THE UNIVERSITY OF CHICAGO

Physician Capture in Clinical Trials

The Impact of Broken Blinds through Side Effects on Sponsorship Bias in Pharmaceutical Clinical Trials

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1 Introduction *

1.1 Statement of Research Question

To develop a potential new drug costs an average of $430 million dollars out of the pocket of a pharmaceutical company (DiMasi, Grabowski, and Hansen 2016). After such a high cost of development, the new drug is evaluated through three phases of clinical trials for efficacy and toxicity, with only a 12% chance of making it to market.[2] If these clinical trials show positive results, the drug will not only become legal for prescription in the US,[3] it will be patent protected for 17 years, granting the company a monopoly over their new chemical compound. Furthermore, the clinical trial's results influence physician decisions about which drug to prescribe to their patients.

Since the profits generated by a drug hinge on the results of these clinical trials, the financial incentives for positive[4] results are quite strong. It stands to reason pharmaceutical companies will do what they can to exert influence towards a positive result from these trials. In fact, empirical research shows that the sponsor of the trial plays a role in how effective a clinical trial finds the drug to be. Researchers have demonstrated that drug trials sponsored by the pharmaceutical industry yield more positive[4] results than publicly funded trials even when the trials are otherwise identical (Lexchin et al. 2003 Lexchin 2012).

Since the outcome of a clinical trial is influenced by sponsorship, clinical trials are an impure signal of actual drug efficacy. In particular, corporate sponsored trials are biased to favor their own drug. One mechanism of bias in clinical trials could be that industry sponsored select physician participants in clinical trials who are more captured. Capture is defined as "institutions using power to influence their regulators" (Zingales 2020). In this paper, capture means pharmaceutical companies using their power to influence the doctors who should be observing unbiased impacts of their drugs. There are two types of capture at play here: the "indirect capture" faced by all physicians in clinical trials due to their close proximity to and frequent interaction with the pharmaceutical industry, and "direct capture" caused by being on the pharmaceutical industry's payroll for the duration of a clinical trial. The pharmaceutical industry may chose physicians who are more subject to indirect capture to participate in their trials but more importantly, physicians in sponsored trials are aware

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[2]Phase 3 Clinical trials make up greater than 50% of spending on development by pharmaceutical companies DiMasi, Grabowski, and Hansen 2016.

[3]This paper will focus on prescription pharmaceuticals in the United States.

[4]Throughout the course of this paper, I will say positive trial results. The meaning of this is clinical trials which demonstrate that the sponsored drug is an effective treatment in placebo controlled trials, or better than its peers (better meaning either in side effect burden or chance of treating the disease or cures more of the disease) in cross sectional drug trials.

of who is signing their paychecks, making them further disposed to produce captured work.

Aware of the industry conflict of interest in trial sponsorship, and to prevent captured physicians from influencing clinical trial results, many clinical trials are double blind. In a double blind trial, a physician does not know a priori whether the patient is on an antidepressant or a placebo. However, in meeting with the patient, the physician observes a patient exhibiting the side effects of the drug. The physician has strong reason to believe this patient is taking the real drug not the placebo. This is called a broken blind.

Psychology discusses a theory of "expectation bias": humans are biased in their reporting based on whether or not they expect something to work. Hence, physicians expecting the drug to work would report greater improvement in patients exhibiting side effects associated with the drug; they expect the treated patients to show improvement and thus see this improvement. I expect pharmaceutical companies select more captured physicians or physicians more optimistic of their drug's prospects to participate in their clinical trials. Hence, the industry sponsored clinical trials report higher results due to capture or expectation bias influencing the results of patients who have broken physician blinds.

Like any industry in today's economy, physicians are susceptible to capture. Double blind trials are intended to protect against capture. However, blinds may be broken by side effects. Since physicians recognize that patients with side effects are more likely to be on the drug, they may report more positive results. Therefore, this paper investigates the theory that physician capture drives part of the difference in measured efficacy between sponsored and publicly funded clinical trials. To do this, I test whether differences in measured efficacy are greater in drugs where side effects are more pronounced.[5] The drugs in which I investigate this phenomena are antidepressants. Antidepressants are a good place to study this phenomena since depression patient improvement is more challenging to measure and potentially more subjective while the burden of side effects from antidepressants can be severe.

1.2 Literature Review

Pharmaceutical economics has garnered much interest in the research community. Some of this is due to information asymmetries (patients don't have the background to make informed decisions), the presence of insurance (patients do not pay for their choices), and the fact that drugs influence health, which many people view as a merit good (there is a public interest in the health outcomes of private individuals). In addition, the high prices of drugs, consistently contested patent structure, and high costs[6] associated with the development of new treatments make it one of today's policy issues.

[5]Pronounced meaning common and distinctive side effects.

[6]It costs $2.9 billion in 2013 dollars in research and development costs to bring a drug to market, including post approval studies (DiMasi, Grabowski, and Hansen 2016).

Much of the research is geared towards controlling spending on drugs without discouraging innovation[7] and finding mechanisms to prevent pharmaceutical rent seeking.[8] As American healthcare spending rises dramatically,[9] policy makers look for ways to limit Medicare/Medicaid spending in order to alleviate the burden it places on tax payers.

The rise in pharmaceutical spending on lobbying, "me too drugs", and marketing coupled with public scandals like Martin Shkreli[10] or the Opioid crisis[11] have lead the American public to believe that pharmaceutical companies are evil (McCarthy 2019). Recent media attacked the American National Institutes of Health (NIH) for funding preliminary research later used by pharmaceutical companies to develop drugs for profit (Cleary et al. 2018).[12] Public displeasure with health spending has caused the the budget of the NIH to fall 24% in the past ten years (Ehrhardt, Appel, and Meinert 2015). At the same time, industry funded trials have risen 43% (Ehrhardt, Appel, and Meinert 2015).

However, industry funding of clinical trials is a clear conflict of interest for pharmaceutical companies since their own earnings depend on the drugs they are testing. As a result, industry funded clinical trials, compared to publicly funded peers, almost universally find the sponsor's drug more effective. The bias in sponsored clinical trial results mean clinical trials are an imperfect signal for drug efficacy. This is a problem because it means the clinical trials physicians use to prescribe drugs to patients are not good signals for actual drug efficacy.

Yet, publicly funded trials decrease due to cuts to NIH funding. Thus, the efficacy of pharmaceuticals is more difficult to measure due to the additional biases introduced in industry funded trials. Moreover, it becomes more difficult to gauge the efficacy of various antidepressants, and more difficult for prescribers to know which drug is best for their patient. In 2003, Joel Lexchin tied indus-

[7]Approximately 27% of a pharmaceutical company's US budget every year goes towards marketing, compared to only 17% spent on research and 19% profits. Advertising pharmaceuticals to consumers is unique to the United States since US freedom of speech laws protect it, but it is illegal is Europe. Marketing in pharmaceuticals can be expanded to include rerunning successful clinical trials with new doctors to expose them to how effective the new drugs are, and even money to publish pro-drug studies in journals Belk 2011

[8]Me too drugs and other forms of incremental innovation are considered rent seeking since the pharmaceutical companies behind these drugs are tweaking current treatments or finding new uses for the same treatments in order to extend patent duration and prevent generics from threatening their profit margins rather than pursuing radically innovative new treatments. (Morgan, Lopert, and Greyson 2008)

[9]Healthcare spending (per capita) has grown more than 31-fold in the past forty years see Kamal, McDermott, and Cox 2019.

[10]Martin Shkreli became well known for hiking the price of an anti-parasitic drug (Daraprim) 56 fold.

[11]The Sackler family, owners of Purdue Pharmaceuticals will spend north of $10 billion settling with states for their role in the Opioid crisis. Johnson and Johnson is also being sued but company policy is not to settle (Hals and Spector 2020).

[12]I would argue the criticism is unfounded since preliminary funding is the only mechanism the NIH has for influencing pharmaceutical companies' research agenda. A classic example given here is the Hepatitis C vaccine which Johnson and Johnson nor Gilead wish to fund research towards since they provide the expensive post contraction treatments for hepatitis C patients.

try sponsorship to more positive outcomes for pharmaceutical efficacy, citing an odds ratio of 4 for an outcome in trial which favored the sponsor of the clinical trial (Lexchin et al. 2003). He also notes none of the published outcomes in his sample were negative. This sponsorship difference is established in antidepressant drugs by Baker et al. 2013. Researchers since present many potential explanations for the divergence between sponsored and unsponsored trials (Oomstrom 2020) In Sismondo's 2008 article "How pharmaceutical industry funding affects trial outcomes: Causal structures and responses", Sismondo outlines the explanations for this bias (Sismondo 2008). He mentions a design bias, using methods known to yield positive results in multiple trials, interpretive results, physician misconduct and publication bias. My research controls for these biases where possible by: using data from after all trials were required to be registered, using only double blind trials, and using raw data rather than reading the articles, there is still a clear trend of residual positive results of industry sponsorship in pharmaceutical clinical trials. By controlling for known biases, this paper seeks to explore a new explanation for the remaining unexplained sponsorship bias. I postulate that physicians are subject to capture, particularly those who are on industry payroll.

The first bias Sismondo discusses is called publication bias. Pharmaceutical companies pursue publication only positive results from trials, discarding neutral and negative results or ending likely negative trials early (Flacco et al. 2015; Melander, Ahlqvist-Rastad, and Meijer 2003). In addition, pharmaceutical companies publish the same positive results in many reputable journals; Melander, Ahlqvist-Rastad, and Meijer 2003 found an average of 2 or as many as 5 influential medical journals have articles about the same industry funded positive studies. The power of these publication biases has been studied intensively by many researchers (Guyatt et al. 2011; Hall, Antueno, and Webber 2007; Johnson and Dickersin 2007) including its impact of antidepressants in Turner et al. 2008. Hoping to prevent some of the selective reporting bias, the NIH now requires registration of all clinical trials prior to beginning the trial, and required result reporting on clinicaltrials.gov. Since this requirement was implemented,[13] Oomstrom 2020 finds the impact of sponsorship bias in clinical trial reporting of antidepressants has decreased significantly; and finds that approximately 50% of the sponsorship difference can be explained by this publication bias.

It is worth noting that a recent court case has rendered this requirement essentially useless. Charles Seife and Peter Lurie sued the Department of Health and Human Services (HHS), claiming the FDA failed to publish ten years of required clinical trial results. Judge Buchwald determined the FDA should publish this data, but it is the FDA's job to enforce the required disclosures from the companies who have failed to post it. Even though the FDA has never enforced these disclosures, it also cannot be compelled to enforce reporting by

[13] July 1, 2005.

the court (Wicks and Clissold 2020).[14][15] Prior to the conclusion of this case, the law requiring these disclosures was demonstrated to significantly decrease the difference in industry and non-industry findings of drug efficacy. The purpose of this law was to eradicate publication bias by forcing companies to report all trials. Seeing that the FDA cannot be compelled to enforce result publication and has never enforced it, the bias may return. However, Oomstrom 2020 suggests this bias was[16] gone or significantly diminished.

In addition to the frequency of publication, and positive studies being selected for publication, researchers also identify bias in how results are reported, paper phrasing, and researcher conclusions (Ebrahim et al. 2014). The authors of papers spin negative results positively (Angell 2009; Thornton and Lee 2000). In Oomstrom 2020, Oomstrom discusses an example of multiple studies performing a direct comparison of Venlafaxine and Sertraline for treating depression. In the Venlafaxine sponsored study, authors find Venlafaxine is statistically significantly better. In the study sponsored by Sertraline's manufacturer, authors find Sertraline and Venlafaxine similarly effective though Sertraline to have less onerous side effects. However, the Oomstrom dataset, only uses numerical results, preventing the report's text from swaying the trial results.

Another potential source of bias is trial design; researchers suspected that in an attempt to attain more positive results industry sponsored trials might use larger sample sizes or perform single blind trials. Following a successful trial, pharmaceutical companies also run additional clinical trials, as a form of marketing to new physicians, to replicate positive trials (Berenson 2005).[17] By running additional trials in the same manner as the original clinical trials, which resulted in the desired positive outcome, pharmaceutical companies can market their efficacy to new physicians participating in these trials, who will also observe their drug as positive. And, at the end of these successful trials, pharmaceutical companies will be able to produce more positive literature around their drug.

It is possible that pharmaceutical companies use inferior methodology in their clinical trials, compared to publicly sponsored trials (Lexchin et al. 2003). Industry sponsored trial size is typically larger, which makes it more disposed to yield a statistically significant result but may be due to pharmaceutical companies' deeper pockets. However, it is disputed whether larger trials should be considered a bias.[18] To control for this, Oomstrom 2020 uses only double blind

[14]The failure of the FDA to enforce this law suggests that the FDA may be subject to some capture of its own, with researchers moving between the FDA and pharmaceutical industry, but this is beyond the scope of this paper.

[15]While clearly the lack of enforcement means some companies opted not to report results of negative trials anyways, researchers can use Heckman corrections to predict actual results in cases where much of the data is missing.

[16]I say "was" because I expect this bias to return but the impact of the court case is too soon to say since this court case occurred in March of 2020. At the time of publishing this paper, there is insufficient data to draw any conclusion from this case's impact yet.

[17]While new physicians might immediately seem to counteract my capture theory, new physicians who expected the drug to work because of previous positive trial results would enable replication of the capture result using their expectation bias result.

[18]Lexchin et al. 2003 says no while Djulbegovic et al. 2000 and Bekelman, Li, and Gross

trials, and has both cross trials and single drug vs placebo trials.

There is also the issue of a broken patient double blind, and the impact of the placebo effect[19] on a patients reported efficacy of antidepressants. In the book "The Emperor's New Drug: Exploding the Antidepressant myth" (Kirsch 2011), Irving Kirsch discusses the impact of side effects on patients. Patients experience side effects in a blind trial, and thus believe they are taking the drug. These patients will then see their mental health improve because they expect it to. In fact, experiencing side effects is 96% correlated with experiencing improvement from antidepressants. This is a very statistically significant finding.

On patients, I postulate that broken blinds should be equally prevalent or impactful in both industry and publicly funded trials, since patients are less conscious of who funds the trial. The same cannot be said of physician bias. What my paper seeks to explore is the role, if any, that side effects play in physician bias because of the role they play in a physician's ability to predict which patients are taking the drug vs. placebo. Possibly, physicians are hired for their capture; or they are captured by working for a pharmaceutical company. Either way, physicians would like to see the drug in testing work, and the question is how they might go about this. After controlling for other biases wherever possible, my paper hypothesizes that the remaining difference between industry sponsored and publicly sponsored trials is caused by captured physicians who, when the trial blind is broken, influence the results.

Capture is not corruption of physicians, so much as a product of the system they work within. Typically capture occurs because pharmaceutical companies have a wealth of resources to support research (money, data, contacts, etc.) and give those resources to researchers who support their cause. With capture, "the most popular and successful researchers will be those who cater to business" (Zingales 2013). Conscious or unconscious of the bias in their own work, physicians who cater to pharmaceuticals will be rewarded accordingly[20] Considering the incentives of physicians, it is clear their reporting may not be without bias.

Much of the actual empirical work in this paper is inspired by Oomstrom's paper "Funding of Clinical Trials and Reported Drug Efficacy". Among other things, Oomstrom's paper analyzes the impact of sponsorship on measured antidepressant efficacy, both for drug compared with placebo and a cross comparison between antidepressants. To a lesser degree, she also investigates the same in anti-psychotics. She finds that industry funded (sponsored) trials yield results about 36% more effective than the same trial publicly funded (unsponsored) (Oomstrom 2020). Oomstrom estimates 50% of bias can be explained by publication bias using changes in trial registration requirements. However, the remaining 50% is due to characteristics or selection invisible within her data.

2008 argue yes.

[19]Patients taking placebos who are unsure whether they are on the real drug or not can experience both side effects and real improvement due to their expectation of getting better.

[20]The Sunshine Act created database "openpayments.cms.gov" enables researchers to see some of this compensation (meals, transportation to exotic conferences, etc.) but it cannot capture the network effect–pharmaceutical companies ability to get papers published, and build networks.

This paper seeks to explain one of those characteristics invisible to her data: a physician's ability to break a blind, expecting physicians in sponsored trials to use this broken blind to yield more positive results for their benefactors. How this is done–whether consciously, by expectation bias, or some other unconscious capture factor–is not the subject of this paper.

2 Model

Publicly funded clinical trials do not experience a conflict of interest to the same extent privately funded trials do. For example, the sponsor of the trial does not have a strong financial interest in the outcome of the trial. Likewise, physicians are not conscious of being sponsored by a drug manufacturer while they report on patient improvement.[21] Only if doctors were on industry payroll would I expect capture to strongly influence their results. If on industry payroll, physicians would be inclined to inflate improvement of patients whom they suspect to be taking the sponsored drug.

Thus, a physician's report of patient improvement is based on a few factors. First, their report contains the actual effect the drug has had on patients. Second, if the trial is sponsored, the physicians ability to correctly identify patients taking the sponsored drug multiplied by how captured the physician is. Third, other forms of bias such as the placebo effect. How much greater a sponsored trial is than its unsponsored peers, is thus defined by how captured the physicians are multiplied by how easily they can identify treated patients. The capture may be driven by expectation bias (and companies hiring physicians with this bias) or by a conscious decision on the part of the physician (corruption).

The resulting model equation is:

$$Y_i = A_i + \beta \times Sp \times X_i + G \times X_i + \epsilon \tag{1}$$

where:

Y is the trial outcome.

Sp is an indicator for industry sponsored trial.

X_i is the difference in side effect profiles between drug and placebo or the two drugs being compared (an instrument for broken blind).

A is the actual drug efficacy.

β is the impact of broken blind through capture (exists only in industry sponsored trials).

G is the impact of broken blind on other biases (exists in all trials).

[21]It would be interesting to see whether in cases where the public good hinges on the outcome of a trial, where the physicians really are hoping this treatment will work, such as break through cancer treatments or COVID-19 vaccines, the difference in difference of efficacy was less intense since the physicians really did want the drug to work.

ϵ is the error term.

While it is important to understand the physicians decision making process, my data analysis is done at a drug trial(s) level. So, assuming the physicians of sponsored clinical trials are some level of captured, I want to investigate correlation between severity of side effects and difference in the effectiveness of pharmaceuticals between industry sponsored and publicly sponsored clinical trials.

This paper is trying to model the impact of capture on physician reported clinical trial results (through a mechanism of broken blinds). However, capture is not easily measured, and so I use side effects to measure broken blinds enabling the physician to exert his capture. I use mean difference between publicly funded clinical trials and industry funded clinical trials to estimate the impact of this capture on the clinical trial results.

When I compare sponsored and unsponsored trials, I get:

	True efficacy	**Capture**	**Other biases**
Sponsored drug v. placebo	A_{i_p}	$\beta \times X_{i_p}$	$G \times X_{i_p}$
Unsponsored drug v. placebo	A_{i_p}		$G \times X_{i_p}$
Difference in Difference		$\beta \times X_{i_p}$	
Sponsored drug v. drug	A_{i_p}	$\beta \times X_{i_p}$	$G \times X_{i_p}$
Unsponsored drug v. drug	A_{i_p}		$G \times X_{i_p}$
Difference in Difference		$\beta \times X_{i_p}$	

Table 1: This table shows how I expect sponsored and unsponsored trials get their resulting efficacies. They can be subtracted to get a regression relating the difference in differences to the capture bias with other factors subtracted out

Using a difference in difference model controls for the true efficacy of the drug, because it is subtracted out in the sponsored minus unsponsored result. Likewise, it controls for other biases which would be equally prevalent in both types of trials, even biases which are driven by side effects but present in both trials such as broken patient blinds driving the placebo effect. As a result, using the difference in difference allows me to better isolate physician capture, and regress it based on side effects.

Taking the difference in differences as the dependent variable, and subtracting out true efficiency and biases which are controlled for or present in both sponsored and sponsored trials, the resulting regression is:

$$Y_{Ii} - Y_{Gi} = \beta X_i + \beta_0 + \epsilon \tag{2}$$

where:

Y_{Ii} is the reported efficacy of drug i by the industry.

Y_{Gi} is the reported efficacy of drug i by the government.

X_i is the estimated difference between the side effects of the drug its competing drug or placebo, meaning how well a doctor would be able to identify this drug.

β is how much the side effects impact the trial outcome. My paper postulates β will be positive and significant if side effects break blinds and physicians are captured.

β_0 is the intercept in this model.

I also run a one sample two sided hypothesis test for correlation, with a null Hypothesis that $\beta = 0$. If this null hypothesis holds, then either physicians are not captured or that side effects do not enable physicians to identify patients who were taking the drug.

3 Data Sources and Data Set Construction

For this paper, I use data on the difference between public and industry sponsored trials, and data on the prevalence of side effects of each drug.

For data on the difference between public and industry sponsored trials – the Y_i values in my model – I use data generously provided to me by Tamar Oomstrom, which she uses in her paper (Oomstrom 2020) about the impact of sponsorship on antidepressant efficacy. The Oomstrom data is collected from primary source clinical trials results, with an entry for each drug in the trial. Her data is compiled from a meta analysis of double blind random controlled trials, using all available antidepressant data,[22] the earliest of which was from 1979, and continues through January 8, 2016. Her antidepressant data is sourced from Andrea Ciprani's 2018 paper "Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis", which sources its data from the Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature, Embase, Latin American and Caribbean Health Sciences Literature database, Medine, Medline In-Process, PsycINFO, the websites of regulatory agencies, and international registers for all published and unpublished, double-blind RCTs.

In her data, there are two types of antidepressant trials which are analyzed: Active vs. Placebo and Active vs. Active. In the former case, the drug is compared against the placebo, and clearly only the active drug can be sponsored. In the latter case, of Drug A vs. Drug B, Oomstrom analyses changes in the sponsorship of Drug A, holding the sponsorship of Drug B constant (sponsored or not). Note here that the actual numbers for efficacy are the difference between the sponsored drug and its competitor's (Drug B or placebo) efficacy rate in a sponsored and unsponsored trial of Drug A.

[22] Oomstrom 2020 also analyzes antipsychotics but those were dropped from this paper due to approximately 50% of the drugs analyzed not being reported on Daily Med.

Some of these trials are publicly sponsored while others are sponsored by one (or more) companies in the pharmaceutical industry. She analyses the same drug combinations, while varying sponsorship in order to get difference in differences values, one for each drug pair or drug vs. placebo which she has variation between industry sponsored and publicly sponsored. I use the Oomstrom data difference in differences results for anti depressants published in tables 2 and 3 of Oomstrom 2020, which are visible as figure 4 and figure 5 in the appendix of this paper. From her paper results, I am able to get estimates of the difference between industry and publicly sponsored trials by drug.

For drug side effects, I used publicly available outcomes of clinical trials posted on dailymed.nlm.nih.gov, the NIH sponsored database which provides physicians with information about drugs. In the case of all reported drugs, I used both the incidence of the side effect in the drug against the incidence of the same side effects in the placebo. All of these were recorded as percentages of the patient populations so they are better comparable between drugs.[23]

In this paper, I regress how different the side effects are between pairs of drugs against the difference in their found efficacy driven by industry sponsorship. However, in order to do this, I need a way to quantify how effectively the side effects of drugs would alert doctors to whether a patient is Drug A vs. Drug B (or placebo).

To quantify this, I group the side effect data reported on Daily Med into categories, and categorize each side effect accordingly. A full table of these categorizations and side effects is available in table 5 of the appendix.

Within each category, I added up the percentage of patients experiencing each side effect for Drug A, and subtracted the same sum of Drug B (or placebo). Then, I summed the absolute value of these differences over all categories, to get a resulting calculation of how common and different unique the side effects were between two drugs/drug and placebo. [24] [25]

[23]Data Notes: Trazodone data was from outpatients only; Paliperidone data is fixed dose data only; Clozapine only has cross studies available online so those were used; Lurasidone only includes impact on depression patients. My data had one outlier, Clomipramine, whose side effects were about 5x as bad as any other drug. I chose to omit this drug because I suspect it's side effects were reported somehow differently on Daily Med.

[24]Note: the data I used only includes side effects with higher instance in the drug than the placebo. The absolute values are unimportant here but were left in for the sake of consistency.

[25]I used the percentages as decimals meaning the resulting sum of percentages would be on the order of 1 rather than on the order of 100.

In cases of drug vs. placebo, I used the following calculation:

$$\sum_{j=1}^{m} \Big| \sum_{i \in E_j} D_i - P_i \Big| \tag{3}$$

where:

E_j is a category of side effect containing each i, which is a side effect.[26]
D_i is the instance of any side effect i in the drug.
P_i is the instance of the same side effect in the placebo.
m is the 11 categories I broke my data down into, see table 5.

For the cross section between two drugs, I performed a similar calculation with a few adjustments to better differentiate between two drugs:

$$\sum_{j=1}^{m} \Big| \sum_{i \in X_j} A_i - B_i \Big| \tag{4}$$

where:

E_j is a category of side effect containing each i which is a side effect.
A_i is the instance of any side effect i in Drug A.
B_i is the instance of the same side effect in Drug B.

Notice here that two drugs with different side effects within the same category would still have a low score, since a physician would likely have a hard time telling them apart.

As a result, two drugs that both induce a lot of gastrointestinal problems that would be hard to tell apart will have a low index number, whereas if one drug caused neurological problems and another caused gastrointestinal problems a doctor would find them easy to tell apart and the pair would have a high index number. Likewise, this method means the comparison of a drug which has rare instances of cardiovascular problems against one with none would gain a small increase in index score from this, since patients with cardiovascular problems would clearly be on one drug but the overall impact on the trial would be small since the side effect is rare.

One drawback of this measure is it treats the side effects as unrelated events. I am unable to find a covariance of side effects value to use in my paper. I expect that a patient who comes in with many side effects is a much more clearly broken blind than a patient coming in with a single condition. Having this covariance coefficient would heighten the effect of side effects on broken blinds since physicians would have a better idea of whether a patient is taking

[26]For example, E_j is gastrointestinal and i is vomiting; or E_j is cardiovascular and i is heart palpitations.

the drug. By not including it I have a conservative estimate of the influence of broken blinds on differences in differences.

Unfortunately, two drugs Oomstrom analyzes are not available on this data site.[27] As a result, I omit them in my analysis. This omission presents a slight selection bias in my data set, since these drugs would not be prescribed in the US because their efficacy is too low, or their side effect burden is too high. Since I analyze difference between industry and publicly sponsored efficacy, the true efficacy of a drug is less important, but it is possible that companies with inefficient drugs would have larger industry - publicly funded results since they would need results more positively skewed than an actually effective drug. Likewise, drugs whose side effects were quite severe would not be legalized in the US.

4 Findings

My final regression on the depression sample was of size 22. 5 of drug vs. placebo, and 17 on Drug A vs. Drug B. For each of the two data points, one input was the difference in reported efficacy between industry funded trials and publicly funded trials, drawing on 146 different trials. The difference in differences was calculated in Oomstrom 2020. The overall results of regression were:

	Full Sample	**Drug v Placebo**	**Drug v Drug**
Sample size	N=22	N=5	N=17
Slope	0.1911	0.134	0.2268
Intercept	-0.2117	-0.1132	-0.2729
Slope 95% CI	0.071-0.311	0.061-0.393	0.047-0.221
R-squared	0.354	0.889	0.361

Table 2: This table summarizes the results of regressing the difference in differences against their side effect metrics

The focus of this paper is a correlation of reasonable strength (given both x and y are instruments, and both of their quantities are estimates) and a positive coefficient. As can be seen in figure 1, the coefficient of determination is .35, meaning that 35% of variation in reported efficacy is correlated with the severity or difference of the side effects.

Moreover, for every unique category of side effect, a 100% instance of every side effect in one drug but not the other arm (drug/placebo) causes a .2 difference in reported efficacy. Additionally, the 95% confidence interval for beta is between 0.071 and 0.311.

[27]Reboxetine since it is not legal in the United States. Amitriptyline is visible on daily med but did not have precise side effect instance data. I am able to get the data from a different source to use in comparison against its placebo, but did not compare Amitriptyline with other drugs since this didn't seem a fair comparison.

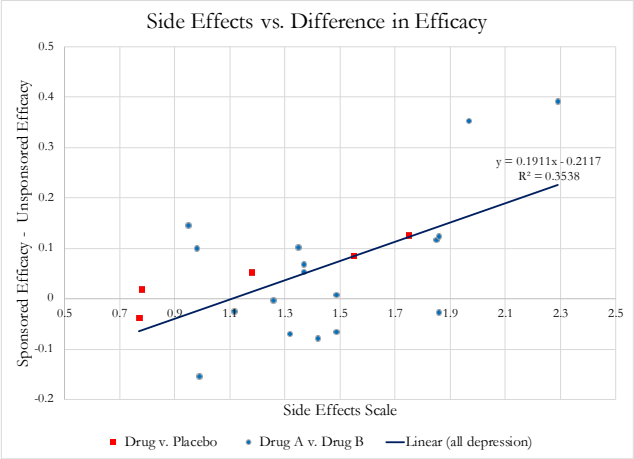

Figure 1: Scatter of side effects vs. the difference in efficacy between industry clinical trials and publicly funded ones, with one line of best fit.

It is worth noting that there is no pattern in the the position of the residuals of the regression. Moreover, their trend line essentially flat, meaning there is no clear heteroskedasticity within the data set. The residuals plot is figure 3 .

In figure 2 the Drug vs. Placebo data has a visibly lower error than a cross section between drugs. The R squared is .89 rather than .35. I suspect this may be due to the clear lack of side effects of a placebo, meaning doctors are less likely to make mistakes on whether a patient is taking a drug, than on figuring out what drug a patient is taking. However, I performed a t test between the two data sets, and found them insignificantly different. This means it is reasonable to regress the two data sets together, and treat them as one regression.

I also ran a significance test on the slope of my regression inspired by Zaiontz 2020.

$$H_0 : \beta_1 = 0 \tag{5}$$

The results of this test were significant. Significant results from this coefficient t test are important because they suggest a statistically significant relationship between side effects and difference in difference of clinical trials. Applying my capture and broken blinds theory, drugs in sponsored trials with greater instance of broken blinds will result in more positive differences due to captured physicians better being able to predict which patients are being treated with the sponsored drug. It is worth noting that all three data sets (combined, drug/placebo, and drug/drug) pass this Hypothesis test independently as well.

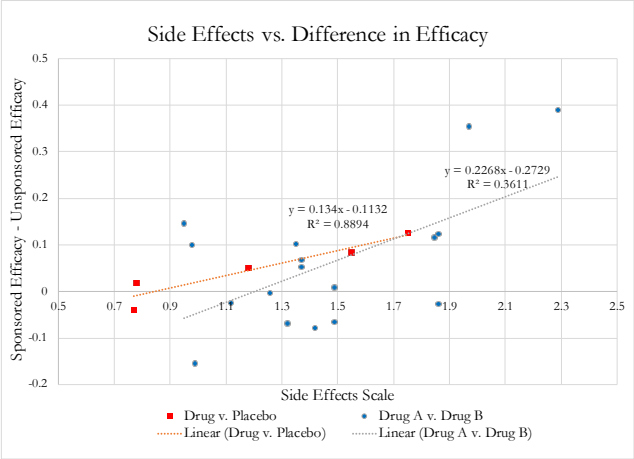

Figure 2: Scatter of side effects vs. the difference in efficacy between industry clinical trials and publicly funded ones, with lines of best fit for Drug vs. Placebo and Drug A vs. Drug B separated out

	Full Sample v. H_0	**Drug/Placebo v. Drug/Drug**
p-values	0.003	0.275
Significant?	yes	no
Slope CI	0.071-0.311	N/A

Table 3: This table summarizes the results of the two t tests performed in this paper. The left side summarizes the results of a t test against the full antidepressant sample of 22 drug pairs against the null hypothesis that the slope of this regression is zero, and get a significant rejection. The right hand side summarizes the results of a t test between the placebo/drug sample and the Drug A/Drug B sample which found the two are not statistically significantly different in a regression t test

5 Conclusion

5.1 Summary

There is strong evidence that clinical trials are biased according to the organization who pays for the trial, and therefore are an imperfect indicator of actual drug efficacy. This paper is based on two postulates: that physicians in industry funded clinical trials are captured and want the sponsored drug to work, more than physicians in unsponsored trials, and that side effects break the double blind and enable physician reports to be biased by this capture. The

pharmaceutical clinical trials explored in this paper were antidepressants. It is possible that alleviation of depression might be more challenging to quantify and thus more subject to physician bias making it a logical first clinical trial area to explore.

In order to do this, side effects were considered an instrument for broken blinds, since side effects are the way a physician might know whether a patient was taking the drug. The data for side effects was pulled from the NIH's Daily Med website which reports instance of side effects in one clinical trial for the use of physicians prescribing this drug. The precise calculation for a single number from a list of side effects and instances can be seen in equation (3).

The gauge for sponsorship bias was the difference between differences in the efficacy of drug A in sponsored trials and the efficacy of its competitor in clinical trials (drug B or placebo) less the difference between the efficacy of drug A in unsponsored trials and the efficacy of its competitor in clinical trials (drug B or placebo). In this way, the difference in how effective drug A is against competition is measured. This data was sourced from Oomstrom 2020.

A regression was done based on the model in equation (2) for the impact of a distinctive side effect profile for the study drug on the difference in efficacy found between sponsored and publicly funded trials of a certain drug. The most important findings of this paper were that there is a significant positive relationship between side effects and difference in reported efficacy found for drugs in sponsorship. The results of the regression can be seen in table 2, or that there is a positive relationship between side effects and difference in efficacy of clinical trials.

Parameter	**Results**
Slope: β	0.19
Intercept	-0.21
95% Slope CI	0.07 to 0.31
R^2	.35
$H_0 : \beta = 0$	reject
p-value	0.003

Table 4: This table is a summary of the main results from the paper

To summarize, there is a significant result that side effects have a positive impact on difference in difference. Using correlation ttests, this relationship was found to statistically significantly positive. It is also worth noting that the t-test between drug v placebo and cross drug analysis was found insignificant, and the residuals were sufficiently randomly distributed figure 3.

5.2 Directions for Future Work

This paper postulates that physicians in clinical trials are captured, and the double blinds which are supposed to control for this capture fail. These are concerning conclusions, since they lead to further questions about conflict of

interest. For example, consider a pharmaceutical company with the knowledge that side effects break double blind trials. Knowing that captured physicians are reporting on their drug in the clinical trial this company has sponsored, this pharmaceutical company might consider adding ingredients to enhance these side effects to better break blinds. Clearly, this paper is only the beginning of research into the question of how broken blinds impact clinical trial differences in sponsorship.

If given a longer time horizon, there is more work I would do using the same data set. The next step for this paper would be to weight the difference in efficacy numbers by the number of clinical trials/patient results backing each trial and rerun the regression. Since the difference in differences is an estimated term, and some differences have more data behind them than others, I would want to give terms which are more certain more weighting. Another potential experiment with the same data set would be to further explore the same theory, using drug trials rather than difference in differences. While difference in difference value allows me to control for the actual effect of the drug and other biases, it also makes the data set much smaller. I would be interested to know if broader patterns in the data set are consistent with my narrower result.

In the process of doing this paper, I explored using the antipsychotic data on Oomstrom 2020. However, approzimately half of the antipsychotic cross studies contained drugs not legal in the US and therefore not contained in the Daily Med database I used for side effects. Unable to use the full data set, and unable to find a correlation with the few drugs I did have, I abandoned the thin antipsychotic dataset and focused my efforts on the more robust depression data set. However, one way to build upon this paper, would be to analyze a different type of drugs to see if this correlation continues in other types of drugs.

The best way to build on this paper with addition information would be to find a dependence coefficient between side effects. It is quite unlikely that the side effects of drugs are entirely independent events. Moreover, a patient who comes to a doctor exhibiting a few side effects is much more clearly identifiable for whether/what drug they are taking than a patient who comes in complaining of only one side effect. To do this, one would need to dig into the primary source clinical trial data–much of which is sealed under hippa–to discover what the typical number and distribution of side effects a patient comes in with. Moreover, the coefficient would be more meaningful if the dataset were the expected number of patients a doctor could correctly identify, rather than just a summation metric of side effects–it would tell me exactly what percent of patients would have a different result based on their side effect profile.

It would also be interesting to see whether this capture coefficient has risen or fallen over time. It would be difficult to work around the endogeneity of publication bias on trials, but this would also be interesting to explore.

If able to get data at a patient by patient and doctor by doctor level, it would also be interesting to see whether some doctors were more responsive to patients exhibiting side effects for positive response or not–it is entirely possible that only a few doctors in an industry funded clinical trial need to be quite captured in order to boost the efficacy. Likewise, it would be interesting to see

how accurately doctors were able to guess whether a patient on a certain drug, if physician guesses was part of clinical trial reporting. Otherwise, experimenting to estimate these coefficients would be equally interesting for how efficiently given some number of side effects a doctor could guess between the two drugs which a patient was on. That would help researchers quantify the impact of capture better, or estimate how captured physicians as a whole are.

Also, as mentioned in a footnote, I would love to explore cases where the FDA might have a higher incentive (probably not a financial incentive, but public opinion) for a drug which would save many lives, and seeing if in cases of extreme need for a drug, the gap between publicly sponsored and privately sponsored drugs closes because the public entity wants the drug to succeed just as badly as the private company, thought for moral reasons rather than profit based ones.

There is a lot more research to be done into broken blinds in clinical trials, and their impact on the gap between industry funded and publicly funded trials. However, this might help to explain the divergence beyond other biases already explored.

There are also a few public policy implications of this paper. Firstly, is suggests that the NIH funding clinical trials is hugely important to ensuring clinical trials are good signals of drug efficacy. Since most clinical trials are outsources to Contract Research Organizations (CROs), I would suggest that the NIH take a closer look at these CROs or even investigate instituting some kind of control for the physicians who participate in clinical trials. Another approach to controlling for the issues in this paper would be to require public reporting of broken blinds when they occur. However, this again places the onus of reporting on the same physicians whose unbiased reporting this paper questioned, so the benefits of this solution are unclear. There is certainly some policy exploration to be done from this paper to ensure clinical trials are pure measures of drug efficacy.

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6 Appendix

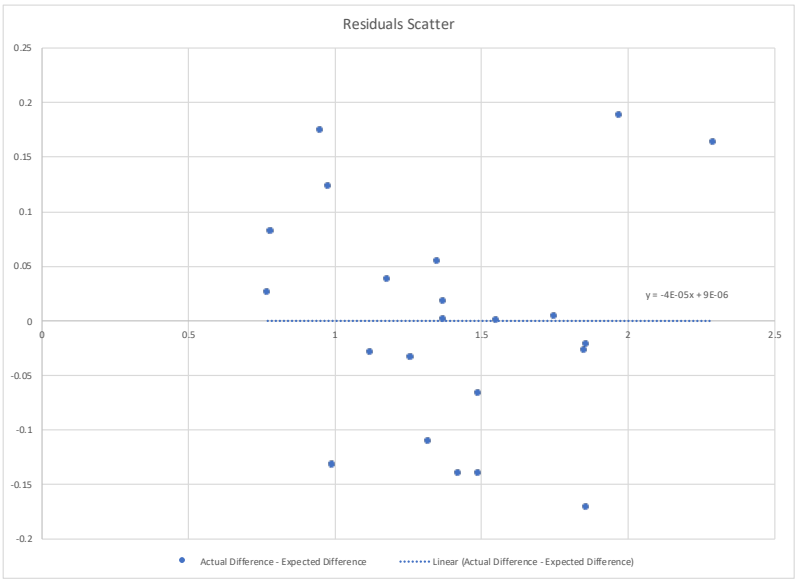


Figure 3: Scatter of residuals from regression, the x axis is the side effect scale, and the y axis is how much the residuals deviate from the model.

Table 2: Difference in Difference: Active versus Placebo Studies

	Sponsored				Not Sponsored				
	Share Respond				Share Respond				
	Drug	Placebo	*Diff*	# Papers	Drug	Placebo	*Diff*	# Papers	DD
All Studies	0.491	0.303	0.188	59	0.441	0.301	0.140	8	0.048
Paroxetine	0.469	0.320	0.149	32	0.250	0.226	0.024	1	0.126
Sertraline	0.453	0.360	0.093	12	0.476	0.433	0.042	2	0.051
Citalopram	0.513	0.399	0.114	8	0.303	0.209	0.095	1	0.019
Trazodone	0.458	0.158	0.300	6	0.568	0.353	0.215	1	0.085
Amitriptyline	0.564	0.278	0.286	1	0.607	0.282	0.325	3	-0.039

Notes: Table presents the difference-in-difference estimate of the sponsorship effect for "Active vs. Placebo" studies. 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 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.

Figure 4: Figures from Oomstrom 2020 which shows her calculation differences of differences for drugs vs. placebos based on sponsored and unsponsored trials.

Table 3: Difference in Difference: Active versus Active Antidepressant Studies

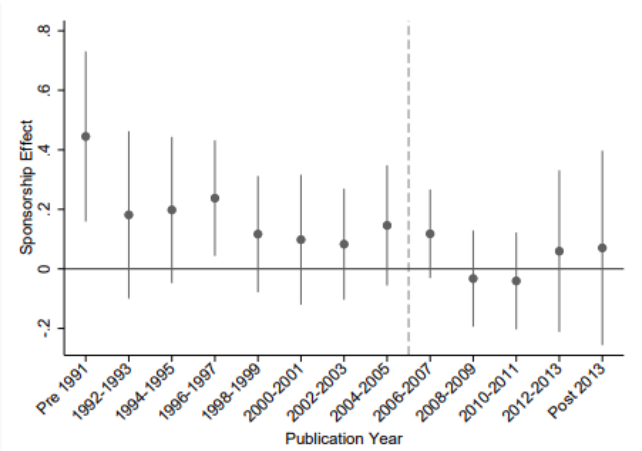
	Sponsored				Not Sponsored				
	Share Respond				Share Respond				
	Drug	Other Arm	*Diff*	# Papers	Drug	Other Arm	*Diff*	# Papers	DD
All Studies	0.640	0.595	0.045	56	0.560	0.578	-0.019	73	0.064
Amitriptyline vs. Paroxetine	0.658	0.648	0.010	1	0.465	0.474	-0.008	14	0.018
Amitriptyline vs. Fluoxetine	0.653	0.564	0.088	3	0.500	0.522	-0.022	10	0.111
Fluoxetine vs. Venlafaxine	0.764	0.745	0.018	1	0.587	0.636	-0.049	10	0.067
Venlafaxine vs. Fluoxetine	0.636	0.587	0.049	10	0.704	0.707	-0.003	1	0.052
Citalopram vs. Escitalopram	0.794	0.815	-0.021	6	0.639	0.760	-0.120	3	0.099
Paroxetine vs. Fluoxetine	0.525	0.473	0.052	7	0.683	0.565	0.119	1	-0.067
Clomipramine vs. Paroxetine	0.535	0.371	0.164	1	0.566	0.657	-0.091	5	0.255
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
Sertraline vs. Venlafaxine	0.549	0.628	-0.079	1	0.570	0.622	-0.052	2	-0.028
Amitriptyline vs. Citalopram	0.650	0.625	0.025	1	0.516	0.548	-0.031	1	0.056
Clomipramine vs. Venlafaxine	0.672	0.533	0.139	1	0.400	0.577	-0.177	1	0.316
Fluvoxamine vs. Milnacipran	0.537	0.660	-0.123	1	0.571	0.702	-0.130	1	0.007
Paroxetine vs. Bupropion	0.395	0.400	-0.005	1	0.507	0.507	-0.000	1	-0.005
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
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: Table presents the difference-in-difference estimate of the sponsorship effect for "Active vs. Active" studies. The first set of columns compares the share of patients that respond to treatment when the first listed drug is sponsored; the next set compare the share of patients that respond 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 share of patients that respond to a given drug and the share that respond to 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.

Figure 5: Figures from Oomstrom 2020 which shows her calculation differences of differences for drugs A vs. drug B based on sponsored and unsponsored trials.

Figure 6: Introduction of Clinical Trial Pre-registration

(a) Sponsorship Effect by Calendar Year



(b) Treatment Intensity by Calendar Year

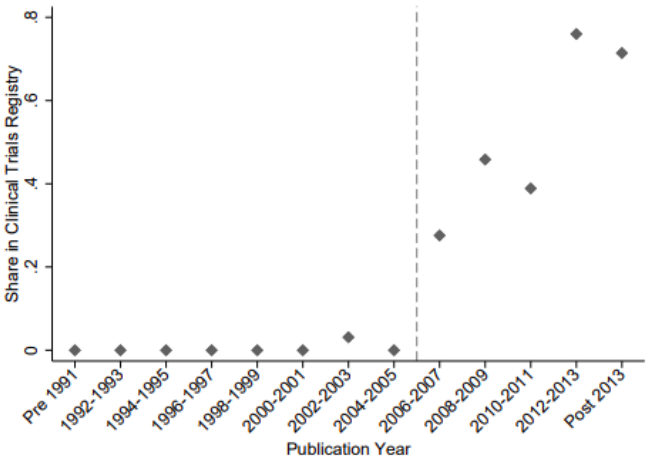


Figure 6: Figures from Oomstrom 2020 which discuss the impact of sponsorship before and after FDA regulation was implemented requiring registration pre-clinical trial, and result publication on clinicaltrials.gov following completion of trials.

CATEGORY	SIDE EFFECTS CONTAINED
GENERAL DISORDERS	Chest pain Chills Chest discomfort Flu syndrome/influenza Syncope/faiting/orthostatic hypertension Fatigue Fever
GASTROINTESTINAL DISORDERS	Nausea Constipation Vomiting Dry mouth Indigestion Abdominal pain/Gastrointestinal disorder Gastroenteritis decreased appetite/increased Tooth disorder Diarrhea Dyspepsia Flatulence Oropharynx disorder/Dysphagia /Trouble swallowing Salivary Hypersecretion Weight loss/gain
NERVOUS SYSTEM DISORDERS	Headache Dizziness Migraine Paresthesia Libido Decrease confusion drugged feeling/lightheadedness/sedation Thinking abnormally nervousness Extrapyramidal disorders/Myoclonus somnolence/drowsiness Tremor Hypoesthesia/Akathisia/restlessness Twitching/ Dystonia/muscle spasms/seizures Hypertonia/dystonia Bradykinesia central nervous system stimulation Tension headache
PSYCHIATRIC DISORDERS	Insomnia sleep disorder Abnormal dreams Trauma/ Psychosomatic disorder Depersonalization Agitation /restlessness Anorexia emotional lability/emotional volatility/altered mood Abnormal gait/ataxia concentration decrease Articulation impairment/speech disorder/Dysarthria irritability memory decrease/impairment Asthenia depression schizophrenia Anxiety

CATEGORY	SIDE EFFECTS CONTAINED
RESPIRATORY SYSTEM DISORDERS	Rhinitis Cough increased Sinusitis Dyspnea/shortness of breath/bronchospasm yawn respiratory tract infection epistaxis/bloody nose Pharyngitis/sore throat/dysphagia /Pharyngolaryngeal pain/Nasopharyngitis
MUSCULOSKELETAL DISORDERS	Myopathy/muscle stiffness/rigidity Myalgia/aches and pains Myasthenia Extremity pain (other than joint) Joint pain/Arthralgia Ecchymosis/bruising Back pain/neck rigidity Accidental injury/incoordination /psychomotor retardation Peripheral edema/edema
CARDIOVASCULAR DISORDERS	Hot flush Hypertension/Hypotension Postural hypertension Flushing Vasodilatation Palpitations Tachycardia
SENSE DISORDERS	Abnormal vision Tinnitus/Ringing in ears Mydriasis/Pupils dilation/Vision defect Taste perversion/ Dysgeusia Amblyopia Vision Blurred/Abnormal Lacrimation (tears)
SKIN DISORDERS AND INFECTIONS	Hyperhidrosis/sweating Rash/acne urticaria/hives/Dermatitis dry skin purpura/spots/application site irritation Pruritus Infection
GENITAL DISORDERS	Ejaculatory Disturbance/disorder/delay ejaculation failure/impotence/abnormal orgasm Other Male Genital Disorders(including ED) Urinary/Micturition Frequency Urination Disorder /impaired /Micturition disorder/hesitation urinary retention Urinary incontinence cystitis Urinary tract infection Dysmenorrhea/period made worse/menstrual disorder Female Genital Disorders /orgasm disturbance /anorgasmia/vaginitis Lactation nonpuerperal/Brest pain
INVESTIGATIONS	Heart rate increased leukopenia/hepatic enzyme increase Blood pressure increased

Table 5: This table breaks down my categories of side effects into the individual side effects which make up each category.

Parameter	**Whole Sample**	**cross section**	**drug v. placebo**
n	22	17	5
r	0.595	0.601	0.943
σ_x	0.402	0.382	0.443
σ_y	0.129	0.144	0.063
β	0.191	0.227	0.134
σ_{yx}	0.106	0.119	0.024
σ_β	0.058	0.078	0.027
t	3.309	2.912	4.912
df	20.000	15.000	3.000
p value	0.003	0.011	0.016
α	0.05	0.05	0.05
t crit	2.086	2.131	3.182
significant?	yes	yes	yes
CI 95% upper	0.311	0.393	0.221
CI 95% lower	0.071	0.061	0.047

Table 6: This table breaks runs the ttest of H_0 defined in equation (5) for each data set separately as well as together. Note that the ttset showing that cross section and drug v. placebo are not statistically significantly different can be found at table 3.