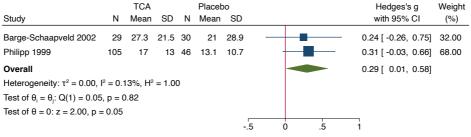
Stata

Supplementary figure S132: Meta-analysis of tricyclic antidepressants versus placebo on remission (sensitivity analysis).





Supplementary figure S133: Meta-analysis of tricyclic antidepressants versus placebo on quality of life (standardised mean difference).



Random-effects Sidik-Jonkman model





PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE	:-		
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Selection criteria
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Search strategy and selection criteria
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Data extraction and risk of bias assessment
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Data extraction and risk of bias assessment
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Outcomes and subgroup analyses
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Protocol
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Data extraction and risk of bias assessment
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Protocol
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Protocol
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Protocol
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses. Protocol or Asset statistical and classifications are statistical and classifications.	essment of inical significance
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Assessment of statistical and clinical significance
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Outcomes and subgroup analyses
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Protocol
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Protocol + data extraction and risk of bias assessme



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. Assessment of state	istical and clinical	signi
RESULTS				
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Supplementary	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplementary	l
Study characteristics	17	Cite each included study and present its characteristics.	Supplementary	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Results + supplementary	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Results	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Results + supplementary	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Results	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Results	l
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Results + supplementary	
DISCUSSION				l
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion	
	23b	Discuss any limitations of the evidence included in the review.	Discussion	l
	23c	Discuss any limitations of the review processes used.	Discussion	
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion	
OTHER INFORMATION				ļ
Registration and	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Abstract + method	ods
protocol	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Abstract + method	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Differences between orotocol and the	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Funding	l
Competing interests	26	Declare any competing interests of review authors.	Competing interes	ests
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supplementary	

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi:10.1136/bmj.n71

For more information, visit: www.prisma-statement.org.

Search strategies for 'Tricyclic antidepressants for major depressive disorder' (C Kamp)

Updated searches performed 27 January 2023

Total number of records identified: 47981 records
Number of duplicates excluded: 15478 records
Number of records in final list: 32483 records
Number of new records sent to authors: 8334 records

Cochrane Central Register of Controlled Trials (2023; Issue 1) in the Cochrane Library (10093 hits)

- #1 MeSH descriptor: [Antidepressive Agents] explode all trees
- #2 (antidepress* or (moodstimula* or mood-stimula*) or thymoanaleptic* or thymoleptic*)
- (amineptine or amitriptyline or amoxapine or butriptyline or clomipramine or desipramine or dibenzepin or dosulepin or doxepin or imipramine or iprindole or lofepramine or maprotiline or nortriptyline or opipramol or protriptyline or tianeptine or trimipramine or cianopramine or demexiptiline or dothiepin or melitracen or metapramine or noxiptiline or quinupramine)
- #4 #1 or #2 or #3
- #5 MeSH descriptor: [Depressive Disorder, Major] explode all trees
- #6 MeSH descriptor: [Depressive Disorder] this term only
- #7 MeSH descriptor: [Seasonal Affective Disorder] explode all trees
- #8 MeSH descriptor: [Dysthymic Disorder] explode all trees
- #9 MeSH descriptor: [Depression] explode all trees
- #10 MeSH descriptor: [Affective Symptoms] this term only
- #11 ((depress* or affective or dysthym*) and (disorder* or disease* or symptom*))
- #12 #5 or #6 or #7 or #8 or #9 or #10 or #11
- #13 #4 and #12

MEDLINE Ovid (1946 to 27 January 2023) (11606 hits)

- 1. exp Antidepressive Agents/
- 2. (antidepress* or (moodstimula* or mood-stimula*) or thymoanaleptic* or thymoleptic*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 3. (amineptine or amitriptyline or amoxapine or butriptyline or clomipramine or desipramine or dibenzepin or doxulepin or doxepin or imipramine or iprindole or lofepramine or maprotiline or nortriptyline or opipramol or protriptyline or tianeptine or trimipramine or cianopramine or demexiptiline or dothiepin or melitracen or metapramine or noxiptiline or quinupramine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 4. 1 or 2 or 3
- 5. exp Depressive Disorder, Major/
- 6. Depressive Disorder/
- 7. exp Seasonal Affective Disorder/
- 8. exp Dysthymic Disorder/
- 9. exp Depression/
- 10. Affective Symptoms/
- 11. ((depress* or affective or dysthym*) and (disorder* or disease* or symptom*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 12. 5 or 6 or 7 or 8 or 9 or 10 or 11
- 13 4 and 12
- 14. (randomized controlled trial or controlled clinical trial).pt. or clinical trials as topic.sh. or trial.ti.

- 15. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
 16. 13 and (14 or 15)
- 17. limit 16 to ("all adult (19 plus years)" or "adolescent (13 to 18 years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")

Embase Ovid (1974 to 27 January 2023) (16488 hits)

- 1. exp antidepressant agent/
- 2. (antidepress* or (moodstimula* or mood-stimula*) or thymoanaleptic* or thymoleptic*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 3. (amineptine or amitriptyline or amoxapine or butriptyline or clomipramine or desipramine or dibenzepin or doxulepin or doxepin or imipramine or iprindole or lofepramine or maprotiline or nortriptyline or opipramol or protriptyline or tianeptine or trimipramine or cianopramine or demexiptiline or dothiepin or melitracen or metapramine or noxiptiline or quinupramine).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 4. 1 or 2 or 3
- 5. exp major depression/
- 6. depression/
- 7. exp seasonal affective disorder/
- 8. exp dysthymia/
- 9. emotional disorder/
- 10. ((depress* or affective or dysthym*) and (disorder* or disease* or symptom*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
- 11. 5 or 6 or 7 or 8 or 9 or 10
- 12. 4 and 11
- 13. Randomized controlled trial/ or Controlled clinical study/ or trial.ti.
- 14. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
 15. 12 and (13 or 14)
- 16. limit 15 to (adult <18 to 64 years> or aged <65+ years>)

LILACS (VHL Regional Portal; 1982 to 27 January 2023) (1161 hits)

((antidepress* OR (moodstimula* OR mood-stimula*) OR thymoanaleptic* OR thymoleptic*) OR (amineptine OR amitriptyline OR amoxapine OR butriptyline OR clomipramine OR desipramine OR dibenzepin OR dosulepin OR doxepin OR imipramine OR iprindole OR lofepramine OR maprotiline OR nortriptyline OR opipramol OR protriptyline OR tianeptine OR trimipramine OR cianopramine OR demexiptiline OR dothiepin OR melitracen OR metapramine OR noxiptiline OR quinupramine)) AND (((depress* OR affective OR dysthym*) AND (disorder* OR disease* OR symptom*))) AND (db:("LILACS"))

PsycINFO (EBSCO host; 1806 to 27 January 2023) (3693 hits)

- S17 S15 AND S16
- S16 TI adult* or Elder* or older or Geriatri* or Senil* or Old Age* or Late Life or Aged OR AB adult* or Elder* or older or Geriatri* or Senil* or Old Age* or Late Life or Aged
- S15 S13 AND S14
- S14 TX ((random* or blind* or placebo* or meta-analys*)) OR TI trial*
- S13 S4 AND S12
- S12 S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
- S11 TX ((depress* or affective or dysthym*) and (disorder* or disease* or symptom*))
- S10 MA Affective Symptoms
- S9 MA Depression

- S8 MA Dysthymic Disorder
- S7 MA Seasonal Affective Disorder
- S6 MA Depressive Disorder Expanders
- S5 MA Depressive Disorder, Major
- S4 S1 OR S2 OR S3
- S3 TX (amineptine or amitriptyline or amoxapine or butriptyline or clomipramine or desipramine or dibenzepin or dosulepin or doxepin or imipramine or iprindole or lofepramine or maprotiline or nortriptyline or opipramol or protriptyline or tianeptine or trimipramine or cianopramine or demexiptiline or dothiepin or melitracen or metapramine or noxiptiline or quinupramine)
- S2 TX (antidepress* or (moodstimula* or mood-stimula*) or thymoanaleptic* or thymoleptic*)
- S1 MA Antidepressive Agents

Science Citation Index Expanded (Web of Science; 1900 to 27 January 2023); Conference Proceedings Citation Index – Science (Web of Science; 1990 to 27 January 2023); Social Sciences Citation Index (Web of Science; 1956 to 27 January 2023), and Conference Proceedings Citation Index-Social Science & Humanities (Web of Science; 1990 to 27 January 2023) (4940 hits)

- #9 #8 AND #7
- #8 TS=(adult* or Elder* or older or Geriatri* or Senil* or Old Age* or Late Life or Aged)
- #7 #6 AND #5
- #6 TI=(random* or blind* or placebo* or meta-analys* or trial*) OR TS=(random* or blind* or placebo* or meta-analys*)
- #5 #4 AND #3
- #4 TS=((depress* or affective or dysthym*) and (disorder* or disease* or symptom*))
- #3 #2 OR #1
- #2 TS=(amineptine or amitriptyline or amoxapine or butriptyline or clomipramine or desipramine or dibenzepin or dosulepin or doxepin or imipramine or iprindole or lofepramine or maprotiline or nortriptyline or opipramol or protriptyline or tianeptine or trimipramine or cianopramine or demexiptiline or dothiepin or melitracen or metapramine or noxiptiline or quinupramine)
- #1 TS=(antidepress* or (moodstimula* or mood-stimula*) or thymoanaleptic* or thymoleptic*)

Exploratory outcomes

Serious adverse events (as reported by trialists)

Four trials reported serious adverse events as a composite outcome (**supplementary table S2**).[1-4] Trials using 'active placebo' were not included in this meta-analysis. All trials only assessed outcomes at the end of the treatment period, i.e. from six to eight weeks after randomisation. A total of 3/320 (0.9%) experimental participants had one or more serious adverse events compared with 6/253 (2.4%) control participants. Meta-analysis showed no evidence of a difference between tricyclic antidepressants and placebo on serious adverse events (odds ratio (OR) 0.52; 95% CI 0.15 to 1.77; p = 0.30; 4 trials) (**supplementary figure S68**). Visual inspection of the forest plot and statistical tests ($1^2 = 0.0\%$) indicated no clear signs of heterogeneity. Trial Sequential Analysis showed that we did not have enough information to confirm or reject the hypothesis that tricyclic antidepressants increased the risk of serious adverse events with a relative risk reduction of 20% (no graph produced as we only had 1.15% of the required information size). This outcome result was assessed as overall high risk of bias.

MADRS, BDI, and HDRS-6

Fourteen trials reported results on MADRS, BDI, or HDRS-6.[5-19] All trials only assessed outcomes at the end of the treatment period, i.e. from 3 to 12 weeks after randomisation. Meta-analysis using standardised mean difference (SMD) showed evidence of a beneficial effect of tricyclic antidepressants on the MADRS and BDI scores (SMD -0.30; 95% CI -0.49 to -0.12; p < 0.01; 14 trials) (**supplementary figure S69**). Visual inspection of the forest plot and statistical tests ($\tau = 0.3$; $I^2 = 72.0\%$) indicated heterogeneity that could not be resolved. This outcome result was assessed as overall high risk of bias.

Suicidal ideation

Two trials reported suicidal ideation [10, 20]. All trials only assessed outcomes at the end of the treatment period, i.e. from six to nine weeks after randomisation. Meta-analysis showed no evidence of a difference between tricyclic antidepressants and placebo on suicidal ideation (RR 0.39; 95% CI 0.07 to 2.30; p = 0.30; 2 trials) (**supplementary figure S70**). Visual inspection of the forest plot and statistical tests ($\tau = 0.6$; $I^2 = 15.0\%$) indicated no clear signs of heterogeneity. This outcome result was assessed as overall high risk of bias.

Response

Thirty-five trials reported on response [1-4, 7, 9, 10, 15, 20-46]. All trials only assessed outcomes at

the end of the treatment period, i.e. from four to nine weeks after randomisation. Meta-analysis

showed evidence of a beneficial effect of tricyclic antidepressants on response (RR 1.49; 95% CI

1.33 to 1.67; p < 0.01; 35 trials) (supplementary figure S71). Visual inspection of the forest plot and

statistical tests ($\tau = 0.2$; $I^2 = 55.3\%$) indicated heterogeneity that could not be resolved. This outcome

result was assessed as overall high risk of bias.

Remission

Three trials reported on remission [38, 40, 47]. All trials only assessed outcomes at the end of the

treatment period, i.e., from 7 to 12 weeks after randomisation. Meta-analysis showed evidence of a

beneficial effect of tricyclic antidepressants on remission (RR 1.87; 95% CI 1.16 to 3.03; p = 0.01; 3

trials) (supplementary figure S72). Visual inspection of the forest plot and statistical tests ($\tau = 0.3$;

 $I^2 = 32.4\%$) indicated heterogeneity that could not be resolved. This outcome result was assessed as

overall high risk of bias.

Remaining results

We performed all meta-analyses as both fixed-effect and random-effects meta-analyses and reported

the most conservative results as the main results. For the less conservative results, please see

supplementary figures S73-S133.

95% prediction intervals

Tricyclic antidepressants versus placebo on HDRS-17: -10.97 to 3.51

Tricyclic antidepressants versus placebo on mania: 0.06 to 29.81

Tricyclic antidepressants versus placebo on anxiety: 0.13 to 4.38

Tricyclic antidepressants versus placebo on urinary retention: 0.17 to 215.00

Tricyclic antidepressants versus placebo on sexual dysfunction: 0.52 to 23.50

Tricyclic antidepressants versus placebo on anorexia: 0.06 to 20.62

Tricyclic antidepressants versus placebo on taste alteration: 0.12 to 139.81

Tricyclic antidepressants versus placebo on hypotension: 0.82 to 13.41

Tricyclic antidepressants versus placebo on syncope: 0.00 to 1.9e+05

Tricyclic antidepressants versus placebo on amblyopia: 1.37 to 8.05

Tricyclic antidepressants versus placebo on non-serious adverse events: 0.63 to 7.05

Tricyclic antidepressants versus placebo on dry mouth: 1.28 to 9.20

Tricyclic antidepressants versus placebo on somnolence: 1.18 to 5.99

Tricyclic antidepressants versus placebo on constipation: 0.84 to 9.39

Tricyclic antidepressants versus placebo on dyspepsia: 0.34 to 14.23

Tricyclic antidepressants versus placebo on nervousness: 0.32 to 13.25

Tricyclic antidepressants versus placebo on asthenia: 0.98 to 3.71

Tricyclic antidepressants versus placebo on nausea: 0.38 to 4.51

Tricyclic antidepressants versus placebo on tremor: 0.91 to 24.39

Tricyclic antidepressants versus placebo on rash: 0.05 to 51.42

Tricyclic antidepressants versus placebo on headache: 0.40 to 2.36

Tricyclic antidepressants versus placebo on increased appetite: 0.97 to 9.13

Tricyclic antidepressants versus placebo on dizziness: 0.83 to 6.75

Tricyclic antidepressants versus placebo on weight gain: 0.31 to 28.87

Tricyclic antidepressants versus placebo on blurred vision: 1.61 to 5.44

Tricyclic antidepressants versus placebo on pharyngitis: 0.01 to 89.56

Tricyclic antidepressants versus placebo on confusion: 1.23 to 9.61

Tricyclic antidepressants versus placebo on tachycardia: 0.73 to 11.40

Tricyclic antidepressants versus placebo on agitation: 0.18 to 6.61

Tricyclic antidepressants versus placebo on diarrhoea: 0.16 to 1.34

Tricyclic antidepressants versus placebo on sweating: 0.97 to 13.70

Tricyclic antidepressants versus placebo on anticholinergic symptoms: 0.44 to 12.48

Tricyclic antidepressants versus placebo on micturition disorder: 0.00 to 2.0e+04

Tricyclic antidepressants versus placebo on sedation: 0.53 to 5.30

Tricyclic antidepressants versus placebo on decreased appetite: 0.24 to 24.28

Tricyclic antidepressants versus placebo on paraesthesia: 0.38 to 16.96

Tricyclic antidepressants versus placebo on rhinitis: 0.07 to 16.40

Tricyclic antidepressants versus placebo on vasodilatation: 0.00 to 1.0e+08

Tricyclic antidepressants versus placebo on infection: 0.00 to 86.51

Tricyclic antidepressants versus placebo on CNS: 0.01 to 99.48

Tricyclic antidepressants versus placebo on MADRS, BDI, or HDRS-6: -1.02 to 0.41

Tricyclic antidepressants versus placebo on suicidal ideation: 0.00 to 4.2e+05

Tricyclic antidepressants versus placebo on remission: 0.38 to 9.24

Tricyclic antidepressants versus placebo on response: 0.89 to 2.48

References

- [1] Bakish D, Bradwejn J, Nair N, McClure J, Remick R, Bulger L. A comparison of moclobemide, amitriptyline and placebo in depression: a Canadian multicentre study. Psychopharmacology (Berl). 1992;106 Suppl:S98-101.
- [2] Emsley R, Ahokas A, Suarez A, Marinescu D, Doci I, Lehtmets A, et al. Efficacy of Tianeptine 25-50 mg in Elderly Patients With Recurrent Major Depressive Disorder: An 8-Week Placebo- and Escitalopram-Controlled Study. J Clin Psychiatry. 2018;79(4).
- [3] Fabre L, Birkhimer LJ, Zaborny BA, Wong LF, Kapik BM. Fluvoxamine versus imipramine and placebo: a double-blind comparison in depressed patients. Int Clin Psychopharmacol. 1996;11(2):119-27.
- [4] Philipp M, Kohnen R, Hiller KO. Hypericum extract versus imipramine or placebo in patients with moderate depression: randomised multicentre study of treatment for eight weeks. BMJ. 1999;319(7224):1534-8.
- [5] Georgotas A, Krakowski M, Gershon S. Controlled trial of zimelidine, a 5-HT reuptake inhibitor, for treatment of depression. Am J Psychiatry. 1982;139(8):1057-8.
- [6] Mynors-Wallis LM, Gath DH, Lloyd-Thomas AR, Tomlinson D. Randomised controlled trial comparing problem solving treatment with amitriptyline and placebo for major depression in primary care. BMJ. 1995;310(6977):441-5.
- [7] Lydiard RB, Stahl SM, Hertzman M, Harrison WM. A double-blind, placebo-controlled study comparing the effects of sertraline versus amitriptyline in the treatment of major depression. J Clin Psychiatry. 1997;58(11):484-91.
- [8] Cassano GB, Heinze G, LÔO H, Mendlewicz J, Sousa MPd. A double-blind comparison of tianeptine, imipramine and placebo in the treatment of major depressive episodes. European Psychiatry. 1996;11(5):254-9.
- [9] Costa e Silva JA, Ruschel SI, Caetano D, Rocha FL, da Silva Lippi JR, Arruda S, et al. Placebo-controlled study of tianeptine in major depressive episodes. Neuropsychobiology. 1997;35(1):24-9.
- [10] Ferguson JM, Mendels J, Manowitz NR. Dothiepin versus doxepin in major depression: results of a multicenter, placebo-controlled trial. Prothiaden Collaborative Study Group. J Clin Psychiatry. 1994;55(6):258-63.
- [11] Ginestet D. Efficacy of tianeptine in major depressive disorders with or without melancholia. European Neuropsychopharmacology. 1997;7:S341-S5.
- [12] Murphy GE, Simons AD, Wetzel RD, Lustman PJ. Cognitive therapy and pharmacotherapy. Singly and together in the treatment of depression. Arch Gen Psychiatry. 1984;41(1):33-41.
- [13] Niklson IA, Reimitz PE, Sennef C. Factors that influence the outcome of placebocontrolled antidepressant clinical trials. Psychopharmacol Bull. 1997;33(1):41-51.
- [14] Roth D, Mattes J, Sheehan KH, Sheehan DV. A double-blind comparison of fluvoxamine, desipramine and placebo in outpatients with depression. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 1990;14(6):929-39.
- [15] Schweizer E, Feighner J, Mandos LA, Rickels K. Comparison of venlafaxine and imipramine in the acute treatment of major depression in outpatients. J Clin Psychiatry. 1994;55(3):104-8.
- [16] Prasko J, Horacek J, Klaschka J, Kosova J, Ondrackova I, Sipek J. Bright light therapy and/or imipramine for inpatients with recurrent non-seasonal depression. Neuro Endocrinol Lett. 2002;23(2):109-13.

- Organon 3-020. Unpublished data. In: Bech, P. Meta-analysis of placebo-controlled trials with mirtazapine using the core items of the Hamilton Depression Scale as evidence of a pure antidepressive effect in the short-term treatment of major depression. International Journal of Neuropsychopharmacology 2001;4:337-45. DOI: 10.1017/S1461145701002565.
- [18] Organon 84062. Unpublished data. In: Bech, P. Meta-analysis of placebo-controlled trials with mirtazapine using the core items of the Hamilton Depression Scale as evidence of a pure antidepressive effect in the short-term treatment of major depression. International Journal of Neuropsychopharmacology 2001;4:337-45. DOI: 10.1017/S1461145701002565.
- [19] Jacobson AF. Comparison of ORG-3770 and amitriptyline in depressed outpatients. 1990. In: Bech, P. Meta-analysis of placebo-controlled trials with mirtazapine using the core items of the Hamilton Depression Scale as evidence of a pure antidepressive effect in the short-term treatment of major depression. International Journal of Neuropsychopharmacology 2001;4:337-45. DOI: 10.1017/S1461145701002565.
- [20] Doogan DP, Langdon CJ. A double-blind, placebo-controlled comparison of sertraline and dothiepin in the treatment of major depression in general practice. Int Clin Psychopharmacol. 1994;9(2):95-100.
- [21] Amin MM, Ananth JV, Coleman BS, Darcourt G, Farkas T, Goldstein B, et al. Fluvoxamine: Antidepressant effects confirmed in a placebo-controlled international study. Clinical neuropharmacology. 1984;7:317.
- [22] Amsterdam JD, Case WG, Csanalosi E, Singer M, Rickels K. A double-blind comparative trial of zimelidine, amitriptyline, and placebo in patients with mixed anxiety and depression. Pharmacopsychiatry. 1986;19(3):115-9.
- [23] Ban TA, Gaszner P, Aguglia E, Batista R, Castillo A, Lipcsey A, et al. Clinical efficacy of reboxetine: a comparative study with desipramine, with methodological considerations. Human Psychopharmacology: Clinical and Experimental. 1998;13(S1):S29-S39.
- [24] Bremner JD. Doppelblindvergleich von Mirtazapin, Amitriptylin und Plazebo bei »Major Depression«. Nervenheilkunde. 1996;15:533-40.
- [25] Claghorn J, Gershon S, Goldstein BJ. Zimeldine tolerability in comparison to amitriptyline and placebo: findings from a multicentre trial. Acta Psychiatr Scand Suppl. 1983;308:104-14.
- [26] Cohn CK, Robinson DS, Roberts DL, Schwiderski UE, O'Brien K, Ieni JR. Responders to antidepressant drug treatment: a study comparing nefazodone, imipramine, and placebo in patients with major depression. J Clin Psychiatry. 1996;57 Suppl 2:15-8.
- [27] Cohn JB, Wilcox C. A comparison of fluoxetine, imipramine, and placebo in patients with major depressive disorder. J Clin Psychiatry. 1985;46(3 Pt 2):26-31.
- [28] Dominguez RA, Goldstein BJ, Jacobson AF, Steinbook RM. A double-blind placebo-controlled study of fluvoxamine and imipramine in depression. J Clin Psychiatry. 1985;46(3):84-7.
- [29] Edwards JG, Goldie A. Mianserin, maprotiline and intracardiac conduction. Br J Clin Pharmacol. 1983;15 Suppl 2:249S-54S.
- [30] Escobar JI, Gomez J, Constain C, Rey J, Santacruz H. Controlled clinical trial with trazodone, a novel antidepressant. A South American experience. J Clin Pharmacol. 1980;20(2-3):124-30.
- [31] Feighner JP. Trazodone, a triazolopyridine derivative, in primary depressive disorder. J Clin Psychiatry. 1980;41(7):250-5.
- [32] Fontaine R, Ontiveros A, Elie R, Kensler TT, Roberts DL, Kaplita S, et al. A double-blind comparison of nefazodone, imipramine, and placebo in major depression. J Clin Psychiatry. 1994;55(6):234-41.

- [33] Gershon S, Newton R. Lack of anticholinergic side effects with a new antidepressent-trazodone. J Clin Psychiatry. 1980;41(3):100-4.
- [34] Katz MM, Tekell JL, Bowden CL, Brannan S, Houston JP, Berman N, et al. Onset and early behavioral effects of pharmacologically different antidepressants and placebo in depression. Neuropsychopharmacology. 2004;29(3):566-79.
- [35] Lapierre YD, Browne M, Horn E, Oyewumi LK, Sarantidis D, Roberts N, et al. Treatment of major affective disorder with fluvoxamine. J Clin Psychiatry. 1987;48(2):65-8.
- [36] Mann JJ, Georgotas A, Newton R, Gershon S. A controlled study of trazodone, imipramine, and placebo in outpatients with endogenous depression. J Clin Psychopharmacol. 1981;1(2):75-80.
- [37] Merideth CH, Feighner JP. A double-blind, controlled evaluation of zimeldine, imipramine and placebo in patients with primary affective disorders. Acta Psychiatr Scand Suppl. 1983;308:70-9.
- [38] Nair NP, Amin M, Holm P, Katona C, Klitgaard N, Ng Ying Kin NM, et al. Moclobemide and nortriptyline in elderly depressed patients. A randomized, multicentre trial against placebo. J Affect Disord. 1995;33(1):1-9.
- [39] Reimherr FW, Chouinard G, Cohn CK, Cole JO, Itil TM, LaPierre YD, et al. Antidepressant efficacy of sertraline: a double-blind, placebo- and amitriptyline-controlled, multicenter comparison study in outpatients with major depression. J Clin Psychiatry. 1990;51 Suppl B:18-27.
- [40] Reynolds CF, Miller MD, Pasternak RE, Frank E, Perel JM, Cornes C, et al. Treatment of Bereavement-Related Major Depressive Episodes in Later Life: A Controlled Study of Acute and Continuation Treatment With Nortriptyline and Interpersonal Psychotherapy. American Journal of Psychiatry. 1999;156(2):202-8.
- [41] Rickels K, Chung HR, Csanalosi IB, Hurowitz AM, London J, Wiseman K, et al. Alprazolam, diazepam, imipramine, and placebo in outpatients with major depression. Arch Gen Psychiatry. 1987;44(10):862-6.
- [42] Schweizer E, Rickels K, Hassman H, Garcia-Espana F. Buspirone and imipramine for the treatment of major depression in the elderly. J Clin Psychiatry. 1998;59(4):175-83.
- [43] Smith WT, Glaudin V, Panagides J, Gilvary E. Mirtazapine vs. amitriptyline vs. placebo in the treatment of major depressive disorder. Psychopharmacol Bull. 1990;26(2):191-6.
- [44] Stark P, Hardison CD. A review of multicenter controlled studies of fluoxetine vs. imipramine and placebo in outpatients with major depressive disorder. J Clin Psychiatry. 1985;46(3 Pt 2):53-8.
- [45] Wilcox CS, Cohn JB, Katz BB, Mijares CP, Guarino JJ, Panagides J, et al. A double-blind, placebo-controlled study comparing mianserin and amitriptyline in moderately depressed outpatients. Int Clin Psychopharmacol. 1994;9(4):271-9.
- [46] Gelenberg AJ, Wojcik JD, Falk WE, Spring B, Brotman AW, Galvin-Nadeau M. Clovoxamine in the treatment of depressed outpatients: A double-blind, parallel-group comparison against amitriptyline and placebo. Comprehensive Psychiatry. 1990;31(4):307-14.
- [47] Thomson J, Rankin H, Ashcroft GW, Yates CM, McQueen JK, Cummings SW. The treatment of depression in general practice: a comparison of L-tryptophan, amitriptyline, and a combination of L-tryptophan and amitriptyline with placebo. Psychol Med. 1982;12(4):741-51.

List of non-serious adverse events combined for meta-analyses:

- Nausea + nausea/vomiting + vomiting
- Somnolence + drowsiness
- Blurred vision + vision abnormalities + visual disorder
- Rash + skin rash + skin
- Dizziness + lightheaded
- Weight gain + weight increase
- Tachycardia + palpitations
- Agitation + motor agitation
- Sweating + increased sweating + hyperhidrosis
- Anticholinergic symptoms + Anticholinergic, composite + anticholinergic adverse events
- Urination impaired + Impaired urination
- Vivid dreams + abnormal dreaming
- Infection + viral infection

Characteristics of the inc Trial ID	Registry/	Risk of for-	Inclusion criteria	Exclusion criteria	Experimental	Dose range	Control	Placebo	Length of	No.	No.	Baseline	Baseline	Co-interventions
Akhondzadeh 2003	published protocol	profit bias		Description of the following production of the following p	Imipramine	(mg/day) 100	intervention	washout	intervention period 4 weeks	randomised to TCA Unclear	randomised to control Unclear	HDRS TCA 19.5	HDRS control 19.5	Lavandula
Akthondzadeh ZUU3	No	Yes	Patients have a baseline Hamilton Rating Scale for Depression (HAM-D 17- item) (Hamilton, 1960) score of at least 18.	excluded: current cognitive disorder in the last year, or current or past history of bippair desorder, schizopherenia, and schizolystap leoparty disorder. Patients were required to be free of all psychotrogic medications for a less at weeks before study entry. Patients were selected to range in age from 18 to 54 years of age. As depression is a serious and potentially life-threatering condition and the participants were outpatients, extensive safeguards were needed. Patients were coulded, if they post a significant risk of suicle at any time during participation. Persons who scored greater than 2 on the suicide ideal ideation or potential in the view of an investigator were excluded. Turther, any clinically significant deterioration in the condition of the subject from baseline would result in exclusion. Pregnant women or women not using medically accepted means of birth control were	Imipramine	100	Placebo	No	4 weeks	Unclear	Undear	19.5	19.5	Lavandusi Angustifolia (lamiacae)
Amin 1984	No	Yes	Each test center investigated either outgatents or hospitalized patients. Control for Inclusion were a dispositio of a major depression (major affection disposition) were a disposition of a major depression (major affective disorder, depressive epitode) after DSM III (American Psychiatric Association, 1980), the presence of a for the eighner criteria of depression (Feighner, 1972) and a total score of > 15 in the 17-item version of the Hamiston Rating Scale for Depression (MADI). The depressive disorder was to be pathological, and not curable by social contact alone.	cachindre. Studied from the study were recognizable suicidal, psychotic and alcoholo of onge-dependent patients, further exclusion orders were accommended to onge-dependent patients, further exclusion orders were concombant medication that could not be descontinued for medical reasons. Pregnant women and women of child-bearing age not practing a realisel form of contraception were also excluded. Finally, patients who had received destruction which we have been suited to the previous weeks, Mulci Inhibitors in the previous week, or tricyclic antidepressants on the 3 days preceding the study were excluded from participation in the study.	Imipramine	Mean: 149	Placebo	Yes	4-6 weeks	Unclear	Unclear	25.92	25.60	No
Amsterdam 1986	No	Yes	All patients were suffering from a moderate to severe mixed anniety/depression syndrome, for which an antidepressant medication appeared the treatment of choice. However, the subjects also fulfilled an RDC diagnosis for major depression, had a minimum Hamilton Depression faiting score (HDRS) of at least 18 on 2.3 t-tem scale, a minimum score of 3 on the taskin Depression scale and an 8 on the Coxf. Innsely scale after the placeton which is the coxf. Innsely scale after the placeton scale and the coxf. Innsely scale after the placeton.	Patients were excluded if they had symptoms or a history of schrophrenia, accurating for a history of place in a schrophrenia, accurating for a history of schrophrenia, accurating the schrophrenia of the schrophrenia of dementia, mental retardation, substance abuse, significant medical lines which might contradicate the use of a T.O. significant hepatic, renal, endocrine or cardiovascular disorders.	Amitriptyline	100-300	Placebo	Yes	4 weeks	55	54	24.5	23.4	No
Bakish 1992	No	Yes	Out-patients of either exe, aged 13.6 S years, suffering from a major depressive poison, according to DSM III.R and scoring a minimum of 18 points on the 17-item Hamilton Depression Scale (INAN-D) were included. Patients had to weigh within 20% of the norm of their height.	The main exclusion criteria were high suicidal risk, depression associated with model-mongrenet pythoric features, main or acute confusional states, significant organic disease, alcohol or drug abuse) and recent treatment with Mod inhibitor, within the past vessib, stricyclic antidepressants (within the past vessib) or electrocomulation treatment (within the past or month). Momes with childrenizing treatment (within the past is month), Momes with childrenizing potential who were not using an effective form of contraception (oral contraception) and women with owner pregnant or luctaling were also excluded. Concomitant use of antihypertensive, duretic, antichildrenize or sympathomimetic agents was prohibited. All patients gave writter informed consent to their participation in the	Amitriptyline	50-150	Placebo	Yes	6 weeks	58	56	22.81	23.04	No
Ban 1998	No	Yes	Hospitalized patients between the age of 18 and 65 years with a DSA-III of 86 agencies of major depression of a least 1 month duration and a total score of 36 or higher on the 17-tem Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960) were eligible for admission.	to the control of the paper in	Desipramine	100-200	Placebo	Yes	4 weeks	Unclear	Unclear	26	25	No
Barge-Schaapveld 2002	No	Yes	83 patients with a DSM-III-R/DSM-IV diagnosis of current major depressive disorder were recruited in 8 primary care practices in the Netherlands. Age between 18 and 65 years, a score at entry of >/= 18 on the C6J.	Exclusion criteria included current use of psychotropic medations and major medical disorders.	Imipramine	50-200	Placebo	No	6 weeks	32	31	24.0	23.5	No
Bhatia 1991	No	Yes	In order to be eligible for the study each patient had to fulfill the DSM-III criteria for major depression with melantonia as determined by the screening and initial evaluations. In addition, each patient was required to have a Hamitton (Institution, 1967) Depression fasting facile over of y- 26 and a Raskin Depression Stale (Raskin et al., 1967) of y- 10. Each patient was evaluated with a complete physical examination, electrocardiagram, and laboratory tests for hepatic, renal, pancreatic, hematopoietic and throat function. They were included in the study if assessed to be free of significant medical disorders. A serum human chorionic gonadotropin was evaluated in order to exclude pregnant females.	Patients and control volunteers were excluded from the study if the required other psychotropic medications, opiate analgesics, advenegic agonists or antagonists. A patient could not have received electroconsulsive therapy or monomalme oxidase inhibitors of years and a superior of the country of the country of which are the country of the country of which are the country of the country of Auriter day careen was utilized to determine the reliability of patient drug history and to exclude patients with positive results for abused drugs including alcohol.	Amitriptyline	200-300	Placebo	No	8 weeks	Unclear	Unclear	Unclear	Unclear	No
Bremner 1996	No	Yes	Outpatients of both sees at least 15-year-old with a DSN-III diagnosis of a moderate-to-ever-major'de presides project (26.5 c. 2 p. 26.5 a) and total score >/= 18 on the first 17 tems of the Hamilton Rating Scale for Depression (HAM-D) who were assessed as able to complete the Zung Self Rating Depression Scale (SDS) entered the study. A fixed upper age limit was not incorporated in the inclusion criteria for this study.	Eduction criteria included a primary diagnosis of schizophrenia dispirated preserves typel, bipolar disorder, or adjustment disorder; anniety as the primary disorder; known active suicidal tendencies; anniety as the primary disorder; known active suicidal tendencies; annivers and anothor of oreig abuse during the last 16 months. Patients with symptoms or a history of the following disease were also excluded: relevant renal, hepatic, respiratory, cardiovascular, or cerebrovascular diseases; narrow-nig algoroma; clinically significant pros- table, heperthorpich, relevant disorders; drug allegy or other hippertensitivity reaction to trucyclic antidepressants or resisted compounds; hipperthorpic mad clinically significant abnormal EEG. Women who were pregnant or intended to become pregnant during the study or were practicing a method of birth control assessed as unrealized by the investigations and nursing required transment with concomitant psychrotropic medication including hemodiatespines and those treated with electroconsultive theory within 30 months of baseline, or other psychrotropic medication rulning despendency and proportion of the control of specific and a well as patients with a 30 days of baseline, monopamine oxidate inhibitors within 30 days of baseline, monopamine oxidate inhibitors within 30 days of baseline, monopamine oxidate inhibitors within 30 days of baseline, which are psychrotropic medication including antidepressants within 7 days of baseline were excluded as well as patients with a total NAMAD socre recition of 30 cBirl and 32 days of baseline were excluded as well as patients with a total NAMAD socre recition of 30 cBirl and 32 days of baseline were excluded as well as patients with a total NAMAD socre recition of 30 cBirl and 32 days of baseline were excluded as well as patients with a total NAMAD socre recition of 30 cBirl and 32 days of baseline were excluded as well as patients with a soul NAMAD socre recition of 30 cBirl and 32 days of baseline were excluded as well as patients with	Amitriptyline	40-280	Placebo	Yes	6 weeks	Unclear	Unclear	27.3	26.6	No
Buchsbaum 1988 - amoxapine	No	Yes	All patients had been free of psychoactive medication for a minimum of 2 weeks before the study began (confirmed by history and urine-drug screening) and were in good health based on medical history, physical examination, and laboratory analyses. Patients were diagnosed according to SDAH-III criteral by a psychiatrist before the study, and all had a minimum score of 30 on the Hamilton Rating Scale for Depression, a minimum score of 4 on the Rakin Scale, and a minimum score of 45 on	-	Amoxapine	150	Placebo	No	2 days	7	3	Unclear	Unclear	No
Buchsbaum 1988 - imipramine	No	Yes	the Zune Self-Ratins Scale for Depression. All patients had been free of psychosactive medication for a minimum of 2 weeks before the study began (confirmed by history and urine-drug screening) and were in good health based on medical history, physical or examination, and laboratory analyses. Patients were diagnosed according cosmination, and laboratory analyses. Patients were diagnosed according cosmination, and laboratory analyses. Patients were diagnosed according cosmination, and 20 on the latent on the Self for the Self for the Self Self for Self Self for the Self for the Self Self for Self fo		Imipramine		Placebo	No	2 days	6	4	Unclear	Unclear	No
Carman 1991	No	Yes	This study was a randomized, double-blind, active- and placebo-controlled investigation of minaserin in apputation of moderately to severely depressed outpatients, age 18 years or older, with the diagnosis of major depression according to DSM-III (Janerdan Psychiatric Association 1980). All patients gave informed consent in writing, All Fertile females used adequate contraceptive means throughout. All patients were free of major or unstable medical problems and were free of other primary psychiatric diagnose. Eligible patients underwerent 3 - week placebo washout and were subsequently randomized to one of three treatment groups if their total 7-tem Hamilton fasting Scale for Depression (PAMD-D, Hamilton 1960) score was 18 or greater, and the total HAMD-D 21-tem scale had not been reduced by 2D percent or more from its screen value.		Amitriptyline		Placebo	Yes	6 weeks	50	50	27.6	26.7	No
Cassano 1996 - imipramine	No	Yes	Patients of both sees, aged between 18 and 60 years, had to fulfil DSAH. In Citeria for Mol (single episode or current) or bipod disorder (depresses), without psychotic features or melancholia. Initial severity of the depression was controlled by a MADRS score greater than or equal to 25.	Other types of depression, such or chronic psychosis, non-responders to two different antidepseants for the current episode, necessity of ECT, treatement within seven days of pre-inclusion with non MAOL treatement within a days of pre-inclusion with a reverselse MAOL treatement within or most of the pre-inclusion with a non-reversible MAOL treatement within or most of pre-inclusion with a non-reversible MAOL treatement within or most of pre-inclusion with a non-reversible MAOL treatement within or most of pre-inclusion with a non-reversible MAOL treatement within or most of pre-inclusion with a non-reversible MAOL treatement within or most of pre-inclusion with a non-reversible MAOL treatement within or most order and pre-inclusion with a non-reversible MAOL treatement within one order and pre-inclusion with a non-reversible MAOL treatement within one most order and pre-inclusion with a non-reversible MAOL treatement within on most order and pre-inclusion with a non-reversible MAOL treatement within on most order and pre-inclusion with a non-reversible MAOL treatement within on most order pre-inclusion with a non-reversible MAOL treatement within on most order pre-inclusion with a non-reversible MAOL treatement within on most order pre-inclusion with a non-reversible MAOL treatement within on most order pre-inclusion with a non-reversible MAOL treatement within on most order pre-inclusion with a non-reversible MAOL treatement within on most order pre-inclusion with a non-reversible MAOL treatement within on most order pre-inclusion with a non-reversible MAOL treatement within on most order pre-inclusion with a non-reversible MAOL treatement within on most order pre-inclusion with a non-reversible MAOL treatement within on most order pre-inclusion with a non-reversible MAOL treatement within on most order pre-inclusion with a non-reversible MAOL treatement within on most order pre-inclusion with a non-reversible MAOL treatement within order pre-inclusion with a non-reversible MAOL treatement within order pre-inc	Imipramine	Mean: 154.5	Placebo	Yes	42 days	64	29	31.4	31.0	No
Cassano 1996 - tianeptine	No	Yes	Patients of both seens, aged between 18 and 60 years, had to fulfill DSAH. In Citerals for Mich Guigle episido or currently of bypoid disorder (depresses), without psychotic features or melancholia. Initial severity of the depression was controlled by a MADRS score greater than or equal to 25.	Other types of depression, acute or chronic psychosis, non-responders to two different antidepseants for the current episode, necessity of ECT, treatement within seven days of pre-inclusion with non MAOL treatement within 3 days of pre-inclusion with a reverseller MAOL treatement within on the pre-inclusion with a non-reversible MAOL treatement within on combined to the company of the pre-inclusion with a non-reversible MAOL treatement within on combined design of explaining with a non-reversible MAOL treatement within on combined design of the inclusion with a non-reversible MAOL treatement within on combined design of an on-reversible many combined design of the m	Tianeptine	Mean: 39	Placebo	Yes	42 days	64	30	31.2	31.0	No

Claghorn 1983	No	Yes	Patients considered for entry were males and females aged 18-65 years, with a diagnosis of Major Depressive Disorder as defined by the Research Diagnostic Criteria of Spitzer et al. (2). All patients had dysphoric mood and at least four of the following symptoms; poor appetite or weight loss, sizep difficulty, loss of interest or pleasure in usual activities including social contact or ser, feelings of self-reprosch or guit, difficulty	Females of childbearing potential were excluded from entry if the possibility of pregnancy could not be definitely excluded during the study. Patients with somatic illness, pre-existing psychiatric conditions such as schizophrenia, schizoaffective disorders, epilepsy, and alcohol or drug dependence were also excluded, as were lactating and pregnant women.	Amitriptyline	75-300	Placebo	Yes	4 weeks	127	139	26	27.25	No
			concentrating, and recurrent thoughts of death or suicide. They also had to have no evidence of other pre-existing psychiatric disorders and their current episode of illners had to be of at least 2 weeks' duration. A minimum total score of 18 on the 21-titem Hamilton Depression (HAM-D) scale (8) modified according to the Early Clinical Drug Evaluation programme (ECDEU) manual (9) was required at entry as well as at the end of a piacebo washout period of 37-days.											
Claghorn 1996	No	Yes	Patients fulfilled the DSM-III-R criteria for major depressive disorder (single or recurrent episode without psychotic features or only mood- congruent psychotic features) and who had given informed consent, were enrolled in the trial. The procedures and possible side effects were explained to the subjects, who were obtained through self-referral or	-	Imipramine	80-240	Placebo	Yes	6 weeks	50	50	25.93	26.42	No
			health care professionals; informed consent was obtained according to federal regulations before the performance of any study-related procedures. All subjects were free of any significant health problems, as determined by a physical examination and clinical laboratory tests (blood chemistry, heamtology, urinalysis, serum pregnancy test) and electrocardiograms (ECGs). Subjects also had to be free of psychoactive medications for a test 37 days before study start.											
Cohn 1984	No	Yes	Individuals aged 60 or older were selected from outpa-tient populations at two centers. To participate in the study, subjects were required to have diagnoses of primary affect-twe disorder-depression, based on the Primary Affecture Disorders Checkist (dapted from Feighner et al.), which resembles the critical for major depressive epi-sode. Duration of the present episode was to be between 1 and 6 months. Patients were also required to have minimum total sozes of 20 on the Hamilton Depression Rating Scale (HDRS) and 14 on the Beck Depression Inventory, additional baseline ratings included the Rasino Presention Scale and Cod Anaety	Potential subjects who had past or present significant abnormal clinical findings, or medical conditions that might affect drug metabolism, were evoluted. Other exclusion raties were sensitivity to tricyclic antidepressants, requirement of ECT or any psychotro-pic medication other than chloral hydrate, and drivoric alcohol or drug abuse.	Imipramine	75-200	Placebo	Yes	4 weeks	Unclear	Unclear	27	28	No
Cohn 1985	No	Yes	Scale. Patients eligible for inclusion were outpatients diagnosed as having major depressive illness according to DSM-III criteria, except that our patients had to have had the illness for at least 1 month rather than 2 weeks. The	Patients were excluded because of concomitant physical conditions or histories of conditions that would interfere with therapy or evaluation.	Imipramine	Maximum: 300	Placebo	Yes	6 weeks	54	58	25.9	25.14	No
Cohn 1990	No	Yes	HAM-D total score of each patient had to be equal to or greater than 20. Recurrent or single episode, 18+ years old, 18 or more om HAMD-17, no more than 20% decrease between screen and baseline, RDS of at least 8	Schizophrenia, atypical type, anxiety, bipolar, drug or alcohol abuse, medical conditions.	Imipramine	65-275	Placebo	Yes	6 weeks	Unclear	Unclear	24.5	25.6	No
Cohn 1996	No	Yes	and higher than Covi Anxiety scale. HAMD-17 of at least 20, 18+ years	-	Imipramine		Placebo	No	8 weeks	11	13	23.6	23.4	No
Costa e Silva 1997	No	Yes	18 - to 60-year-old patients, eligible for the study, had to fulfill DSM-III as retrieval for Major Depression or Biplos Diorder. De-pressed, of Biplos diorder. De-pressed, of Major Diorder. Despressed, of moderate or severe intensity without psychotic features, with or without criteria for melancholic type and with a total Montgomery-Asberg Depression Rating Scale (MADRS) score of at least 25 [22], The patients were in- or out-patients.	Patients could not be included if they were defined as treatment resistant after prescription of two different antidespressants, each antidespressant having been prescribed for at least 4 weeks, with all some regarded as being in the therapeutic range. Patients with all severe or uncontrolled disease, with a history of drug abuse or depen- dence, or with excessed enfishing habits, women of ridli-bearing potential without effective contraception, or those pregnant or breast- feeding has to be excluded.	Tianeptine	25-50	Placebo	Yes	6 weeks	Unclear	Unclear	35.2	35.6	No
Dominguez 1985	No	Yes	Patients between the ages of 21 and 65 who meet DSM-III criterio of MDD (Single or recurrent), All had establishes primary depressive symptoms of at least 2 weeks duration, with a minimum score of 15 on the HAM-D17	Patients were excluded if their depression was secondary to any other prophetatic illness, if they had any significant physical condition, or had a history of recent or continued substance abuse. Patients were also excluded of they were pregnant or of childbearing potential. Other exclusion criteria were exposure to antidepressants within 3 days, lithium within a week and/or Mol hiblibitors, ECT or investigational drugs within 1 month of the washout phase.		100-300	Placebo	Yes	4 weeks	35	31	22.0	20.9	No
Doogan 1994	No	Yes	Patients were eligible for inclusion if they were attending a general practitioner for treatment of a primary najor depressive prosupote that met IDSM-IIB. Rotteria (American Psychiatric Association, 1587), were aged over 18 years, and ager informed consort. They also had to have a score on the Montgomery-Auberg Depression Rating Scale (MADRS, Montgomery and Abserg, 1979) of 27 or more, and a severity score of 4 or more on the Clinical Global Impression (CGI) scale (Guy, 1976).	MADRS; [2] risk of saudole (MAD RS item 10 nated over 3); [3] current pregnancy, lactation or risk of pregnancy, [displication corresponding, lactation or risk of pregnancy, [displication corresponding pregnancy, lactation or risk of pregnancy, [displication or cardiac shyperplass; [7] history of hypotension; [8] concurrent hereapy with ethanistic, ethicoguie, or guanethidine; [9] concurrent thereapy with sympathorimmetics or guanethidine; [9] concurrent thereapy with sympathorimmetics or guanethidine; [9] concurrent thereapy with the preceding 3 months; [11] a history of intolerance, resistance, or sensitivity to either tricyclic antidepressants or 5-HT resplance inhibitors; [2] presistant depression [6] or more weeks' treatment with antidepressants for the current episode of over I years'; [13] narrow-angle glaucoms; [14] depression secondary to other psychiatric disease; [2], shidopyrein, dementals or to organic disease; [15] history of epilepsy, [16] current use of other psychotropic medication (part from a short-acting nonsharbiturate	Dothiepin	75-150	Placebo	Yes	6 weeks	108	101	27.3	27.4	No
Dunbar 1991	No	Yes	Outpatients who fulfilled the DSM-III criteria for major depression and had a score of 18 or more on NAMD-17. Their baseline Raskin depression score had to be higher than their Covi anxiety score.	International Control of the Study occurred if patients had any other primary psychiatric diagnosis or progressively unstable physical linkses. Women childbearing potential were excluded for the initial part of the study (FGA requirement). During the latter stages of the trial, women cutsing adequate contraception or who were leasting were excluded. Therapy lasted 6 weeks following a 4-14 day placebo runin period. Any patients who had a 2 20% reaction in the HAMD score over this period were excluded, the remaining subjects being randomised to either provident, impriment or placebo.	Imipramine	65-275	Placebo	Yes	6 weeks	241	244	26.2	26.6	No
Edwards 1983	No	Yes	Outpatients of both sexes between the ages of 18 and 66 years were selected from those referred to the Psychatric (Division of the Royal South Hants Hospital, Southampton. To be included in the study petitions must have had a unipolar depressive lines which had become established as an autonomous process and whose course was largely independent of environmental influences even though threaful events might have been studied in the Medical Research Council Control for programs depressive lines (Medical Research Council, 1955) and the criteria of reighter and his colleague (Feigher et al., 1972). They corresponded to the DSM-III category of 'major depression' and no patients had a soore of less than 17 on the Hamitton Rating Scale for Depression (Hamilton, 1956).	Patients who had received treatment with a therapeutic dose of mianserin or majorotiline at any time during the course of their present illness were excluded. Plateints were ablo excluded if they had a serious physical illness, organic brain syndrome, epilepsy, mental sustommatility, a hierory of actival or illegal drug abuse or had been given ECT during the preceding as months. Pregnant women or women lakely to become pregnant during treatment were also excluded.	Maprotiline	75-225	Placebo	No	6 weeks	20	19	22.1	24.1	No
Emsley 2018	Yes	Yes	Outpatients, at least 65 year, moderate to severe episodes of recurrent MOD.	MDD single epidose, bipolar I and II, dysthymic disorder, depression superimposed or dysthymic disorder, Alzheimers, dementia, mild cognitive impairment, panic disorder, gaorapholas, specific flobia, social phobia, OCD, PTSD, acute stress disorder, psychotic disorder according III DSM-YTR. Unstale medical conditions, alcohol or drug abuse. Not responded to 2 drugs, has EET or structured psychoterapy.	Tianeptine	25-50	Placebo	Yes	8 weeks	105	107	26.7	26.6	No
Escobar 1980	No	Yes	[1] diagnosis of endogenous major depressive disorder according to the Research Diagnostic Criteria (RDC) 8 of the New York State Psychiatric Institute; [2] no Abstroy of other psychiatric disorder or major physical illness; [3] baseline total scores in the Hamilton Depression Scale (HMA-0) of 18 or higher, (4) seem of 21 youngons of depression as Isted in Table 1 distributed in at least three of the five symptom clusters; and [5)	By the end of the washout period, total scores in the Hamilton Depression Scale had to be 18 or higher for the patient to go into the double-blind portion of the study.	Imipramine	100-300	Placebo	Yes	4 weeks	15	12	31.3	30.9	No
Fabre 1996	No	Yes	Sinend informed consent. Females (using a medically acceptable method of birth control) and males aged 18 to 65 years who met DSM-111-R criteria for major depressive disorder were recruited on an outpatient basis. All subjects had a minimum score of 20 on the 21-tem Hamilton Depression Rating Scale for Depression (HAMP-0) and a minimum score of 20 not the 45 depressed mood* flem at screening and baseline. A minimum Raskin Depression Scale score lost and a Cox Anacley Scale score less than the Raskin Score were also required at the screening and baseline visits.	unstable medical condition, clinically significant abnormal laboratory findings and patients who demonstrated aptechor response clarked as < 20% improvement in HAMA-D total score) during the washout phase.		40-240	Placebo	Yes	6 weeks	50	50	26.5	26.0	No
Feiger 1996	No	Yes	Nation and formate outlyiers ages 15 or other with the diagnosis off either single or recurrent reploated of migh or persons in were eligible for this study. At least 8 + 4 day baseline period and to be five of diminally relevant consucts of psychotropic ages for for an appropriate time. A 3-week washout period was required for patients who had been treated for more than 3 months with antidepressacts or annihold forging beliefs could not have been treated with another investigational drug within 2 months of the baseline period. Subjects were required to have a score of at least 20 on the HAMO-17 at the end of the baseline period.	Solget were excluded if they were pregnent to lactating or were soundly active and table to bear children to were not using adequate contraception. Other exclusion criteria included dasis 1 psychiatric diagnosis, deducion a ballacination of using current episode of depression, high probability of needing other treatments during the course of study (percept choral hybarte of seeps), asplination current medical conditions, meeting (SMA-ill R criteria for psychoactive substance used disorder within the pior 12 months, allergy or hypersensitivity to asperones or tricyclic antidepressants, significant scide risk, electronomidate therapy within fin months of the study, and a history of glaucoma, urinary retention, or seizure disorders.	Imipramine	50-300	Placebo	Yes	8 weeks	41	40	24	24	No
Feighner 1980	No	Yes	Patients considered for this study were males and females, 18 to 6.5 years of age, with a polyshirt diag-nois of primary depression according to the criteria of Feighner et al. 14 in addition, these patients were required to have at least seven of the 2.1 gins comprising the Symptom Profile for Depression or to exhibit symptoms distributed among at least three of the Nex categories encompassed by the Profile (manifest or reported depression, somatic disturbance, depressive ideation, re- tarded thought psychomotrod disturbance, la addition, a total score of 13 or more on the Hamilton Psychiatric Rating Scale for Depression was required.	Females at risk of conception were not permitted to enter the study. Also excluded were patients with other psycholic disease or new psycholic disease or new psycholic disease or psycholic disease or new psycholic disease poor psycholic disease psycholic	Imipramine	100-300	Placebo	Yes	4 weeks	20	12	36.6	36.0	No

Feighner 1983	No	Yes	Outpatients suffering from moderate to severe symptoms of a Unipolar Maylor Operative Noticer for at least in moth were selected for the study. They met the Feighenr Diagnostic Criteria for primary depression (13), which are secretally interchangeable with the DSM-11 criteria for Major Operative piscode (14). The Feighenr criteria include dysphoric mood and at least level of the following symptoms: poor appetitior or weight loss, deep difficulty, loss of energy, agitation or retardation, loss of interest in usual activities or decreases in insual drive, feighings of guilt, complaints of diminished ability, and thoughts of death or suicide. Additionally, participants were required to have minimum baseline baseline score as follows: 18 or more on the 21-time Hamilton Charles of the Control of	Patients were excluded who suffered from bipolar major affective disorders, predominantly psychmotor readed depression or depression secondary to other non-affective psychiatric fillers. Patients with chinically mustable medical disorders were excluded as were any patients known to be hypersensitive to benociateprines or TCX. Is addition, patients who required anti-chiningies, CN Scattle anti-hypertensives, or other psychotropic medications, except chlorohydrate, were excluded.	Imipramine	50-225	Placebo	Yes	6 weeks	Unclear	Unclear	30.4	30.0	No
Feighner 1989a	No	Yes	Inclusion criteria: 18-70, an intal 21-item HAMD score of at least 20, a minimum Raskin Depression Scale score of 8, and a Cow Anxiety Scale score less than or equal to the Raskin.	Patients were excluded if they were pregnant, not practicing medically acceptable contraception, or if they poxed a serious suicide risk. Organic brain aydrome, schizophrenia, a history of setzum gor or alcohol abuse within the past year, or a contraindication to imprimen, such as glucumon or chronic unitary tetention. Also excluded after wash-out if their HAMD score was less than 20 or had decreased by 20% or more.	Imipramine	Unclear	Placebo	Yes	6 weeks	Unclear	Unclear	25.96	25.9	No
Feighner 1989b Feighner 1989c	No No	Yes Yes	DSM-III major depression MDD according to DSM-III for at least 4 weeks. Minimum score of 18 on	SECULAR OF EAR OF HIGHE.	Imipramine Imipramine	150-300 25-250	Placebo Placebo	Yes Yes	6 weeks	36 15	19 15	27 Unclear	25 Unclear	No No
Ferguson 1994 -	No	Yes	HAMD-17. Age 18-70 Outpatients aged 18 to 75 years with a diagnosis of major depression	Exclusion criteria included active suicidal ideation or suicide attempts	Dothiepin	50-150	Placebo	Yes	10 weeks	194	96	23.9	23.6	No
dothiepin Ferguson 1994 - doxepin		Yes	without psychotic features (DSM-III-R) criteria) were screened at 15 centers. Patients were required to have a total score of at least 20 on the 17-titem Hamilton Rating Scale for Depression (HAM-D), a score of at least 9 on the Raskin Depression Scale, a score on the Covi Anxiety Scale 10 less	in the last 2.1 months, schizophrenia, organic mental syndromes, or seizure disorders, faiture to respond to an adequate course of satisfeepersant therapy, recent bistory of alcohol or drug abuse, electrocensulule therapy within 30 days of the study, monoamine oxidese inhibitors or neuroleptics within 14 days of active drug treatment; and our offerth antidepersants or analoptics within 7 factures or criteria included active suicidal ideation or saided attempts, in the last 21 months, schizophrenia, organic mental syndromes, or seiture disorders; failure to respond to an adequate course of antidepersant therapy, recent history of abone) or finely abuse,	Doxepin	50-150	Placebo	Yes	9 weeks	193	96	23.8	23.6	No
			than the Raskin score, and a moderate or greater severity of illness on the Clinical Global Impressions (CGI) scale.	oxidase inhibitors or neuroleptics within 14 days of active drug treatment; and use of other antidepressants or anxiolytics within 7										
Fontaine 1994	No	Yes	Inclusion criteria included age between 18 and 65 years, diagnosis of MDD (modified to require dysphoric features of 41 teast 4 weeks' duration), minimum pertentients come 22 con the first 31 trens of the Hamilton Rating Scale for Depression (MAM-0-17), and written informed consent.	date of baseline. Alterial were excluded from entry into the study for any of the following reasons: primary psychiatric diagnosis other than depression, Istory of bipolar disorder, or gains mental disorder, or schizophrenis, symptoms of urinary retention or prostatic hypertrophy, or glasmosi, DSAH-ledflered diagnosis of storollar or substance above within the past year; significant medical disorder except mile hyperterison controlled with drugs other than except mile hyperterison controlled with drugs other than except mile hyperterison controlled with drugs other than extend the story of the s	Imipramine	50-250	Placebo	Yes	6 weeks	45	45	25.8	25.9	No
Gelenberg 1990a	No	Yes	For inclusion patients had to meet DSM-III criteria for major depression and relighter criteria for primary depression. They also had to socre at least 16 on the first 17 items of the Hamilton Rating Scale for Depression (HAM-D) at the end of a "washout" period.	We excluded women who were or who might become pregnant, patients with other polyhatir for serious medical illnesse, or patients with chemical dependencies. Further, patients must have been free of lithium for at least 7 days, MAO inhibitors for at least 2 weeks, tricyclic or other antidepressants for at least 3 days, and any other investigational drug for at least 4 weeks, and must not have had electrocomoulsive therapy within at least 4 weeks.	Amitriptyline		Placebo	Yes	6 weeks	19	22	24.8	23.6	No
Gelenberg 1990b	No	Yes	Men and women (without childbearing potential) outpatients, ages 18 to 75 years, with a definite diagnosis of major depressive disorder per Research Diagnostic Criteria (RDC) (Spitzer et al., 1978) and an entry score of 3/=20 on a modified Hamilton Depression Rating Scale (HAM-D), adapted to include symptoms of hypersomnia, hyperphagia, and weight gain (see Appendix).	We excluded patients with a history of mania, symptoms of psychosis or a diagnosis of schizophrenia, those unable to give informed consent, or patients with a current diagnosis of al-coholism, other drug addiction, epilepsy or clinical evidence of serious suicidal risk with poor past response to antidepressant therapy or with medical illnesses that might interfere with treatment.	Imipramine	Unclear	Placebo	No	4 weeks	Unclear	Unclear	24.3	24.5	No
Georgotas 1982	No	Yes	Patients were selected for the study on the basis of the following criteria: i) evidence of major depressive disorder according to Research Diagnostic Criteria (RDC) (9), 2) age between 18 and 65 years, and 3) minimal baseline total score of 18 on the Hamilton Rating Scale for Depression .	Exclusion criteria were intercurrent medical illness, childbearing potential, and the need to take other medications. The patients were predominantly middle aged. For two-thirds of them the current depressive episode had lasted 6 months or more. All patients provided informed consent.	Amitriptyline	150-300	Placebo	Yes	4 weeks	Unclear	Unclear	28.5	28.6	No
Georgotas 1986	No	Yes	Men and women, 55 years of age and older, complaining of depressive symptoms, were evaluated for entry into this outpatient study. Fatients included in the study were independintly diagnosed by two psychiatrists as suffering from a major depressive disorder as defined by the Research Oligosotist Citerita (Spitzer et al. 1976). A score of 15 or greater on the Hamilton Rating Scale for Depression was also required for inclusion. The depressives subspec (endogenous/honendogenous) according to RDC was also ascertained.	<u>Journals from Uniform</u> . They showed evidence of moderate to severe demental, drug or allohold dependence as defined by DSM-III, mental relatedation, evinos mentalogical disorders, other presenting major psychiatric disorders, sevious medical films disorders, other presenting major psychiatric disorders, sevious medical films (TSM LONG). The seventify of the depression or its resistance to previous treatment was on a deterrent to inclusion, provided that patients were not actively suicidal and that they had a repoposible friend or family member who was in frequent contract with our research of family member who was in frequent contract with our research.	Nortriptyline	Mean: 79	Placebo	Yes	7 weeks	Unclear	Unclear	23.6	23.1	No
Gerner 1980	No	Yes	60 years of age and older with a diagnosis of unipolar depression by the Research Diagnostic Criteria (48) and with a Hamilton Depression Score of	Patients were excluded because of significant hepatic, renal, cardiovascular, peurological, or other medical problems, or use of	Imipramine	50-200	Placebo	Yes	4 weeks	21	20	25	25	No
Gershon 1980	No	Yes	at least 18 were included in this study. Admission criteria were primary depressive disor-der of the endogenous type, a minimum score of 18 on the Hamilton Rating Scale for Depression at a score of at least 7 of the 21 symptoms in at least three of the five categories of the Symptom Profile for Depression (Table 1). The Categories of the Symptom Profile for Depression (Table 1). The Diagnostic and Statiscal Manual (DAWI) criteria for a major depressive disorder were met by 361 of the 263 patients included in the analysis of Pickary, Patients with other psychotic on resulted disorders, im-pared physical health, a history of brain trauma, also-holsin, drug addiction, sexture disorders, nernal deficiency, and fix of pregnancy were excluded from the trial. All patients gave written informed consent for the study after an explanation of the possible risks and benefits was provided.	prescribed or other drugs (including alcohol).	Imipramine	100-300	Placebo	Yes	4 weeks	Unclear	Unclear	31	30	No
Ginestet 1997 - 37.5 mg	No No	Yes	The patients included were in or outpatients, 18–65 years. They had to meet DSA-Hill Retires for major depression. Depression was of moderate or severe infensity, without psycholic features, meeting or not criteria for melanchoic type. AMORIS score had to be of all east 25 Montgomery and Abberg, 1979) at the end of the placebo period and provided that, in case of a score decrease, this reduction was less than 30% of the initial score. The patients included were in-or outpatients, 18–65 years. They had to	Patients who could not be included were: patients defined as nonresponders after pricription of an antidipressant for at least 4 weeks for the current episode with ality doses regarded as being within the therapeutic range; patients with sweere or uncontrolled somatic diseases, patients with a history of drug or alcohol abuse; pregnant women or women of childreshirp potential without effective contraception. Patients who could not be included were patients defined as	Tianeptine Tianeptine	37.5 75	Placebo	Yes	6 weeks	84	38	31.6	31.7	No
	No		meet DSM-III-R criteria for major depression. Depression was of moderate or severe intensity, without psychotic features, meeting or not criteria for melancholic type. MADRS score had to be of at least 25 (Montgomery and Asberg, 3179) at the end of the placebo period and provided that, in case of a score decrease, this reduction was less than 30% of the initial score.	nonresponders after prescription of an antidepressant for at least 4 weeks for the current episode with daily doses regarded as being within the therapeutic range; patients with severe or uncontrolled somatic diseases, patients with a history of drug or alcohol abuse, pregnant women or women of childbearing potential without effective contraceation										
Hicks 1988	No	Yes	referral or in response to a newspaper advertisement. They were included in the study if the riginary prochiatric diagnosis me DSM-Ill criteria for major depression with melancholia (American Psychiatric Association, 1380). Also required were a minimum score of 26 on the Hamilton Rating Scale for Depression (Hamilton, 1560) and 10 on the Raskin Depression (Scale (Raskin et al., 1567), and a Covi Anxiety Scale score (Covi et al., 1379) below the Raskin score.	Patients were excluded from the study if they were pregnant, had major medical illense, pallensy, glaucona, hypothyroidism, or active alcohol or drug abuse. Also excluded were those who had received electroconvolutive therapy, monoamie oxidase inhibitors, or an investigational drug in the previous 2 weeks. Psychotropic medications were tapered and discontinued? drugs before hospitalization. Patients were admitted as inpatients to the Clinical Beaventh Central value there in the Clinical Seasons's Central value of the Clinical Seasons's Central value their restantiant for Clinical Seasons's Central value of the Clinical Seasons's Central v	Amitriptyline		Placebo	Yes	6 weeks	16	15	30.8	29.4	No
Itil 1983	No	Yes	Patients were selected who reported an episode of primary depression of a least 2 weeks duration, in which the lateration of mondo exceeded customary sadness and could not be relieved by social contact. Patients and tatalized an immum of 15 points on the first 17 items of the Hamilton Rating Scale for Depression (HAMD; Hamilton, 1967). All patients had aminimum of 100 exect symptom, thus complying with the Research Diagnostic Criteria for depressive disorders (DSM, 1980). All patients met depression of the control of the depression of th	Pregnant women and women of childbearing potential were eccluded, as were patients whose depression was secondary to another illness. Patients receiving the following therapy were also eccluded: imparamia, MAOI inhibitors within 2 weeks of study commencement, electrocomouldes therapy within 4 weeks of study commencement, thinhour andowate, or any short or follogetime medication which might interact with either study drug.		50-300	Placebo	Yes	4 weeks	25	22	21.9	19.7	No
Itil 1993 - doxepin	No No	Yes Yes	Diagnosis of Major Depressive Episode (DSM-III-R 296.2, 296.3) Diagnosis of Major Depressive Episode (DSM-III-R 296.2, 296.3)	Psychotic features Psychotic features		50-150 50-150		Yes Yes	9 weeks 9 weeks	Unclear Unclear	Unclear Unclear	24.9 23.4	22.8	No No
Jacobson 1990	No	Yes	Psychiatric outpatients meeting DSM-III criteria for a major depressive epicode (single or recurrent), baseline 17-Item HAM-D >= 18	25% decrease in total MAM-D score during the placebo wash-out period, history of skrolphrelia or derbe psychoses, atypical depression, adjustment disorder, drug or alcohol abuse, drug overdose in the previous 4 months, active suicidal tendencies; patients with clinically relevant renal, cardiovascular, respiratory or enerbrovascular disease, protatic hypertophy, narrow angle glaucoma, urinary retention, unstable disbetes, seizure disorder or dicinically relevant feet danges, not ECT in the periodus 3 months, adequate dosor of an antidepressant (>150 mg amtiriphyline or qualwaleff or at least fewelsh) in the month preceding the trial; women of shidbearing potential without adequate contraception, monthers sintle breastfeding or 6 months not autrum	Amitriptyline	Mean: 115.1	Placebo	Yes	4-6 weeks (unclear)	Unclear	Unclear	21.6	21.4	No
Javors 2000 Katz 1990	No No	Yes No	Patients meeting DSM-IV criteria for unipolar major depression Consenting, medically stable subjects with persistent symptoms of major	-	Desipramine Nortriptyline		Placebo Placebo	No Yes	6 weeks 7 weeks	5 Unclear	4 Unclear	Unclear 21.7	Unclear 23.7	No No
			depression, a score on the 21-item Hamilton Rating Scale for Depression of at least 18, and no medical contraindications to the use of nortriptyline											

Katz 1993b Katz 2004	No	Yes	For both protocols, patients were required to attaitly then-current DSM criteria for major depressive episode or protocol 03, DSM-III in Criteria were to be statisfied, and for protocol 01, DSM-III in Criteria were to be statisfied. However, protocol 01 also specifically excluded patients with atypicality and double depressions. Thus, for both protocols the inclusion criteria for affective disorder were close. In addition, for both protocols patients were required to statisfy a sevenity criterion of 13 or greater on the hamilton Depression Rating Scale, reflective were required to be 18-65 years old. Protocol 01 also allowed entry of patients 66-70 years old following medical constitution. Patients with a diagnosis of primary major depression, unipolar type,	Patients were excluded on standard medical grounds including distincibly significant heptacit clauses, glasmoun, seture discorder, hypertension, endourie disorder, prostats (hypertension), renal disease, cerebral vascular disease, cardiovascular diseases (including significant electrocardiogram (ECC) findings), climical laboratory findings, bom entro electrocardiogram (ECC) findings), dimical laboratory tricyclic or tetracyclic anticepressants. Women of childbearing potential, preprant, and nursing women were not to be entered. Patients who were judged at risk for suicide were excluded. All patients provided written informed comen, and conduct of this particular values of the patients provided written informed comen, and conduct of this particular values and provided at each site by an institutional review band.	Amitriptyline Desipramine	75-225	Placebo	Yes	4 weeks	93	104	23.6	23.2	No No
			single, or recurrent episode were identified from newly admitted in- patients at two Teas Veterans Admiration (IVA) hospitals. All subjects provided written informed consent and the study was carried out as approved by the University of Teas shelth Center at San Antonio's institutional Review Board (IRB) and the Dallas IVA Medical Center's IRB. Olagonical interviews were conducted using the Structured Clinical interview for DSM-III (SCIID, Spitzer and Williams, 1953). Patients were required to soze or 36 on the HAMD (21-time version) (Hamilton, 1960).											
Klieser 1988	No	Yes	The patients all suffered from severe vitalized depression corresponding to the DSM-III classification "major depressive disorder". The severity of the disease was so pronounced that the treatment had to be carried out on a closed ward.	-	Amitriptyline	150	Placebo	No	3 weeks	12	14	34	31	Cognitive behavioural therapy, group therapy, occupational
Klieser 1989	No	Yes	Severe vitalized depressions or acute schizophrenia, and for whom locked	-	Amitriptyline	150	Placebo	No	21 days	10	14	Unclear	Unclear	therapy No
Kocsis 1985	No	Yes	ward-based treatment was indicated. Subjects were included if they (1) Midfiled DSM-III criteria for dysthymic disorder, in, depressed or dysphoric mood for at least two continuous years plus at least three associated symptoms; (2) had a Global Assessment Scale (GAS) score of 70 or less; (3) had a score on the 24-tem version of the Hamitton Depression Scale (IAMA-D)[10 of greater than 13; and (4) had given signed informed consent.	Patients were excluded if they had a history of bipolar disorder, ie, mania or hypomania, or 'secondary depression' as indicated by a history of psychosis, schools or substance abuse, or severe or chronic medical iliness. Also excluded were patients having a contraindication to imipramine or an apparently adequate trial of antidepressant medication within the past six months. The presence of Asis I and Asis I disorders other than those already stated was systematically assessed but was not used to exclude patients from the study.	Imipramine	100-300	Placebo	Yes	6 weeks	29	25	25.6	22.1	No
Kupfer 1979	No	No	All forty-seen patients were hospitalized on the Clinical Research Unit (CRU) at Western Psychiatric institute and Clinica (WPIG. 14 the time of admission, all patients had a traditional psychiatric interview and a physical examination. In addition, collegar information was obtained from their families and from case records of previous hospitalizations. During a two-week dury-free price of the price of production tests, an electroencephalogram, and any other tests that, based on their history or physical examination, were indicated. All patients thus underwerd an electroencephalogram, and any other tests that, based on their history or physical examination, were indicated. All patients thus underwerd an electroencephalogram, and any other exists that, based on their history or physical examination, were indicated. All patients thus underwerd an electroencephalogram of the production of their production. The production of the productio		Amitriptyline	50-200	Placebo	Yes	4 weeks	30	17	40.3	45.5	No
Langlois 1985	No	Yes	Patients were diagnosed by two psychiatrists as suffering from a major depressive disorder according to RDC and DSA-III criteria [9, 10]. A minimum total score of 20 on the Hamilton Rating Scale for Depression III) was required to enter the study. None of the patients had received an antidepressant or an antipsychotic drug for at least 2 weeks prior to	-	Amitriptyline	150-225	Placebo	No	4 weeks	15	15	Unclear	Unclear	No
Lapierre 1987	No	Yes	entering the study. Minimum 15 on HAMD-17	Other psychiatric diagnoses, significant organic disease, dependent on licit or illicit drugs, recieving ECT within 4 weeks, lithium carbonate within one week, MAO inhibitors within 2 weeks, other antidepressants during wash-out, any drug which could not be discontinued and might interact with study drug.	Imipramine	Maximum: 300	Placebo	Yes	6 weeks	21	20	24	22	No
Larsen 1989	No	Yes	in- and outpatients of either sex, above 17 years of age, suffering from major depressive disorder (DSM-111) (2) dissified as reactive depression according to the hexexastel it scale (3) were eligible for this double-blind trial. At 2 successive examinations 1 week apart the patients scored at least 15 on the first 17 items of the Hamilton Rating Scale for Depression (HRSD) (4)	Exclusion criteria were: previous manic episodes, adequate treatment already instituted, need for ECT, obvious suicide risk, history of drug or alcohol abuse, noncooperation or unreliability, pregnancy, lactation, abnormal hepatic or renal function and known haematopoietic, metabolic or hormonal disorders, diastolic blood pressure above 100 mmHg and any contraindication for tricyclic	Clomipramin e	75-150	Placebo	No	6 weeks	20	18	Unclear	Unclear	No
Lydiard 1989	No	Yes	Subjects were male and female, 18 years or above, who were not on psychotropic medications (no lithium within 6 months of study entry) and who met the DSM-III (American Psychiatric Association 1980) criteria for major depressive disorder. Patients had a score of at least 22 on the Hamilton Depression Rating Scale (HAM-D).	antidenressants. Exclusions included psychotic disorders, organic brain syndrome, bipolar affective disorder, current depressive symptoms of < 1 month or > 1 8 months duration, a current substance use disorder, or clear suicidal intent.	Imipramine	100-300	Placebo	Yes	6 weeks	18	18	26.4	26.0	No
Lydiard 1997	No	Yes	At least 18 years old, pulgathers with DSA-BIHR grinary ask 1 of major deprecision (night or recurrent), current regioned not less than a weeks. HAMD-17 score 18 or more. No more than slight improvement during placebo washout, max 3 points on CGH	IDAM-IB is criteria for : autor/chronic organic mental islander, organic tablin syndrome, opkrivmia, blookal disorders, severe generalized anxiety disorder, COD, psychotic disorders, severe personality disorder. Significant medical illense, recent history of substance abuse or depence, current suicide risk, history of neurologic disease, narrow- angle glasurome or significant protates unpyritems. Additional psychotropic drugs during study, previously receivederstraine, within 1 month in other study, failed to respond to adequate trails of two or more antidepressants, received any deport neurolegist, says daily processed and the study of the contraction of the contraction of the study of the contraction of the contraction of the study of the contraction of the contraction of the study of study of	Amitriptyline	50-200	Placebo	Yes	8 weeks	131	129	22.1	22.1	No
Mann 1981	No	Yes	Admission criteria included a diagnosis of a major depressive disorder, endogenous subtype, according to research diagnostic criteria 25 of sufficient severity to score at least 18 on the Hamilton depression scale	Patients with other significant neurotic or psychotic disorders, alcohol or drug abuse, seizure disorders, mental retardation, brain trauma, significant physical disease, or females in whom the possibility of pregnancy could not be reasonably excluded were not admitted to the study.	Imipramine	100-300	Placebo	Yes	4 weeks	Unclear	Unclear	24	22.5	No
March 1990 McGrath 2000	No No	Yes	Admission orderfa included an illness duration between 1 and 18 months (researsED-79.54 c. range 1.17 month) and a minimum zone of 2.2 on the first 17 items of the Hamilton Rating Scale for Depression (HAM-D). Subjects were men and women, age 18 to 65 years, who met DSM-IV	The following subjects were excluded from participation: pregnant women, lactating women, or women of utilizerating potential who were taking inadequate contraceptive measures; patients with schapphrenia, potential verbound of the production within 1 year of substance abuse or atchdoling patients with a cardiovascular, predict, rend, gastroinefaith, pulmonary, metabolic, teatherms, or assessment of depression; patients with or required treatment, or assessment of depression; patients with or required treatment with any concurrent medication that might interact with or obscure the action of the study medication; patients with officially spatients with multiple drug allergies; patients who had received any continuous production of the preceding 1 weeks, and patients with officially in the 2 weeks preceding study entry or with had received any other antidepressant drugs in the preceding 1 weeks, and patients with officially on a received any other antidepressant drugs in the preceding 1 weeks, and patients with officially on a received any other antidepressant drugs in the preceding 1 weeks, and patients with officially on a received any other antidepressant drugs in the preceding 1 weeks, and patients with official and received any other antidepressant drugs in the preceding 1 weeks, and patients with official and received any other antidepressant drugs in the preceding 1 weeks and patients with a directived any other antidepressant drugs in the preceding 1 weeks and patients with a directived any other antidepressant drugs in the preceding 1 weeks and patients with a directived any other antidepressant drugs in the precipital and the preceding 1 weeks and patients with a directived any other antidepressant drugs in the precipital and the patients and the pat	Imipramine	50-300	Placebo	Yes	6 weeks	18	18	25.5 Unclear	26.5 Unclear	No
			criteria for a major depressive episode for at least 1 month and also met the Columbia criteria for atypical depression (9). Unlike DSA-VL, which requires two associated symptoms together with moof reactivity for a slappois of altypical depression, the Columbia criteria require only one associated symptom among the following four-overeating, oversleeping, severe anergy, and particological resolutive to interpression rejection. The requirement for only one symptom is based on treatment outcome studies showing that the presence of one associated symptom appears sufficient to observe the advantage of MADIo over tricyclics (3, 4) and evidence indicating that all associated symptoms were equivalent in predicting MADI advantage (23), in addition, biologic, course-of-lifesa, and family study data indicate that patients with a single associated symptom more closely resemble those with more associated features than throw with none (1)	lactation, or unwillingness to use effective Brith control in women, 3) untable and serious physical lines, 4,9 abstroy of seizure, 5) psychosis or organic mental syndrome, 6) substance use disorders active within 6 months, except for include dependence, 7) history of mania, 8) antisocial personality disorder, 9) history of nonresponse to an adequate truit of Towastine (defined as greater than 150 mg/ day for 2 consecutive weeks and weeks lost interment), 10) history of nonresponse to any other SSRI, and 11) laboratory evidence of hypothyroidism.	armpe di ime		- mod UU		- WCCMS			an and all	arman 201	
Merideth 1983	No	Yes	Patients with a diagnosis of MDD as defined by RDC, 18+ on HAM-D21	Patients with somatic diseases, drug allergy, schizophrenia, epilepsy or a history of drug or alcohol abuse were excluded from the trial, as were women of child-bearing potential and lactating or pregnant women.	Imipramine	Mean: 134- 215	Placebo	Yes	6weeks	Unclear	Unclear	26	26	No
Merideth 1984	No	Yes	Patients who participated in this study were at least 60 years old and met criteria for primary affective disorder opersion, based on the Primary Affective Disorders Depression Checklist adapted from Feighner et al. These criteria resemble tools for major depressive episode in Patients were also required to have, at baseline, moderate or severe symptoms of depression that produced stratal score of at least 18 on the symptoms of depression that produced stratal score of at least 18 on the symptoms of depression that produced stratal score of at least 18 on the symptoms of depression that produced stratal score of a least 18 on the symptoms of depression that produced stratal score and or more for the item depressed mood. Efforts were made to enroll patients whose current episode of illness had lasted at least 1 month, but not more than 6 months.	Patients who met any one of the following criteria were excluded from the study. 13 guillificate abnormal findings on physical examination or clinical laboratory study. 21 a medical or surgical examination or clinical laboratory study. 21 a medical or surgical condition that could interfere with the absorption, metabolism, distribution, or excretion of either test drug; 3) instory of significant to psychotro- pic drugs themically similar to comiferations or some distribution of the study of the	Imipramine	50-200	Placebo	Yes	5 weeks	Unclear	Unclear	26	29	No
Miller 2001	No	Yes	All subjects gave oral and written informed consent before entry in the study. Patients meeting DSM-III-R criteria for Major Depression were	-	Imipramine	Unclear	Placebo	No	6 weeks	Unclear	Unclear	Unclear	Unclear	No
Minelli 2010	No	Yes	randomly assigned to receive treatment. MDD as diagnosed on the basis of DSM-IV criteria. All were judged	No patient presented psychotic symptoms or comorbility disorders in	Clomipramin	25	Placebo	No	1 hour	Unclear	Unclear	Unclear	Unclear	No
			treatment-resistant depressed patients. Treatment resistance to ADs was defined as two or more unsuccessful trials of ADs at an adequate dose for at least 4 weeks.	Axis II and Axis III of DSM-IV	e									

14 t 4004 CT	In.	Iv	United to 40 CO and all 20 and the control of the c	From the second	Inches de la	Inches	In.	In.	42	Inches	Utestan	20.55	40.03	C
Murphy 1984 - vs CT Murphy 1984 - vs CT +	No No	Yes	Unipolar, 18-60 years old, 20 or higher on BDI, 14 or higher on HAMD-17. Unipolar, 18-60 years old, 20 or higher on BDI, 14 or higher on HAMD-17.	Free of psychotropic medication, neurologic disorders, medical disorders requiring medication other than diuretic. Free of psychotropic medication, neurologic disorders, medical	Nortriptyline Nortriptyline	Unclear	No intervention Active	No No	12 weeks 12 weeks	Unclear	Unclear	20.55	18.83	Cognitive therapy Cognitive therapy
Murphy 1984 - vs CT + placebo Mynors-Wallis 1995	No No	Yes	Unipolar, 18-60 years old, 20 or higher on BDI, 14 or higher on HAMD-17. The main criterion for inclusion was that patients met the research	Free of psychotropic medication, neurologic disorders, medical disorders requiring medication other than diuretic. Criteria for exclusion included having another psychiatric disorder	Nortriptyline	Unclear 50-150	Active placebo Placebo	No No	12 weeks	Unclear 31	Unclear 30	20.55	21.35	Cognitive therapy Problem solving
			diagnostic criteria for major depression-namely, that they had experienced low mod accompanied by at least four key symptoms of depression, such as appetite disturbance, skep difficulty, loss of energy, poor concentration, guitt, suidold thlowalth, loss of interest or pleasure in usual activities, and psychomotor retardation, for at least two weeks. In addition, patients And to soors 12 or more on the Hamilton craiting scale for depression (17 items), which measures the severity of depression.	(other than anxiety disorder) before the onset of the depression, receiving current psychological or antidepressant drug restament, having current psychologic and real though the control suicidal intent, having a history of skillapprient; excent drug or alcohol missue, or physical problems that would preclude being able to take amitriptyline.										
Nair 1995	No	Yes	In- and out-patients of 60-90 years of age, meeting the DSM-IIR is criteria for major depression, been eligible. At randmixtation (baseline), the total score on the first 17 items of the Hamilton Rating Scale for Depression (HISO), Hamilton, 1950, elselin, 1951 was at least 18. The duration of the current episode was a minimum of a weeks and the severity at least moderate as rated on a clinicar's Global impression of Severity Scale (COS) which covers the following categories: very severely il, severely il, middly il, minimally ili, or not ill.	Educision criteria were any other psychiatric or neurological diagnosis, however several consequence of the control control significant abnormal laboratory findings, including ECG, sitting blood pressure of 2 27000 dom set good and heart rate of 4 500 or 1000 byen, orthorostatic systolic fall in blood pressure of > 30 mm leg after lying for 5 min and, sind, any control anadication to the trial drugs. Patients who were uncooperative, those with a history of drug or alcohol abuse or having energiest of click under pressure in the presenting week, McOlds and effective control control sind pressure of the pressure of the control control control effective control control control control control control control sections of control control control control control effective control control control control control sections of the control control control control control sections of the control control control control control sections of the control control sections of the control control sections of the control control sections of the control section sections of the control section section sections	Nortriptyline	25-100	Placebo	Yes	7 weeks	38	35	23.5	24.0	No
Niklson 1997	No	Yes	MDD according to DSM-II-R, age 18-70 years, HAMD-17 of 18 or greater, duration of present episode at least 2 weeks, but not longer than 12 months since diagnosis was made.	Any other primary psychiatric diagnosis, if they had received relevant antidepressants within 5 half-lives or ECT within 1 year. Patients with clinically relevant renal, hepatic, cardiovascular or cerebrovascular disease, diabetic or epileptic, women not adequately protected against pregnance.	Imipramine	Maximum: 150	Placebo	No	6 weeks	142	108	22.7	24.0	No
NIMH trial 1989	Yes	No	To be included in the study, patients had to meet Research Diagnostic Criteria for a current episode of eliethic major depressive discorder (with the additional criterion that the required symptoms had to be present for at least the periodic 2 weeks) and had how have a score of 14 or greater on an amended version of the 17-item Hamilton Rating Scale for Depression (HSSD).	Educision risteria included specific additional psychiatric disorders (definite bipolar in and probable or definite bipolar in partic disorders, alcoholism, drug use disorder, antisocala personality disorders, filterules' syndrome, and Research Dispositic Cirleria diagnosis ofmajor depressive disorder, psycholic subtype), two or more schoolpysif estures, history of schizopheria, organic brain syndrome, mental eriandistion, concurrent treatment, presence of specific disording antisory of the protection of the protection of the disording antisory and presence of a clinical state inconsistent with participating in the research protocol, eg. current active suicide posternial or need for immediate treatment.	Imipramine	Mean: 185	Placebo	No	16 weeks	63	62	Unclear	Unclear	Minimal supportive therapy
Organon 3-020	No	Yes	Psychiatric outpatients meeting DSM-III criteria for a major depressive episode (single or recurrent), baseline 17-item HAM-D $>$ 18	255% decrease in total IAMA-D score during the placebo wash-out period, history of skinolphrenia or other psychose, shypical depression, adjustment disorder, drug or alcohol ablace, drug overdose in the previous 4 morths, active suididal tendencies; patients with clinically relevant renal, cardiovascular, respiratory or cerebrovascular disease, prostatic hypertopy, narrow-negle glaucoma, urinary retention, unstable disbetes, seizure disorder or clinically relevant Est Danges; no IECT in the previous 3 months, adequate dose of an antidepressant (>150 mg amitripytine or equivalent for at least 6 weekly in the month preceding the trial; women of dildbearing potential without adequate contraception, mothers called hereafteding or 6 months not narrum	Amitriptyline	Mean: 133.7	Placebo	Yes	6 weeks	Unclear	Unclear	24.9	25.2	No
Organon 84062	No	Yes	Psychiatric outpatients meeting DSM-III criteria for a major depressive episode (single or recurrent), baseline 17-item HAM-D >= 18	-	Amitriptyline	Unclear	Placebo	No	6 weeks	Unclear	Unclear	Unclear	Unclear	No
Peselow 1989	No	Yes	All patients who gave consent were treated as out-patients at the Foundation for Depression-Manie Depression. All patients involved in the trial met DSM-III criteria for major depression, were 18 years of age or older, and had a minimum score of 18 on the first 17 items of the 21-item Hamilton depression scale	All patients who participated in the trial were free from active medical illness, endocrinopathy and current substance abuse	Imipramine	65-275	Placebo	Yes	6 weeks	Unclear	Unclear	Unclear	Unclear	No
Philipp 1999	No	Yes	Inclusion: Men and women aged 18-65: Diagnosis of a moderate depressive episode according to ICD-10 (International classification of diseases, 10th revision) codes F32.1 and F33.1 - Minimum total score of diseases, 10th revision) codes F32.1 and F33.1 - Minimum total score of diseases, 10th revision for the maintenance depression rating scale: A clinical global impressions rating of a veerify (tiem. 1) of moderately, and admit a little production of the moderate of the mode	Edusion - Mild and severe depressive disorders according to (CI-1) doctor=120, 173, 0122, 173, 1732, 173, 0133, 18 pick and disorders according to (CI-1) Cooker 513.** Comorbidity from alcohol or drug dependence according to (CI-1) doctor=151-13-jusicial six (assessed by tem 10 of the Montgomery Ablang depression rating (assessed by tem 10 of the Montgomery Ablang depression rating (assessed by tem 10 of the Montgomery Ablang depression rating montgomery). The control of the Montgomery Ablang depression rating varieties and varieties of the Montgomery Ablang depression rating varieties and varie	Imipramine	50-100	Placebo	No	8 weeks	110	47	22.2	22.7	No
Pomara 2001	No	No	Participation was open to males and females between the age of 18 and 58 with a psychiatric diagnosis of maley depressive episode. Memirian Psychiatric Association, 1987) [DSM-III-R] and a baseline score of 18 on the 21-tiem Hamilton Depression Rating Sciele (IDRS). Patients were also diagnosed as having definite, primary, unipolar depression using Research Diagnostic Citrist (ROC) [Spitzer et al., 1977) based on the Schedule for Affective Disorders and Schizophrenia (Spitzer and Endicot, 1979).	Patients using other psychotropic medications within 14 days of entry into the study were also excluded.	Nortriptyline	50-150	Placebo	Yes	6 weeks	Unclear	Unclear	20.3	21.3	No
Prasko 2002	No	No	1 Age 20-60 years. 2) Meeting the DSA-HIR diagnostic criteria for eccurrent major depressive disorder of moderate or severe type (296.32 and 296.33) without sessonal pattern. 3) At least 2 episodes of major depression in life time, and at least one episode of major depression during the last 2 years previous the current episode, at least one episode in another season than the current one. 4) total score of the 21-time hamilton Psychiatric Rating Scale for Depression (10) higher than 20.5) Written informed consent.	1) The presence of any of the following mental conditions: a Biplian depression b. Paint Giorder. c. Alcoholism or drug abuse. d. Antisocial personality disorder. e. Histrionic personality disorder. f. Histrionic personality disorder. f. Histrionic personality disorder. f. History of schoolpheria. g. Organic brain impairment. h. Mental net artestation. 19 Presence of specify laysical lilless or medical contrandications for using imprantine; endocrine disease in history. 3) Pregnancy. 4) Treatment by drug causing depression in the last month. 5) Eye diseases (such as the aphabic condition, retinal diseases, inlammatory diseases, flatunmat. canterdats and optic nere disease).	Imipramine	150	Placebo	Yes	3 weeks	13	11	23	23.1	Bright light therapy
Raft 1981 Raisi 2007	No No	No No	Patients strending the N.C. Memorial Hoppital Plan Clinical in 1974 were screened for the presence of definite primary depression, according to the criteria of Feighter et al. (6.) If they were judged to require antidepressant therapy and gave informed consent, they were assigned to receive an adouble-blind basis. All subjects met the Diagnostic and Statistical Manual of Mental Disorders, Forth edition (22) (DOM-My criteria for MOD, based on the Disorders, Forth edition (22) (DOM-My criteria for MOD, based on the Dating Scale for Depression (HAM-D, 17 term) (23) score of at least 20.	Patients with history of other psychiatric disorders such as bipolar disorder, personality disorder, aniety disorder, substance abuse and were excluded. Also patients were occluded they were psychotic or posed a significant risk of skidde at any time during the trial. Pregnant or lactative women were excluded as well. All patients were	Amitriptyline Nortriptyline		Placebo	No No	5 weeks 8 weeks	23	7 22	32	31	No Citalopram
				free of unstable medical disorders including cardiovascular, hepatic, renal, gastrointestinal, pulmonary, metabolic, endocrine or hematological illnesses. All patients gave a complete medical and psychiatric history and were physically examined before entring the study.					-					
Ravindran 1995 Reimherr 1990	No No	Yes Yes	18-65, DSM-III-R, minimum score of 15 on HAMD-17 Male or female patients between the ages of 18 and 65 years who met the DSM-III criteria for major depression were considered eligible. After a	No other axis I disorder, free of physical or organic disorders Patients excluded from the study included those not meeting DSM-III criteria for major depression, pregnant or lactating females, and	Desipramine Amitriptyline	50-225	Placebo Placebo	Yes Yes	8 weeks 8 weeks	37 149	26 150	20.7	23.43	No No
			one colors and state in a major inspired where the considerated regions considered in graphs allund, placed washout period color 70 to 4 of a state of the color graphs allund placed washout period color 10 to 4 of a state of the color than 10 to 4 of the color o	statistic of high-frequency legislation scalarity using an adequate member of childrening potential rutp researchy using an adequate member of childrening potential rutp research using an adequate concurrent psychotherapeutic medication or concomitant medications other has estrogers, progretores, and disuretics; patients with other significant medical conditions; patients receiving another investigational drug within 4 weeks of enrolling in this patients with a history of serious intolerance or resistance to antidepressant medications; patients with an alcohol or drug abuse condition; and patients with schizophrenia or schizoaffective disorder.										
Reynolds 1999 – nortriptyline	No	No	To be included in the study, potential subjects were required to meet the criteria of the Schedule for Affective Disorders and Schlzophrenia—Lifetime Version (\$405-1) (15) and the Research Diagnostic Circles (160) (16) for a definice current major depressive episode (nonpsychotic and nonbipolar, with no history of chronic intermittent depression or dysthymal, for through the control of the con		Nortriptyline		Placebo	Yes	8 weeks	25	22	19.0	20.1	No
Reynolds 1999 – nortriptyline + IP	No	No	To be included in the study, potential subjects were required to meet the criteria of the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-1) (15) and the Research Diagnostic Citeria (BIO (18) for a definite current major depressive episode (nonpsychotic and nonbipolar, with no history of chronic intermittent depression or dysthymal, for thy or disorders and the CODAP (12), which replace the SchiZoS-1 as our primary diagnostic CODAP (12), which replace the SchiZoS-1 as our primary diagnostic value of the CODAP (12), which replace the SchiZoS-1 as our primary diagnostic value of the CODAP (12), which replace the SchiZoS-1 as our primary diagnostic. Which is the control to the control of the CODAP (12), which replace the SchiZoS-1 as our primary diagnostic. No their diagnost, with the exception of generalized anxiety disorder, panic disorder, and posturamist is treas disorder, were allowed. Diagnostic reliability was ensured through the use of a structured diagnostic assessment together with independent inicial confirmation by a serior psychiatrist (M.D.M., R.E.P.). A bereavement intensity score of 45 or more on the Teasa Review diversion of Gent (18) was required as an indication of active grieving. Finally, to be eligible for the study, subjects were required to provide written informed connext.		Nortriptyline	Unclear	Placebo	Yes	8 weeks	16	17	20.5	19.9	Interpersonal psychotherapy

Bishale 4003-	le-	In-	The subjects for the study		Amilton **	100 20-	Discrit	No	6 m 1	60	50	Hart	Hart	No
Rickels 1982a	No	No Yes	The subjects for the study were 202 nonpsychotic unipolar depressed outpatients; 120 patients were treated in private family practice and 82 patients in psychiatric practice. All participating physicians were trained by our research group in clinical research and were closely supervised (8). To enter the trial, patients had to suffer from at least a moderate degree	Patients were excluded if than were assensed bacteties as al-	Amitriptyline	50-225	Placebo	No	6 weeks	68	57	Unclear	Unclear	No No
	NO	143	To enter the trial, patients had to suffer from at least a moderate degree of depression (y-) one month), have a soon of y-5 on the register purposes of the properties of the	Patients were excluded if they were pregnant, lactating or planned to become pregnant. Also excluded from the study were patients suffering from schlasphrenia, organic brain syndrome, mental externation, actionly, sociopathy, schlas-affective disorder or taleolar depression and metandroila. Patients with serious impairment of hepatic and rental functions, cardiovacid or metabolic disease, and those with known hypersensitivity to the study drugs were also activated with the study of the study drugs were also activated to the study and study of the study drugs were also activated to the study of the study drugs were also activated to the study of the study drugs were also activated to the study of the study of the study and study of the s	ampramine	30*223	- racebo	NU	weeks		37	oncleaf	ondesf	110
Rickels 1982c - imipramine	No	Yes	To enter the trail, patients had to suffer from moderate to severe depression for which antidepression from windcation was considered the treatment of choice and had to be free of all psychotropic medications for least 1 week, and for 2 weeks if they were taking NACO inhibitors. Patients had to be depressed for at least 1 month, had to have a score of 10 months of 10	Patients were excluded if they were pregnant, lactating, or planned to become pregnant, lock occluded were patients with schloophenia, organic brain syndrome, or mental retardation, as well as patients suffering from serious impair—ment of heaptor or renal functions, or cardiovascular or metabolic disease, and those with horown hyperesticityly to be study drugs. Commontant therapy with other paychorogic drugs was not permitted. Patients had to be willing and able to understand and age a written informed consent form.	Imipramine	75-150	Placebo	No	6 weeks	Unclear	Unclear	Unclear	Unclear	No
Rickels 1982c - lofepramine	No	Yes	To enter the trail, patients had to suffer from moderate to severe depression for whoch antidepression from windcation was considered the treatment of choice and had to be free of all psychotropic medications for least 1 week, and for 2 weeks if they were taking NAC inhibitions. Patients had to be depressed for at least 1 month, had to have a score of 25 on the Feighten et al. (1927)), a score of 27 on the Feighten et perspection Scale (Teastin et al. (1970)), and a score of the feath of the depression Scale (Teastin et al. (1970)), and a score of 1990).	Patients were excluded if they were pregnant, lactating, or planned to become pregnant. Also excluded were pretines with schizophrenia, organic brain syndrome, or mental retardation, as well as patients, organic brain syndrome, or mental retardation, as well as patients suffering from serious impair—ment of hepatic or renal functions, or cardiovascular or metabolic disease, and those with known hyperemetalivity to be study drugs. Committent therapy with other psychotropic drugs was not permitted. Patients had to be willing and able to undestand and age a written informed consent form.	Lofepramine	105-210	Placebo	No	6 weeks	Unclear	Unclear	Unclear	Unclear	No
Rickels 1982d	No	Yes	an order to enter the drug stall, patients had to suffer from at least a moderate degree of depression for which antidepression rediction was considered the treatment of choice. Patients had to be depressed for at the stall month, have a minimum baseline score of 20 on the 21-tem Hamilton Depression Scale (105), have a minimum score of 5 on the Rasin Depression Scale (105), have a minimum score of 5 on the Rasin Depression Scale, and on the Feighner Depression (hecklist they had to exhibit dispélhoric mood plus at least five additional items. These intake criteria this identified each patient as suffering from a major depressive disorder as specified in the DSM III.	Leduced from the study were patients under the age of 18 and over he age of 60, patients with strong sociopath trends, alcholium, organic brain syndrome, or evidence of schizophrenia. Patients with shidors of univary retention, protate hypertrophy or glaucoma, requiring gausenthiem, and pregnant or lactating women were also excluded. Patients had to be free from psychotropic medication for at least? J days and free from MAO rinibilitor for at least 2 weeks prior to study participation. No psychotropic or hypnotic medication ofter than an occasional forloral hydrate was allowed during the study. Finally, patients whose laboratory data were not within normal range were excluded.	Imipramine	100-200	Placebo	No	6 weeks	Unclear	Unclear	Unclear	Unclear	No
Rickels 1985 - amitriptyline	No	Yes	Patients valuntarily participated in the study and signed an informed consent form thefore enrolling. To qualify for inclusions, patients that to meet the Fregieren engonate Consent for property reduces a certain which have been experienced to the consent of property reduces and the study of the consent of the consent of property reduces and the consent of the con		Amitriptyline	50-225	Placebo	Yes	6 weeks	124	65	25.48	26.38	No
Rickels 1985 - doxepin	No	Yes	Patients voluntarily participated in the study and signed an informed consent form before enrolling. To qualify for inclusion, patients had to meet the Feighier Diagnostic Cirtler's for primary depression, which have since been determined to be concordant with the DSA-III criteria for major depressive projection. The Feighier criteria include application cond and at least fine of the following symptoms: poor appetite or weight passes gaing difficulty, loss of energy, application or restrations, loss of interest in usual activities or decrease in sexual drive, feelings of guilt, complaints of diminished ability, and thoughts of deem or suicide. In addition, patients were required to have a score on the Raskin Depression Scale of 8 or more, five tensor more endorsed on the Feighier Depression Checklist, a HAM-O L21-tient) score of 18 or more, and a Covi Anxiety Scale score less than or equal to the Raskin score.		Doxepin	50-225	Placebo	Yes	6 weeks	122	65	25.85	26.38	No
Rickets 1987	No	Yes	To qualify for inclusion in the trial, patients had to fulfill DSM-III criteria for MDD, single or recurrent subtype, and had to have a zore of 18 or ingler on the MAND-21 and a zore of 30 or more on the Rakin Depression Scale, with the CoV Almelry Scale score being less than or equal to the Rakin score. Arrival at the DSM-III diagnosis was facilitated by a physician checklist that also allowed subtyping of patients as to whether or not they belonged to the metandicula subtype. Female patients and the scale of the subtype contraction of the present lines and to be one mother or foreign, a slightly stricter criterion than used by the DSM-III.	Study exclusions included the following: psychopathy or psychosis; bipolar, involutional, schlosoffective, or secondary depression; severe have or kidner disease; uncontrolled cardiovasidar, pulmonary, endocrinological, or collagen diseases; glaucome, hatlory of urmary endocrinological, or collagen diseases; glaucome, hatlory of urmary extention, paralytic limes, convolvide deoders, and any disorder contraindicating the use of tirtyclic medication. Pstetests known to be estudied to be decident profit in the contraints and the programmediates the contraints of the contraints of the sentitle to be made large sent programmed or, methydoga, or thyroid medications were also excluded: the use of any psychotropic medication other than study medication was prohibited.	Imipramine	75-225	Placebo	Yes	6 weeks	63	61	24.4	24.5	No
Rickels 1994	No	Yes	Moderate to severe major depressive disorder or bipolar disorder, depressed type but without rapid cycling. Patients had to be 18 years of age and had to have a total source of 20 or above on the HRSD at baseline. Female patients, if sexually active, had to use medically accepted contracective methods.	Standard medical and psychiatric exclusions were utilised.	Imipramine	50-300	Placebo	No	8 weeks	92	95	24.3	23.5	No
Roffman 1982	No	Yes	Depressed on Equations .18 to 65 years of age with a diagnosis of a major depressive disorder according to the Diagnosis Statistical Manual 128e. 2, 286.3 of the American Psychiatric Association and with a score of at least 18 on the Hamilton Depression Rating Scale (HORS) were used in this study.	Edution criteria consisted of history or evidence of clinically significant renal disease, Blun Or credition evolutions, hepatic disease, SOIT, SOFT, or alkaline phosphatase elevations, cardiovascular disease, emabblic disease, Seriure disorders, hypersensitivity to tricyclic antidopressants or related compounds, hypersensitivity to tricyclic antidopressants or related compounds. Albo patients with adjustment disorders, manifectpressive illness, correlatives with adjustment disorders, manifectpressive illness, corrective types chilophereia and primary antiety disorder were excluded. In addition, ingestion of cafferine was limited to 40 oz. of caffeniated beverages per day, informed consent for participation in	Amitriptyline	75-150	Placebo	Yes	4 weeks	Unclear	Unclear	24.3	25.0	No
Roth 1990	No	Yes	To quality for inclusion in the trial, patients had to fulfill DSAH ill criterio trialpic represerve fipiode (Splart, 1890). A current episode duration of all less one month, a zone of 22 on the first 17 items of the Hamilton of all less one month, a zone of 22 on the first 17 items of the Hamilton Depression Scale, and signed informed consent were required. The complete structured clinical interview for DSAH III (SCD-P) (278) Splatter et al., 3850) was used during screening to ensure diagnostic accuracy and the homogeneity of the sample at the USF site. Eligible patients were outpatients of either see, age 18 and older.	the study was obtained from each sattern! Women who were pregnant, lactating, or not using reliable contraception were excluded. Also excluded were patients with a heatery of any other uniquid Assi psychiatric disorder, including mania study of any other uniquid Assi psychiatric disorder, including mania could interfer with the diagnost, violatined or associated of depression as well as patients with any included inscription of the diagnost of the analysis of the diagnost and t	Desipramine	50-300	Placebo	Yes	6 weeks	30	30	29.5	28.9	No
Rothblum 1982	No	Yes	Make and female outpatients between the ages of 50 and 55 years, with NOAH its diagnosis of moderate to severe maple depression, were included. The diagnoses were made following an assessment on the Schedule for Affective Boorders and Schizophrens's Servity of depressions was measured by the Raskin Depression Scale, and a score of at least 7 of a total of 15 was required for admission. The initial telephone screening interview attempted to rule out serious medical and psychiatric disorders. Patients could not be receiving due the psychiatric treatment with a patients could not be receiving due the psychiatric treatment with a patients could not be receiving due the psychiatric treatment with an and able to read and understand English.	stude baseline were also excluded. Exclusion retries included diagnosed schizophrenia; addiction to alcohol or other drugs; significant dementia; uncontrolled liver, identificant or pinnomany disease; glaucoma; spelepsy or seizures as determined by physical examination, laboratory tests, and/or history, and allegies to be toxidogenipee or tricyclic antidepresents. Also excluded were patients receiving concomitant therapy with psychrotopic medications or thyroid medication with the exception of conjugated estrogens, nonnarcotic mild analgesics, antimigration emedications and diuretic; or patients who had received tranquillares or benodiaepines in the preceding 7 day, or lithium carbonate or antidepresentals (including mononamine oxidae inhibitors) in any regular daily dose during the preceding month. All participation was by informed written concent.	Imipramine	25-225	Placebo	No	6 weeks	13	12	20.5	22.5	No
Schweizer 1994	No	Yes	Patients aged 18 years or older over netrouted who met DSA-IR-R ortical reagar depression for antinium of weeks. The 21 steen Humilton Rating Scale for Depression (HAM-D) total score had to be at least 20 at both the initial score evolutation and the perteretament seasion. The score should not have decreased by more than 20% during the screening period.	Patients were encluded if their affective lines was lipidar, required subspitalization, or as primarily problect. Patients also were excluded if they reported marked suicidal ideation, recent lip in the past 2 years) also hold or four, dependence or abuse, any acute or unable of becoming pregnant were required to use a melicularly approved from of birth control and were admitted to the study only if a human chronice genadories net was negative. Concentiating hypotherior indication (other than chloral hydrate as needed) was excluded during the study, and for at least 1 day before double-blind	Imipramine	25-225	Placebo	Yes	6 weeks	73	78	24.2	24.6	No
Schweizer 1998	No	Yes	At least 65 of age, live in community setting and not a nursing home, DSM-III-R criteria for major depressive episode, unipolar type with minimum duration of illness of 3 months, minimum severity score of 18 on HAMD-17.	treatment began (14 days for MAO inhibitors and 30 days for pourdebitis). Albheimers disease or other dementa, current or past history of psychosis, schizophrenia, shizoaffective disorder, bipolar disorder, setures or glaucoma, any autor or unstable medical codition, including parkinsons disease, unstable endortine dyfurtions, or cancer in past 5 years. Concomitant psychotropic medication was not permitted and use of abroha was disocuraged. History in past year of alcoholism or drug deprendence including daily use of betwoodsarpiers for more than 6 continuous weeks was also reason	Imipramine	50-150	Placebo	No	8 weeks	60	60	23.9	24.1	No
Shipley 1981	No	Yes	The 76 subjects studied were inpatients on the Clinical Research Unit at Western Psychiatric institute and Clinic. When admitted, a psychiatric institute and Clinic. When admitted, a psychiatric interview and physical examination were completed, routine islabratory data including thyroid function tests were obtained, and an EEG and any other tests deemed necessary were completed. After a 2-weed rung-free period, the Schedule for Affective Bisorders and Schizophrenia (SAGS) (Spitzer et al., 1975) was completed by the psychiatrists and used together with collateral information from previous hospitalizations, case excords, and interviews, with farally members to establish the diagnosis according to the RDC. If the sevenity of depressive symptoms at the end of the 2-week drug free period was still smarted (17-freen HSE) accorded at least 30 using the sum of two raters), then patients were entered into the protocoid.	for exclusion.	Amitriptyline	Maximum: 200	Placebo	Yes	Unclear	Unclear	Unclear	38.5	44.2	No

Silverstone 1994	No	Yes	Patients aged 18-65 with a diagnosis of a major depressive epicode as defined by DSM-Hin Circline entered the study. At entry participants were required to have a minimum score of 16 on the 17-item Hamilton Depression Rating Scale (HDRS).	Patients at risk of suicide, with mood-incongruent symptoms, continuional states of whose depression was due to another psychiatric liness or organic factor were excluded from the trial. Patients with any significant physical disease, or a history of increased intraocular pressure, glaucoma or micturition disturbances were also cuduled. Patients who had received deteroconsulvise therapy (ECT) or an investigational drug within the last 4 weeks, an MAOI within the last 2 weeks or nemarked antidepressant, filmbum or carbannaspine within the last 7 days were excluded. With the exception of benoadagenipse, all other antidepressant medication, ECT and psychoactive drugs (including anticonvulsants, barbiturates and phenoblasize derivatives) were prohibited. Patients established on a single benoadasepine prior to entering the study were allowed to continue with the same treatment; the use of ternaspean was permitted for night sedation. No dietary restrictions were imposed.	Imipramine	75-150	Placebo	No	6 weeks	83	83	25.4	24.4	No
Smith 1990	No	Yes	The study population consisted of 150 outpatients with a diagnosis of major depressive illness, DSMI-180 2c. 276.3 (American Psychiatric Association 1580) and a minimum baseline score of 15 on the first 17 items of the Hamilton Rating Scale for Depression (HAM-7), Hamilton 1500). Patients who had a 20 percent or greater reduction in total HAM-100 core during the placebo washout period were considered placebo responders and were not randomized into the study. Additionally, patients were required to be at least 15 years of age, fire of significant renul, hepatic, respiratory, accordinately, or cerebrovascular disease, and accordinate of the control of the cont	Furthermore, patients were excluded if their primary diagnosis was schraphrenia, alystical depression, annexive, guistrument, or bipolar disorder, or if they were known drug or alcohol abusers or had known active suicidal tendencies or known cognitive deficiencies.	Amitriptyline	80-280	Placebo	Yes	6 weeks	50	50	23.7	23.3	No
Stark 1985	No	Yes	Patients eligible for inclusion were outpatients diagnosed as having major depressive illness according to DSM-ill criteria, except that our patients had to have had the illness for at least 1 month rather than 2 weeks. The HAM-D total score of each patient had to be equal to or greater than 20.	Patients were excluded because of concomitant phy sical conditions or histories of conditions that would interfere with therapy or evaluation.	Imipramine	Maximum: 300	Placebo	Yes	6 weeks	Unclear	Unclear	28.2	28.1	No
	No	Yes	HAMD below 19, 18-65 years.	-	Desipramine		Placebo	Yes	6 weeks	Unclear	Unclear	Unclear		No
Stratas 1984 - dothiepin	No	Yes	Candidates for this study, evaluated in a psychiatric outpatient clinic, were required to fulfill the following diagnostic criteria at a perstudy visit: BIO Citiagnosis of major despressive disorder; score of 18 or more on the 21 term Hamilton Depression Rafting Scale (HORS) and rating of 2 or more for the Items "depressed mood" and "work activities," rating of at least "moderately III" (2) a on a global severity scale of 0-6, where 0 = normall; and presence of depressive symptoms for at least 2 weeks prior to study entrances.	participate in the study.	Dothiepin	50-300	Placebo	Yes	6 weeks	Unclear	Unclear	Unclear	Unclear	No
Stratas 1984 - amitriptyline	No	Yes	Candidates for this study, evaluated in a psychiatric outpatient clinic, were required to fulfill the following diagnostic criteria at a perstudy visit: BCC diagnosis of major deepressive disorder; score of 18 or more on the 21 time thamilton Depression Rating Scale (HDRS) and rating of 2 or more for the term "depressed mood" and "work activities;" rating of at least "moderately ill" (2-3 on a global severity scale 01 Ge, where 0 = normal); and presence of depressive symptoms for at least 2 weeks prior to study entrance.	Patients were excluded for those physical and psychiatric disorders which are standard contraindications for tricyclics. All patients who fulfilled the inclusion criteria gave written informed consent to participate in the study.	Amitriptyline	50-300	Placebo	Yes	6 weeks	Unclear	Unclear	Unclear	Unclear	No
Thomson 1982	No	Yes	The general practitioners selected a group of patients complaining of depression of all star2 veels' duration, who were considered by their practitioner to require antidepressant drug treatment but not to need psychiatric referral. The patients were goal 18-65 years, and were required to have a total Hamitton Depression Rating Scale (HOS) (Hamilton, 1906) zone of 12 or more on entry into the study. Patients who had received antidepressants in the previous 2 weeks, or in whom the use of freychic antidepressants was contrandicated, were excluded. Patients were allowed to take disaspam 5 mg/dby or intrazepam as a hyproprict, but if affared this was continued throughout the study.		Amitriptyline	75-150	Placebo	Yes	12 weeks	31	28	17.4	19.4	No
Van De Merwe 1984	No	Yes	Patients included in the study were of either sos, between ages 18 and 60 years and in good physical health without disease in any organ system. Patients with any cardiovascular or other psychiatric illness were excluded (this included organic brain disease, alcoholism, addiction or mental handicap).	Patients who had been treated in adequate doage and time with auditopersoants or with electronouslust herapy in the period prior to referral were excluded, as were patients with depression severe recoupl to war- end electronouslustic breapy, individuals receiving known enzyme-indusing or enzyme-indusing or enzyme-indusing or enzyme-indusing and electronouslustic breapy, individuals receiving known enzyme-indusing or enzyme-indusing or expected sounds unable to comprehend the purpose of the study or unable to comply with the program were excluded. Women of childbearing and the observation of the program of the prog	Amitriptyline	Mean: 95.3		Yes	28 days	Unclear	Unclear	Unclear	Unclear	No
Versiani 1989	No	Yes	Male and female, 18-65, diagnosis of major depressive episode according to DSM-III. minimum score of 17 on HAMD-21	High suicide risk, concomitant psychiatric diseases, drug or alcohol dependence, significant organic disease, pregnancy, allergy	Imipramine	33-200	Placebo	No	6 weeks	Unclear	Unclear	25.8	23.3	No
White 1984 Wilcox 1994	No No	Yes	Subjects were patients at the Adult Psychiatric Citics of the Los Angeles County-University of Southern California Medical Center. For inclusion, such patients were required to meet Research Diagnostic Criteria (Spitzer et al. 1977) for major depressived sizorisch, confirmed in independent interviews by two clinicians, generally a psychologist and a psychiatrist. All patients were between the age of 13 and 60, and all agreed informed consent to participate. At the point of starting treatment with study medications, all patients were five or other psychotherapseutic drugs for sharp and the properties of the properties of the psychotherapseutic drugs for sharp and the properties of the psychotherapseutic drugs for sharp and the psychotherapseutic drugs for concurrently administered during the true.	Sedusion criteria any of the following histories • Clinically significant Education Any of the following histories: • Clinically significant Education criteria Any of the following histories: • Clinically significant	Nortriptyline	75-150 60-300	Placebo	No Yes	4 weeks	50	59	25.2	27.0	No No
VVIICOX 1994	ΝO	res	Outpatients: • Oliganosis of major depressive illnes (pSM+III 296.2 or 205.3) + HAM-D-17 core at baseline - 7,16 * Age > -7 18 years • Ability to complete the Zung Self-Rating Depression Scale	Educision criteria Any of the following histories: - Clinically significant exacts discussed in the content of	amuriptyline	00-300	ristee00	125	u weeks	30	143	24.2	23.3	nu

Trial ID	Experimental Intervention	TCA participants a			nts assessed for serious e events
		Numbers and types of serious adverse events	Proportion of participants with a serious adverse event	Numbers and types of serious adverse events	Proportion of participants with a serious adverse event
		reaction, 4 anorexia, 4 hyperkinesia, 2		4 hyperkinesia, 4 anorexia, 3 hypotension, 2 manic	
Amin 1984	Imipramine	hypokinesia	* out of 153	reaction, 1 hypokinesia	* out of 149
Bakish 1992 Ban 1998	Amitriptyline Desipramine	1 kidney infection 7 hypotension	1 out of 57 7 out of 89	4 hypotension	0 out of 55 4 out of 85
Bremner 1996	Amitriptyline	4 impotence, 4 amblyopia	* out of 50	-	0 out of 50
Carman 1991	Amitriptyline	16 amblyopia, 6 urinary retention	* out of 50	5 amblyopia	5 out of 50
		4 hepatitis, 1 delirium, 1			
Cassano 1996 - imipramine	Imipramine	suicide attempt	* out of 64	-	0 out of 29
Cassano 1996 - tianeptine	Tianeptine	1 suicide attempt	1 out of 64	1 suicide attempt	1 out of 30
Claghorn 1983	Amitriptyline	21 hypotension postural, 11 hypokinesia, 9 hyperkinesia	* out of 85	11 hypokinesia, 10 hyperkinesia, 3 hypotension postural	* out of 87
Claghorn 1996	Imipramine	hostility, 1 anorexia, 1 anxiety	* out of 45	4 hypertonia, 2 hostility, 1 anxiety	* out of 46
-		7 syncope/dizziness, 3			
Dominguez 1985	Imipramine	9 taste alteration, 9 drugged feeling, 7 libido decreased, 5 tinnitus, 5	7 out of 35	-	0 out of 31
Dunbar 1991 Emsley 2018	Imipramine Tianeptine	abnormal ejaculation 2 anxiety, 1 breast cancer, 1 arthritis, 1 dysgeusia	2 out of 105	2 fall, 1 paraesthesia, 1 panic attack, 1 anxiety	0 out of 240 2 out of 107
,		5 anorexia, 1 abnormal		1 ruptured ectopic	
Fabre 1996	Imipramine	ejaculation	* out of 48	pregnancy, 1 hernia repair	* out of 44
Feiger 1996	Imipramine	5 orthostatic dizziness, 6 tinnitus, 1 loss of libido	* out of 41	3 tinnitus	3 out of 40
Feighner 1989a	Imipramine	5 anxiety	5 out of 58	8 anxiety	8 out of 59
Ferguson 1994 - dothiepin	Dothiepin	16 amblyopia	16 out of 188	3 amblyopia	3 out of 95
Ferguson 1994 - doxepin	Doxepin	18 amblyopia	18 out of 186	3 amblyopia	3 out of 94
- Q		7.1		7-1-	
Fontaine 1994	Imipramine	23 orthostatic symptoms 15 orthostatic effects, 15	23 out of 45	3 orthostatic symptoms 10 syncope, 6 orthostatic	3 out of 45
Georgotas 1986	Nortriptyline	syncope	* out of 25	effects	* out of 28
Gerner 1980	Imipramine	1 atrial fibrillation	1 out of 21	-	0 out of 20
Itil 1983	Imipramine Imipramine	5 dizziness/syncope, 2 manic episodes, 1 depressive stupor, 1 overdose of fluvazepam	* out of 21	1 suicide attempt 2 dizziness/syncope, 1 manic episodes, hypomania and hyperactivity	1 out of 22 * out of 20
March 1990	Imipramine	-	0 out of 15	1 suicide attempt	1 out of 12
Nair 1995	Nortriptyline	events	16 out of 37	events	9 out of 35
Philipp 1999	Imipramine		0 out of 110	1 suicide attempt	1 out of 47
Prasko 2002	Imipramine	1 hypomania	1 out of 11	1 hypomania	1 out of 9
Raft 1981	Amitriptyline	3 urinary retention, 3 decrease of libido, 3 anorexia, 3 orthostatic hypotension, 1	0 out of 7	2 forgetfulnuess 5 anorexia, 3 urinary retention, 3 decrease of libido, 2 anorgasmia, 1	2 out of 6
Raisi 2007	Nortriptyline	anorgasmia	* out of 19	orthostatic hypotension	* out of 19
Ravindran 1995	Desipramine	6 amnesia, 6 taste alteration, 5 sexual	9 out of 37	5 anorexia, 1 taste alteration, 1 amnesia, 1	2 out of 26
Reimherr 1990	Amitriptyline	dysfunction, 1 anorexia	* out of 149	sexual dysfunction	* out of 150
Rickels 1987	Imipramine	5 cognitive deficite 7 urinary retention, 7	5 out of 63	4 cognitive deficite	4 out of 61
Rickels 1994	Imipramine	postural hypotension	* out of 92	4	0 out of 95
Schweizer 1998	Imipramine	13 urinary retention	* out of 60	1 urinary retention	* out of 60
Silverstone 1994	Imipramine	1 suicide hypotension, 6 dyscoordination, 6	1 out of 83	suicide 3 hypertension, 2 hypotension, 2 amblyopia,	* out of 83
Smith 1990	Amitriptyline	hypertension 9 anxiety, 7 taste change,	* out of 50	1 dyscoordination	* out of 50
Stark 1985	Imipramine	4 sexual dysfunction, 2 anorexia	* out of 186	12 anxiety, 3 taste change, 2 anorexia	* out of 169

<u> </u>					
Wilcox 1994	Amitrintyline	9 amhlyonia	9 out of 50	3 amblyonia	3 out of 49

 $\ensuremath{^{*}}$ The overall proportion of serious adverse events was unclear.

Number needed to	harm for serio	ous adverse ev	ents.					
	Number of trials							
	reporting		TCA	Control	Control	Relative risk (95%		
Events	the event	TCA events	analysed	events	analysed	CI)	P-value	NNH
Hypotension	10	111	636	31	633	3.31 (1.93, 5.68)	< 0.01	7
Urinary retention	5	36	266	4	270	6.07 (1.66, 22.19)	0.01	8
Amblyopia	5	73	574	16	388	3.32 (1.94, 5.66)	< 0.01	11
Sexual dysfunction	8	25	651	4	650	3.50 (1.29, 9.48)	0.01	31
Taste alteration	4	23	677	4	666	4.04 (1.23, 13.24)	0.02	35
Amnesia	2	6	150	3	153	1.20 (0.04, 32.84)	0.92	
Anorexia	7	19	616	16	592	1.15 (0.39, 3.37)	0.80	
Anxiety	4	17	377	22	359	0.74 (0.38, 1.46)	0.39	
Dyscoordination	2	6	107	1	110	3.74 (0.46, 30.20)	0.22	
Hyperkinesia	2	13	225	14	222	0.94 (0.45, 1.93)	0.86	
Hypertension	2	6	149	3	154	1.86 (0.52, 6.65)	0.34	
Hypokinesia	2	13	225	12	224	1.10 (0.50, 2.41)	0.82	
Mania	4	7	261	5	256	1.29 (0.39, 4.31)	0.68	
Syncope	3	27	54	12	67	2.42 (0.80, 7.34)	0.12	
Tinnitus	2	11	267	3	277	3.12 (0.58, 16.75)	0.18	

Number nee	ded to treat fo	or non-serious	adverse ever	nts.				
	Number of							
	trials							
	reporting		TCA	Control	Control	Relative risk		
Events	the event	TCA events	analysed	events	analysed	(95% CI)	P-value	NNT
Diarrhoea	13	35	895	82	886	0.46 (0.29, 0.	< 0.01	19
Infection	3	9	279	21	259	0.41 (0.19, 0.	0.02	2:

Number needed to harm for nor	-serious adve	rse events.						
	Number of							
	trials							
	reporting		TCA	Control	Control			
Events	the event	TCA events	analysed	events	analysed	Relative risk (95% CI)	P-value	NNH
Dry mouth	45	1863	3399	452	3066	3.43 (2.87, 4.10)	< 0.01	2
Anticholinergic symptoms	5	184	297	74	257	2.35 (1.46, 3.78)	< 0.01	3
Somnolence	33	919	2616	300	2393	2.65 (2.20, 3.21)	< 0.01	4
Sedation	5	98	301	54	272	1.67 (1.08, 2.58)	0.02	7
Dizziness	34	584	2753	209	2472	2.37 (1.87, 3.01)	< 0.01	7
Constipation	38	617	3082	196	2795	2.81 (2.16, 3.65)	< 0.01	7
Sweating	21	239	1563	54	1531	3.64 (2.41, 5.50)	< 0.01	8
Tremor	28	305	2321	47	2010	4.70 (3.02, 7.30)	< 0.01	9
Blurred vision	20	216	1485	66	1419	2.96 (2.21, 3.96)	< 0.01	10
Flushing	2	26	231	4	214	5.86 (1.33, 25.72)	0.02	10
Weight gain	8	78	671	16	469	2.98 (1.31, 6.77)	0.01	12
Abnormal dreams	2	8	86			5.55 (1.00, 30.71)	0.049	12
Nervousness	14	153	886			2.07 (1.19, 3.59)	0.01	12
Increased appetite	5	76	650	19	463	2.97 (1.70, 5.18)	< 0.01	13
Micturition disorder	3	25	259	6	265	3.97 (1.40, 11.22)	0.01	13
Asthenia	20	252	1937	119	1732	1.91 (1.47, 2.47)	< 0.01	16
Impaired urination	2	23	422	C		23.07 (3.14, 169.75)	< 0.01	18
Tachycardia	14	85	1095	25		2.89 (1.63, 5.13)	< 0.01	18
Confusion	7	59	806	13		3.44 (1.86, 6.35)	< 0.01	19
Dyspepsia	11	127	1283	50		2.20 (1.21, 4.00)	0.01	19
Urinary hesitancy	2		183	2		4.46 (1.00, 19.83)	0.0495	22
Appetite decreased	4	32	465	13		2.39 (1.10, 5.16)	0.03	24
Paraesthesia	7	52	872	16	688	2.55 (1.17, 5.56)	0.02	27
Agitation	10	62	771	49		1.10 (0.57, 2.11)	0.77	
CNS	2	24	115	19		1.05 (0.59, 1.87)	0.88	
Headache	33	466	2586	389		0.97 (0.79, 1.20)	0.79	
Insomnia	26	163	2188	174		0.85 (0.62, 1.16)	0.30	
Nausea	32	337	2604	234		1.31 (0.99, 1.73)	0.06	
Pharyngitis	2	49	482	29		0.85 (0.50, 1.47)	0.57	
Rash	5		377	12		1.59 (0.50, 5.00)	0.43	
Rhinitis	2	58	419	31		1.04 (0.69, 1.57)	0.87	
Upper respiratory tract infection	2		291	11		1.00 (0.45, 2.22)	1.00	
Vasodilatation	3	28	330	4		4.64 (0.92, 23.32)	0.06	
Yawning	2	0	342	C	347	1.02 (0.06, 16.16)	0.99	