Online Appendix to: "Funding of Clinical Trials and Reported Drug Efficacy"

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Appendix

A Antidepressant and Antipsychotic Drugs

Antidepressants and antipsychotics are both large and lucrative types of drugs. In 2006, five out of the 35 drugs with the largest sales in the United States were antidepressants, and each of these drugs had annual sales of more than a billion dollars (Ioannidis, 2008).[34] Total revenue fell in later years as some of these blockbusters went off patent, but the quantity of antidepressant prescriptions has increased over time. For example, the share of the U.S. adult population that takes antidepressants has increased 64% from 1999–2014 (Moore and Mattison, 2017).

Both drug types have many substitutable drugs and a vibrant debate regarding their efficacy. Antidepressants were developed in several waves, beginning with the monoamine oxidase inhibitors in 1958 (Hillhouse and Porter, 2015). The earliest drugs in the analysis are two tricyclic antidepressants: amitriptyline, which was approved by the FDA in 1961, and clomipramine, which was approved in Europe in 1970. Both are on the World Health Organization's Model List of Essential Medications. The analysis also includes all second-generation antidepressants approved either in the United States, Europe, or Japan, plus trazodone and nefazodone. Second-generation antidepressants include selective serotonin reuptake inhibitors (SSRIs) such as escitalopram (brand name Lexapro). It also includes atypical antidepressants such as bupropion (brand name Wellbutrin) and serotonin-norepinphrine reuptake inhibitors (SNRIs) such as duloxetine (brand name Cymbalta). For antipsychotics, this analysis includes the first-generation antipsychotics chlorpromazine (approved in 1957) and haloperidol (approved in 1967) along with thirteen second generations antipsychotics. The full sample of included drugs is shown in appendix figure A8.

B Statistical Significance Calculation

In table 1 column (4), the outcome is an indicator for whether the drug was statistically significantly more effective than the placebo arm or least effective arm in that trial. The efficacy outcome—the proportion of patients that responded to treatment—was considered statistically significant if the Z-score, computed as

$$Z = \frac{p_1 - p_2}{\sqrt{\hat{p}\,(1-\hat{p})\left(\frac{1}{n_1}+\frac{1}{n_2}\right)}} \tag{8}$$

[34] These blockbuster drugs include venlafaxine (brand name Effexor), escitalopram (Lexapro), sertraline (Zoloft), bupropion (Wellbutrin), and duloxetine (Cymbalta).

was significant at the 5% level. With an infinite sample, this Z-score cutoff was 1.64 for placebo-controlled trials and 1.96 for head-to-head trials. Here p is the proportion of patients that respond to treatment. The numeric indexing in equation 8 refers to the first or second arm, and $\hat{p}$ is the overall proportion for both arms. The variable n refers to the number of patients in each arm. For schizophrenia trials, the Z-score was computed as

$$Z = \frac{e_1 - e_2}{\sqrt{\left(\frac{\sigma_1^2}{n_1} + \frac{\sigma_2^2}{n_2}\right)}} \tag{9}$$

where e is the decline in schizophrenia score, σ is the standard deviation of this decline, and n is the sample size in that arm.

C Absolute versus Relative Efficacy

This main outcome in this paper is the efficacy of a drug, relative to the placebo or least effective arm. This paper focuses on relative rather than absolute efficacy, since regulatory and publication decisions are based on relative efficacy. For example, if a company sponsored a drug against a placebo and finds a large absolute effect, but a small or negative effect relative to the placebo effect, this trial would be considered a failure, not a success.[35] Most abstracts for these trials discuss relative efficacy e.g. "both vortioxetine doses were statistically superior to placebo" (Boulenger et al., 2014) or "the treatment groups did not differ significantly in the percentage of responders" (Shelton et al., 2006).

Table A5 shows that publication and approval more strongly related to relative efficacy than absolute efficacy. In columns (1)-(3), I estimate:

$$1\{Published_j\} = \alpha + y_{ij} + X_{ij}\gamma + G_{d(i),p(j)} + \varepsilon_{ij} \tag{10}$$

where the outcome is an indicator for whether trial j was published. The coefficient of interest is on y_{ij}, the relative or absolute efficacy of a given arm i in trial j. The rest of the terms are the same as in equation 1, though X_{ij} now includes only the type of measurement scale. Relative efficacy is much more strongly related to publication (column (1)) than absolute efficacy (column (2)), though both coefficients are statistically significant. Column (3) includes both relative and absolute efficacy. In this regression, only relative efficacy is significant and positive.

Columns (4)-(6) analyze the relationship between efficacy and drug approval. For each drug, I calculate the average relative and absolute efficacy in all trials published before that drug gained FDA approval. If the drug was never approved, all published trials are included. There are 30 drugs included

[35] As an example, the abstract of Boulenger et al. (2014) states "Duloxetine separated from placebo, thus validating the study," indicating that efficacy relative to the placebo is necessary for a successful trial.

in the initial Cipriani et al. (2018) and Leucht et al. (2013) samples. Of these, 23 (77%) were approved by the FDA. The other drugs were approved in other countries. I regress an indicator for whether the drug was approved on the relative and absolute efficacy in pre-approval trials. The relative efficacy of a drug in pre-approval trials is positively related to FDA approval, while absolute efficacy is actually negatively related to approval. A drug with a low absolute efficacy may be approved if the alternative is nothing, but once there are other effective alternatives a drug with a high absolute efficacy (but a low relative efficacy) may be rejected.

D Sponsorship Effect Specifications

Appendix table A8 presents results for drug set (column 1), drug pair (column 2), and less restrictive fixed effects: only drug controls (column 3), or no controls (column 4). The panel (a) the outcome is relative efficacy, while in panel (b) the outcome is absolute efficacy. In columns (1) and (2), the estimates with relative and absolute efficacy are both positive and statistically significant, though the estimates with absolute efficacy are larger. This is because, within a drug and drug pair, sponsored arms improve the efficacy of both the sponsored drug and the least effective drug in the trial (see columns (1)-(3) of appendix table A6). Sponsored trials have larger sample sizes and lower dropout rates, both of which are correlated with higher efficacy. Panel (a) using relative efficacy accounts for this change in the control arms of the trial.

The estimates in columns (3) and (4) are presented for completeness, but do not represent a causal sponsorship effect. Column (3) includes drug fixed effects. The estimate with relative efficacy as an outcome is positive and statistically significant, while the estimate with absolute efficacy is positive and not statistically significant. This is because sponsored drugs are often tested against weaker competitors. This is shown in column (4) of appendix table A6. For each drug and trial, I compute the mean absolute efficacy of that drug, leaving out the efficacy of that drug in that trial. Then I regress

$$y_{-ij} = \alpha + \beta Sponsor_{ij} + G_{d(i),p(j)} + \varepsilon_{ij} \tag{11}$$

which is similar to the main equation 1 but the outcome $y_{-i,j}$ is now the absolute efficacy of the other drug, *not* drug i, in trial j. This measures the leave-out mean efficacy of the control arm for that drug. Column (4) of table A6 shows that the leave-out mean efficacy of the control arm is 0.13 standard deviations lower in sponsored trials, compared to non-sponsored trials. Therefore, within a drug, sponsored trials are tested against weaker competitors. Therefore, a sponsored trial needs to have a lower absolute efficacy to still report favorable findings relative to the other arms in the trial. Reassuringly, within a

drug pair, the leave-out mean efficacy of the control arm is the same for sponsored and non-sponsored arms.[36]

Finally, the estimate in column (4) of table A8 is positive and statistically significant. However, this simply reflects that industry often chooses to test more effective drugs than government or academics. In addition, active drugs are both more effective and more likely to be sponsored than placebo drugs.

E Comparability of Sponsored and Not Sponsored Arms

Figure A4 presents differences in general characteristics and trial design for sponsored relative to unsponsored arms. The left panel presents the overall, unconditional differences between sponsored and unsponsored arms. For each characteristic k_{ij} for arm i in trial j, I estimate

$$k_{ij} = \alpha + \beta Sponsor_{ij} + \varepsilon_{ij} \tag{12}$$

and plot the coefficient on $Sponsor_{ij}$ along with 95% confidence intervals clustered at the trial level. As shown in the left panel of figure A4, sponsored and unsponsored arms are very similar in terms of registration status, length of trial, whether the outcome was a standard metric, the baseline severity of patients, the dosage, and the share of female patients. Sponsored arms occur in trials one standard deviation, or approximately ten years, earlier relative to the drug's approval year. This reiterates the findings from figure 2; drugs are more likely to be sponsored earlier in their life cycle.

The right panel presents the differences between sponsored and unsponsored arms within a drug pair. In this case, I estimate

$$k_{ij} = \alpha + \beta Sponsor_{ij} + G_{d(i),p(j)} + \varepsilon_{ij} \tag{13}$$

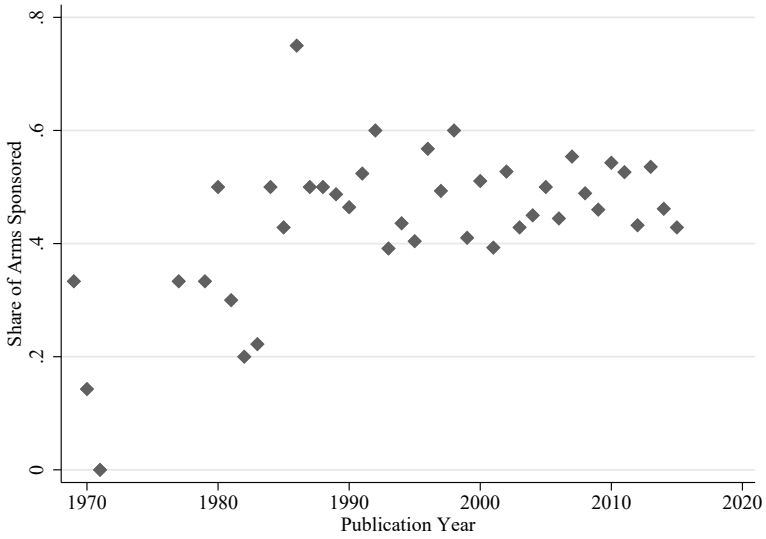
and plot the coefficient on $Sponsor_{ij}$. Here, $G_{d(i),p(j)}$ is a fixed effect for each drug in each drug pair, as defined in section 3.3. Within drug pairs, sponsored arms occur only 0.4 standard deviations or about four years earlier. Similarly, while in panel (a) sponsored arms enroll 0.2 standard deviation or 15 more patients per arm, within a drug pair, sponsored arms enroll only a statistically insignificant 0.1 standard deviations more patients. This pattern is also seen with the dropout rate; sponsored arms have a 0.18 standard deviation lower dropout rate, while within drug pairs, the difference in dropout rates is statistically insignificant and lowered to -0.09 standard deviations. Within a drug pair, the only statistically significant differences in characteristics are the mean age of enrollees (which is considered and rejected as a mechanism in section 4.1) and the aforementioned trial timing.

[36] This estimate is slightly different from zero due to noise in calculating the leave-out mean estimates.

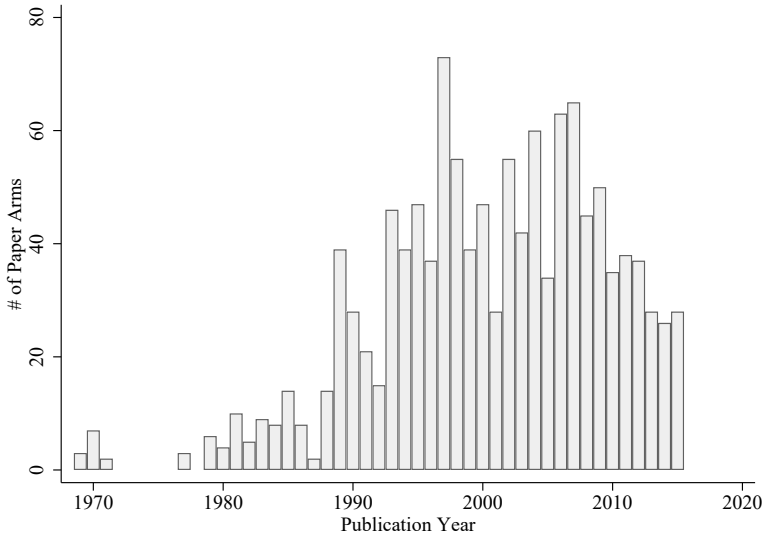
F Additional Tables and Figures

Figure A1: Variation in Sponsorship by Calendar Year

(A) Sponsorship

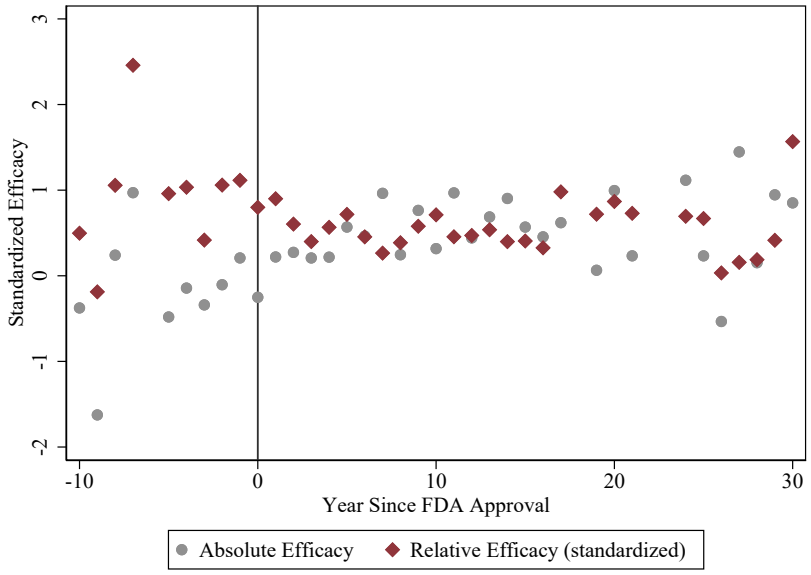


(B) Sample Size



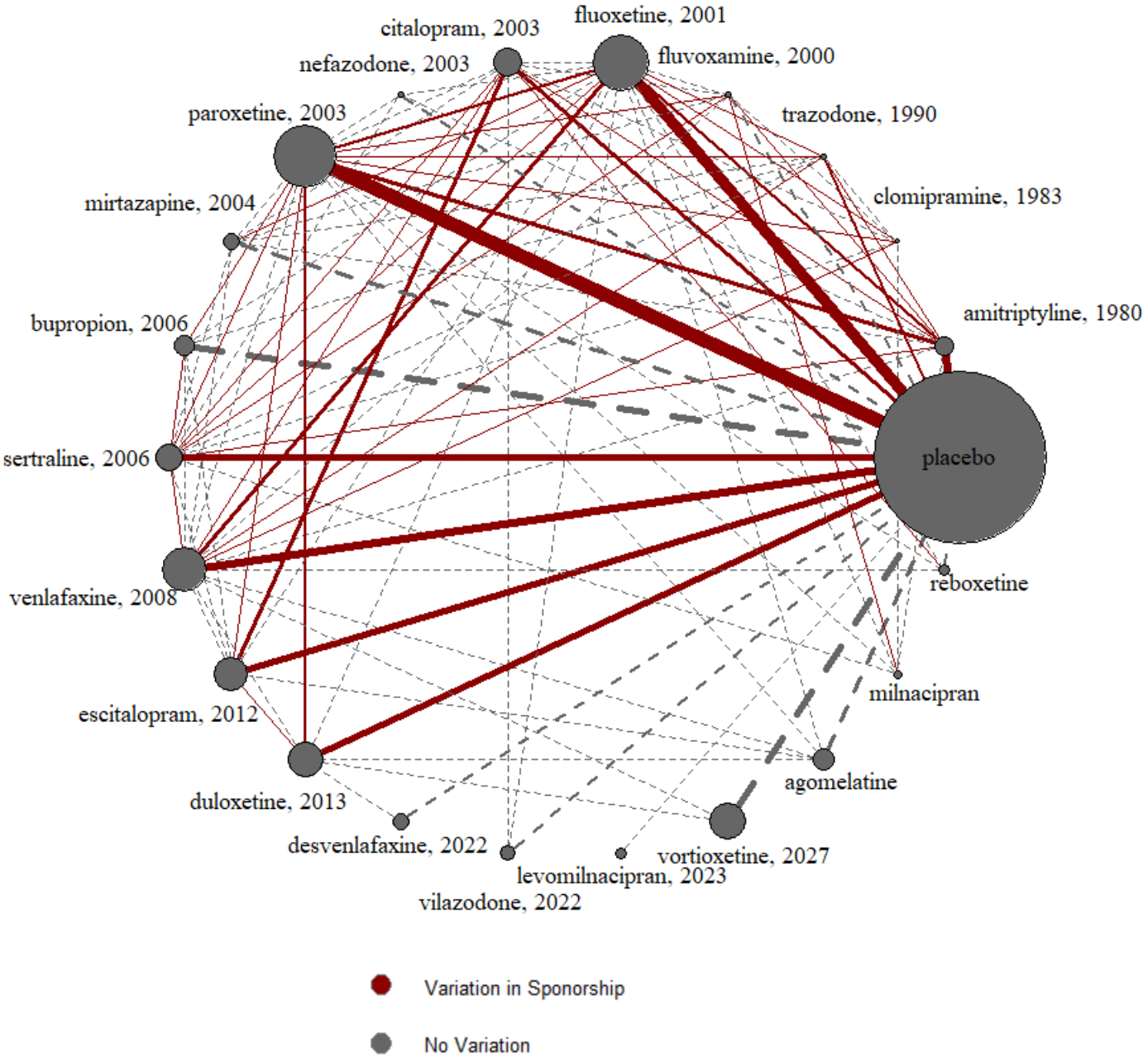
Notes: Panel (a) presents the average share of sponsored arms over time. The x-axis plots the publication year of the arm's trial. The y-axis plots the share of those arms that are sponsored. This figure excludes drugs that are not approved by the FDA (agomelatine, amisulpride, milnacipran, reboxetine, sertindole, and zotepine). Panel (b) presents the number of trial arms in the sample by their publication year.

Figure A2: Efficacy by Year Since Drug Approval



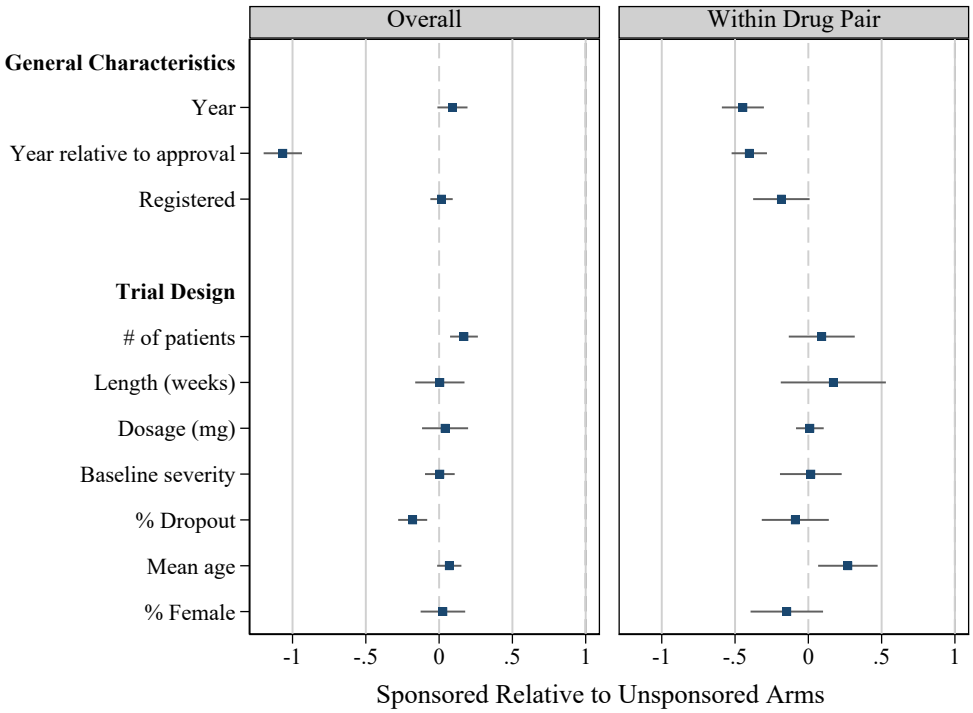
Notes: This figure presents the relationship between effectiveness and year since FDA approval. The x-axis plots the year the arm was published relative to the FDA approval year for that drug. The y-axis plots the average standardized absolute efficacy, or the standardized relative efficacy in each relative year. This sample is restricted to sponsored arms to remove sponsorship dynamics over time.

Figure A3: Network of Trials for Antidepressants



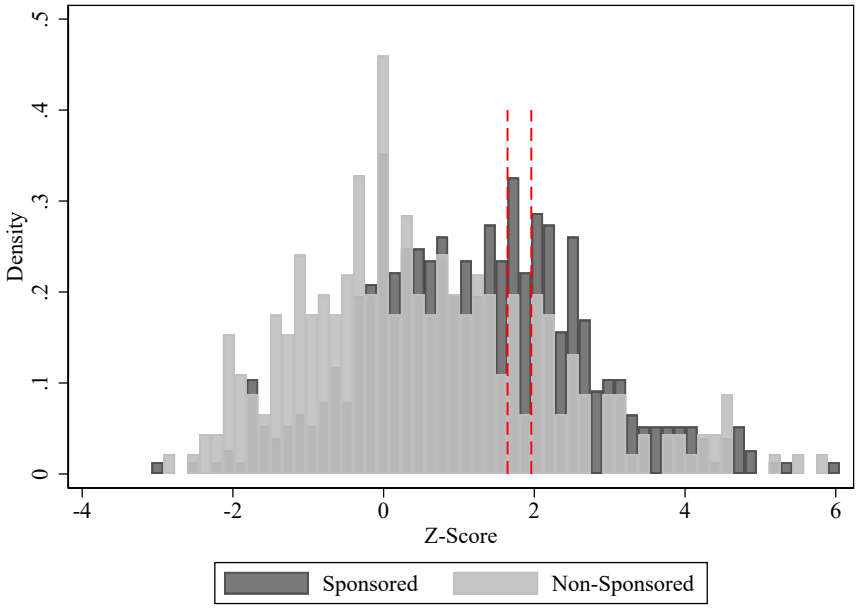
Notes: This figure presents the network of comparisons within antidepressants. Each node represents a drug and is labeled with the year that a generic formulation entered the United States market (years after 2023 are estimates). The size of the circle is proportional to the number of randomly assigned participants. Each line represents a clinical trial comparing the two drugs. A trial with three or more drugs would have a line between every pair of drugs tested. The width of the lines is proportional to the number of trials comparing every pair of treatments. Lines in solid red denote that the sponsorship status of at least one of the drugs varies within the trials; lines in dashed gray denote that the sponsorship status of both drugs is constant.

Figure A4: Characteristics of Sponsored Relative to Unsponsored Arms



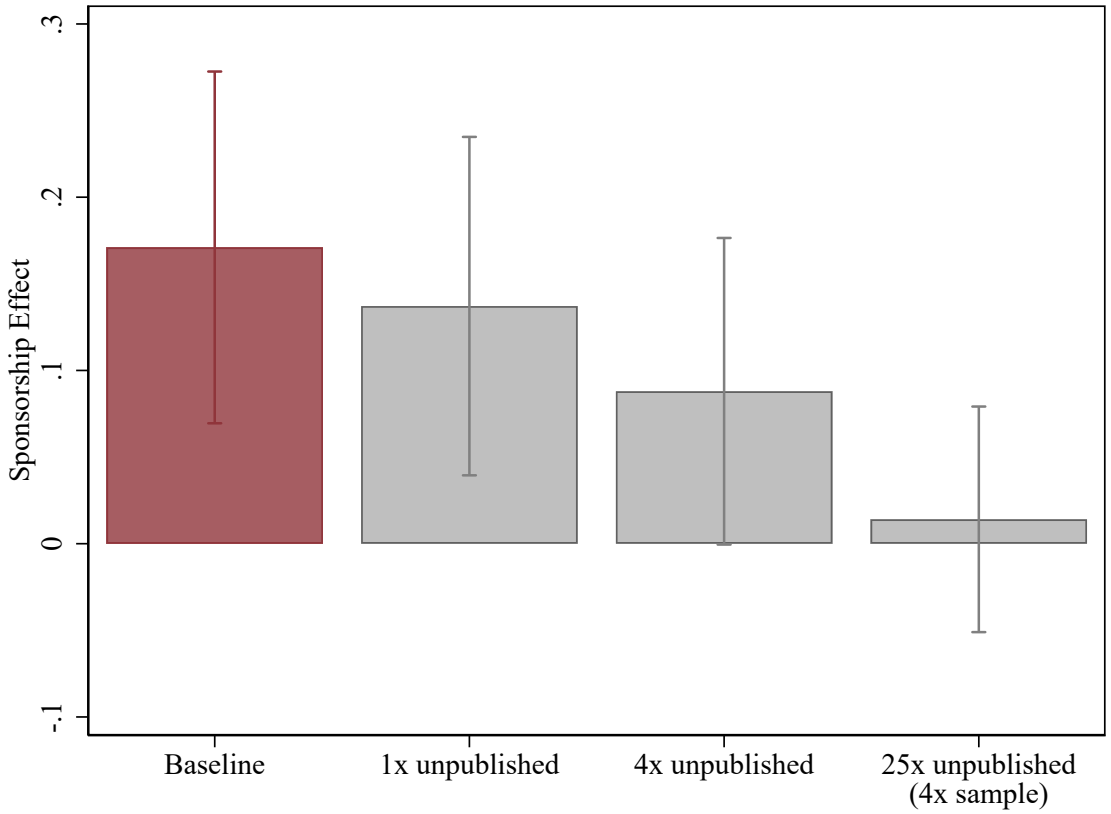
Notes: This figure presents the difference in characteristics for sponsored relative to unsponsored arms. The left panel presents the overall difference in trial characteristics between all sponsored and unsponsored arms. The right panel presents the difference in trial characteristics controlling for drug pairs. These differences were calculated using regression coefficients from the estimation of equation 12 and 13 as described in appendix section E. Error bars represent 95 percent confidence intervals. Standard errors are clustered at the trial level.

Figure A5: Distribution of Z-Scores Conditional on Publication



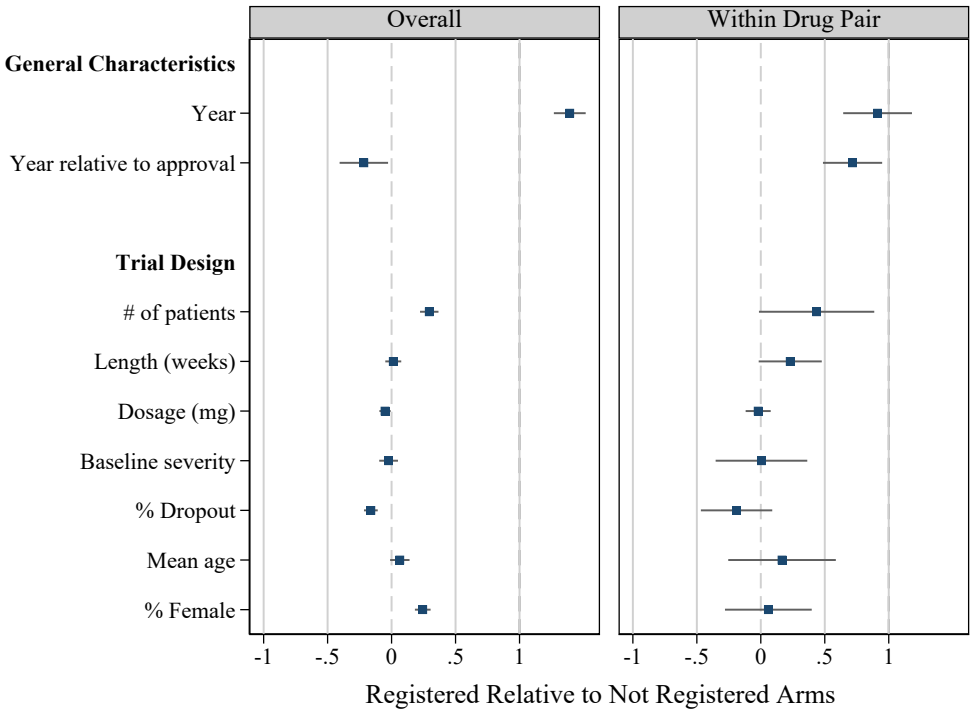
Notes: This figure presents the distribution of z-scores for drug efficacy in published trials. Both placebo-controlled and head-to-head trials are included. I omit placebo arms. I test for bunching at $Z = 1.645$ (5%, one sided, 10%, two sided) and $Z = 1.96$ (5%, two sided).

Figure A6: Counterfactual Sponsorship Effect under Alternate Publication Assumptions



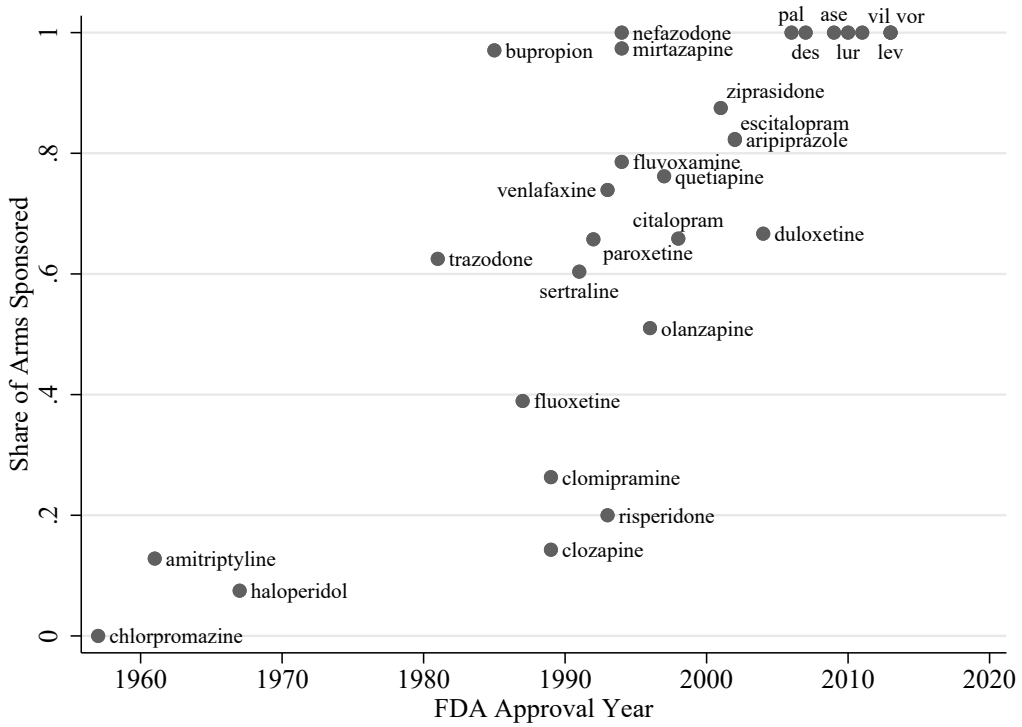
Notes: This figure presents the coefficients on $Sponsor_{ij}$ from the estimation of equation 1 with alternate samples. The left-most bar in solid maroon presents the baseline estimates including only published trials, replicating table 1, column (2). The second bar presents estimates including each unpublished trial once. The third bar presents estimates including each unpublished trial four times. The last bar presents estimates with the baseline sample size increased by a factor of four. This is accomplished by including each unpublished trial nineteen times, see section 4.2.2. 95% confidences intervals are presented as lines on each bar graph. Standard errors are clustered at the trial level. The weighted number of arms is 1,215 (baseline), 1,412 (Add 1x unpublished), 2,003 (Add 4x unpublished), and 4,958 (Add 19x unpublished, 4x sample).

Figure A7: Characteristics of Registered Relative to Non-Registered Arms



Notes: This figure presents the difference in characteristics for pre-registered relative to non-registered arms. The left panel presents the overall difference in trial characteristics between all registered versus non-registered arms. The right panel presents the difference in trial characteristics controlling for drug pairs. These differences were calculated using the procedure in appendix section E, using an indicator for pre-registered instead of sponsored. Error bars represent 95 percent confidence intervals. Standard errors are clustered at the trial level.

Figure A8: Included Drugs



Notes: This figure presents the antidepressant and antipsychotic drugs included in this analysis. The x-axis presents the year of FDA approval for the drug, while the y-axis plots the share of arms in which that drug is sponsored. The label "ase" refers to asenapine, "lur" refers to lurasidone, "vil" refers to vilazodone, "lev" refers to levomilnacipran, and "vor" refers to vortioxetine. The analysis sample also includes agomelatine, amisulpride, milnacipran, reboxetine, sertindole, and zotepine which are not yet approved in the United States and thus not shown in this figure.

Table A1: Summary Statistics: Full and Variation Samples

	Full Sample			Sample with Variation Within: Drug Sets			Sample with Variation Within: Drug Pairs		
	Mean	Std Dev.	% Missing	Mean	Std Dev.	% Missing	Mean	Std Dev.	% Missing
Trial Year	2001	8.8	0	1999	7.7	0	2000	8.1	0
FDA approval year	1990	13	29	1987	12	18	1988	12	25
Share:									
Sponsored	0.48	0.50	0	0.50	0.50	0	0.41	0.49	0
Sponsored w/o COI	0.41	0.49	0	0.39	0.49	0	0.32	0.47	0
Antidepressant	0.74	0.44	0	0.79	0.41	0	0.79	0.41	0
Registered	0.12	0.33	0	0.05	0.21	0	0.09	0.28	0
Post approval	0.86	0.35	29	0.88	0.32	18	0.91	0.29	25
Trial design:									
# of patients	100	86	0	89	101	0	92	91	0
Length (weeks)	9.0	8.0	0	8.6	6.6	0	9.3	8.6	0
Dosage (mg)	69	104	23	59	92	15	59	87	23
Baseline severity	-0.0	1.0	6	0.0	1.0	4	-0.1	1.0	6
% Dropout	29	15	11	29	15	12	30	16	13
Mean age	42	9	16	44	11	15	43	10	15
% Female	51	21	45	51	20	52	50	20	51
Total arms	1,215			453			778		
Total trials	509			208			348		

Notes: This table presents the mean and standard deviation for trial arm characteristics, along with the percent of trial arms with missing values. These summary statistics are shown for the full sample, the subsample with variation in sponsorship within drug sets, and the subsample with variation in sponsorship within drug pairs. Year refers to the year the trial was published. FDA approval year is the year that arm of the trial obtained FDA approval. Sponsored is defined as in section 2.2.2, and COI refers to conflicts of interest. Registered means the trial was registered on ClinicalTrials.gov and post approval means that trial was conducted after that arm had FDA approval. This outcome, as well as "FDA approval year" is missing for placebo arms. Placebo arms are also never sponsored. Baseline severity is standardized to have a mean of zero and a standard deviation of one.

Table A2: Difference in Difference: Antidepressants

Panel A: Active versus Placebo									
	Sponsored				Not Sponsored				
	Drug	Placebo	*Diff*	# Arms	Drug	Placebo	*Diff*	# Arms	DD
All Drug Sets	0.473	0.302	0.172	51	0.366	0.289	0.077	8	0.095
Paroxetine	0.465	0.305	0.160	29	0.250	0.226	0.024	1	0.137
Sertraline	0.460	0.361	0.099	11	0.476	0.433	0.042	2	0.057
Trazodone	0.458	0.158	0.300	6	0.568	0.353	0.215	1	0.085
Citalopram	0.509	0.350	0.160	4	0.303	0.209	0.095	1	0.065
Amitriptyline	0.564	0.278	0.286	1	0.607	0.282	0.325	3	-0.039

Panel B: Active versus Active									
	Sponsored				Not Sponsored				
	Drug	Other Arm	*Diff*	# Arms	Drug	Other Arm	*Diff*	# Arms	DD
All Drug Sets	0.647	0.597	0.049	50	0.567	0.583	-0.016	60	0.066
Amitriptyline vs. Fluoxetine	0.653	0.564	0.088	3	0.500	0.522	-0.022	10	0.111
Amitriptyline vs. Paroxetine	0.658	0.648	0.010	1	0.466	0.473	-0.008	8	0.017
Citalopram vs. Escitalopram	0.794	0.815	-0.021	6	0.639	0.760	-0.120	3	0.099
Fluoxetine vs. Venlafaxine	0.764	0.745	0.018	1	0.613	0.687	-0.074	7	0.092
Venlafaxine vs. Fluoxetine	0.687	0.613	0.074	7	0.704	0.707	-0.003	1	0.077
Paroxetine vs. Fluoxetine	0.531	0.475	0.056	6	0.683	0.565	0.119	1	-0.063
Clomipramine vs. Paroxetine	0.535	0.371	0.164	1	0.607	0.649	-0.042	4	0.205
Mirtazapine vs. Fluoxetine	0.713	0.518	0.196	4	0.667	0.444	0.222	1	-0.027
Sertraline vs. Fluoxetine	0.559	0.505	0.054	4	0.673	0.464	0.209	1	-0.155
Amitriptyline vs. Sertraline	0.500	0.529	-0.029	1	0.526	0.452	0.074	3	-0.104
Amitriptyline vs. Trazodone	0.557	0.435	0.122	2	0.566	0.467	0.099	2	0.023
Clomipramine vs. Fluoxetine	0.733	0.800	-0.067	1	0.552	0.665	-0.113	3	0.046
Trazodone vs. Fluoxetine	0.765	0.476	0.289	1	0.431	0.496	-0.065	3	0.353
Amitriptyline vs. Fluvoxamine	0.618	0.371	0.246	1	0.368	0.507	-0.139	2	0.385
Amitriptyline vs. Citalopram	0.650	0.625	0.025	1	0.516	0.548	-0.031	1	0.056
Fluvoxamine vs. Milnacipran	0.537	0.660	-0.123	1	0.571	0.702	-0.130	1	0.007
Paroxetine vs. Escitalopram	0.564	0.621	-0.057	1	0.698	0.675	0.023	1	-0.080
Paroxetine vs. Fluvoxamine	0.436	0.369	0.067	1	0.533	0.567	-0.033	1	0.101
Reboxetine vs. Citalopram	0.421	0.557	-0.136	1	0.609	0.600	0.009	1	-0.145
Sertraline vs. Citalopram	0.695	0.680	0.015	1	0.231	0.360	-0.129	1	0.144
Sertraline vs. Fluvoxamine	0.583	0.725	-0.142	1	0.479	0.551	-0.072	1	-0.070
Sertraline vs. Venlafaxine	0.549	0.628	-0.079	1	0.569	0.653	-0.084	1	0.005
Trazodone vs. Paroxetine	0.873	0.906	-0.033	1	0.413	0.560	-0.148	1	0.115
Venlafaxine vs. Citalopram	0.645	0.667	-0.022	1	0.429	0.840	-0.411	1	0.390
Venlafaxine vs. Sertraline	0.628	0.549	0.079	1	0.667	0.709	-0.042	1	0.122

Notes: This table presents the difference-in-difference estimate of the sponsorship effect for "Active versus Placebo" drug sets (panel (a)) and "Active versus Active" drug sets (panel (b)) . The first set of columns compares the share of patients that respond to treatment when the drug is sponsored; the next set compare these results when the drug is not sponsored. The difference between the share of patients that respond to a given drug and the share that respond to the placebo group (or other arm) is given in the column labeled "Diff" for "Difference." The last column reports the difference between the two difference columns. This difference in difference (DD) is analogous to the sponsorship effect in equation 1.

Table A3: Difference in Difference: Antipsychotics

	Sponsored				Not Sponsored				
	Drug	Other Arm	*Diff*	# Arms	Drug	Other Arm	*Diff*	# Arms	DD
All Drug Sets	18.48	14.70	3.78	26	15.59	15.62	-0.04	27	3.82
Risperidone vs. Haloperidol	13.80	4.60	9.20	1	21.73	22.06	-0.34	12	9.54
Olanzapine vs. Haloperidol	21.09	16.51	4.57	10	6.57	4.37	2.20	2	2.37
Amisulpride vs. Risperidone	24.47	23.17	1.30	3	24.10	28.40	-4.30	1	5.60
Olanzapine vs. Aripiprazole	31.50	27.30	4.20	1	24.32	23.93	0.39	3	3.81
Olanzapine vs. Amisulpride	1.90	2.40	-0.50	1	22.56	20.85	1.72	2	-2.22
Risperidone vs. Olanzapine	11.25	11.00	0.25	2	4.90	4.70	0.20	1	0.05
Ziprasidone vs. Olanzapine	13.13	14.53	-1.40	2	26.00	35.70	-9.70	1	8.31
Zotepine vs. Haloperidol	13.82	14.78	-0.97	2	5.00	6.20	-1.20	1	0.24
Amisulpride vs. Haloperidol	27.30	21.90	5.40	1	20.90	17.30	3.60	1	1.80
Amisulpride vs. Olanzapine	25.00	28.00	-3.00	1	2.40	1.90	0.50	1	-3.50
Clozapine vs. Chlorpromazine	21.10	20.80	0.30	1	19.94	14.48	5.46	1	-5.16
Olanzapine vs. Risperidone	28.10	24.90	3.20	1	4.70	4.90	-0.20	1	3.40

Notes: This table reports the difference-in-difference estimate of the sponsorship effect for "Active vs. Active" schizophrenia drug sets. The first set of columns compares the decline in the schizophrenia score when the first listed drug is sponsored; the next set compare these results when the first listed drug is not sponsored. In all cases, the second listed drug has no change in sponsorship interests. The difference between the decline in the schizophrenia score for a given drug and the decline for the other arm is given in the column labeled "Diff" for "Difference." The last column reports the difference between the two difference columns. This difference in difference (DD) is analogous to the sponsorship effect in equation 1.

Table A4: Fixed Effect Example

	(1) Drug by Drug Set Fixed Effects		(2) Drug by Drug Pair Fixed Effects	
Trial	$G_{d(i),s(j)}$	Drug	$G_{d(i),p(j)}$	Drug
X	1	Drug A	1	Drug A
X		Placebo		*Placebo*
Y	1	Drug A	1	Drug A
Y		Placebo		*Placebo*
Z	2	Drug A	1	Drug A
Z		Herbal Supplement		Herbal Supplement
Z		Placebo		*Placebo*
W	3	Drug A	1	Drug A
W		Drug B		Drug B
W		Placebo		*Placebo*
W			2	Drug A
W				Drug B
W				Placebo
K	4	Drug A	2	Drug A
K		Drug B		Drug B
Q	5	Drug A	3	Drug A
Q		Drug C		Drug C

Notes: This table provides an example of the fixed effects in equation 1 based on six hypothetical trials: X,Y, Z, W, K, and Q. Each row represents a treatment arm (i.e. drug) in the sample. The $G_{d(i),s(j)}$ and $G_{d(i),p(j)}$ columns present the fixed effects for Drug A; each number represents a different fixed effect. The fixed effects for the other drugs are omitted. Column (1) presents the more restrictive drug-by-drug set fixed effects $G_{d(i),s(j)}$. In this case, each trial j maps to a unique drug set $s(j)$. Each different drug set has a separate fixed effect for Drug A. The first two trials assess the same drug set, so Drug A has the same fixed effect in those two trials. Each of the other four trials assess a different drug set, so Drug A has four separate fixed effect in these trials. Column (2) presents the less restrictive drug-by-drug pair fixed effects $G_{d(i),p(j)}$. In this case, Drug A gets a separate fixed effect for each different drug it is directly compared against. Here, Drug A has the same fixed effect for the first four trials, where it is compared with a placebo. In trial W, Drug A also has a separate fixed effect since it is compared with Drug B as well; this is the same fixed effect as in trial K. In this case, trial W would be re-weighted so that this arm is not double counted.

Table A5: Absolute versus Relative Efficacy

	Published			Approved		
	(1)	(2)	(3)	(4)	(5)	(6)
Relative Efficacy	0.107***		0.103***	0.453**		0.247
	(0.021)		(0.025)	(0.202)		(0.219)
Absolute Efficacy		0.029*	0.009		-0.395***	-0.310*
		(0.017)	(0.018)		(0.139)	(0.158)
Controls	X	X	X			
Drug by Drug Pair F.E.	X	X	X			
Mean Outcome	0.86	0.86	0.86	0.77	0.77	0.77
Weighted N	1,412	1,412	1,412	30	30	30

Note: This table presents the coefficients on absolute efficacy, relative efficacy, or both from the estimation of equation 10 in columns (1)-(3). Columns (4)-(6) present the coefficients from a regression where each observation is a unique drug. For each drug, I compute the average absolute efficacy, relative efficacy, or both, in all pre-approval trials. For drugs not approved by the FDA, all trials are pre-approval trials. The table reports the coefficients on these average efficacy measures when regressed on an indicator for whether a drug was approved by the FDA. Standard errors are clustered are reported in parentheses, with $^{*}p < 0.10$, $^{**}p < 0.05$ and $^{***}p < 0.01$.

Table A6: Understanding Control Arms in the Sponsorship Effect

	Relative Efficacy	Absolute Efficacy	Efficacy of Least Effective Drug in Pair	Leave-out Mean Efficacy of Control Drug	
	(1)	(2)	(3)	(4)	(5)
$Sponsor_{ij}$	0.171***	0.259**	0.098	-0.126***	-0.003
	(0.052)	(0.103)	(0.101)	(0.043)	(0.002)
Controls	X	X	X		
Drug Combination Fixed Effects	Drug by Drug Pair	Drug by Drug Pair	Drug by Drug Pair	Drug	Drug by Drug Pair
Mean Outcome	0.35	0.06	-0.40	0.03	0.03
Weighted N	1,215	1,215	1,215	1,215	1,215

Note: Columns (1) and (2) replicate table 1, columns (2) and (3). The outcome in column (3) is the efficacy of the placebo or least effective arm in that drug pair. Columns (4) and (5) present the coefficients on $Sponsor_{ij}$ from the estimation of equation 11, where the outcome y_{-ij} is the absolute efficacy of the other arm in the trial. Column (4) has only drug fixed effects while column (5) has the baseline drug by drug pair fixed effects. Controls include the trial's publication year and the type of psychiatric score used. Standard errors are clustered at the trial level and reported in parentheses, with $^{*}p < 0.10$, $^{**}p < 0.05$ and $^{***}p < 0.01$.

Table A7: Effect of Sponsorship on Drug Efficacy within Drug Set

	Relative efficacy		Absolute efficacy	Significantly better at 0.05 level	Most effective in trial	% Decline
	(1)	(2)	(3)	(4)	(5)	(6)
$Sponsor_{ij}$	0.179**	0.183**	0.384**	0.102**	0.190**	0.022*
	(0.083)	(0.081)	(0.168)	(0.043)	(0.091)	(0.012)
Controls		X	X	X	X	X
Drug by Drug Set F.E.	X	X	X	X	X	X
Mean Outcome	0.45	0.45	0.06	0.24	0.39	0.05
N	1,215	1,215	1,215	1,087	1,215	798

Note: This table presents the coefficients on $Sponsor_{ij}$ from the estimation of equation 1, but where the fixed effects $G_{d(i),s(j)}$ control for each drug in each unique drug set. See section 3.3 for more detail. In columns 1 and 2, the dependent variable y_{ij} is the standardized efficacy measure, relative to the placebo arm if available or least effective arm in that trial otherwise. In column 3, the outcome is the standardized efficacy measure. The outcome in column 4 is an indicator for whether arm i in trial j was found to be statistically significantly different from the other arms in that trial at the 0.05 level. In column 5, the outcome is an indicator for whether arm i was the most effective arm in trial j. The outcome in column (6) is the percent decline in the psychotic score, relative to the placebo or least effective arm. Controls include the trial's publication year and the type of psychiatric score used. Standard errors are clustered at the trial level and reported in parentheses, with $^{*}p < 0.10$, $^{**}p < 0.05$ and $^{***}p < 0.01$.

Table A8: Alternate Specifications

Panel A:	Relative Efficacy			
	(1a)	(2a)	(3a)	(4a)
$Sponsor_{ij}$	0.183**	0.171***	0.177***	0.376***
	(0.081)	(0.052)	(0.048)	(0.035)
Controls	X	X	X	X
Drug Combination Fixed Effects	Drug by Drug Set	Drug by Drug Pair	Drug	None
Mean Outcome	0.45	0.35	0.45	0.45
Weighted N	1,215	1,215	1,215	1,215

Panel B:	Absolute Efficacy			
	(1b)	(2b)	(3b)	(4b)
$Sponsor_{ij}$	0.384**	0.259**	0.093	0.414***
	(0.168)	(0.103)	(0.087)	(0.053)
Controls	X	X	X	X
Drug Combination Fixed Effects	Drug by Drug Set	Drug by Drug Pair	Drug	None
Mean Outcome	0.06	0.06	0.06	0.06
Weighted N	1,215	1,215	1,215	1,215

Note: This table presents estimates of the sponsorship effect with alternate specifications. Column (1) presents the coefficients on $Sponsor_{ij}$ from the estimation of equation 1, but where the fixed effects $G_{d(i),s(j)}$ control for each drug in each unique drug set. Column (2) presents coefficients from the estimation of equation 1, where the fixed effects $G_{d(i),p(j)}$ control for each drug in each drug pair. In column (3) I include only drug fixed effects, and column (4) has no drug-specific fixed effects. See section 3.3 for more detail. In the top panel, the dependent variable is the standardized efficacy measure, relative to the placebo arm if available or least effective arm otherwise. In the bottom panel, the dependent variable y_{ij} is the standardized absolute efficacy measure for arm i in trial j. Columns (2a) and (2b) replicate the results from table 1, column (2) and column (3). Controls include the trial's publication year and the type of psychiatric score used. Standard errors are clustered at the trial level and reported in parentheses, with $^{*}p < 0.10$, $^{**}p < 0.05$ and $^{***}p < 0.01$.

Table A9: Sponsorship Variation by Characteristics

	# Arms	Share with Variation
Full Sample	1,215	0.64
Drug Type - Antidepressants		
Tricyclic	67	0.88
Atypical	160	0.28
SSRI	333	0.79
SNRI	124	0.60
Drug Type - Antipsychotics		
1st Gen	52	0.75
2nd Gen	201	0.62
Placebo	260	0.67
Approval Year		
Prior to 1990	278	0.77
1990 - 1996	305	0.68
1997 or after	231	0.50
Patent Expiry Year		
Prior to 2000	167	0.80
2000 - 2007	395	0.70
2008 or after	311	0.59

Note: This table presents the share of arms with each characteristic that have variation in sponsorship. In this table, variation in sponsorship is defined within drug pairs.

Table A10: Sponsorship Effect by Years

	Relative Efficacy	
	Baseline	Drop Pre-1991
	(1)	(2)
$Sponsor_{ij}$	0.171***	0.100**
	(0.052)	(0.049)
Controls	X	X
Drug by Drug Pair F.E.	X	X
Mean Outcome	0.35	0.32
Weighted N	1,215	1,053

Note: This table presents coefficients from the estimation of equation 1, where the fixed effects $G_{d(i),p(j)}$ control for each drug in each drug pair. Column (1) replicates the baseline estimate from table 1, column (2), where the outcome is relative efficacy. The dependent variable is the same in all subsequent columns. Column (2) drops trials that were conducted before 1991. Standard errors are clustered at the trial level and reported in parentheses, with $^{*}p < 0.10$, $^{**}p < 0.05$ and $^{***}p < 0.01$.

Table A11: Sponsorship Effect Interacted with Pre-Registration and Publication

	Relative Efficacy
	(1)
$Sponsor_{ij}$	0.183***
	(0.052)
$Sponsor_{ij}$ x Pre-Registered	-0.122
	(0.077)
$Sponsor_{ij}$ x Unpublished	-0.364***
	(0.087)
$Sponsor_{ij}$ x Pre-Registered x Unpublished	-0.240
	(0.147)
Controls	X
Drug by Drug Pair F.E.	X
Mean Outcome	0.31
Weighted N	1,412

Note: Table presents the coefficients from the estimation of equation 1 with $Sponsor_{Ij}$ interacted with several indicators. Pre-registered is an indicator for whether the trial was pre-registered on ClinicalTrials.gov. Unpublished is an indicator for whether the trial was unpublished. The sample in this table includes both published and unpublished trials. Controls include the trial's publication year and the type of psychiatric score used. Standard errors are clustered at the trial level and reported in parentheses, with $^{*}p < 0.10$, $^{**}p < 0.05$ and $^{***}p < 0.01$.