Forest plots for review question: For adults with a new episode of more severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?

Subgroup analyses

Subgroup analyses of older adults (60 years and older) compared to younger adults (younger than 60 years)

SSRIs versus placebo

Figure 21: Depression symptoms endpoint

_	Exp	eriment	al	(control	-		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
76.1.1 Older adults (mean age >	60 year	's)							
Emsley 2018	13.1	6.6	98	17.1	6.9	106	3.9%	-0.59 [-0.87, -0.31]	-
Nyth 1992	13.1	10	60	17.5	8.5	32	2.0%	-0.46 [-0.89, -0.02]	~
Tollefson 1993/1995 Subtotal (95% CI)	14	7.7	326 484	15.7	7.4	329 467	7.5% 13.5%	-0.22 [-0.38, -0.07] -0.40 [-0.65, -0.14]	•
Heterogeneity: Tau² = 0.03; Chi²: Test for overall effect: Z = 2.99 (P			= 0.07)	I ² = 63	%				
76.1.2 Younger adults (mean ag	e <60 ye	ars)							
003-048	12.3	7.08	179	13.2	7.73	59	3.7%	-0.12 [-0.42, 0.17]	+
Bjerkenstedt 2005	14.9	8.4	54	15.5	6.7	55	2.6%	-0.08 [-0.45, 0.30]	+
Byerley 1988	12.8	7.7	20	19.7	6.5	16	0.9%	-0.94 [-1.63, -0.24]	
CAGO178A2303	14	7.53	163	17.3	7.92	158	5.3%	-0.43 [-0.65, -0.20]	-
CL3-20098-022	13.3	7.6	133	15.9	8.6	147	4.9%	-0.32 [-0.55, -0.08]	-
CL3-20098-023	12.2	8.1	137	13.8	8	137	4.9%	-0.20 [-0.44, 0.04]	4
CL3-20098-024	12.5	7.4	146	13.4	8.4	158	5.2%	-0.11 [-0.34, 0.11]	+
Fava 1998a		10.12	109	12.2	9	19	1.7%	0.04 [-0.45, 0.53]	+
Fava 2005	13.3	7.3	47	12.6	6.4	43	2.2%	0.10 [-0.31, 0.51]	+
Forest Laboratories 2000		10.38	243		10.86	125	5.4%	-0.18 [-0.39, 0.04]	4
Forest Research Institute 2003		10.89	143	20.5		151	5.1%	-0.31 [-0.54, -0.08]	-
Godlewska 2012	19.8	7.8	21	20	4.3	21	1.1%	-0.03 [-0.64, 0.57]	+
Hirayasu 2011a	9.32	7.15	197	9.3	6.6	100	4.8%	0.00 [-0.24, 0.24]	+
Hirayasu 2011b		10.35	360	18.3	10.1	124	5.8%	-0.24 [-0.45, -0.04]	-
Hunter 2011	13.5	8.25		12.09	8.23	11	0.6%	0.16 [-0.65, 0.98]	+
Komulainen 2018	20.2	4.56	17	22.3	4.95	15	0.9%	-0.43 [-1.13, 0.27]	
Loo 2002	13.09	8.37		15.34	8.87	136	4.9%	-0.26 [-0.50, -0.03]	-
Lopez-Rodriguez 2004	6	8.59	10	14	8.59	10	0.5%	-0.89 [-1.82, 0.04]	
Macias-Cortes 2015	11.7	3.7	46	15	3.7	43	2.0%	-0.88 [-1.32, -0.45]	
Mathews 2015		10.04	280	18.2		281	7.0%	-0.26 [-0.42, -0.09]	-
Mundt 2012	11.5	5.8	55	13.9	6.4	50	2.5%	-0.39 [-0.78, -0.00]	~
PAR 279 MDUK	13.7	5.61	19	15.6	5.61	10	0.7%	-0.33 [-1.10, 0.44]	+
Rudolph 1999	14.2	4.14	103	14.8	4.02	97	4.0%	-0.15 [-0.42, 0.13]	4
Sheehan 2009b	18.09	8.89	99	18.4	9.2	95	3.9%	-0.03 [-0.32, 0.25]	+
Wade 2002 Subtotal (95% CI)	14.3	9.1	188 2925	16.7	9.1	189 2250	5.8% 86.5%	-0.26 [-0.47, -0.06] -0.23 [-0.30, -0.16]	7
Heterogeneity: Tau* = 0.01; Chi*: Test for overall effect: Z = 6.31 (P				0); f*= :	27%	EEGO	00.0%	-0.20 [-0.00, -0.10]	
Total (95% CI)			3409			2717	100.0%	-0.25 [-0.31, -0.18]	-
Heterogeneity: Tau* = 0.01; Chi*: Test for overall effect: Z = 7.10 (P			P = 0.0)5); (*= :	33%				-10 -5 0 5 1
Test for subgroup differences: C			(P = 0.	22), I*=	34.8%				Favours SSRI Favours placebo

Figure 22: De	pression svn	nptoms chang	ae score
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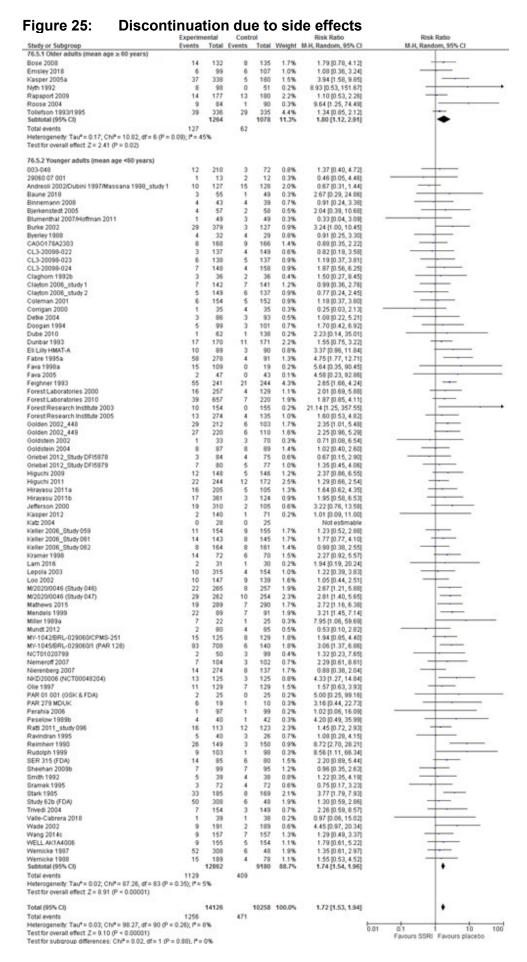
igule 22. Deplessio			1113	U	Control	٠٠.	•	Std. Maan Difference	Std. Maan Difference
tudy or Subgroup	Mean	experimental SD	Total	Mean	Control SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% CI
5.2.1 Older adults (mean age ≥ 60 years)									
ose 2008	-12.1	10.22	129	-10.6	10.42	134	1.9%	-0.14 [-0.39, 0.10]	+
msley 2018	-13.6		98	-9.5	4.82804308	106	1.7%	-0.86 [-1.14, -0.57]	-
th 1992	-13.1	7.07106781	60	-6.7	5.97578447	32	1.0%	-0.95 [-1.40, -0.49]	
apaport 2009	-12.11	8.02	173	-8.85	8	178	2.1%	-0.41 [-0.62, -0.19]	-
illefson 1993/1995	-8.1	7.6	326	-6.4	7.1	329	2.5%	-0.23 [-0.38, -0.08]	4
btotal (95% CI)			786			779	9.1%	-0.48 [-0.74, -0.21]	•
sterogeneity: Tau* = 0.07; Chi* = 23.85, df = 4 (P < 0	0.00017/19	F= 83%							1
st for overall effect: Z = 3.52 (P = 0.0004)	0.0001),1	-00%							
i.2.2 Younger adults (mean age <60 years)									
060 07 001	-13.08	10.2191	12	-10.91	9.386048	11	0.4%	-0.21 [-1.03, 0.61]	+
dreoli 2002/Dubini 1997/Massana 1998_study 1	-13.3	4.6	127	-8.6	4.47	128	1.8%	-1.03 [-1.29, -0.77]	-
une 2018	-15.96	8.58	52	-8	8.38	48	1.1%	-0.93 [-1.34, -0.52]	-
nnemann 2008	-13.42	7.61	30	-10.18	7.57	31	0.8%	-0.42 [-0.93, 0.09]	-
erkenstedt 2005	-8.9	8	54	-9.7	7	55	1.2%	0.11 [-0.27, 0.48]	+
umenthal 2007/Hoffman 2011	-6.1	6.7	49	-6.1	7.3	49	1.2%	0.00 [-0.40, 0.40]	+
arke 2002	-12.9		366	-9.4	9.82	119	2.1%	-0.37 [-0.58, -0.16]	-
aghorn 1992a	-10.72		32	-4.59	9.35	27	0.8%		-
						27		-0.65 [-1.17, -0.12]	
aghorn 1992b	-11.44		32	-5.49	8.31		0.8%	-0.71 [-1.23, -0.18]	
ayton 2006_study 1	-14.2		133	-12.1	7.98	130	1.9%	-0.26 [-0.50, -0.02]	1
ayton 2006_study 2	-12.9		133	-11.9	7.86	126	1.9%	-0.13 [-0.37, 0.12]	1
etice 2004	-11.7	4.61	85	-8.8	4.82	93	1.6%	-0.61 [-0.91, -0.31]	-
ibe 2010	-15		54	-13	8.84	122	1.5%	-0.23 [-0.55, 0.10]	4
LIIIy HMAT-A	-7.4	6.44	87	-4.78	6.42	89	1.6%	-0.41 [-0.70, -0.11]	⊣
abre 1992	-9.13	8.14	38	-3.06	8.1	36	0.9%	-0.74 [-1.21, -0.27]	
bre 1995a	-9.89		261	-7.6	7.5	86	1.9%	-0.27 [-0.52, -0.03]	4
wa 1998a	-10.95		109	-11.6	8.9	19	0.9%	0.07 [-0.42, 0.56]	+
wa 2005	-6.3		47	-7.3	4.6400431	43	1.1%	0.20 [-0.22, 0.61]	<u>_</u>
orest Laboratories 2000	-12.95			-11.2	10.35	125	2.1%	-0.17 [-0.39, 0.04]	J
			243]
rest Laboratories 2010	-11.55		637	-8.5	8.8		2.5%	-0.32 [-0.47, -0.16]]
rest Research Institute 2003	-13.3		143	-10	10.57	151	2.0%	-0.31 [-0.54, -0.08]	1
rest Research Institute 2005	-16.26		266	-12.4	10.34	132	2.1%	-0.37 [-0.58, -0.16]	7
odlewska 2012	-4.4	5.16139516	21	-3.3	3.11688948	21	0.6%	-0.25 [-0.86, 0.35]	+
olden 2002_448	-11.89	8.19	206	-9.9	8.04	101	1.9%	-0.24 [-0.48, -0.00]	4
olden 2002_449	-12.69	8.2	218	-10.2	8.18	110	2.0%	-0.30 [-0.53, -0.07]	4
guchi 2009	-9.4		148	-8.3	5.8	145	2.0%	-0.17 [-0.40, 0.06]	4
guchi 2011	-12.7		241	-10.4	8.11	171	2.2%	-0.30 (-0.49, -0.10)	-
unter 2011	-9.67		12	-8.64	5.99548163	11	0.4%	-0.17 [-0.99, 0.65]	_
fferson 2000	-14.7	10.56	296	-12.1	11.05	101	2.0%	-0.24 [-0.47, -0.02]	
ksper 2012	-19		139	-13.4	9.27	71	1.6%	-0.55 [-0.84, -0.26]	
eller 2006_Study 062	-17.25		161	-14	8.87	154	2.0%	-0.38 [-0.61, -0.16]	٦
omulainen 2018	-1.9		17		3.29146624	15	0.5%	0.09 [-0.60, 0.79]	
rangler 2006_Group A	-10.8	6.5	89	-9.6	7.8	100	1.7%	-0.17 [-0.45, 0.12]	4
am 2016	-8.8	9.9	31	-6.5	9.6	30	0.8%	-0.23 [-0.74, 0.27]	+
00 2002	-14.21	6.23938298	144	-12.06	6.85867334	136	2.0%	-0.33 [-0.56, -0.09]	4
(2020/0046 (Study 046)	-12.5	8.45	243	-11.5	8.45	247	2.3%	-0.12 [-0.30, 0.06]	4
2020/0046 (Study 047)	-11.8	7.64	242	-10.1	7.27	239	2.3%	-0.23 [-0.41, -0.05]	4
acias-Cortes 2015	-8.9		46	-5.7		43	1.0%	-1.29 [-1.75, -0.83]	-
withews 2015	-15.9		280	-13.6	10.06		2.4%	-0.23 [-0.39, -0.06]	1
				-6.2	7.2				_
Iller 1989a	-6		19				0.6%	0.03 [-0.58, 0.64]	
undt 2012	-13.4		55	-10.7	6.6	50	1.2%	-0.44 [-0.82, -0.05]	
Y-1042/BRL-029060/CPMS-251	-10.23		120	-8.25	7.56		1.9%	-0.26 [-0.51, -0.01]	7
Y-1045/BRL-029060/1 (PAR 128)	-12.39		694	-9	8.63	136	2.3%	-0.39 [-0.57, -0.20]	1
CT01020799	-11.7		49	-11.45	10.18	94	1.4%	-0.02 [-0.37, 0.32]	Ť
erenberg 2007	-7.22	6.62	274	-5.97	6.79		2.1%	-0.19 [-0.39, 0.02]	1
KD20006 (NCT00048204)	-11.1	7.9	117	-10.9	7.8	118	1.8%	-0.03 [-0.28, 0.23]	†
IR 01 001 (GSK & FDA)	-13.36	7.93		-11.33	7.93	21	0.6%	-0.25 [-0.85, 0.35]	+
eimherr 1990	-11.66		142	-8.16	7.85		2.0%	-0.43 [-0.67, -0.20]	-1
ER 315 (FDA)	-8.9		76	-7.8	8		1.5%	-0.17 [-0.49, 0.15]	4
neehan 2009b		6.46107963		-11.02	6.86603233	95	1.7%	-0.06 [-0.34, 0.22]	1
			72	-6.4		70			
amek 1995	-8.6				6.7		1.4%	-0.34 [-0.67, -0.01]]
ark 1985	-11	10.1	185	-8.2	9	169	2.1%	-0.29 [-0.50, -0.08]]
udy 62b (FDA)	-8.82	8.71	297	-5.69	8.65	48	1.6%	-0.36 [-0.66, -0.05]	٦
udy F1.J-MC-HMAQ - Study Group B	-7.63		37	-7.1	6.96	72	1.2%	-0.08 [-0.47, 0.32]	Ť
ade 2002	-14.9	6.56658206	188	-12	6.78196137	189	2.2%	-0.43 [-0.64, -0.23]	*
ELL AK1A4006	-13.9	10.87	146	-12.2	9.73	148	2.0%	-0.16 [-0.39, 0.06]	4
ernicke 1987	-8.83			-5.7	8.6		1.6%	-0.36 [-0.67, -0.05]	4
ernicke 1988	-10.6			-7	8.6		1.8%	-0.43 [-0.70, -0.16]	-
ubtotal (95% CI)	10.0	0.3	8596		0.0	5669	90.9%	-0.30 [-0.36, -0.25]	il
eterogeneity: Tau* = 0.02; Chi* = 121.45, df = 57 (P est for overall effect: Z = 10.81 (P < 0.00001)	< 0.0000	1); I*= 53%							
			0000				400.00		
otal (95% CI)			9382			6448	100.0%	-0.31 [-0.37, -0.26]	
eterogeneity: Tau* = 0.02; Chi* = 147.09, df = 62 (P	< 0.0000	1); P = 58%							10 5 0 5
A 6 - A 6 -									
st for overall effect: Z = 11.33 (P < 0.00001)									Favours SSRI Favours placebo

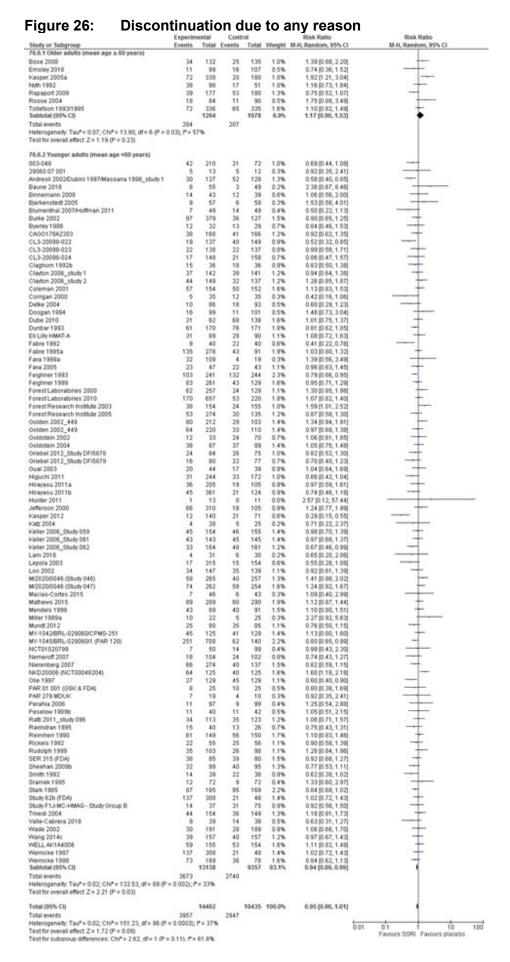
Figure 23: Remission

igure 23:	Remission							
Chada as Cabassas		Experim		Contr		Majaba	Risk Ratio	Risk Ratio
tudy or Subgroup		Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
6.3.1 Older adults (me	an age ≥ 60 years)							
Bose 2008		44	132	39	135	2.7%	1.15 [0.81, 1.65]	
Kasper 2005a		117	338	76	180	4.3%	0.82 [0.65, 1.03]	-
Rapaport 2009		71	177	50	180	3.3%	1.44 [1.07, 1.94]	-
toose 2004		27	84	30	90	2.1%	0.96 [0.63, 1.48]	
ollefson 1993/1995		71	336	44	335	2.8%	1.61 [1.14, 2.27]	
ubtotal (95% CI)			1067		920	15.2%	1.16 [0.88, 1.53]	•
otal events		330		239				
leterogeneity: Tau* = 0.	07; Chi ² = 15.10, df = 4 (P = 0	0.004); I*=	74%					
est for overall effect: Z :	: 1.02 (P = 0.31)							
6.3.2 Younger adults (r	mean age <60 years)							
	97/Massana 1998_study 1	57	127	34	128	2.8%	1.69 [1.19, 2.39]	-
innemann 2008	077ma00ana 1000_00ay 1	18	43	8	39	0.9%	2.04 [1.00, 4.16]	
jerkenstedt 2005		15	57	4	58	0.5%	3.82 [1.35, 10.80]	
lumenthal 2007/Hoffm	an 2011	23	49	15	49	1.6%	1.53 [0.92, 2.57]	
AGO178A2303	JII 2011	37	168	22	166	1.8%	1.66 [1.03, 2.69]	
		25	137	24				
L3-20098-022		36	138	27	149	1.6%	1.13 [0.68, 1.89]	
L3-20098-023						2.0%	1.32 [0.85, 2.05]	
L3-20098-024		30	148	38	158	2.1%	0.84 [0.55, 1.29]	
layton 2006_study 1		65	142	40	141	3.1%	1.61 [1.17, 2.22]	
layton 2006_study 2		56	149	48	137	3.2%	1.07 [0.79, 1.46]	工
oleman 2001		58	154	46	152	3.1%	1.24 [0.91, 1.71]	
etke 2004		38	86	28	93	2.4%	1.47 [0.99, 2.17]	
ube 2010		23	62	38	138	2.1%	1.35 [0.88, 2.06]	_
II LIIIy HMAT-A		31	89	18	90	1.7%	1.74 [1.05, 2.88]	
ava 2005		14	47	9	43	0.9%	1.42 [0.69, 2.95]	
eighner 1993		59	241	31	244	2.3%	1.93 [1.30, 2.87]	
orest Research Institut	e 2003	42	154	27	155	2.1%	1.57 [1.02, 2.40]	
orest Research Institut	e 2005	122	274	36	135	3.2%	1.67 [1.23, 2.28]	
olden 2002_448		94	212	38	103	3.4%	1.20 [0.90, 1.61]	+-
olden 2002_449		105	220	37	110	3.3%	1.42 [1.05, 1.91]	-
oldstein 2002		10	33	22	70	1.2%	0.96 [0.52, 1.80]	
oldstein 2004		31	87	26	89	2.1%	1.22 [0.79, 1.87]	+
liguchi 2009		49	148	32	146	2.5%	1.51 [1.03, 2.21]	
liguchi 2011		86	244	40	172	3.1%	1.52 [1.10, 2.09]	-
lunter 2011		3	13	3	11	0.3%	0.85 [0.21, 3.38]	
efferson 2000		79	310	19	105	2.0%	1.41 [0.90, 2.21]	+
asper 2012		57	140	14	71	1.6%	2.06 [1.24, 3.44]	
ramer 1998		24	72	12	70	1.2%	1.94 [1.06, 3.58]	
am 2016		6	31	9	30	0.6%	0.65 [0.26, 1.59]	
00 2002		37	147	21	139	1.8%		
acias-Cortes 2015		7	46	21	43	0.2%	1.67 [1.03, 2.70]	
		10		12	99	0.2%	3.27 [0.72, 14.89]	
CT01020799			50				1.65 [0.77, 3.55]	
emeroff 2007		28	104	22	102	1.7%	1.25 [0.77, 2.03]	
ierenberg 2007	10.0	69	274	27	137	2.4%	1.28 [0.86, 1.90]	
KD20006 (NCT00048)	(04)	32	125	29	125	2.0%	1.10 [0.71, 1.71]	
erahia 2006		42	97	33	99	2.7%	1.30 [0.91, 1.86]	T.
atti 2011_study 096		58	113	48	123	3.5%	1.32 [0.99, 1.75]	_
udolph 1999		23	103	17	98	1.4%	1.29 [0.73, 2.26]	
heehan 2009b		15	99	14	95	1.0%	1.03 [0.53, 2.01]	
tudy F1J-MC-HMAQ - S	tudy Group B	11	37	21	75	1.2%	1.06 [0.57, 1.96]	_
alle-Cabrera 2018		20	39	6	38	0.8%	3.25 [1.47, 7.20]	
ang 2014c		62	157	54	157	3.4%	1.15 [0.86, 1.53]	+
ELL AK1A4006		55	155	51	154	3.2%	1.07 [0.79, 1.46]	+
ubtotal (95% CI)			5321		4673	84.8%	1.37 [1.28, 1.47]	
otal events		1762		1102				
eterogeneity: Tau² = 0. est for overall effect: Z =	00; Chi² = 45.66, df = 42 (P = = 9.07 (P < 0.00001)	0.32); *=	8%					
etal (DEN CD			6388		5593	100.0%	1.34 [1.24, 1.44]	
otal (95% Cli		2002	-300	1341			(men man)	l'
otal (95% CI)								
otal events	12: Chit = 60 52 4f = 47 42 =	2092	21%	1341				
otal events	02; Chi² = 68.53, df = 47 (P =		31%	1341				0.01 0.1 10 Favours placebo Favours SSRI

Figure	24:	Response
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	Response							
tudy or Subgroup	-	Experim Events		Contr Events		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
6.4.1 Older adults (mean	age ≥ 60 years)	210		2101110	1000	The same		
ose 2008		59	132	51	135	1.5%	1.18 [0.89, 1.58]	+
msley 2018		54	99	36	107	1.3%	1.62 [1.18, 2.24]	
asper 2005a		139 32	338 98	85 9	180	2.1%	0.87 [0.71, 1.06]	1
lyth 1992 Papaport 2009		100	177	71	51 180	1.9%	1.85 [0.96, 3.57] 1.43 [1.15, 1.79]	_
toose 2004		32	84	34	90	1.0%	1.01 [0.69, 1.47]	_
ollefson 1993/1995		121	336	90	335	1.9%	1.34 [1.07, 1.68]	-
ubtotal (95% CI)			1264	-	1078	10.1%	1.25 [1.03, 1.51]	*
otal events		537		376				
leterogeneity: Tau* = 0.04;	Chi ² = 19.09, df = 6 (P = 6	0.004); *=	69%					
est for overall effect: Z = 2	22 (P = 0.03)							
6.4.2 Younger adults (me								
ndreoli 2002/Dubini 1997.	Massana 1998_study 1	72	127	43	128	1.5%	1.69 [1.27, 2.25]	
innemann 2008		25	43	17	39	0.8%	1.33 [0.86, 2.07]	
jerkenstedt 2005		20	57	21	58	0.7%	0.97 [0.59, 1.58]	
urke 2002 yerley 1988		179 14	379 32	33 4	127 29	1.3%	1.82 [1.33, 2.48] 3.17 [1.18, 8.55]	
AGO178A2303		91	168	61	166	1.8%	1.47 [1.16, 1.88]	-
L3-20098-022		77	137	69	149	1.9%	1.21 [0.97, 1.52]	-
L3-20098-024		89	148	91	158	2.2%	1.04 [0.87, 1.26]	+
laghorn 1992b		15	36	6	36	0.3%	2.50 [1.09, 5.71]	
layton 2006_study 1		90	142	69	141	2.0%	1.30 [1.05, 1.60]	-
layton 2006_study 2		82	149	64	137	1.9%	1.18 [0.94, 1.48]	+
oleman 2001		83	154	73	152	1.9%	1.12 [0.90, 1.40]	+
orrigan 2000		17	35	9	35	0.4%	1.89 [0.98, 3.65]	
letke 2004		64	86	41	93	1.7%	1.69 [1.30, 2.19]	
oogan 1994 lube 2010		50	99	40	101	1.4%	1.28 [0.94, 1.74]	
ube 2010 unbar 1993		29 72	62 170	59 30	138	1.3%	1.09 [0.79, 1.52]	Τ
unbar 1993 Ii Lilly HMAT-A		38	170	24	90	0.9%	2.41 [1.67, 3.49] 1.60 [1.05, 2.43]	
abre 1995a		128	278	32	91	1.4%	1.31 [0.96, 1.78]	-
ava 1998a		63	109	10	19	0.8%	1.10 [0.70, 1.73]	+
orest Laboratories 2000		118	257	51	129	1.7%	1.16 [0.90, 1.49]	+
orest Research Institute 2	003	70	154	45	155	1.4%	1.57 [1.16, 2.12]	-
orest Research Institute 2	005	162	274	56	135	1.9%	1.43 [1.14, 1.78]	-
oldstein 2002		17	33	33	70	0.9%	1.09 [0.72, 1.65]	+
oldstein 2004		34	87	27	89	0.9%	1.29 [0.86, 1.94]	_
ual 2003		19	44	15	39	0.6%	1.12 [0.67, 1.89]	
liguchi 2009		78	148	56	146	1.7%	1.37 [1.06, 1.78]	
liguchi 2011		146	244	78	172	2.2%	1.32 [1.09, 1.60]	Γ
lirayasu 2011a Iirayasu 2011b		133 179	205 361	66 45	105	1.7%	1.03 [0.86, 1.23] 1.37 [1.06, 1.76]	_
lunter 2010_study 1		6	14	6	14	0.3%	1.00 [0.43, 2.35]	
lunter 2011		6	13	6	11	0.3%	0.85 [0.38, 1.88]	
efferson 2000		145	310	36	105	1.5%	1.36 [1.02, 1.82]	-
asper 2012		96	140	33	71	1.6%	1.48 [1.12, 1.94]	-
atz 2004		11	28	6	25	0.3%	1.64 [0.71, 3.78]	+
ramer 1998		33	72	20	70	0.8%	1.60 [1.03, 2.51]	-
ranzler 2006_Group A		33	89	26	100	0.9%	1.43 [0.93, 2.19]	_
am 2016		9	31	10	30	0.3%	0.87 [0.41, 1.84]	
epola 2003		183	315	74	154	2.2%	1.21 [1.00, 1.46]	<u></u>
00 2002		81	147	63	139	1.8%	1.22 [0.96, 1.54]	Γ
V2020/0046 (Study 046)		156	265	136	257 254	2.5%	1.11 [0.95, 1.30]	L
V2020/0046 (Study 047) facias-Cortes 2015		128 19	262 46	108 5	43	0.2%	1.15 [0.95, 1.39] 3.55 [1.45, 8.68]	
lathews 2015		176	289	142	290	2.6%	1.24 [1.07, 1.44]	-
lendels 1999		37	89	24	91	0.9%	1.58 [1.03, 2.41]	-
lundt 2012		33	80	20	85	0.8%	1.75 [1.10, 2.79]	
Y-1042/BRL-029060/CPN	19-251	56	125	44	129	1.4%	1.31 [0.96, 1.79]	-
Y-1045/BRL-029060/1 (P.	AR 128)	461	708	69	140	2.3%	1.32 [1.11, 1.58]	-
CT01020799		14	50	31	99	0.6%	0.89 [0.53, 1.52]	+
lemeroff 2007		45	104	37	102	1.2%	1.19 [0.85, 1.67]	+
lierenberg 2007		94	274	36	137	1.3%	1.31 [0.94, 1.81]	
KD20006 (NCT00048204)	57	125	59	125	1.6%	0.97 [0.74, 1.26]	T
(lie 1997 AP 01 001 (GSV 8 FDA)		71	129	45	129	1.5%	1.58 [1.19, 2.09]	
AR 01 001 (GSK & FDA) erahia 2006		11 59	25 97	8 51	25 99	0.4% 1.7%	1.38 [0.67, 2.83] 1.18 [0.92, 1.51]	
erania 2006 eselow 1989a		17	34	14	39	0.6%	1.39 [0.81, 2.38]	
eselow 1989b		19	40	14	42	0.6%	1.43 [0.83, 2.44]	+
atti 2011_study 096		65	113	73	123	2.0%	0.97 [0.78, 1.20]	+
avindran 1995		17	40	7	26	0.4%	1.58 [0.76, 3.27]	+
eimherr 1990		77	149	49	150	1.5%	1.58 [1.20, 2.09]	
tickels 1992		22	55	10	56	0.4%	2.24 [1.17, 4.28]	
udolph 1999		52	103	41	98	1.4%	1.21 [0.89, 1.63]	+
		27	99	23	95	0.7%	1.13 [0.70, 1.82]	
heehan 2009b		15	39	8	38	0.4%	1.83 [0.88, 3.80]	
heehan 2009b mith 1992		77	185	39	169	1.3%	1.80 [1.30, 2.49]	
heehan 2009b mith 1992 tark 1985	v Group P		37	28	75	0.7%	1.09 [0.67, 1.77]	T
heehan 2009b mith 1992 tark 1985 tudy F1J-MC-HMAQ - Stud	y Group B	15			38	0.7%	2.27 [1.37, 3.78]	
heehan 2009b mith 1992 tark 1985 tudy F1J-MC-HMAQ - Stud alle-Cabrera 2018	y Group B	15 28	39	12	100	2.006		
heehan 2009b mith 1992 tark 1985 tudy F1J-MC-HMAQ - Stud alle-Cabrera 2018 (ade 2002	y Group B	15 28 103	39 191	79	189	2.0%	1.29 [1.04, 1.60]	
heehan 2009b mith 1992 tark 1985 tudy F1J-MC-HMAQ - Stud alle-Cabrera 2018 (ade 2002 (ang 2014c	y Group B	15 28 103 91	39 191 157	79 78	157	2.1%	1.29 [1.04, 1.60] 1.17 [0.95, 1.43]	E
heehan 2009b mith 1992 tark 1985 tudy F1J-MC-HMAQ - Stud alle-Cabrera 2018 (ade 2002 fang 2014c (ELL AK1A4006	y Group B	15 28 103 91 88	39 191 157 155	79 78 78	157 154	2.1%	1.29 [1.04, 1.60] 1.17 [0.95, 1.43] 1.12 [0.91, 1.38]	_
heehan 2009b mith 1992 tark 1985 tudy F1J-MC-HMAQ - Stud alle-Cabrera 2018 fade 2002 fang 2014c ÆLL AK1A4005 fernicke 1987	y Group B	15 28 103 91 88 112	39 191 157 155 308	79 78 78 9	157 154 48	2.1% 2.0% 0.5%	1.29 [1.04, 1.60] 1.17 [0.95, 1.43] 1.12 [0.91, 1.38] 1.94 [1.06, 3.56]	=
heehan 2009b mith 1992 tark 1985 tudy F1J-MC-HMAQ - Stud alle-Cabrera 2018 (ade 2002 fang 2014c (ELL AK1A4006	y Group B	15 28 103 91 88	39 191 157 155	79 78 78	157 154	2.1%	1.29 [1.04, 1.60] 1.17 [0.95, 1.43] 1.12 [0.91, 1.38]	=
heehan 2009b mith 1992 tark 1985 tudy F1J-MC-HMAQ - Stud alle-Cabrera 2018 rade 2002 rang 2014c ÆLL AK1A4006 fermicke 1987 ermicke 1988 ubtotal (95% CI)	y Group B	15 28 103 91 88 112	39 191 157 155 308 189	79 78 78 9	157 154 48 78	2.1% 2.0% 0.5% 0.9%	1.29 [1.04, 1.60] 1.17 [0.95, 1.43] 1.12 [0.91, 1.38] 1.94 [1.06, 3.56] 2.04 [1.32, 3.14]	=
heehan 2009b mith 1992 tark 1985 tudy F1,J-MC-HMAQ - Stud alle-Cabrera 2018 rade 2002 rang 2014c rELL, AK1A4006 remicke 1987 remicke 1988 ubtotad (95% CI) otal events leterogeneth; Tau*= 0.01;	ChiP= 113.89, df= 71 (P	15 28 103 91 88 112 89	39 191 157 155 308 189 10067	79 78 78 9 18	157 154 48 78	2.1% 2.0% 0.5% 0.9%	1.29 [1.04, 1.60] 1.17 [0.95, 1.43] 1.12 [0.91, 1.38] 1.94 [1.06, 3.56] 2.04 [1.32, 3.14]	=
heehan 2009b mith 1992 tark 1985 tudy F1,J-MC-HMAQ - Stud alle-Cabrera 2018 rade 2002 rang 2014c rELL, AK1A4006 remicke 1987 remicke 1988 ubtotad (95% CI) otal events leterogeneth; Tau*= 0.01;	ChiP= 113.89, df= 71 (P	15 28 103 91 88 112 89	39 191 157 155 308 189 10067	79 78 78 9 18	157 154 48 78	2.1% 2.0% 0.5% 0.9%	1.29 [1.04, 1.60] 1.17 [0.95, 1.43] 1.12 [0.91, 1.38] 1.94 [1.06, 3.56] 2.04 [1.32, 3.14]	
heehan 2009b mith 1992 tark 1995 tudy FIJ-MC-HMAQ - Stud alle-Cabrera 2018 rade 2002 rang 2014c remicke 1987 remicke 1988 ubtotal (95% CI) otal events elerogeneity: Tau* = 0.01; est for overall effect: Z = 1	ChiP= 113.89, df= 71 (P	15 28 103 91 88 112 89	39 191 157 155 308 189 10067	79 78 78 9 18	157 154 48 78 7521	2.1% 2.0% 0.5% 0.9%	1.29 [1.04, 1.60] 1.17 [0.95, 1.43] 1.12 [0.91, 1.38] 1.94 [1.06, 3.56] 2.04 [1.32, 3.14]	
heehan 2009b mith 1992 tark 1985 tudy F1J-MC-HMAQ - Stud alle-Cabrera 2018 rade 2002 rang 2014c rELL AVITA4005 (remicke 1987 fernicke 1988	ChiP= 113.89, df= 71 (P	15 28 103 91 88 112 89	39 191 157 155 308 189 10067	79 78 78 9 18	157 154 48 78 7521	2.1% 2.0% 0.5% 0.9% 89.9%	1.29 [1.04, 1.60] 1.17 [0.95, 1.43] 1.12 [0.91, 1.38] 1.94 [1.06, 3.56] 2.04 [1.32, 3.14] 1.31 [1.25, 1.37]	-
heehan 2009b mith 1992 tark 1985 tudy F1,J-MC-HMAQ - Stud alle-Cabrera 2018 fade 2002 fang 2014c fELL, AK1A4006 fermicke 1987 fermicke 1988 ublotati (95% Cl) otal events est for overall effect: Z = 1 otal (95% Cl)	ChiP= 113.89, df= 71 (P 1.30 (P < 0.00001) ChiP= 134.01, df= 78 (P	15 28 103 91 88 112 89 5188 = 0.0009);	39 191 157 155 308 189 10067 P= 38%	79 78 78 9 18 2943	157 154 48 78 7521	2.1% 2.0% 0.5% 0.9% 89.9%	1.29 [1.04, 1.60] 1.17 [0.95, 1.43] 1.12 [0.91, 1.38] 1.94 [1.06, 3.56] 2.04 [1.32, 3.14] 1.31 [1.25, 1.37]	0.01 0.1 10

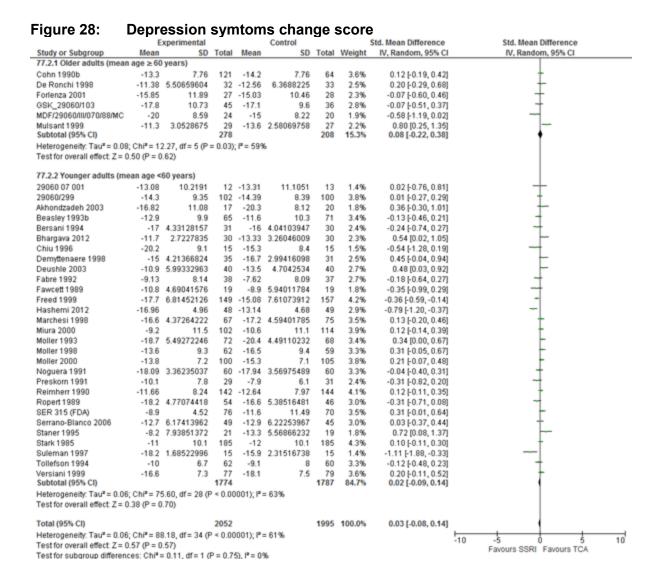


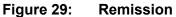


SSRIs versus TCAs

Figure 27: Depression symptoms endpoint

J	Exp	eriment	al	(Control		•	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
77.1.1 Older adults (mean	age ≥ 6	0 years	;)						
De Ronchi 1998	14.22	8.31	32	13.94	9.4	33	2.9%	0.03 [-0.46, 0.52]	+
Forlenza 2001	14.44	12.35	27	12.71	11.8	28	2.6%	0.14 [-0.39, 0.67]	+
GSK_29060/103	13.5	11.4	45	13.8	8.4	36	3.2%	-0.03 [-0.47, 0.41]	+
Mulsant 1999	9.6	4.6	29	8.8	3	27	2.6%	0.20 [-0.32, 0.73]	+
Subtotal (95% CI)			133			124	11.2%	0.07 [-0.17, 0.32]	•
Heterogeneity: Tau ² = 0.00	; Chi*= (0.53, df	= 3 (P =	= 0.91);	$I^2 = 0\%$				
Test for overall effect $Z = 0$									
77.1.2 Younger adults (me	ean age	<60 yea	irs)						
Bersani 1994	16	6.5	31	16	6.1	30	2.7%	0.00 [-0.50, 0.50]	+
Bhargava 2012	14.23	3.51	-	13.67	4.74	30	2.7%	0.13 [-0.37, 0.64]	+
Byerley 1988	12.8	7.7	20	13.7	8.5	24	2.2%	-0.11 [-0.70, 0.49]	+
Chiu 1996	7.4	9.6	15	11.7	8.1	15	1.6%	-0.47 [-1.20, 0.26]	-
Christiansen 1996	8.1	5.9	56	6.9	6.2	57	3.9%	0.20 [-0.17, 0.57]	+
Cohn 1984b	14.72	8.81	35	14.54	8.85	31	2.9%	0.02 [-0.46, 0.50]	+
Demyttenaere 1998	9.9	6.3	35	7.2	4.5	31	2.8%	0.48 [-0.01, 0.97]	-
Deushle 2003	12.7	8.2	40	10.5	7.1	40	3.2%	0.28 [-0.16, 0.72]	<u> </u>
Fawcett 1989	12.8	6.5	19	14.6	7.9	19	2.0%	-0.24 [-0.88, 0.39]	
Freed 1999		10.24	149	16.58	10.89	157	5.6%	-0.27 [-0.50, -0.05]	_
Hashemi 2012	16.16	4.02		19.71	4.21	49	3.4%	-0.86 [-1.27, -0.44]	_
Judd 1993	9.6	6.2	23	11.6	4.21	23	2.3%	-0.32 [-0.90, 0.26]	
Laakmann 1991	9.47	7.56	62	9.65	7.86	62	4.1%	-0.02 [-0.38, 0.33]	1
Marchesi 1998	8.9	6.6	67	8.1	6.9	75	4.1%	0.12 [-0.21, 0.45]	<u> </u>
Moller 1993	11.5	8.3	72	9.3	6.3	68	4.3%		
Noguera 1991	6.21	4.57	60	6.66	4.93	60	4.0%	0.30 [-0.04, 0.63]	
			21					-0.09 [-0.45, 0.26]	_
Ontiveros Sanchez 1998	7.8	6.21		5.8	5.45	21	2.1%	0.34 [-0.27, 0.95]	
PAR 29060/281	16.1	8.59	76	12.4	8.59	79	4.4%	0.43 [0.11, 0.75]	
PAR MDUK 032	12	8.07	29	12.2	8.07	30	2.7%	-0.02 [-0.53, 0.49]	I
Peters 1990	10	6	41	11	9	40	3.3%	-0.13 [-0.57, 0.31]	I
Ropert 1989	9.4		54	11.8	8	46	3.6%	-0.32 [-0.71, 0.08]]
SER-CHN-1	5.53	6.94	113	6.47	7.24	118	5.2%	-0.13 [-0.39, 0.13]	1
Serrano-Blanco 2006	9.5	8.2	49	8.8	8.2	45	3.5%	0.08 [-0.32, 0.49]	T
Staner 1995	17.8	11.3	21	10.7	7.9	19	2.0%	0.71 [0.07, 1.35]	_
Suleman 1997	7.2	2.5	15	7	2.6	15	1.7%	0.08 [-0.64, 0.79]	T
Tollefson 1994	11.6	7.6	62	12.2	7.9	60	4.0%	-0.08 [-0.43, 0.28]	Ť
Versiani 1999 Subtotal (95% CI)	9.9	8.4	77 1320	8.1	7	79 1323	4.5% 88.8%	0.23 [-0.08, 0.55] 0.01 [-0.11, 0.13]	Ţ
Heterogeneity: Tau* = 0.05	; Chi*= 5	54.83, d	f= 26 (P = 0.01	008); (800	53%			
Test for overall effect Z = 0									
Total (95% CI)			1453			1447	100.0%	0.02 [-0.09, 0.12]	1
Heterogeneity: Tau ² = 0.04	Chi*= f	55.69. d		P = 0.00	03): I ² =				
Test for overall effect: Z = 0	-			0.01	/	- 5 70			-10 -5 0 5 1
	ces: Chi								Favours SSRI Favours TCA





	Experim	ental	Contr	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
77.3.1 Older adults (mean age ≥ 60 years)							
Forlenza 2001	13	27	11	28	3.4%	1.23 [0.67, 2.24]	-
Geretsegger 1995	22	44	18	47	4.9%	1.31 [0.82, 2.08]	+-
Guillibert 1989	20	40	19	39	5.2%	1.03 [0.66, 1.60]	+
Hutchinson 1992	38	58	18	32	6.8%	1.16 [0.81, 1.67]	+-
<yle 1998<="" td=""><td>96</td><td>179</td><td>99</td><td>186</td><td>11.3%</td><td>1.01 [0.83, 1.22]</td><td>+</td></yle>	96	179	99	186	11.3%	1.01 [0.83, 1.22]	+
MDF/29060/III/070/88/MC	17	32	11	30	3.7%	1.45 [0.82, 2.57]	+
Mulsant 1999	19	43	21	37	5.3%	0.78 [0.50, 1.21]	
Navarro 2001	20	29	25	29	8.6%	0.80 [0.60, 1.06]	
Sneed 2014	14	58	19	52	3.6%	0.66 [0.37, 1.18]	
Subtotal (95% CI)		510		480	52.8%	0.99 [0.86, 1.14]	•
Total events	259		241				
Heterogeneity: Tau* = 0.01; Chi* = 9.63, df = 8 (F	$= 0.29); ^2$	= 17%					
Test for overall effect: Z = 0.13 (P = 0.90)							
77.3.2 Younger adults (mean age <60 years)							
Beasley 1993b	11	65	15	71	2.6%	0.80 [0.40, 1.62]	
Danish University Antidepressant Group 1986	14	57	31	57	4.3%	0.45 [0.27, 0.75]	
Danish University Antidepressant Group 1990	12	62	26	58	3.6%	0.43 [0.24, 0.77]	
Fawcett 1989	4	20	5	20	1.1%	0.80 [0.25, 2.55]	
Feighner 1993	59	241	63	241	8.0%	0.94 [0.69, 1.27]	+
Keegan 1991	14	20	13	22	5.1%	1.18 [0.75, 1.86]	-
Levine 1989	11	30	15	30	3.5%	0.73 [0.41, 1.32]	
Moller 1993	49	112	54	110	8.6%	0.89 [0.67, 1.18]	+
Moon 1996	33	70	32	68	6.9%	1.00 [0.70, 1.43]	+
Tollefson 1994	20	62	14	62	3.5%	1.43 [0.80, 2.56]	+
Subtotal (95% CI)		739		739	47.2%	0.84 [0.68, 1.04]	•
Total events	227		268				
Heterogeneity: Tau* = 0.05; Chi* = 17.78, df = 9 (P = 0.04);	°= 49%					
Test for overall effect: Z = 1.60 (P = 0.11)							
Total (95% CI)		1249		1219	100.0%	0.92 [0.82, 1.05]	•
Total events	486		509				
Heterogeneity: Tau2 = 0.03; Chi2 = 29.21, df = 18	(P = 0.05)	I ² = 38	%				has also de la co
Test for overall effect: Z = 1.22 (P = 0.22)							0.01 0.1 1 10 10 Favours TCA Favours SSRI
Test for subgroup differences: Chi2 = 1.60, df = 1							FAVOURS I CA. FAVOURS SSRI

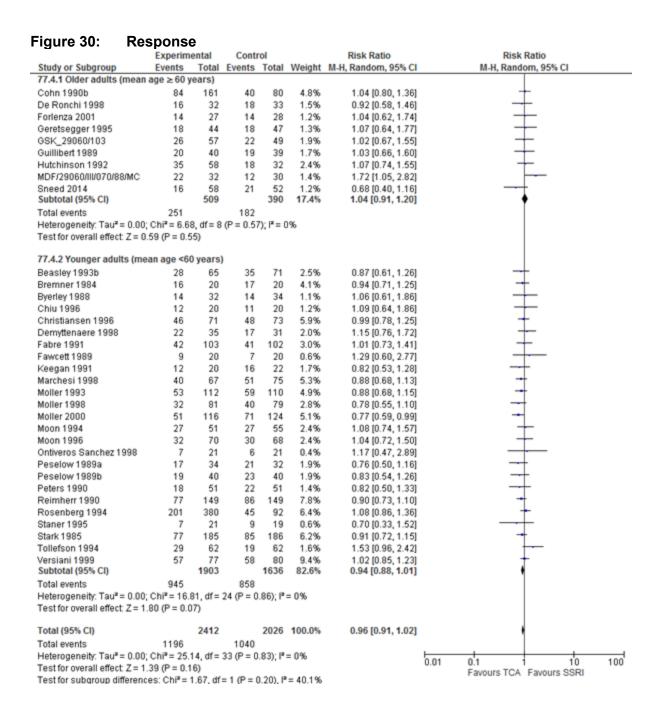


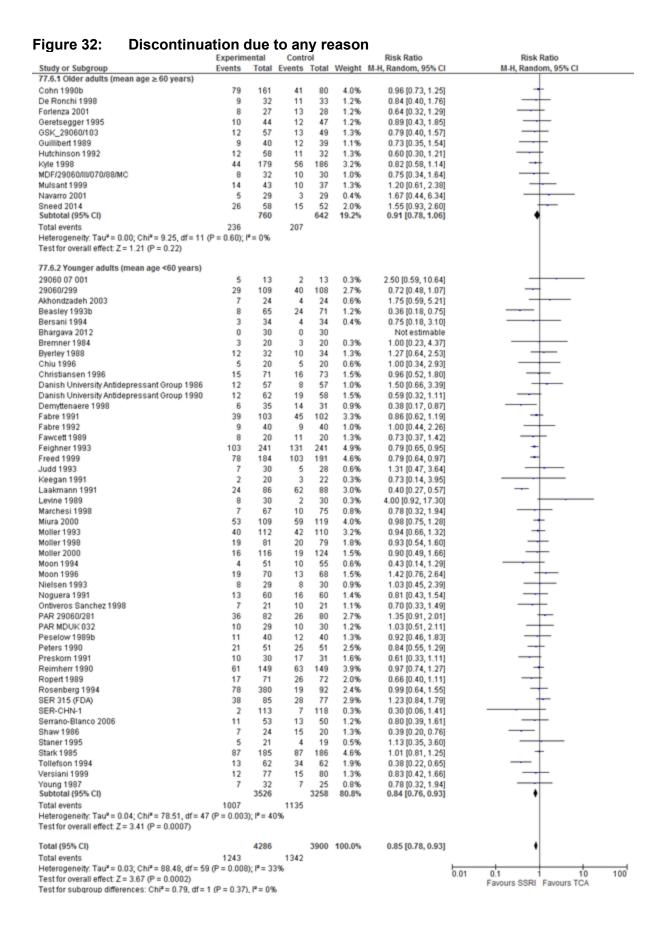
Figure 31: Discontinuation due to side effects Experimental Events Total Risk Ratio Control Risk Ratio Study or Subgroup

77.5.1 Older adults (mean age ≥ 60 years) Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI Cohn 1990b 49 161 80 5.9% 0.87 [0.60, 1.27] 28 0.41 [0.09, 1.97] De Ronchi 1998 32 33 0.8% Forlenza 2001 27 1.7% 0.65 [0.24, 1.73] 28 Geretsegger 1995 9 44 47 2.0% 1.37 [0.56, 3.37] GSK_29060/103 5 57 4 49 1.1% 1.07 [0.31, 3.78] Guillibert 1989 40 5 39 1.0% 0.58 [0.15, 2.28] Hutchinson 1992 58 32 1.8% 0.74 [0.28, 1.93] Kyle 1998 31 179 48 186 5.6% 0.67 [0.45, 1.00] MDF/29060/III/070/88/MC 2 32 5 30 0.8% 0.38 [0.08, 1.79] Mulsant 1999 8 43 5 37 1.6% 1.38 [0.49, 3.85] Navarro 2001 29 0.2% 29 0.20 (0.01, 3.99) 0 Sneed 2014 58 5 52 1.4% 1.08 [0.35, 3.32] Subtotal (95% CI) 760 642 24.0% 0.80 [0.64, 0.99] Total events 128 128 Heterogeneity: Tau2 = 0.00; Chi2 = 6.70, df = 11 (P = 0.82); I2 = 0% Test for overall effect Z = 2.02 (P = 0.04) 77.5.2 Younger adults (mean age <60 years) 29060 07 001 13 0.4% 0.50 [0.05, 4.86] 29060/299 109 12 108 2.0% 0.58 [0.24, 1.41] Akhondzadeh 2003 24 Ü 24 Not estimable 0 Bascara 1989 27 23 0.7% 0.57 [0.10, 3.11] Beasley 1993b 71 0.27 [0.10, 0.77] 65 16 1.6% Bersani 1994 0 34 34 0.2% 0.33 [0.01, 7.91] 30 20 Bhargava 2012 0 Ü 30 Not estimable 0.6% 1.00 [0.16, 6.42] Bremner 1984 2 20 Byerley 1988 32 1.06 [0.29, 3.90] 34 1.1% 20 0.7% 1.50 [0.28, 8.04] Chiu 1996 20 Christiansen 1996 10 71 73 2.3% 1.14 [0.49, 2.64] Danish University Antidepressant Group 1986 0 57 57 0.2% 0.11 [0.01, 2.02] Danish University Antidepressant Group 1990 62 10 58 0.5% 0.09 [0.01, 0.71] Demyttenaere 1998 0.16 [0.04, 0.67] 35 11 31 0.9% 29 0.58 [0.34, 0.99] Fabre 1991 17 103 102 4.2% Fawcett 1989 20 10 20 1.8% 0.40 [0.15, 1.07] Feighner 1993 55 241 85 241 7.1% 0.65 [0.48, 0.86] Freed 1999 23 184 38 191 4.7% 0.63 (0.39, 1.01) 0 Judd 1993 2.81 [0.12, 66.17] 30 28 0.2% 0 22 Keegan 1991 20 0.2% 0.16 [0.01, 2.85] Levine 1989 30 0 30 0.2% 5.00 [0.25, 99.95] Marchesi 1998 3 67 75 0.6% 1.68 [0.29, 9.75] Miura 2000 20 109 19 119 3.9% 1.15 [0.65, 2.04] Moller 1993 12 112 19 110 3.1% 0.62 [0.32, 1.22] Moller 1998 5 81 79 1.1% 1.22 [0.34, 4.37] Moller 2000 124 1.5% 0.67 [0.23, 1.98] 116 Moon 1994 2 51 10 55 0.9% 0.22 [0.05, 0.94] Moon 1996 3 70 68 0.8% 0.97 [0.20, 4.65] Nielsen 1993 4 29 5 30 1.2% 0.83 [0.25, 2.78] Noguera 1991 2 60 0.8% 0.33 [0.07, 1.59] 60 6 Ontiveros Sanchez 1998 21 0.9% 0.29 [0.07, 1.22] PAR 29060/281 22 82 16 80 3.9% 1.34 [0.76, 2.36] PAR MDUK 032 9 29 10 30 2.7% 0.93 [0.44, 1.96] Peselow 1989b 40 40 1.33 [0.32, 5.58] 4 3 0.9% Preskorn 1991 13 0.24 [0.08, 0.75] 30 31 1.3% Reimherr 1990 28 4.7% 0.93 [0.57, 1.51] 26 149 149 Ropert 1989 4 71 12 72 1.5% 0.34 [0.11, 1.00] Rosenberg 1994 32 380 12 92 3.5% 0.65 [0.35, 1.20] SER 315 (FDA) 14 85 6 77 2.0% 2.11 (0.85, 5.23) SER-CHN-1 2 0.30 [0.06, 1.41] 113 118 0.8% 0.17 [0.02, 1.31] Shaw 1986 24 20 0.5% Staner 1995 21 19 0.6% 0.90 [0.14, 5.81] Stark 1985 33 185 52 186 5.8% 0.64 [0.43, 0.94] Tollefson 1994 6 62 27 62 2.4% 0.22 [0.10, 0.50] Versiani 1999 77 80 1.1% 0.45 [0.12, 1.66] Young 1987 0 0.2% 3.94 [0.20, 78.54] 32 ٠ 0.65 [0.54, 0.78] Subtotal (95% CI) 3323 3052 76.0% Total events 359 524 Heterogeneity: Tau^a = 0.09; Chi^a = 62.59, df = 43 (P = 0.03); I^a = 31% Test for overall effect: Z = 4.65 (P < 0.00001) Total (95% CI) 4083 3694 100.0% 0.69 [0.60, 0.80] Total events 487 652 Heterogeneity: Tau2 = 0.05; Chi2 = 70.97, df = 55 (P = 0.07); i2 = 22% 0.01 100

Favours SSRI Favours TCA

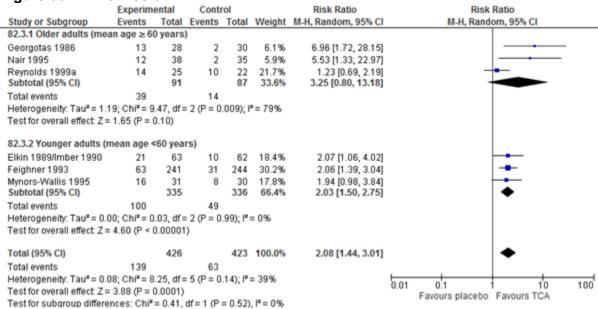
Test for overall effect: Z = 5.05 (P < 0.00001)

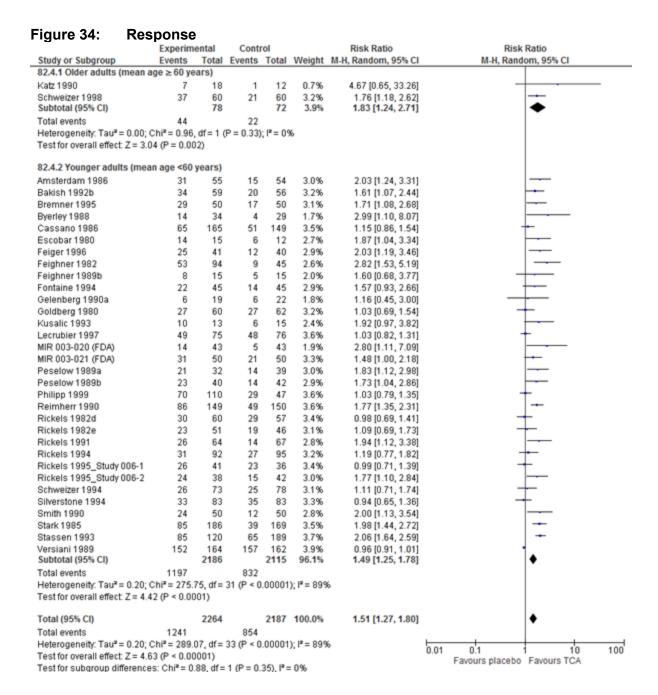
Test for subgroup differences: Chi² = 1.85, df = 1 (P = 0.17), I² = 46.0%

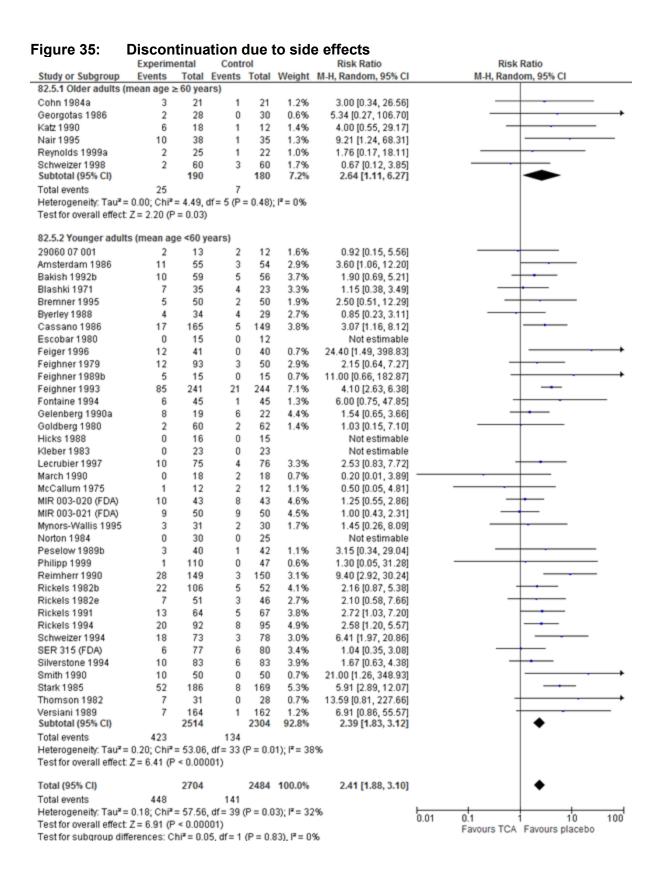


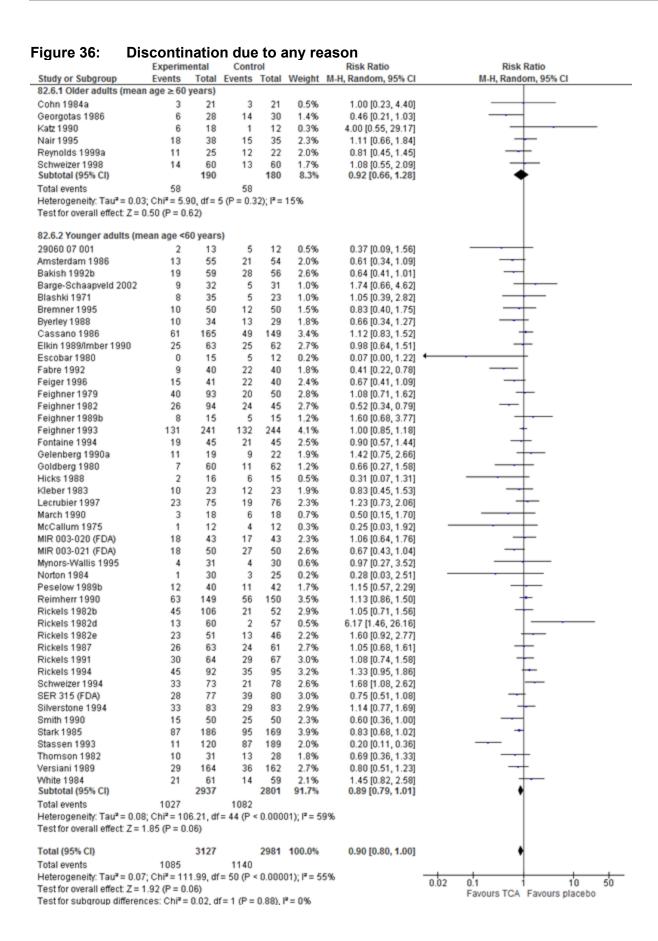
TCAs versus placebo

Figure 33: Remission









SNRIs versus placebo

Figure 37: Depression symptoms change score

		_							
	E	xperimental			Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
85.2.1 Older adults (mean age \geq 60 ye	ars)								
Katona 2012	-15.8	9.7	147	-10.3	9.63	145	5.5%	-0.57 [-0.80, -0.33]	•
Robinson 2014	-7.42	7.37	201	-7.15	7.51	95	5.4%	-0.04 [-0.28, 0.21]	.†
Subtotal (95% CI)			348			240	10.9%	-0.30 [-0.82, 0.22]	•
Heterogeneity: Tau* = 0.13; Chi* = 9.48;	df = 1 (P	= 0.002); (*=	89%						
Test for overall effect: $Z = 1.14$ (P = 0.25	5)								
85.2.2 Younger adults (mean age <60	years)								
Baldwin 2012	-16.8	9.77	149	-14.8	9.63	145	5.5%	-0.21 [-0.43, 0.02]	-
Boulenger 2014	-21.15	9.3	146	-11.7	9.55	158	5.4%	-1.00 [-1.24, -0.76]	-
Brannan 2005	-10.85	7.93	132	-10.27	7.81	136	5.4%	-0.07 [-0.31, 0.17]	+
Detke 2004	-11.55	4.84	186	-8.8	4.82	93	5.3%	-0.57 [-0.82, -0.31]	-
EII LIIIY HMAT-A	-6.31	6.3	81	-4.78	6.42	89	4.7%	-0.24 [-0.54, 0.06]	-
Juelfi 1995	-14.2	9.6	46	-4.8	11	47	3.5%	-0.90 [-1.33, -0.47]	-
lewett 2010	-17	10.56	193	-13.2	10.64	186	5.8%	-0.36 [-0.56, -0.15]	-
liguchi 2009	-10	6.4	74	-8.3	5.8	145	5.0%	-0.28 [-0.56, -0.00]	-
Higuchi 2016	-15.17	10.08	348	-12.41	10.12	182	6.1%	-0.27 [-0.45, -0.09]	4
Chan 1991	-9.07	6.76	67	-4	7.15960893	26	3.2%	-0.73 [-1.20, -0.27]	-
dahableshwarkar 2013	-13.47	9.15	149	-10.5	9.28	149	5.5%	-0.32 [-0.55, -0.09]	-
Mendels 1993	-14.8	9.64	77	-10.53	8.98	75	4.5%	-0.46 [-0.78, -0.13]	-
Nierenberg 2007	-7.61	6.94	273	-5.97	6.79	137	5.8%	-0.24 [-0.44, -0.03]	- 1
Schweizer 1994	-15.6	9.8		-10.2	9.6	78	4.4%	-0.55 [-0.89, -0.22]	+
Sheehan 2009b		7.32900744	91	-11.02	6.86603233	95	4.8%	-0.46 [-0.75, -0.17]	-
Study F1J-MC-HMAQ - Study Group B	-8	6.75	81	-7.1	6.96	72	4.6%	-0.13 [-0.45, 0.19]	†
/EN 600A-303 (FDA)	-10.14	8.45	69	-9.89	8.45	79	4.5%	-0.03 [-0.35, 0.29]	†
/EN 600A-313 (FDA)	-11.39	8.39		-9.49	8.2	75	5.0%	-0.23 [-0.51, 0.05]	
Subtotal (95% CI)			2375			1967	89.1%	-0.38 [-0.49, -0.26]	•
leterogeneity: Tau* = 0.04; Chi* = 58.2	3, df = 17	(P < 0.00001)	$(1^{2} = 71)$	96					
est for overall effect: Z = 6.28 (P < 0.00	0001)								
Total (95% CI)			2723			2207	100.0%	-0.37 [-0.48, -0.26]	
Heterogeneity: Tau* = 0.05; Chi* = 67.9	4, df = 19	(P < 0.00001)	$ c ^2 = 72$	2%				-	1
Test for overall effect: Z = 6.44 (P < 0.00									-10 -5 0 5
Test for subgroup differences: Chi ² = 0.		/D = 0.705 /F	- 004						Favours SNRI Favours placebo



igure 30. Reillissi						Dist. Dati	Pi-t P-ti-
	Experim		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
85.3.1 Older adults (mean age ≥ 60 ye							
Katona 2012	51	151	28	145	3.7%	1.75 [1.17, 2.61]	
Raskin 2007	55	207	15	104	2.7%	1.84 [1.10, 3.10]	
Robinson 2014	74	249	31	121	4.2%	1.16 [0.81, 1.66]	+
Subtotal (95% CI)		607		370	10.6%	1.50 [1.11, 2.03]	•
Total events	180		74				
Heterogeneity: Tau² = 0.03; Chi² = 3.13,	df = 2 (P =	0.21); (°= 36%				
Test for overall effect: $Z = 2.64$ (P = 0.00	18)						
85.3.2 Younger adults (mean age <60)	years)						
Baldwin 2012	52	157	49	152	4.6%	1.03 [0.75, 1.42]	+
Boulenger 2014	79	147	30	158	4.2%	2.83 [1.98, 4.04]	-
Brannan 2005	30	141	33	141	3.4%	0.91 [0.59, 1.41]	-
Cutler 2009	55	151	42	157	4.4%	1.36 [0.98, 1.90]	-
Detke 2002a	55	128	39	139	4.5%	1.53 [1.10, 2.14]	-
Detke 2002b	53	123	18	122	3.1%	2.92 [1.82, 4.68]	
Detke 2004	92	188	28	93	4.3%	1.63 [1.15, 2.29]	-
Eli Lilly HMAT-A	23	84	18	90	2.6%	1.37 [0.80, 2.35]	+
Goldstein 2002	37	70	22	70	3.6%	1.68 [1.12, 2.54]	-
Soldstein 2004	43	91	26	89	3.8%	1.62 [1.10, 2.39]	-
Suelfi 1995	12	46	6	47	1.2%	2.04 [0.84, 4.98]	
lewett 2009	94	187	63	197	5.5%	1.57 [1.23, 2.02]	-
lewett 2010	108	198	71	187	5.9%	1.44 [1.15, 1.80]	-
Higuchi 2009	26	75	32	146	3.4%	1.58 [1.02, 2.45]	-
Levin 2013	26	51	30	52	4.2%	0.88 [0.62, 1.26]	-
Mahableshwarkar 2013	51	152	33	153	4.0%	1.56 [1.07, 2.27]	-
Mahableshwarkar 2015a	38	152	41	161	3.9%	0.98 [0.67, 1.44]	+
Nemeroff 2007	31	102	22	102	3.1%	1.41 [0.88, 2.26]	-
Nierenberg 2007	75	273	27	137	3.8%	1.39 [0.94, 2.06]	-
Perahia 2006	82	196	33	99	4.6%	1.26 [0.91, 1.74]	-
Rudolph 1999	35	100	17	98	2.8%	2.02 [1.21, 3.35]	
Sheehan 2009b	21	95	14	95	2.2%	1.50 [0.81, 2.77]	
Study F1J-MC-HMAQ - Study Group B	32	82	21	75	3.3%	1.39 [0.89, 2.19]	-
Thase 1997	32	95	19	102	2.9%	1.81 [1.10, 2.96]	
Subtotal (95% CI)	32	3084	15	2862	89.4%	1.47 [1.31, 1.66]	♦
otal events	1182		734				
leterogeneity: Tau ² = 0.04; Chi ² = 48.57	7, df = 23 (6)	P = 0.00	1); $I^2 = 5$	3%			
Test for overall effect: $Z = 6.59$ (P < 0.00	001)						
Total (95% CI)		3691		3232	100.0%	1.48 [1.33, 1.64]	•
otal events	1362		808				
Heterogeneity: Tau ² = 0.04; Chi ² = 51.71		P = 0.00		1%			L. J
Test for overall effect: Z = 7.19 (P < 0.00		2.00	-,,,	-			0.01 0.1 1 10 10
							Favours placebo Favours SNRI



igaio do. Roopono	_		_				
	Experime		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
85.4.1 Older adults (mean age ≥ 60 yea							
Katona 2012	93	151	51	145	3.9%	1.75 [1.36, 2.26]	-
Raskin 2007	75	207	19	104	2.1%	1.98 [1.27, 3.09]	
Robinson 2014	88	249	46	121	3.5%	0.93 [0.70, 1.23]	T
Subtotal (95% CI)		607		370	9.5%	1.46 [0.91, 2.34]	_
Total events	256		116				
Heterogeneity: Tau² = 0.15; Chi² = 13.41 Test for overall effect: Z = 1.56 (P = 0.12)		= 0.001); 1= 85	50			
85.4.2 Younger adults (mean age <60 y	ears)						
Baldwin 2012	85	157	68	152	4.2%	1.21 [0.96, 1.52]	-
Boulenger 2014	108	147	51	158	4.0%	2.28 [1.78, 2.91]	-
Brannan 2005	55	141	54	141	3.4%	1.02 [0.76, 1.37]	+
Cunningham 1994	47	72	41	76	3.7%	1.21 [0.93, 1.58]	 -
Cutler 2009	70	151	55	157	3.6%	1.32 [1.01, 1.74]	+
Detke 2002a	83	128	58	139	4.1%	1.55 [1.23, 1.96]	-
Detke 2002b	75	123	33	122	3.1%	2.25 [1.63, 3.12]	_
Detke 2004	128	188	41	93	3.9%	1.54 [1.20, 1.98]	-
Eli Lilly HMAT-A	28	84	24	90	2.0%	1.25 [0.79, 1.97]	
Goldstein 2002	42	70	33	70	3.2%	1.27 [0.93, 1.74]	-
Goldstein 2004	44	91	27	89	2.6%	1.59 [1.09, 2.33]	
Hewett 2009	120	187	91	197	4.7%	1.39 [1.15, 1.67]	-
Hewett 2010	127	198	91	187	4.8%	1.32 [1.10, 1.58]	-
Higuchi 2009	38	75	56	146	3.3%	1.32 [0.98, 1.79]	 -
Hunter 2010_study 2	5	17	5	16	0.5%	0.94 [0.33, 2.65]	
Hunter 2010_study 3	9	18	5	15	0.8%	1.50 [0.64, 3.52]	+
Lecrubier 1997	60	78	48	76	4.4%	1.22 [0.99, 1.50]	+
Levin 2013	32	51	36	52	3.6%	0.91 [0.69, 1.20]	+
Mahableshwarkar 2013	76	152	48	153	3.5%	1.59 [1.20, 2.12]	-
Mahableshwarkar 2015a	80	152	60	161	3.9%	1.41 [1.10, 1.81]	-
Nemeroff 2007	51	102	37	102	3.1%	1.38 [1.00, 1.90]	_
Nierenberg 2007	92	273	36	137	3.1%	1.28 [0.93, 1.78]	
Perahia 2006	129	196	51	99	4.3%	1.28 [1.03, 1.59]	-
Rudolph 1999	54	100	41	98	3.4%	1.29 [0.96, 1.73]	 -
Schweizer 1994	35	73	25	78	2.4%	1.50 [1.00, 2.24]	_
Sheehan 2009b	35	95	23	95	2.1%	1.52 [0.98, 2.37]	_
Study F1J-MC-HMAQ - Study Group B	40	82	28	75	2.7%	1.31 [0.90, 1.89]	_
Thase 1997	40	95	18	102	1.9%	2.39 [1.47, 3.86]	
Subtotal (95% CI)		3296		3076	90.5%	1.39 [1.29, 1.50]	•
Total events	1788		1184				
Heterogeneity: Tau² = 0.02; Chi² = 52.77 Test for overall effect: Z = 8.26 (P < 0.000		P = 0.00	2); I*= 49	3%			
Total (95% CI)		3903		3446	100.0%	1.39 [1.29, 1.51]	•
Total events	2044		1300				
Heterogeneity: Tau ² = 0.03; Chi ² = 66.23		P = 0.00		55%			0.01 0.1 1 10 100
Test for overall effect: Z = 8.21 (P < 0.000							0.01 0.1 1 10 100 Favours placebo Favours SNRI

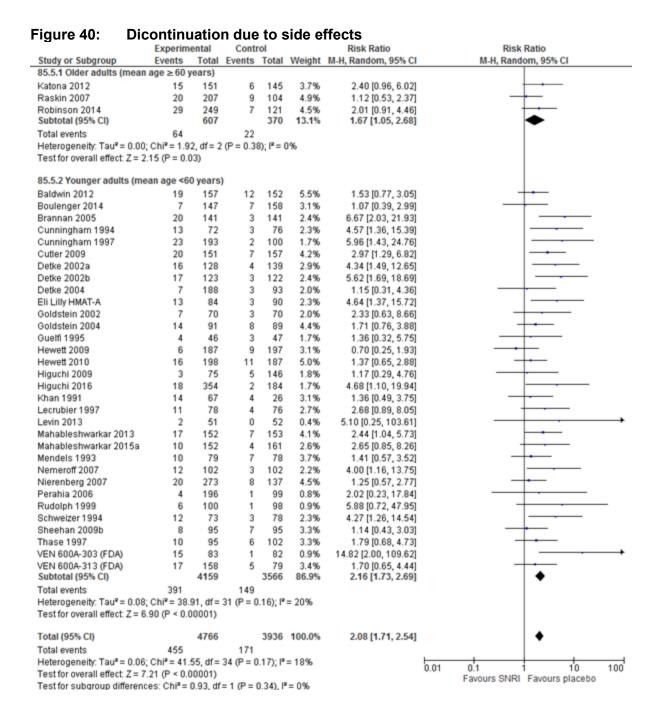


Figure 41: Discontinuation due to any reason

igure 41. Disconti				_	···		Dist. Datis
Chudu as Subassus	Experime		Contr		Malaht	Risk Ratio	Risk Ratio
Study or Subgroup 85.6.1 Older adults (mean age ≥ 60 yea	Events	Total	Events	Total	vveignt	M-H, Random, 95% CI	M-H, Random, 95% CI
			4.7			4 00 10 70 0 00	
Katona 2012	23	151	17	145	2.0%	1.30 [0.72, 2.33]	
Raskin 2007	45	207	24	104	3.0%	0.94 [0.61, 1.46]	
Robinson 2014 Subtotal (95% CI)	70	249 607	43	121 370	4.4% 9.3%	0.79 [0.58, 1.08] 0.91 [0.71, 1.17]	7
	420	007		3/0	9.370	0.91 [0.71, 1.17]	₹
Total events	138	0.000.1	84				
Heterogeneity: Tau* = 0.01; Chi* = 2.25,		0.32); 1	= 11%				
Test for overall effect: $Z = 0.75$ (P = 0.46))						
35.6.2 Younger adults (mean age <60 y	(ears)						
Baldwin 2012	45	157	29	152	3.2%	1.50 [1.00, 2.26]	-
Boulenger 2014	16	147	25	158	1.9%	0.69 [0.38, 1.24]	
Cunningham 1994	25	72	32	76	3.2%	0.82 [0.55, 1.25]	-+
Cunningham 1997	66	193	41	100	4.4%	0.83 [0.61, 1.13]	-+
Cutter 2009	46	151	33	157	3.4%	1.45 [0.98, 2.13]	-
Detke 2002a	50	128	49	139	4.4%	1.11 [0.81, 1.51]	+
Detke 2004	21	188	18	93	2.0%	0.58 [0.32, 1.03]	
Eli Lilly HMAT-A	44	84	29	90	3.7%	1.63 [1.13, 2.34]	
3oldstein 2002	24	70	24	70	2.8%	1.00 [0.63, 1.58]	+
3oldstein 2004	38	91	37	89	3.9%	1.00 [0.71, 1.42]	+
Suelfi 1995	11	46	27	47	2.0%	0.42 [0.24, 0.74]	
lewett 2009	23	187	30	197	2.4%	0.81 [0.49, 1.34]	
lewett 2010	46	198	41	187	3.6%	1.06 [0.73, 1.53]	+
liguchi 2009	9	75	15	146	1.2%	1.17 [0.54, 2.54]	
liguchi 2016	45	354	18	184	2.4%	1.30 [0.78, 2.18]	
ecrubier 1997	23	78	19	76	2.3%	1.18 [0.70, 1.98]	
evin 2013	20	51	19	52	2.5%	1.07 [0.65, 1.76]	
fahableshwarkar 2013	42	152	33	153	3.4%	1.28 [0.86, 1.91]	
Mahableshwarkar 2015a	37	152	32	161	3.1%	1.22 [0.81, 1.86]	-
Mendels 1993	17	79	24	78	2.2%	0.70 [0.41, 1.20]	
Verneroff 2007	24	102	24	102	2.5%	1.00 [0.61, 1.64]	
lierenberg 2007	85	273	40	137	4.3%	1.07 [0.78, 1.46]	_
Perahia 2006	23	196	9	99	1.4%	1.29 [0.62, 2.68]	
Rudolph 1999	28	100	26	98	2.8%	1.06 [0.67, 1.66]	
Schweizer 1991	19	44	8	16	1.9%	0.86 [0.48, 1.57]	
Schweizer 1994	26	73	21	78	2.6%	1.32 [0.82, 2.13]	
Sheehan 2009b	42	95	40	95	4.2%	1.05 [0.76, 1.46]	_
Study F1J-MC-HMAQ - Study Group B	25	82	31	75	3.1%	0.74 [0.48, 1.13]	
hase 1997	26	95	41	102	3.3%	0.68 [0.45, 1.02]	
EN 600A-303 (FDA)	35	83	26	82	3.3%	1.33 [0.89, 1.99]	-
EN 600A-303 (FDA)	39	158	25	79	3.1%	0.78 [0.51, 1.19]	
Subtotal (95% CI)	35	3954	23	3368	90.7%	1.01 [0.91, 1.12]	•
otal events	1020	5554	866	5500	501176	1101 [0101, 1112]	Ĭ
		- 0.02		v.			
Heterogeneity: Tau² = 0.03; Chi² = 48.14 l'est for overall effect: Z = 0.20 (P = 0.84)		- 0.02	/, r = 36	~			
Total (95% CI)		4561		3738	100.0%	1.00 [0.91, 1.10]	l l
otal events	1158	4501	950	3130	.00.079	1.00 [0.01, 1.10]	Ĭ
rotal events Heterogeneity: Tau² = 0.03; Chi² = 51.38		- 0 00		×			
	. ui = 33 (F	= 0.02	7, 1 = 36	70			and the state of t
est for overall effect: Z = 0.06 (P = 0.95)							0.01 0.1 1 10 10 Favours SNRI Favours placebo

SNRIs versus TCAs

Figure 42: Discontinuation due to side effects

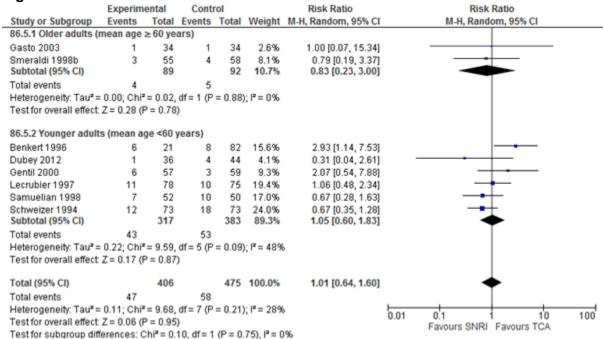
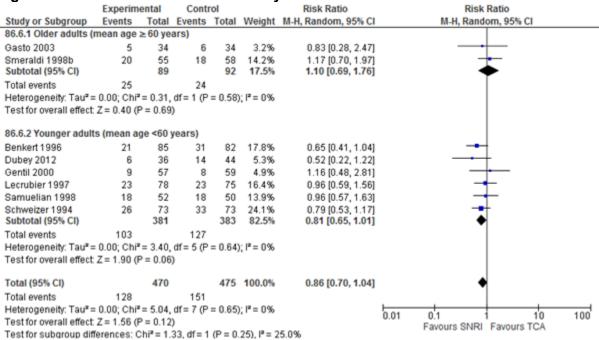


Figure 43: Discontinuation due to any reason



SNRIs versus SSRIs

Figure 44: Remission

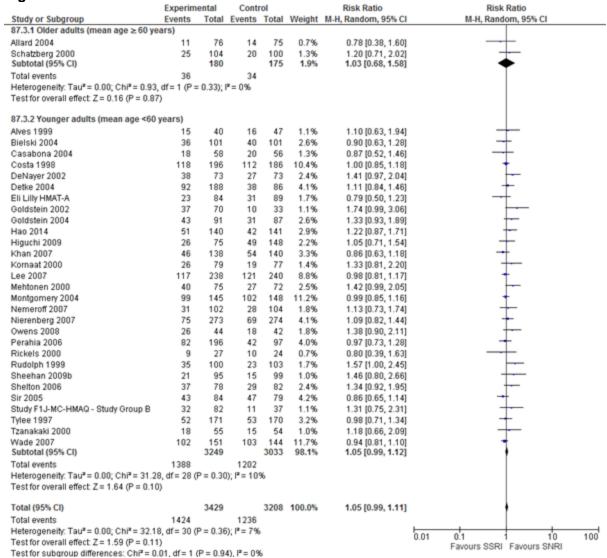
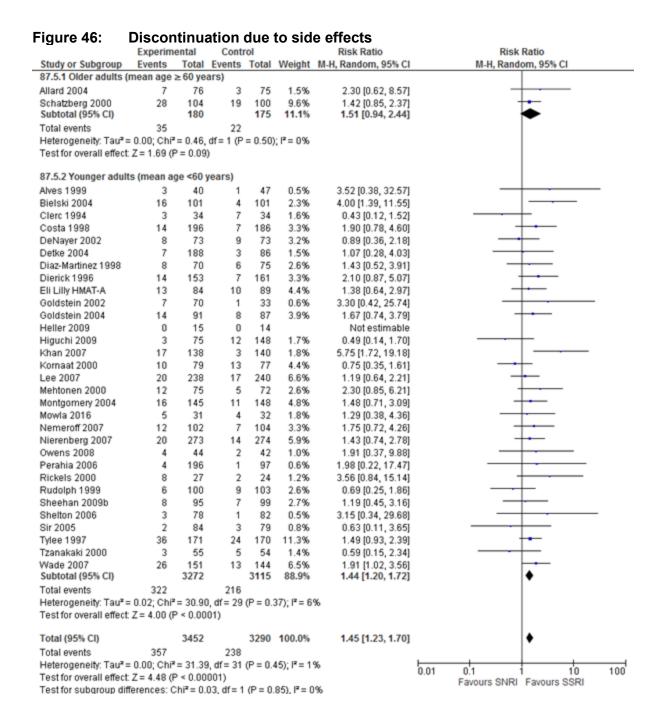
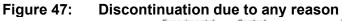


Figure 45:	Response
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guic +o. Resp	Experime	ental	Contr	nol		Risk Ratio	Risk Ratio
tudy or Subgroup	Events				Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
7.4.1 Older adults (mean age ≥		Total	Events	Total	rreight	m-n, nandom, 55% Ci	m-n, random, 55.4 Ci
llard 2004	54	76	55	75	3.5%	0.97 [0.79, 1.18]	<u> </u>
wang 2004	43	52	48	53	4.8%	0.91 [0.78, 1.06]	4
chatzberg 2000	59	104	52	100	2.5%	1.09 [0.85, 1.40]	_
ubtotal (95% CI)	55	232	32	228	10.8%	0.96 [0.86, 1.07]	•
otal events	156		155				1
leterogeneity: Tau* = 0.00; Chi* =	1.78, df = 2 (P =	0.41); [² = 0%				
est for overall effect: Z = 0.72 (P =	0.47)						
7.4.2 Younger adults (mean age	<60 years)						
lves 1999	26	40	28	47	1.6%	1.09 [0.79, 1.51]	+
ielski 2004	47	101	57	101	2.2%	0.82 [0.63, 1.08]	
asabona 2004	43	58	29	56	1.9%	1.43 [1.07, 1.92]	-
lerc 1994	23	34	17	34	1.1%	1.35 [0.90, 2.04]	
osta 1998	158	196	156	186	7.3%	0.96 [0.88, 1.06]	+
eNayer 2002	37	73	27	73	1.3%	1.37 [0.94, 1.99]	-
etke 2004	128	188	64	86	4.6%	0.91 [0.78, 1.07]	+
iaz-Martinez 1998	37	70	45	75	2.0%	0.88 [0.66, 1.18]	-+
ierick 1996	107	153	95	161	4.4%	1.19 [1.00, 1.40]	-
li Lilly HMAT-A	28	84	38	89	1.2%	0.78 [0.53, 1.15]	
oldstein 2002	42	70	17	33	1.2%	1.16 [0.79, 1.71]	+
oldstein 2004	44	91	34	87	1.5%	1.24 [0.88, 1.73]	
ao 2014	86	140	74	141	3.4%	1.17 [0.95, 1.44]	-
iguchi 2009	38	75	78	148	2.2%	0.96 [0.73, 1.26]	+
ang 2017	10	10	16	16	4.8%	1.00 [0.86, 1.17]	+
han 2007	62	138	83	140	2.8%	0.76 [0.60, 0.95]	
ornaat 2000	33	79	33	77	1.3%	0.97 [0.68, 1.41]	_
ee 2007	144	238	157	240	5.4%	0.92 [0.81, 1.06]	4
lehtonen 2000	49	75	41	72	2.4%	1.15 [0.88, 1.49]	_
lontgomery 2004	113	145	113	148	5.9%	1.02 [0.90, 1.16]	<u> </u>
lemeroff 2007	51	102	45	104	1.9%	1.16 [0.86, 1.55]	_
lierenberg 2007	92	273	94	274	2.8%	0.98 [0.78, 1.24]	+
wens 2008	29	44	26	42	1.7%	1.06 [0.77, 1.46]	_
erahia 2006	129	196	59	97	3.7%	1.08 [0.90, 1.31]	<u> </u>
udolph 1999	54	100	52	103	2.3%	1.07 [0.82, 1.39]	_
heehan 2009b	35	95	27	99	1.1%	1.35 [0.89, 2.05]	
helton 2006	48	78	39	82	2.0%	1.29 [0.97, 1.72]	
ir 2005	56	84	56	79	3.3%	0.94 [0.76, 1.16]	1
tudy F1J-MC-HMAQ - Study Grou		82	15	37	0.9%	1.20 [0.77, 1.88]	
rlee 1997	81	171	98	170	3.4%	0.82 [0.67, 1.01]	-
zanakaki 2000	30	55	28	54	1.4%		_
zanakaki 2000 /ade 2007	112	151	115	144	5.9%	1.05 [0.74, 1.50] 0.93 [0.82, 1.05]	1
ubtotal (95% CI)	112	3489	113	3295	89.2%	1.02 [0.97, 1.07]	
otal events	2012		1856			2000, 000,	1
eterogeneity: Tau² = 0.01; Chi² =		= 0.03		%			
est for overall effect Z = 0.67 (P =		- 5.05	71 34				
otal (95% CI)		3721		3523	100.0%	1.01 [0.97, 1.06]	
otal events	2168		2011	3020		[0.0.1, 1.00]	1
otal events leterogeneity: Tau* = 0.01; Chi* =		= 0.05		%.			
		- 0.05	, r = 31	20			0.01 0.1 1 10 1
est for overall effect: Z = 0.45 (P =							Favours SSRI Favours SNRI





	Experim		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
7.6.1 Older adults (mean age ≥ 60 ye	ars)						
llard 2004	18	76	16	75	2.1%	1.11 [0.61, 2.01]	
lwang 2004	3	52	3	53	0.3%	1.02 [0.22, 4.82]	
ubtotal (95% CI)		128		128	2.4%	1.10 [0.63, 1.91]	•
otal events	21		19				
leterogeneity: Tau* = 0.00; Chi* = 0.01,	df = 1 (P =	0.92); F	z = 0%				
est for overall effect: $Z = 0.33$ (P = 0.74)						
37.6.2 Younger adults (mean age <60)	years)						
lives 1999	10	40	9	47	1.2%	1.31 [0.59, 2.89]	
Basterzi 2009	7	21	7	22	1.0%	1.05 [0.44, 2.48]	
Bielski 2004	33	101	24	101	3.5%	1.38 [0.88, 2.15]	+-
Clerc 1994	6	34	12	34	1.0%	0.50 [0.21, 1.18]	
Costa 1998	29	196	18	186	2.4%	1.53 [0.88, 2.66]	
DeNayer 2002	24	73	29	73	3.7%	0.83 [0.54, 1.28]	-
Detke 2004	21	188	10	86	1.5%	0.96 [0.47, 1.95]	
Diaz-Martinez 1998	15	70	20	75	2.1%	0.80 [0.45, 1.44]	-
Dierick 1996	38	153	40	161	4.5%	1.00 [0.68, 1.47]	+
li Lilly HMAT-A	44	84	31	89	5.3%	1.50 [1.06, 2.13]	-
3oldstein 2002	24	70	12	33	2.3%	0.94 [0.54, 1.64]	
3oldstein 2004	38	91	38	87	5.6%	0.96 [0.68, 1.34]	+
Hao 2014	32	140	36	141	4.0%	0.90 [0.59, 1.36]	-
Heller 2009	3	15	5	14	0.5%	0.56 [0.16, 1.92]	
liguchi 2009	9	75	22	148	1.4%	0.81 [0.39, 1.67]	
Chan 2007	47	138	30	140	4.4%	1.59 [1.07, 2.35]	-
Cornaat 2000	15	79	24	77	2.3%	0.61 [0.35, 1.07]	
ee 2007	72	238	57	240	6.9%	1.27 [0.95, 1.72]	-
dehtonen 2000	16	75	12	72	1.6%	1.28 [0.65, 2.51]	
fontgomery 2004	20	145	22	148	2.3%	0.93 [0.53, 1.63]	
dowla 2016	5	31	4	32	0.5%	1.29 [0.38, 4.36]	
Verneroff 2007	24	102	18	104	2.4%	1.36 [0.79, 2.35]	-
Vierenberg 2007	85	273	66	274	7.9%	1.29 [0.98, 1.70]	-
Owens 2008	12	44	10	42	1.4%	1.15 [0.55, 2.36]	
Perahia 2006	23	196	11	97	1.6%	1.03 [0.53, 2.03]	
Rudolph 1999	28	100	35	103	4.0%	0.82 [0.54, 1.25]	
Sheehan 2009b	42	95	32	99	5.0%	1.37 [0.95, 1.97]	
Shelton 2006	11	78	19	82	1.6%	0.61 [0.31, 1.20]	
Sir 2005	25	84	13	79	2.1%		
	25 25	82	14	37	2.1%	1.81 [1.00, 3.28]	
Study F1J-MC-HMAQ - Study Group B				-		0.81 [0.48, 1.36]	1
ylee 1997	47	171	46	170 54	5.4%	1.02 [0.72, 1.44]	
Zanakaki 2000 Kodo 2007	12	55	12		1.5%	0.98 [0.48, 1.99]	
Vade 2007 Subtotal (95% CI)	37	151 3488	32	144 3291	4.0% 97.6%	1.10 [0.73, 1.67] 1.09 [0.99, 1.19]	T
	070	3400	770	3291	37.0%	1.09 [0.99, 1.19]	ř
otal events	879		770				
leterogeneity: Tau² = 0.01; Chi² = 37.33 est for overall effect: Z = 1.73 (P = 0.08		= 0.24); (*= 14	%			
Total (95% CI)		3616		3419	100.0%	1.09 [1.00, 1.19]	
otal events	900	23.0	789			[1100] 1110]	ſ
leterogeneity: Tau* = 0.01; Chi* = 37.34		P = 0.33					
est for overall effect: Z = 1.90 (P = 0.06		- 0.32	/, I = 5%	,			0.01 0.1 1 10
estion overall effect Z = 1.30 (F = 0.06	,						Favours SNRI Favours SSRI

Trazodone versus TCAs

Figure 48: Discontinuation due to side effects

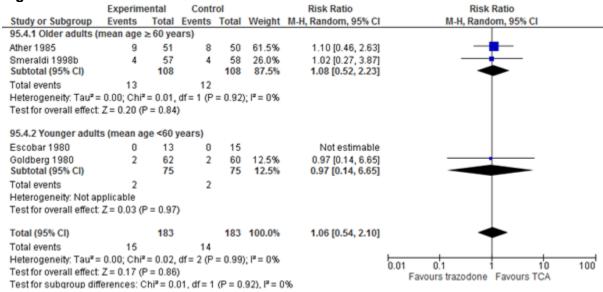
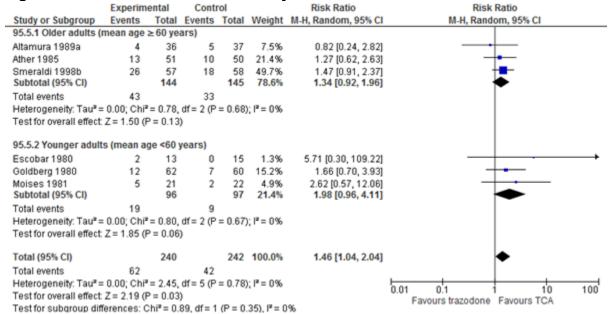


Figure 49: Discontinuation due to any reason



Pairwise meta-analysis of couple interventions (not included in the NMA)

Behavioural couples therapy versus waitlist

Figure 50: Depression symptoms endpoint

	Expe	erimen	tal	0	Control			Std. Mean Difference		Std. Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed	1				
Beach 1992	8.4	6.22	15	20.47	10.68	15	100.0%	-1.34 [-2.15, -0.54]		•					
Total (95% CI)			15			15	100.0%	-1.34 [-2.15, -0.54]		•					
Heterogeneity: Not ap Test for overall effect:			0.001)						-10	-5 Favours BCT	0 Favour	5 s waitlist	10		

Figure 51: Depression symptoms change score

	Expe	rimen	tal	Control				Std. Mean Difference		Std. Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed					
Beach 1992	-15.53	4.91	15	-7.86	7.48	15	100.0%	-1.18 [-1.96, -0.40]		-					
Total (95% CI)			15			15	100.0%	-1.18 [-1.96, -0.40]		•					
Heterogeneity: Not applicable Test for overall effect: Z = 2.95 (P = 0.003)									-10	-5 (Favours BCT) 5 Favours wa	itlist	10		

Figure 52: Marital adjustment endpoint

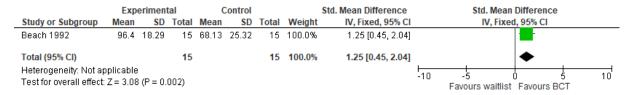
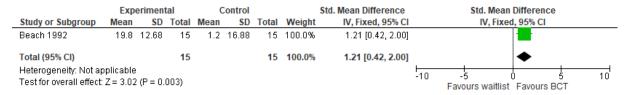


Figure 53: Marital adjustment change score



Behavioural couples therapy versus CBT individual

Figure 54: Depression symptoms endpoint

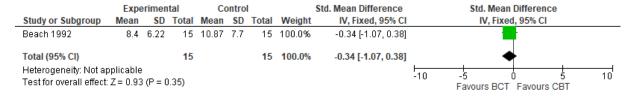


Figure 55: Depression symptoms change score



Figure 56: Marital adjustment endpoint

	(Control			Std. Mean Difference		Std. Mean Difference							
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI				
Beach 1992	96.4	18.29	15	63.6	32.07	15	100.0%	1.22 [0.43, 2.01]			-			
Total (95% CI)			15			15	100.0%	1.22 [0.43, 2.01]			•			
Heterogeneity: Not applicable Test for overall effect: Z = 3.04 (P = 0.002)									-10	-5 Favours	0 CBT Favou	5 Irs BCT	10	

Figure 57: Marital adjustment change score

	Exp	tal	0	Control			Std. Mean Difference		Std. Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fi	xed, 95%	CI	
Beach 1992	19.8	12.68	15	-2.67	21.74	15	100.0%	1.23 [0.44, 2.02]					•
Total (95% CI)			15			15	100.0%	1.23 [0.44, 2.02]			•		
Heterogeneity: Not applicable Test for overall effect: Z = 3.05 (P = 0.002)									-10	-5 Favours Cl	0 BT Favoi	5 Jrs BCT	10

CBT individual versus waitlist

Figure 58: Depression symptoms endpoint

	Expe	erimental Control						Std. Mean Difference	Std. Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI				
Beach 1992	10.87	7.7	15	20.47	10.68	15	100.0%	-1.00 [-1.77, -0.24]						
Total (95% CI)			15			15	100.0%	-1.00 [-1.77, -0.24]			•			
Heterogeneity: Not ap Test for overall effect:	•	(P = 0).01)						-10	-5 Favours	0 S CBT Fav	5 ours waitlist	10	

Figure 59: Depression symptoms change score



Figure 60: Marital adjustment endpoint



Figure 61: Marital adjustment change score

