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Table DS1 Randomised placebo-controlled trials of antidepressants in juvenile depression included for meta-analysis

Study	Quality[a]	Funds[b]	Participants	Age, years	Drug (dose, mg)[c]	Treatment, weeks	Response	Analysis[d]	Drug *v.* placebo responses
Kramer & Feiguine, 1981[19]	3	3	20	12–18	Amitriptyline (200)	6	PRS 'improved'	1	*LOCF:* (8/10) 80% *v.* (6/10) 60% (NS)
Petti & Law, 1982[20]	3	1	6	6–12	Imipramine (145)[e]	6	Clinical: SADLI, BID, CDI 'improved'	1	*LOCF:* (3/3) 100% *v.* (1/3) 33% for all outcomes (all NS)
Puig-Antich *et al*, 1987[21]	3	1	38	9	Imipramine (140)	5	KSADS–P depression + anhedonia to ⩽2	1	*LOCF:* (9/16) 56% *v.* (15/22) 68% (NS)
Bernstein *et al*, 1990[22]	3	2	18	7–18	Imipramine (164); alprazolam	8	Return to school	1	*LOCF:* (5/6) 83% *v.* (3/6) 50%; (ALP (5/6) 83% *v.* PBO (both NS))
Geller *et al*, 1990[23]	3	1	31	12–17	Nortriptyline (139)	8	CDRS ↓ to ⩽25 + KSADS–P ⩽2	1	*LOCF:* (1/12) 8% *v.* (4/19) 21% (NS)
Hughes *et al*, 1990[24]	2	1	27	6–12	Imipramine (87.5)	6	CDRS ↓ ⩾50%	3	*LOCF:* (6/13) 46% *v.* (7/14) 50% (NS)
Simeon *et al*, 1990[25]	1	4	38	13–18	Fluoxetine (200)	7	HRSD, CGI, SCL–58, Raskin, Covi (no criteria)	1 & 2	*LOCF:* (10/19) 53% *v.* (10/19) 53% *Completers:* (10/15) 66% *v.* (10/15) 66% (both NS)
Boulos *et al*, 1991[26]	3	4	43	15–20	Desipramine (200)	6	HRSD ↓ ⩾50%	1 & 2	*LOCF:* (11/22) 50% *v.* (7/21) 33% *Completers:* (6/12) 50% *v.* (6/18) 33% (both NS)
Geller *et al*, 1992[27]	3	1	50	6–12	Nortriptyline (139)	8	CDRS ↓ to ⩽20; or KSADS–P dysphoria + anhedonia to ⩽2	1	*LOCF:* CDRS: (8/26) 31% *v.* (4/24) 17%; KSADS–P: (12/26) 46% *v.* (14/24) 58% (all NS)
Kutcher *et al*, 1994[28]	3	3	42	15–20	Desipramine (200)	6	HRSD ↓50%	1	*LOCF:* (8/17) 48% *v.* (9/25) 35% (NS)
Kye *et al*, 1996[29]	4	1	31	13–17	Amitriptyline (275)	8	HRSD ↓ ⩾50% or to <6	2	***LOCF:*** (13/18) 72% *v.* (11/13) 85%; (10/18) 56% *v.* (2/13) 15% (all NS)
Emslie *et al*, 1997[30]	4	1	96	7–17	Fluoxetine (100)	8	CDRS–R ⩽28 or CGI ⩽2	1 & 2	*LOCF:* CGI: (27/48) 56% *v.* (16/48) 33% (*P*=0.02); CDRS (15/48) 31% *v.* (11/48) 23% (NS) *Completers:* CGI (25/34) 74% *v.* (15/26) 58% (NS)
Sallée *et al*, 1997[33]	2	1	16	14–18	Clomipramine (240, IV)[f]	1	HRSD ↓ ⩾50%	1	*LOCF:* (7/8) 88% *v.* (3/8) 38% (NS)
Birmaher *et al*, 1998[34]	3	1	27	12–18	Amitriptyline (275)	10	HRSD ↓ ⩾50% + to <7; BDI ↓ ⩾50% + to <9; CGI–I to ⩽2	2	*LOCF:* (10/13) 77% *v.* (11/14) 79%; (9/13) 69% *v.* (10/14) 71%; (11/13) 85% *v.* (12/14) 86%; (8/13) 62% *v.* (8/14) 57%; (10/13) 77% *v.* (8/14) 57% (all NS)
Klein *et al*, 1998[35]	3	1	36	13–18	Desipramine (214)	6	CGI–I to ⩽3	1	*LOCF:* (12/18) 67% *v.* (9/18) 50% (NS)
Avci *et al*, 1999[36]	3	4	20	9–15	Moclobemide (150)	5	Clinical status, 5 wks	1	*LOCF:* (8/10) 80% *v.* (8/10) 80% (NS)
Milin *et al*, 1999[37]	4	2	268	13–18	Paroxetine (120)	12	MADRS ↓⩾50%	1 & 2	*LOCF:* (107/177) 61% *v.* (53/91) 58% (NS) *Completers:* (94/126) 75% *v.* (47/66) 71% (NS)
Deas *et al*, 2000[38]	3	1	10	17	Sertraline (120)[g]	12	HRSD ↓ ⩾50%	2	*LOCF:* (2/5) 40% *v.* (4/5) 80% (NS)
Keller *et al*, 2001[39]	4	2	275	12–18	Paroxetine (140); imipramine (206)	8	HRSD↓⩾50% or ⩽8; CGI–I to ⩽2	1 & 2	*LOCF:* HRSD: PRX (60/92) 66% *v.* PBO (44/91) 48% (*P*=0.02); IMI (48/92) 52% *v.* PBO (NS) *Completers:* HRSD: PRX (51/76) 76% *v.* PBO (38/66) 58% (NS); IMI (36/56) 64% *v.* PBO (NS); CGI: PRX (50/76) 66% *v.* PBO (32/66) 48% (*P*=0.02); IMI (29/56) 52% *v.* PBO (NS)

(continued)

Table DS1 *(continued)*

Study	Quality[a]	Funds[b]	Participants	Age, years	Drug (dose, mg)[c]	Treatment, weeks	Response	Analysis[d]	Drug *v.* placebo responses
Emslie *et al*, 2002[31]	3	2	210	8–18	Fluoxetine (100)	9	CDRS–R ↓⩾30%; CGI–I to ⩽2	2	*LOCF* CDRS–R: (77/109) 71% *v.* (56/101) 55% (NS); CGI: (57/109) 52.3% *v.* (37/101) 36.8% (*P*=0.03)
FDA website, 2001[40]	3	2	126	7–17	Mirtazapine (180)	8	HRSD, CDRS–R, CGI	2	*LOCF:* CGI: (49/82) 60% *v.* (25/44) 57% (NS)
FDA website, 2001[40]	3	2	124	7–17	Mirtazapine (180)	8	HRSD, CDRS–R, CGI	2	*LOCF:* CGI: (45/83) 54% *v.* (17/41) 42% (NS)
Rynn *et al*, 2002[41]	2	2	195	12–17	Nefazodone (175)	8	CDRS–R, CGI	2	*LOCF:* CGI: (61/99) 62% *v.* (40/96) 42% (*P*=0.005)
Wagner *et al*, 2003[42]	4	2	376	6–17	Sertraline (157)	10	CDRS–R ↓⩾40%; CGI–I to ⩽2	2	*LOCF:* CDRS–R: (130/189) 69% *v.* (110/187) 59% (*P*<0.05); CGI: (119/189) 63% *v.* (99/187) 53% (*P*<0.05)
Cheung *et al*, 2005[62] (Study 382) & Emslie *et al*, 2007[32]	2	2	161	8–17	Venlafaxine extended release (100–225)	8	CDRS–R ↓⩾35%; HRSD ↓⩾50%;, MADRS, CGI	2	*LOCF:* CGI: (39/78) 50% *v.* (34/83) 41% (NS)
Cheung *et al*, 2005[62] (Study 394) & Emslie *et al*, 2007[32]	2	2	193	8–17	Venlafaxine extended release (100–225)	8	CDRS–R ↓ ⩾35%; HRSD ↓ ⩾50%; MADRS, CGI	2	*LOCF:* CGI: (69/101) 68% *v.* (56/92) 61% (NS)
SmithKline Beecham, 2001[44]	3	2	203	7–17	Paroxetine (102)	8	CDRS–R ↓ CGI–I to ⩽2	1 & 2	*LOCF:* CDRS–R: PRX (101) improved < PBO (102) CGI: PRX (49/101) 49% *v.* PBO (46/102) 45% *Completers:* CGI: PRX (46/68) 68% *v.*. PBO (44/80) 55% (all NS)
March *et al*, 2004[5]	4	1	328[h]	12–17	Fluoxetine (125)[i]	12	CDRS–R ↓ CGI–I to ⩽2	2	*LOCF:* CGI–I: FLX (66/109) 61% *v.* CBT+FLX (76/107) 71% *v.* CBT (48/111) 43% *v.* PBO (39/112) 35% (all FLX *v.* PBO: *P*<0.0001)
Wagner *et al*, 2004[43]	2	2	174	13–19	Citalopram (150)	8	CDRS–R ⩽28	2	*LOCF:* (32/89) 36% CTP *v.* (20/85) 24% PBO (*P*<0.05)

Drug abbreviations are self-defined as representing the stated drugs included in each trial. BID, Bellevue Index of Depression; CDI, Children's Depression Inventory; CDRS, Children's Depression Rating Scale; CDRS–R, CDRS – Revised; CGI, Clinical Global Impression scale; CGI–I, CGI Improvement sub-scale; Covi, Covi Anxiety Scale; HRSD, Hamilton Rating Scale for Depression; IV, intravenous; KSADS–P, Kiddie Schedule for Affective Disorders and Schizophrenia, Present episode; LOCF, last observation carried forward; MADRS, Montgomery–Åsberg Depression Rating Scale; NS, not significant; PBO, placebo; PRS, Psychiatric Rating Scale; Raskin, Raskin Depression Scale; SADLI, School-Aged Depression List Interview; SCL–58, Self-Rating Symptom Checklist.

a. Based on the Jadad *et al*[65] scale from 1 to 4 (best score).

b. Funding: 1, US–NIH or other non-industrial source; 2, pharmaceutical; 3, mixed (non-industrial + pharmaceutical); 4, not stated.

c. Drug doses: imipramine equivalents total mg/day (final or maximum dose).

d. Analysis: 1, responders among completers; 2, responders by last observation carried forward; 3, not specifically reported.

e. Imipramine dose at 5 mg/kg per day: at age 6 (21 kg), 105 mg; at age 12 (37 kg), 185 mg.

f. Clomipramine and placebo given intravenously.

g. With/without group psychotherapy.

h. The meta-analysis used only the comparison of fluoxetine alone *v.* placebo (*N*=216).

i. With/without cognitive–behavioural psychotherapy.

Meta-analyses used 2979 of the 3182 participants in these 29 trials involving 30 total drug/placebo comparisons averaging 8 weeks, for a total of 456 total person-years of treatment exposure.

Table DS2 Crude characteristics of trials in juvenile patients with depression, categorised by type of antidepressant

Measure	TCAs	SRIs	Other	All
Trials, *n*	14	12	4	30
High-quality score, %[a]	85.7	66.7	75.0	76.7
Participants/trial, *n*[b]	31.0 (19.5–42.2)	198 (112–255)	125 (46.0–178)	46.5 (27.0–197)
Duration, weeks[b]	6.00 (6.00–8.00)	8.00 (8.00–11.5)	8.00 (5.75–8.00)	8.00 (6.00–8.00)
Exposure, person-weeks[b,c]	248 (138–302)	1584 (898–2494)	1000 (323–1422)	584 (202–1576)
Dose, IMIeq mg/day[b,c]	200 (140–220)	132 (106–161)	179 (156–180)	160 (136–200)
Baseline depression score, %				
Drug group[b]	33.7 (33.3–67.9)	50.5 (43.2–52.2)	38.6 (23.1–54.2)	49.6 (33.4–56.2)
Placebo group[b]	35.0 (32.2–64.4)	51.2 (43.2–54.1)	37.2 (21.0–53.3)	49.9 (33.4–55.1)
Difference	1.30	0.70	1.40	−0.30
Ratio	0.96	0.99	1.04	0.99
Proportion 'responding', %[d]				
Drug group[b]	61.5 (46.8–80.3)	58.5 (48.9–67.6)	60.7 (55.6–75.4)	60.1 (49.6–71.0)
Placebo group[b]	49.2 (33.3–62.0)	50.5 (36.4–58.7)	49.2 (41.5–74.2)	49.2 (35.7–59.1)
Difference	12.3	8.00	11.5	10.9
Ratio	1.47	1.16	1.23	1.22
'Response' rate, %/week				
Drug group[b]	8.68 (7.40–11.8)	6.57 (5.04–7.77)	7.59 (6.95–13.9)	7.69 (6.20–9.38)
Placebo group[b]	7.06 (5.56–10.2)	5.82 (4.34–6.54)	6.16 (5.19–13.8)	6.04 (5.17–7.98)
Difference	1.62	0.75	1.43	1.65
Ratio	1.23	1.13	1.23	1.27

IMIeq, imipramine equivalent; SRI, serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
a. Proportion of trials with a high Jadad scale quality rating (3 or 4).
b. Medians (25th–75th percentiles).
c. In a logistic regression model contrasting TCAs and SRIs (not shown), exposure differed significantly (6.4-fold higher with SRIs), as did drug dose (34% higher with TCAs).
d. 'Response' typically is defined as >50% reduction in symptom ratings during a trial.

Table DS3 Summary of response rates[a] to antidepressants *v.* placebo and of their meta-analysis

Study[b]	Drug type	'Responders' with drug, *n/N* (%)	'Responders' with placebo, *n/N* (%)	RR	Confidence limits		Weight, %
					Lower	Upper	
Kramer & Feiguine 1981[19]	TCA	8/10 (80.0)	6/10 (60.0)	1.333	0.737	2.414	0.81
Petti & Law, 1982[20]	TCA	3/3 (100)	1/3 (33.0)	3.000	0.606	14.86	0.13
Puig-Antich *et al* 1987[21]	TCA	9/16 (56.3)	15/22 (68.2)	0.825	0.492	1.385	1.70
Bernstein *et al* 1990[22]	TCA	5/6 (83.3)	3/6 (50.0)	1.667	0.694	4.004	0.40
Geller *et al* 1990[23]	TCA	1/12 (8.3)	4/19 (21.1)	0.396	0.050	3.133	0.42
Hughes *et al* 1990[24]	TCA	6/13 (46.2)	7/14 (50.0)	0.923	0.420	2.028	0.91
Simeon *et al* 1990[25]	SRI	10/19 (52.6)	10/19 (52.6)	1.000	0.547	1.828	1.34
Boulos *et al* 1991[26]	TCA	11/22 (50.0)	7/21 (33.3)	1.500	0.719	3.129	0.96
Geller *et al* 1992[27]	TCA	8/26 (30.8)	4/24 (16.7)	1.846	0.637	5.352	0.56
Kutcher *et al* 1994[28]	TCA	8/17 (47.1)	9/25 (36.0)	1.307	0.632	2.702	0.98
Kye *et al* 1996[29]	TCA	13/18 (72.2)	11/13 (84.6)	0.854	0.590	1.234	1.72
Emslie *et al* 1997[30]*	SRI	27/48 (56.3)	16/48 (33.3)	1.688	1.053	2.704	2.15
Sallée *et al* 1997[33]	TCA	7/8 (87.5)	3/8 (37.5)	2.333	0.919	5.927	0.40
Birmaher *et al* 1998[34]	TCA	10/13 (76.9)	11/14 (78.6)	0.979	0.653	1.467	1.42
Klein *et al* 1998[35]	TCA	12/18 (66.7)	9/18 (50.0)	1.333	0.757	2.348	1.21
Avci *et al* 1999[36]	Other	8/10 (80.0)	8/10 (80.0)	1.000	0.645	1.550	1.07
Milin *et al* 1999[37]	SRI	107/177 (60.5)	53/91 (58.2)	1.038	0.841	1.282	9.41
Deas *et al* 2000[38]	SRI	2/5 (40.0)	4/5 (80.0)	0.500	0.157	1.594	0.54
Keller *et al* 2001[39]	TCA	48/92 (52.2)	44/91 (48.4)	1.079	0.808	1.440	5.94
Keller *et al* 2001[39]*	SRI	60/92 (65.2)	44/91 (48.4)	1.349	1.040	1.749	5.94
Emslie *et al* 2002[31]*	SRI	77/109 (70.6)	56/101 (55.4)	1.274	1.030	1.576	7.81
FDA 2001[40]/Cheung *et al* 2005[62]	Other	49/82 (59.8)	25/44 (56.8)	1.052	0.769	1.438	4.37
FDA 2001[40]/Cheung *et al* 2005[62]	Other	45/83 (54.2)	17/41 (41.5)	1.308	0.864	1.978	3.06
Rynn *et al* 2002[41]*	Other	61/99 (61.6)	40/96 (41.7)	1.479	1.114	1.963	5.46
Wagner *et al* 2003[42]*	SRI	130/189 (68.8)	110/187 (58.8)	1.169	1.003	1.363	14.86
Cheung *et al* 2005[62]/Emslie *et al* 2007[32]	SRI	39/78 (50.0)	34/83 (41.0)	1.221	0.868	1.716	4.43
Cheung *et al* 2005[62]/Emslie *et al* 2007[32]	SRI	69/101 (68.3)	56/92 (60.9)	1.122	0.909	1.386	7.87
SmithKline Beecham 2001[44]	SRI	49/101 (48.5)	46/102 (45.1)	1.077	0.802	1.443	6.15
March *et al* 2004[5]*	SRI	66/109 (60.6)	39/112 (34.8)	1.739	1.294	2.336	5.17
Wagner *et al* 2004[43]	SRI	32/89 (36.0)	20/85 (23.5)	1.528	0.952	2.452	2.75
Pooled RR	All	980/1665 (58.9%)	712/1495 (47.6%)	1.223	1.146	1.306	100

RR, rate ratio; TCA, tricyclic antidepressants; SRI, serotonin reuptake inhibitors.
a. Response rates are proportions of participants considered substantially improved in each trial, by criteria defined for each trial and summarised in Table DS1, and used as the basis for meta-analysis. Pooled RR differs statistically highly significantly from the null of 1.0 (z=6.04, P<0.0001), CI limit >1.0, compared with 22/30 trials not finding RR >1.0, at similar rates with all three drug types.
b. Trials that met the criterion that the lower limit of the confidence interval of the trial rate ratio should be >1 are marked with an asterisk.