Comparison of Publication Bias Between Observational and Interventional Studies Evaluating Use of Antidepressants

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BACKGROUND

- Major depressive disorder (MDD) affects 7.1% (17.3 million adults) at least once during their lifetime
- Primary treatments are selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitor (SNRIs)
- Published randomized controlled trials (RCT) are mostly positive (72.5%)
- Very few published RCTs are negative (5.8%)
- RCTs are more likely to be industry-funded

OBJECTIVE

- Determine if RCTs or observational studies have more positive publications and whether it is influenced by funding source

METHODS

Study Design
- Systematic review
- Extensive literature search of Pubmed and www.clinicaltrials.gov
- Data extraction from one reviewer
- Bias assessed with:
  - Cochrane Risk of Bias
  - Newcastle-Ottawa Scale

Inclusion Criteria
- RCTs, cohort or case-control studies
- Primary intervention of SSRI or SNRI (fluoxetine, paroxetine, sertraline, citalopram, escitalopram, and venlafaxine)
- Presence of control group (placebo, non-intervention, standard of care)
- Endpoint of change in depressive symptoms (as measured by validated scale or reduction in suicidal tendency) or frequency of adverse events

Exclusion Criteria
- Studies with data from the same source
- Non-RCT or non-observational design
- Abstract/Protocol-only
- Study not in English

Data Collection
- Author name and date of publication
- Statistically significant improvement in depressive symptoms or reduction of suicide ideation
- Statistically non-significant frequency of adverse drug reactions
- Primary adversely affected organ system
- Study design
- Source of funding

Statistical Analysis
- Descriptive statistics
- Chi Square analysis or Fisher's Exact for primary outcome
- $\alpha = 0.05$

RESULTS

Table 1: Characteristics of included studies

	RCT	Cohort	Case-Control
Number of Studies	52	38	20
Control Type			
Placebo	46	0	0
Standard of Care	6	1	1
Non-exposure	0	37	19
Study Setting			
Inpatient	5	7	3
Outpatient	47	31	17
Primary Endpoint			
Change in Depressive SSx	42	2	3
Safety	1	36	17
Other*	9	0	0
Funding Sources			
None	10	17	8
Industry	16	1	4
Government	24	15	5
Institution	1	4	2
Professional Society	1	0	0
Other**	0	1	1
Clinical Trial Registration			
Yes	25	2	1
No	27	36	19

*Other primary endpoints include: Sleep disturbance, premenstrual dysphoric disorder (PMDD), All-cause mortality, prevention of post-traumatic stress disorder, SUD, risk-taking behaviors, symptomatic relief of functional chest pain, quality of life (QOL), glycemic control, irritable bowel syndrome (IBS), and generalized anxiety disorder (GAD).
**Other sources of funding include: Wellcome Trust and the Western Danish Research Forum for Health Sciences

Table 2: Study Outcomes

	RCT (N = 52)	Cohort (N=38)	Case Control (N=20)
Change in Depressive SSx (%)			
Not included	1 (2%)	36 (95%)	18 (90%)
Significant	23 (44%)	2 (5%)	2 (10%)
Nonsignificant	28 (54%)	0 (0%)	0 (0%)
Common Adverse Events (%)			
Not included	15 (29%)	31 (82%)	19 (95%)
Significant	15 (31%)	5 (13%)	0 (0%)
Nonsignificant	22 (40%)	2 (5%)	1 (5%)
Serious Adverse Events (%)			
Not included	30 (58%)	4 (10%)	2 (10%)
Significant	3 (5%)	20 (53%)	9 (45%)
Nonsignificant	19 (36%)	14 (37%)	9 (45%)

RESULTS

Figure 1: Proportion of positive trials and negative trials in RCT and observational studies

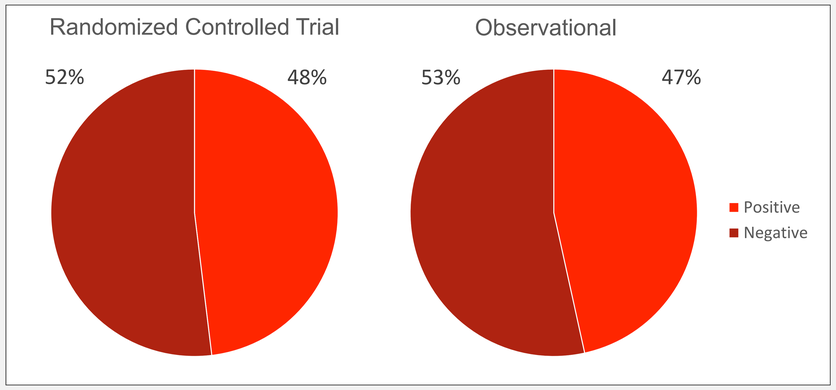

Table 3: Breakdown of positive trials by funding source

	Randomized	Observational
Total Positive Trials	25/52 (48.1%)	27/58 (46.6%)
Funding		
No Funding	5/10 (50%)	14/25 (56%)
Industry	7/16 (43.8%)	1/5 (20%)
Governmental	12/24 (50%)	9/20 (45%)
Institutional	0/1 (0%)	1/6 (20%)
Professional Society	1/1 (100%)	--
Other	--	2/2 (100%)
Primary Endpoint		
Efficacy	22/42 (52.4%)	4/5 (20%)
Safety	1/1 (100%)	23/53 (43.4%)
Other	2/9 (22.2%)	--

CONCLUSION

- The difference in rates of positive outcomes do not differ notably between randomized trial and observation studies for SSRIs and SNRIs.
- Studies that had no listed source of funding tended to be positive slightly more often than studies with listed funding sources

REFERENCES

1. National Institute of Mental Health [Internet]. Bethesda: US Govt; c2019 [cited 2019 May 21]. Office of Science Policy, Planning, and Communications; [about 3 screens]. Available from: https://www.nimh.nih.gov/health/topics/depression/index.shtml
2. American Psychiatric Association. Practice Guideline for the Treatment of Patients with major Depressive Disorder. 3rd ed. District of Columbia (DC): American Psychiatric Association; 2010
3. Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med. 2008 Jan 17;358(3):252-60. doi: 10.1056/NEJMsa065779. PubMed PMID:18199864.

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BACKGROUND

- MDD affects 7.1% (17.3 million adults) at least once during their life\
- Severe impairment occurs in 63.8% episodes
- primary treatment modality: SSRIs and SNRIs
- Published RCT studies mostly positive (72.5%)
- Very few published RCT studies negative (5.8%)
- RCT more likely to receive industry funding

OBJECTIVE

- Determine if RCT or observational studies have more positive results
- Examine the impact of industry financial backing on reported results

METHODS

Study Design
- Database review of Pubmed and Clinicaltrials.gov
- Data extraction from one reviewer
- Bias assessed with:
  - Cochrane Risk of Bias
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Inclusion Criteria
- Study design of RCT, cohort, case control
- primary intervention of SSRI or SNRI
  Included drugs: fluoxetine, paroxetine, sertraline, citalopram, escitalopram, and venlafaxine
- presence of control group (placebo, non-intervention, standard of care)
- Endpoint of change in depressive symptoms (as measured by validated scale or reduction in suicidal tendency) or frequency of adverse events

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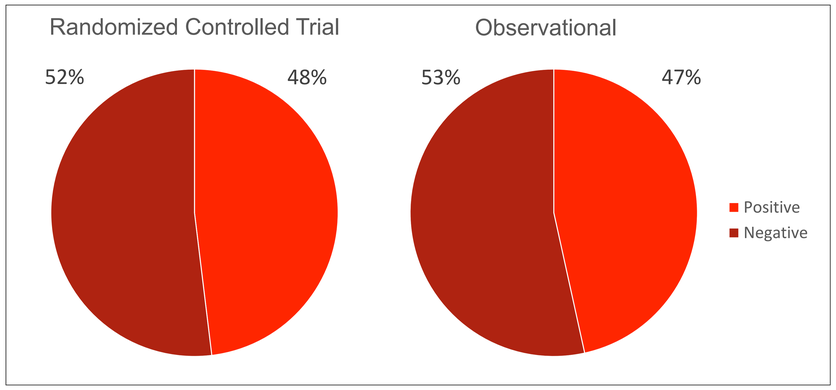

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