

Supplementary Tables and Figures

Table S1. Study Characteristics

Study	Placebo, n (ITT)	Antipsychotics, n (ITT)	Antipsychotics	Mean Age	Mean CGI	Study Completion, %	Duration of illness, year	Gender, % Male	Treatment Duration, weeks
Clark 1970	14	15	Chlorpromazine 1000 mg/d (max)	37.4	4.35	95.5	24.0	7.1	12.0
Clark 1971	18	19	Thioridazine 400 mg	32.3	4.06	85.3		29.4	6.0
Clark 1972	18	18	Loxapine 100mg/d (max)	39.9	4.81	90.9		44.4	12.0
Serafetinides 1972	13	15	Clopenthixol 250 mg (max)	43.9	5.23	93.0	24.0	46.2	12.0
Charalampous 1974	19	20	Thiothixene 60 mg/d (max)	25.9		68.3	2.5	96.7	4.0
Van Der Velde 1975	25	24	Loxapine 100 mg/d	25.6	5.02	85.5		52.0	6.0
Clark 1975	12	12	Trifluoperazine 50 mg/d (max)	36.9	4.5	84.1	9.5	61.5	4.0
Chouinard 1975	24	24	Perphenazine 20 mg/d	39	4.1	83.3		50.0	12.0
Peet 1981	18	16	Chlorpromazine 400 mg/d	51.3	3.75	60.4		66.7	8.0
Cohen 1987	11	26	Piquindone 120 mg/d (max)	36.1		66.7	12.1	100.0	2.0
Chouinard 1990	20	20	Remoxipride 600 mg/d (max)	37.8	6	69.4	13.4	61.9	4.0
Montgomery 1992	23	27	Thioridazine 400 mg	37.9		59.4		87.0	4.0
Chouinard 1993	22	22	Risperidone 6 mg/d	37	4.5	51.9	14.0	71.1	8.0
Marder 1994	64	63	Risperidone 6 mg/d	37.1	3.7	47.2	15.2	89.1	8.0
Fabre 1995	4	8	Quetiapine 25 to 250 mg/d	35	4.3	91.7		100.0	3.0
Taiminen 1996	45		N/A	43.2	5	88.9	16.5	64.4	12.0
Borison 1996	53	53	Quetiapine 75-750 mg/d	37	4.6	45.9	15.0	90.9	6.0
Beasley 1996	62	65	Olanzapine 15/17.5 mg/d	35	4.9	41.5		91.2	6.0
Van Kammen 1996	38	40	Sertindole 20 mg/d	37.1	4.8	51.2	13.8	94.7	5.7
Beasley 1996	49	49	Olanzapine 10 mg/d	36	5	27.0	14.0	65.3	6.0
Small 1997	92	92	Quetiapine 750 mg/d	38	4.9	44.4	16.0	66.7	6.0
Zimbroy 1997	71	65	Sertindole 20 mg/d	38.7	4.7	51.3	16.6	78.1	8.0
Arvanitis 1997	51	51	Quetiapine 600 mg/d	36	4.9	41.3	14.0	80.4	5.7
Kramer 1997	12	26	L745,870 15 mg/d	42	5	57.9		91.7	4.0
Keck 1998	47	41	Ziprasidone 120 mg/d	39	4.7	69.0	17.3	85.4	4.0
Truffinet 1999	34	63	Fananserin 500 mg/d	38.9	4.6	28.9	16.0	88.2	4.0
Daniel 1999	91	104	Ziprasidone 160 mg/d	37.2	4.8	55.0	22.5	68.5	6.0
Cooper 2000	58	61	Zotepine 150-300 mg/d	41.6	4.1	45.4	13.2	72.4	8.0
Cooper 2000	53	53	Zotepine 150-300 mg/d	36.3	4.85	56.0		69.8	8.0
Kane 2002	106	102	Aripiprazole 15mg/d	38.5	4.9	59.9	16.0	69.8	4.0
Arato 2002	71	67	Ziprasidone 160 mg/d	48.7	4.1	35.6	21.6	83.1	6.0
Potkin 2003	103	98	Aripiprazole 20 mg/d	38.8	4.8	59.9		70.9	4.0
Pigott 2003	149	148	Aripiprazole 15 mg/d	41.7	3.5	37.4		58.1	6.0
Bai 2003	20	22	Risperidone 6 mg/d	51.4		85.7		60.0	12.0
Cutler 2006	88	94	Aripiprazole 10 mg/d	42.9	4.7	53.1	18.3	81.8	5.0
Potkin 2006	71	152	Risperidone 4-6 mg/d	36.1	5.4	71.5		63.0	2.0

McEvoy 2007	107	106	Aripiprazole 10 mg/d	41.2	4.6	33.8	16.7	76.9	6.0
Kane 2007	126	129	Paliperidone ER 12 mg	37.1	4.43	65.9	9.1	40.9	6.0
Davidson 2007	120	113	Paliperidone ER 12 mg	37.9	4.62	59.1	13.4	57.5	6.0
Marder 2007	105	111	Paliperidone ER 12 mg	41.6	4.445	43.2		74.0	6.0
Kahn 2007	115	117	Quetiapine XR 600 mg/d	34.1	4.9	75.9	8.0	58.3	6.0
Potkin 2007	62	60	Asenapine 10 mg/d	42	4.6	40.1		79.0	6.0
Casey 2008	114	111	Bifeprunox 20 mg/d	40.8	4.54	30.9		75.4	6.0
Meltzer 2008	351	240	Paliperidone ER 12 mg	39	4.67	45.4		92.0	6.0
Findling 2008	98	97	Aripiprazole 30mg	15.4	4.6	84.8	1.5	61.0	6.0
Potkin 2008	117	115	Iloperidone 12 mg/d	39.3		37.2		70.9	6.0
Potkin 2008	152	141	Iloperidone 20-24 mg/d	38.8		50.3		67.3	6.0
Potkin 2008	152	149	Iloperidone 10-16 mg/d	39		58.1		58.8	6.0
Canuso 2009	80	157	Paliperidone ER	36.1	5.2	86.0	12.5	62.5	2.0
Nakamura 2009	90	90	Lurasidone 80 mg/d	41.9	4.8	43.8		77.8	6.0

TABLE S2. Summary of Placebo Response Findings and Sensitivity Analyses

	Number of studies (Study duration)	SMC (95%CI)	p-value	Quality Rating	Q-statistics (df)	p-value Heterogeneity
Overall placebo response (unbiased)	50 (<12 weeks)	-0.332 (-0.444, -0.220)	<0.001	3 to 7	387.83 (49)	<0.001
Sensitivity Analysis	61 (<12 weeks)	-0.295 (-0.401, -0.188)	<0.001	1 to 7	439.41 (60)	<0.001

Studies were included in the primary analysis sample of 50 studies. Four long-term studies had available data on Week 6 to Week 12, which were extracted and included in the analysis (1-4). The study inclusion criteria were: 1) reported baseline and at least 1 post-baseline assessment (<12 weeks); 2) identified efficacy data using either the Brief Psychiatric Rating Scale (BPRS) or the Positive and Negative Syndrome Scale (PANSS) rating scales (for studies that reported results solely on a graphic basis, data were obtained directly from the published graphs); and, 3) met minimum study quality criteria (omnibus rating score >3 i.e., 'moderately poor' or better) (5). Two sensitivity analyses were conducted: one based on 61 studies, adding the 11 studies with an omnibus rating score of <2 (exceptionally poor or very poor).

Figure S1. Summary of Placebo Response (SMC) Findings

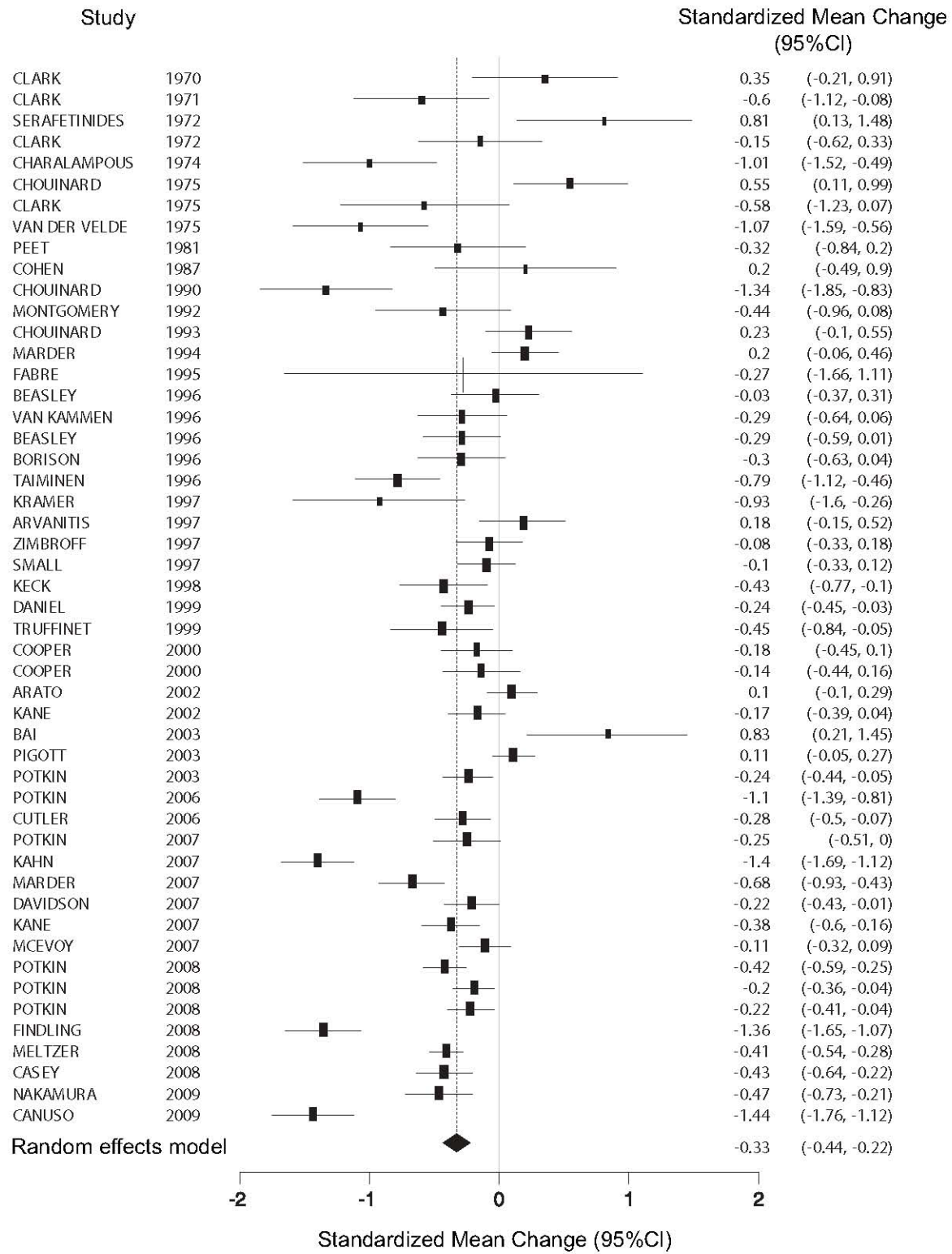
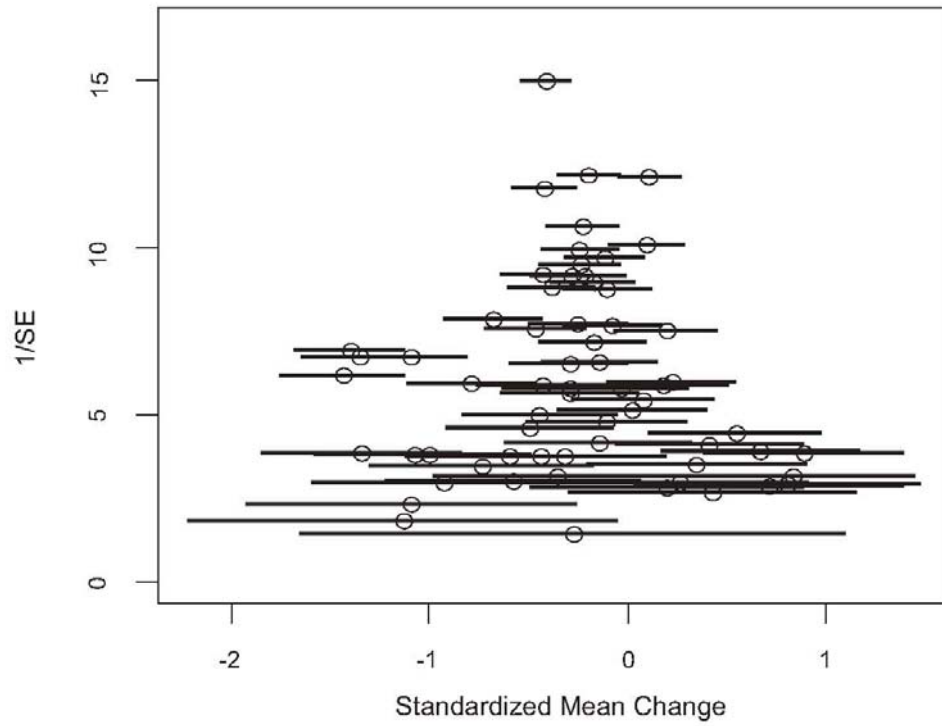
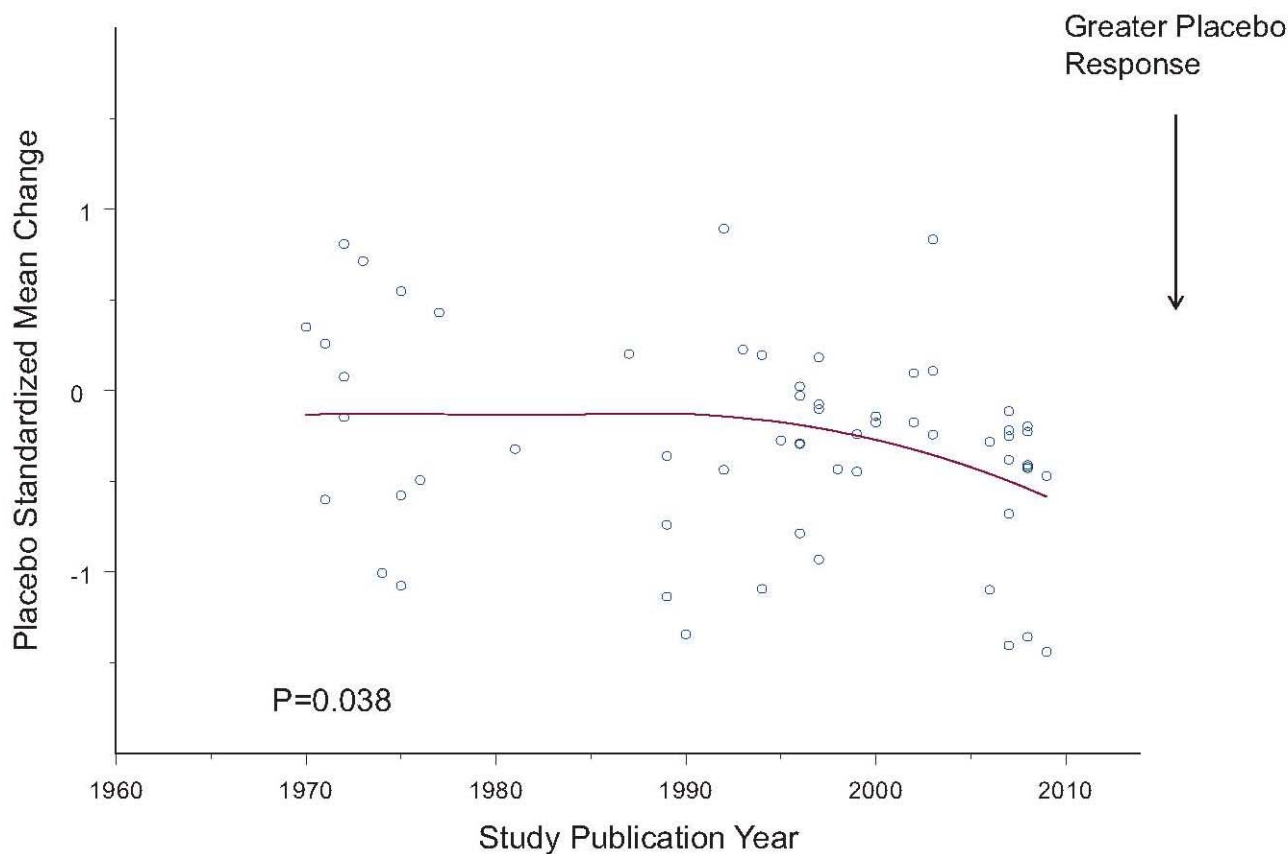


Figure S2. Funnel Plot for Assessing Publication Bias: Placebo Mean Change From Baseline (N=64 Studies)



Symmetric funnel shape indicates publication bias is unlikely.

Figure S3. Placebo Standardized Mean Change (SMC) Over Time



A greater influence of study year on placebo SMC was found in studies published after 1999 (regression coefficient= -0.094 , $SE=0.033$, $p=0.004$, likelihood square LR $\chi^2=8.10$) compared to the time trend in 1970–1999 (regression coefficient= -0.011 , $SE=0.008$, $p=0.195$, LR $\chi^2=1.68$). Moreover, the difference in time trend between the two periods was significant (-0.079 , $SD=0.034$, $p=0.019$, $\chi^2=5.51$ for period-by-year interaction test). A sensitivity analysis was performed using 1993, an earlier cutoff year identified as the watershed year when the trend for increasing placebo response began (4). It showed consistent patterns with greater increase in placebo response in the more recent studies (1993–2010, regression coefficient= -0.031 , $p=0.028$) compared to that in the older studies (prior to 1993, regression coefficient= -0.018 , $p=0.230$). Likewise, similar placebo response patterns were observed after excluding the 11 studies with an omnibus quality rating score of 1 (“exceptionally poor”) or 2 (“very poor”), of which 9 were published in 1971–1992 and the remaining 2 in 1994–1996.

Figure S4. Placebo Response Vs. Number of Investigative Sites

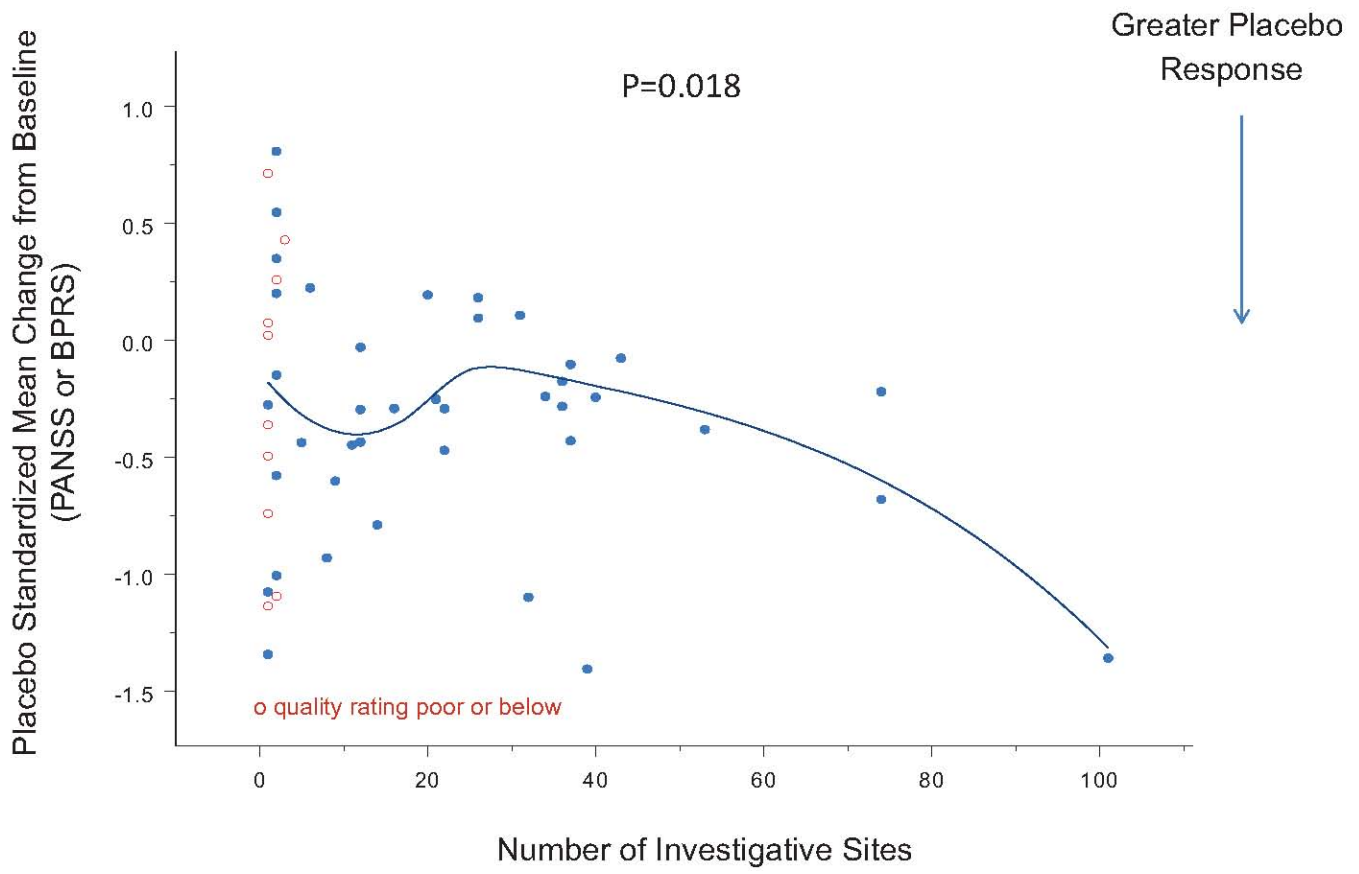
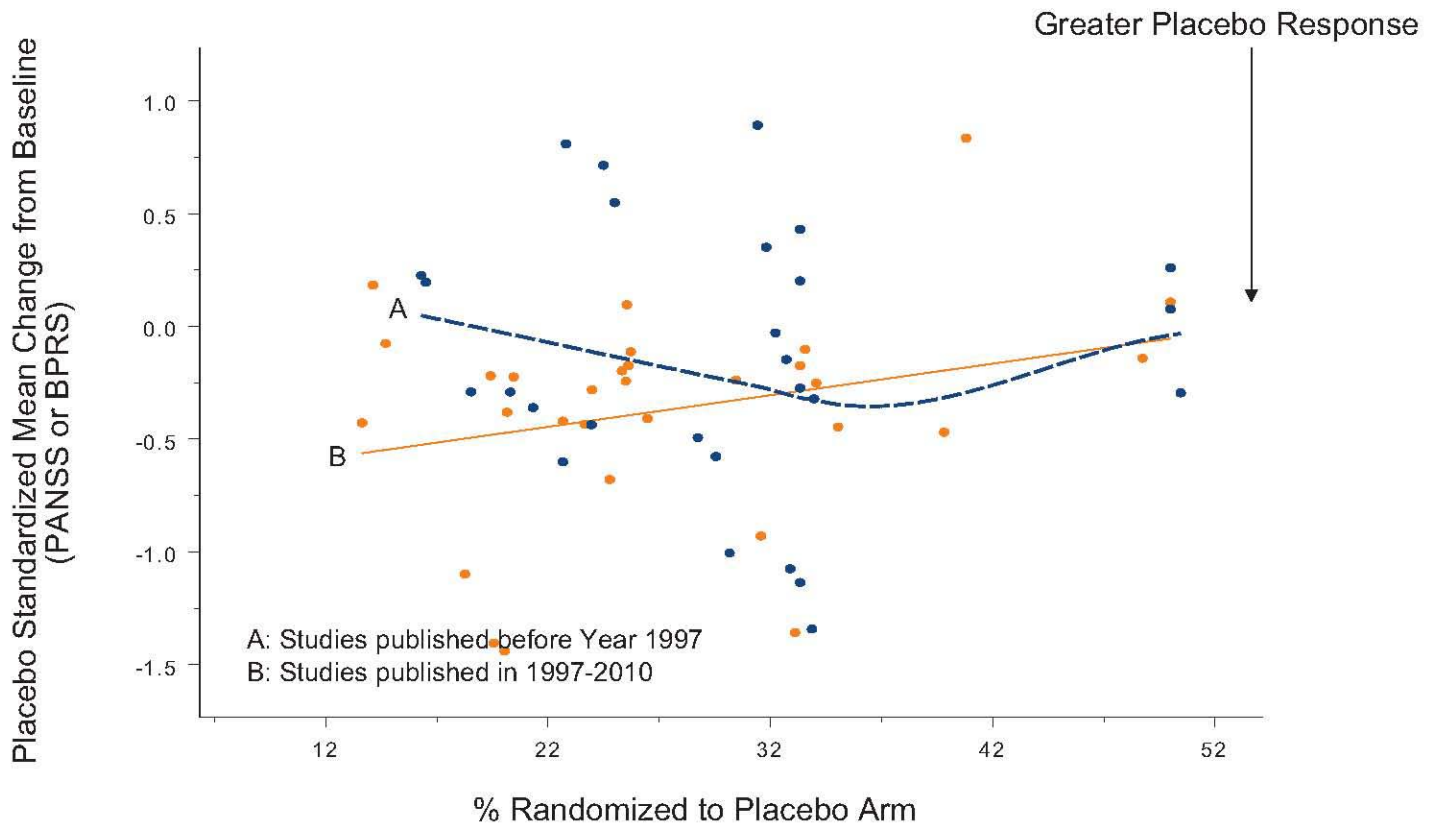


Figure S5. Placebo Response Vs. Percent Randomized to Placebo



Increase in percentage of subjects randomized to placebo was associated with less placebo response (year 1998–2010), but not independent of study year influences.

References

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