

EVALUATING DETAILING PAYMENTS AS A POTENTIAL DRIVER OF
BENZODIAZEPINE PRESCRIBING BEHAVIOR

By

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ABSTRACT

Benzodiazepines are a psychoactive drug class used to treat anxiety, insomnia, and more. While they have a relatively uninteresting prescription pattern when viewed in isolation, their co-prescription rates with opioids are rising. This pattern is associated with increased risk of abuse and mortality in patients and is against public health guidance. To date, detailing payments made from pharmaceutical manufacturers to physicians have not been investigated as a potential driver of benzodiazepine prescription. This study uses the Open Payments database to offer a descriptive analysis of detailing payments made to psychiatrists between 2014 and 2019, a new contribution to pharmaceutical marketing literature. This study argues that detailing payments are unlikely to be drivers of trends in benzodiazepine prescription and benzodiazepine-opioid co-prescription, though further investigation into within-physician effects and different specialties should be pursued. Policymakers, public health officials, and researchers in the field may be interested in the findings.

INTRODUCTION

Benzodiazepine prescriptions continue to increase in the United States, as do rates of benzodiazepine-opioid co-prescription. This trend persists despite regulators' and public health officials' concern about their misuse and their explicit guidance against benzodiazepine-opioid co-prescription. It is likely that a several factors are driving these trends in benzodiazepine prescriptions, among which are variables that routinely explain prescribing behavior across all drug classes. One such variable is pharmaceutical marketing, specifically the use of detailing payments while promoting a drug. "Detailing payments" refers to a marketing technique in which representatives of a pharmaceutical company provide "gifts, information, samples, trips, honoraria and other inducements... to physicians in order to encourage them to prescribe their drugs" (King and Bearman 2017).

Research has demonstrated that pharmaceutical industry detailing payments to physicians are positively correlated with increases in physician prescribing in the United States (Carey et al. 2020). Furthermore, a study in France found that doctors who received as little as a €10 gift associated with benzodiazepine marketing had statistically significant higher levels of benzodiazepine reimbursements in comparison to those who didn't receive a gift (Lagnaoui et al. 2004). To date, no research has specifically investigated whether detailing payments could similarly affect benzodiazepine prescribing behavior in the United States.

This project aimed to evaluate whether detailing payments related to benzodiazepines are likely to explain prescribing behavior for benzodiazepines. Detailing payments related to benzodiazepines are defined as those which are attributable to a benzodiazepine or a selective serotonin reuptake inhibitor, a common benzodiazepine substitute. Previous research suggests that

payments for benzodiazepines will increase prescribing behavior and payments for substitutes will decrease prescribing behavior.

The first audience that will benefit from these findings are public health officials. A more comprehensive understanding of the drivers behind the trend in benzodiazepine-related overdoses will better inform the solutions developed to combat them. Similarly, policymakers concerned about benzodiazepine-related overdoses stand to gain something from this research. This project's findings may help justify existing or new legislation controlling detailing payments in accordance with public health concerns. Pharmaceutical marketing executives may be interested in this research, as well as researchers whose work centers on or is implicated by the effect of detailing payments on prescribing behavior.

LITERATURE REVIEW

Why benzodiazepines?

Benzodiazepines are a psychoactive drug class commonly used as treatment for anxiety, though they are also approved as treatment for insomnia, seizures, alcohol withdrawal, and other afflictions. The first benzodiazepine, Librium, was discovered in 1955 and made commercially available in 1960. Several other brand name benzodiazepines followed, including Valium, Xanax, Klonopin, and more. Seventeen years after the introduction of Librium, benzodiazepines became the most prescribed drug class in the world. By and large, benzodiazepines' popularity owed itself to the drugs' broad set of approved indications and relative safety—that is, when they are prescribed correctly. (Balon et al. 2020)

Benzodiazepines generally work best when prescribed over the course of a few weeks. Long-term benzodiazepine use is associated with a various adverse health effects ranging from physical dependence (Lader, Tylee, and Donoghue 2009) to increased risk of dementia

(Penninkilampi and Eslick 2018). Benzodiazepines also work best when taken without other depressants. When taken in combination with alcohol or other depressants, benzodiazepines can cause severe and potentially fatal respiratory depression (Fraser 1998). This risk is especially prominent in cases of benzodiazepine-opioid co-prescription.

From 1999 to 2019, nearly half a million Americans have overdosed and died using either an illicit or prescription opioid (“Understanding the Epidemic” 2021). Opioid overdose deaths per capita continue to rise year-on-year, as do the desires of all Americans to see this crisis resolved. Benzodiazepine prescriptions and abuse are also on the rise, though these trends are much lower profile than those concerning opioids (Agarwal and Landon 2019). Benzodiazepines generally have a reputation as safe, effective treatments, and have consequently escaped mainstream scrutiny. Increasingly, however, researchers are investigating the ways in which benzodiazepine prescriptions interplay with opioid overdose deaths within the United States.

Research has demonstrated that the mortality risk associated with benzodiazepine-opioid co-prescription is higher than that of prescriptions for either of the drugs on their own (Xu et al. 2020). It is currently against public health guidance for physicians to prescribe benzodiazepines to an opioid user and vice versa. Despite this, the prescription of both drugs individually and in combination are on the rise (Rhee 2019).

Though this growth is higher within the population of patients 65 years of age or older, it is also observed across the total population (Brett et al. 2018). From 2003 to 2015, the rate at which physician visits noted a benzodiazepine or opioid quadrupled, growing from 0.5% to 2%. The co-prescribing rate of benzodiazepines with opioids and other central nervous system depressants nearly tripled across the same period, growing from 1.0% to 2.9%. All in all, it is estimated that benzodiazepines were co-prescribed in 19.2% of visits in which there was also an opioid, and

opioids were co-prescribed in 26.4% of visits in which there was also a benzodiazepine in 2015. Though it is unclear whether these trends generalize globally, benzodiazepine, opioid, and benzodiazepine-opioid prescriptions are on the rise within the United States. (Agrawal et al. 2019)

Unfortunately, this increase in prescription rates is associated with an increase in mortality rates. From 1999 to 2016, benzodiazepine-related mortality increased from 0.6 deaths per 100,000 people to 4.4 deaths per 100,000 people (Agrawal et al. 2019). Given the way the drugs interact and the trends in prescription data, the consensus amongst the literature is that the increase in benzodiazepine-opioid co-prescription is likely driving the increase in benzodiazepine-related mortality.

Why detailing payments?

If co-prescribing these two drugs is against public health guidance and worsens mortality, then why are rates of co-prescription rising? It is likely that no one thing explains this trend, and researchers have only just begun to explore potential factors. Patients with anxiety disorders have benzodiazepine prescriptions at double the rate patients without anxiety disorders do, and patients with a mood disorder have benzodiazepine prescriptions at quadruple the rate patients without mood disorders do (Lagnaoui et al. 2004). Polypharmacy status and chronic care visits are also associated with higher rates of co-prescription, as is being younger and female (Rhee 2019).

All these analyses have used patient attributes to explain prescribing behavior. It is well-established, however, that there are variables completely removed from patients that also explain physicians' prescribing behavior. One such variable is the marketing of prescription drugs.

Broadly speaking, the marketing of a drug is positively associated with its prescription. Research has demonstrated the effectiveness of several marketing practices as a means of influencing prescribing behavior, including direct-to-consumer advertising, drug coupons, and

detailing payments (Carey, Lieber, and Miller 2020). In the pharmaceutical industry, detailing payments are those payments made from a manufacturer to a physician during one-on-one sales interactions. These payments include consulting fees, gifts, entertainment, meals, speaking fees, charitable contributions and more. Estimates widely vary as to how much the pharmaceutical industry spends on detailing per year, as studies vary in how broadly they define the marketing technique (e.g., some studies include the value of free samples in their calculations of detailing payments whereas others do not). It is generally agreed, however, that the value of yearly detailing payments within the United States routinely exceeds tens of billions of dollars (King et al. 2017).

The pharmaceutical industry spends so much on detailing payments because of their ability to consistently increase the prescription of drugs. Detailing has been called the most effective promotional marketing instrument available to pharmaceutical companies, as even small payments have a statistically significant effect on prescribing behavior (Iyer, Derman, and Sanhu 2016). All in all, one study estimates the return-on-investment for detailing payments to be 10-to-1 for new branded drugs and 2-to-1 for all drugs (Schwartz and Woloshin 2019).

There is a clear conflict of interest for physicians accepting these payments (Appelbaum and Gold 2010). The prescription of drugs according to financial incentives as opposed to a medical appropriateness presents issues for patients. No patient would want to be prescribed a drug that (s)he does not need, nor would he want a drug that is suboptimal for his needs. Less obvious though is the economic burden placed on these patients because of detailing. Studies have shown that physicians who receive detailing payments routinely incur higher medical costs than those who do not. One paper estimates that “a 10% or \$25 increase in annual industry payments would be associated with approximately \$1,100 higher medical costs and \$100 higher drug costs” (Meija, Meija, and Pestilli 2019).

Because of these health and financial concerns, legislation has been passed to implement oversight on detailing payments to physicians. Arguably most significant legislation was the Physician Payments Sunshine Act of 2010 (PPSA), passed as part of the Affordable Care Act. The PPSA requires drug manufacturers and medical device companies marketing products in the United States to report all detailing payments greater than \$10 in value (Perlis and Perlis 2019). Along with the value of the payment, the manufacturers need to report to whom they made the payment, what the payment consisted of (e.g., a meal, speaking fees, etc.), when the payment was made, for what product the payment concerned, and more. All this data is publicly available through the Open Payments database.

Much work has been done on detailing payments since the publication of this database in 2013. Within the literature, there is a particular emphasis on opioids and prescription stimulants, two commonly abused drug classes that currently include high-profile, brand-name products (Hadland et al. 2017, Hadland et al. 2020). No study has used the database to investigate what benzodiazepine detailing payments look like in the United States, let alone their development over time. This study aimed to accomplish both and use those findings to judge whether detailing payments could drive prescribing behavior.

METHODS

Data Source

In response to demand for greater oversight of detailing payments, the Obama administration passed the Physician Payments Sunshine Act of 2010 and in doing so created the Open Payments national disclosure program. From 2013 onwards, all detailing payments made from all drug manufacturers to all physicians (so long as they are not residents or employed by the manufacturer) have been recorded and published in a publicly available database. The data in Open

Payments is both granular and far-reaching; all detailing payments of at least \$10 in value are included in the database, accompanied with information about the physician that accepted the payment, the product the payment concerned, and in what form the payment came (e.g., a meal, speaking fees, etc.). Because of its scope and detail, many studies on pharmaceutical marketing use the Open Payments program as a detailing payments data source. This project followed suit out of a desire to be consistent with the literature and to use the most comprehensive data available.

Analysis

This project employed the use of R statistical software to analyze the Open Payments data between 2014 and 2019. These years were selected for two reasons. The earlier bound was selected because pharmaceutical marketing literature already contains several analyses of Open Payments data through 2013. This is likely a reflection of the heightened interest in the data during its first years of being available to researchers. The later bound was selected to prevent COVID-19-related impacts from skewing the results of the analysis. These impacts are not yet well-defined in the literature, though they are likely to have been severe. A surface-level look at payments in 2019 and payments in 2020 show that detailing payments nearly halved in frequency. Further investigation into the effect of COVID-19 on detailing payments to physicians is necessary.

The intended design of this project was a difference-in-difference design to discern the causal effect of detailing payments on benzodiazepine prescriptions and benzodiazepine-opioid co-prescription. After some exploratory data analysis, this design had to be scrapped because detailing payments for benzodiazepines and their substitutes are nearly non-existent. Figure 1 records the number of physicians receiving at least one detailing payment for an SSRI or benzodiazepine product listed as a commonly prescribed medicine for anxiety disorders by the Anxiety Disorders Association of America for a given year. No physician received a detailing

payment for any benzodiazepine product between 2014-2019, and no more than 10 received a detailing payment for any SSRI product across the same period.

Before asking to what extent payments can explain the prescribing of benzodiazepines and other psychoactive drugs, current trends in payments for these drugs must be better understood. This project consequently turned its focus to descriptive analysis of detailing payments between 2014 and 2019, something not yet present in pharmaceutical marketing literature.

Analyzing all detailing payments was too broad of an effort to trace back in any meaningful way to benzodiazepine prescription. After considering a few ideas to narrow down the dataset, this project focused in on detailing payments made to psychiatrists. Psychiatrists were selected as a sub-population for a few reasons. Across all physicians, psychiatrists account for the highest share of benzodiazepine prescriptions in the United States outside of primary care providers (Santo et. al 2020). Psychiatrists also are particularly prone to detailing efforts because of their specialty:

The flexible boundaries of many psychiatric diagnostic categories, in the absence of definitive diagnostic tests, may encourage expansive definitions of affected populations and create opportunities for industry to promote treatments for people who would not previously have been seen as having a disorder... Relative exclusion of psychiatrists from providing psychotherapy—a consequence of many managed care approaches—may also continue to push the field toward a psychopharmacologic orientation. Finally, the existence of similar compounds with roughly equivalent levels of efficacy and similar side-effect profiles (e.g., the selective serotonin reuptake inhibitors) creates an incentive for companies to undertake extensive efforts to distinguish their products from essentially equivalent compounds. (Appelbaum and Gold 2010)

That said, there is a large trade-off here in terms of scope. The results of the following descriptive analysis should be limited in their extrapolation, and further investigation into detailing payments made to all physicians should be pursued.

The descriptive analysis was done along three dimensions: incidence, magnitude, and concentration. The incidence of detailing payments refers to how frequently they occurred. Quantifying the magnitude of detailing payments means to quantify how much pharmaceutical companies paid out to psychiatrists both on an individual and aggregated basis. Lastly, analyzing the concentration of detailing payments refers to analyzing the extent to which payments were concentrated in value to a smaller sub-population of psychiatrists.

RESULTS

Incidence

The number of psychiatrists receiving at least one payment over the course of the year steadily declined between 2014 and 2019. The number of psychiatrists receiving at least one payment peaked in 2014 at 23,346. By 2019, the number declined to 19,642. See Figure 2 for more details.

Relative to other specialties, payments to psychiatrists became slightly less frequent over time. In 2014, 3.73% of payments could be attributed to psychiatrists. By 2019, the number declined to 3.12%. See Figure 3 for more details.

Magnitude

On an aggregated basis, detailing payments to psychiatrists increased between 2014 and 2019. The total of industry payments to psychiatrists rose from \$50,397,807 in 2014 to \$58,652,395 in 2019, an increase of roughly 16%. Payments in 2019 declined slightly from a peak of \$59,011,080 in 2018. See Figure 4 for more details.

Relative to other specialties, the trend is less clear. The proportion of overall payment value attributable to payments made to psychiatrists increased between 2014 and 2019, though it took a sharp downturn in 2019. Regardless, this proportion has remained relatively small over time, never dropping below 2.38% or rising above 2.65%. See Figure 5 for more details.

Detailing payments to psychiatrists also rose on an individual basis. Payments were summed aggregated by physician over the course of the year to account for wide discrepancies in payment value by type. Both the mean and median cumulative payment value per physician increased over time. The average cumulative payment value increased from \$2,159 in 2014 to \$3,014 in 2019, a roughly 39.6% increase. The median increased from \$156 to \$168 over the same period. The discrepancy between the mean and median values are a result of the rightward skew of the distribution of payment values. See Figures 6 and 7 for more details.

Concentration

The mentioned rightward skew of the distribution of payment values is also apparent when analyzing the physicians who received the most detailing payments over the course of a year. Both the 90th and 99th percentile of cumulative payments per psychiatrist increased significantly between 2014 and 2019. In 2014, the 90th and 99th percentile of cumulative payments per psychiatrist were \$1,402 and \$42,627 respectively. In 2019, they were \$1,563 and \$70,972. This represents an increase of roughly 11% and 43% for the 90th and 99th percentiles respectively. See Figures 8 and 9 for more details.

Previous studies of detailing payments analyze the proportion of payments over \$10,000 in value relative to all payments as a way of measuring concentration. This can be done by quantity of payments and value of payments. In 2014, just 3.08% of psychiatrists received payments throughout the year totaling \$10,000 or more in value. Yet, the payments these psychiatrists

received made up 78.9% of the value of all detailing payments made to psychiatrists for that year. In 2019, these figures were 3.79% and 84.7%. While the growth of the number of physicians receiving \$10,000 or more in payments outpaces the growth of the value attributable to these physicians' payments, the overall landscape remains highly concentrated. See Figures 10 and 11 for more details.

DISCUSSION

This project used detailing payments made to psychiatrists can be used as a proxy to study marketing trends behind psychoactive drugs. These payments appear to be 1) decreasing in frequency, 2) increasing in magnitude, and 3) consistently highly concentrated in value among a few physicians. If detailing payments were to have a significant within-physician effects on prescribing behavior, we might expect to see that influence play out in a small number of physicians. Alternatively, detailing payments might exert an effect on prescribing behavior through targeted influencers within certain physician communities.

That said, detailing payments are unlikely to be drivers of benzodiazepine prescribing behavior. Between 2014 and 2019, no detailing payments were made to any physician in the United States. Detailing payments to benzodiazepines' main substitute, SSRIs, were few and far between and concentrated to no more than 10 physicians in a year. For this same reason, it is also unlikely that detailing payments are drivers of benzodiazepine and opioid co-prescription. More likely drivers of benzodiazepine-opioid co-prescription are patient attributes, such as polypharmacy status and chronic care visits. Further investigation with a more rigorous design and representative population should be pursued to confirm this.

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APPENDIX

Figure 1

Drug Class	Drug Name	Number of Physicians Receiving Detailing Payments					
		2014	2015	2016	2017	2018	2019
Benzodiazepines	Atvian	-	-	-	-	-	-
	Dalmane	-	-	-	-	-	-
	Klonopin	-	-	-	-	-	-
	Halcion	-	-	-	-	-	-
	Librium	-	-	-	-	-	-
	Restoril	-	-	-	-	-	-
	Serax	-	-	-	-	-	-
	Tranxene	-	-	-	-	-	-
	Valium	-	-	-	-	-	-
	Xanax	-	-	-	-	-	-
SSRIs	Celexa	1	-	-	-	-	-
	Lexapro	1	-	-	-	-	-
	Luvox	-	-	-	-	-	-
	Luvox CR	-	-	-	-	-	-
	Paxil	-	-	-	-	-	-
	Prozac	3	2	2	-	-	-
	Zoloft	5	2	1	-	-	-

Drugs selected from [the ADAA's medication guidelines](#).

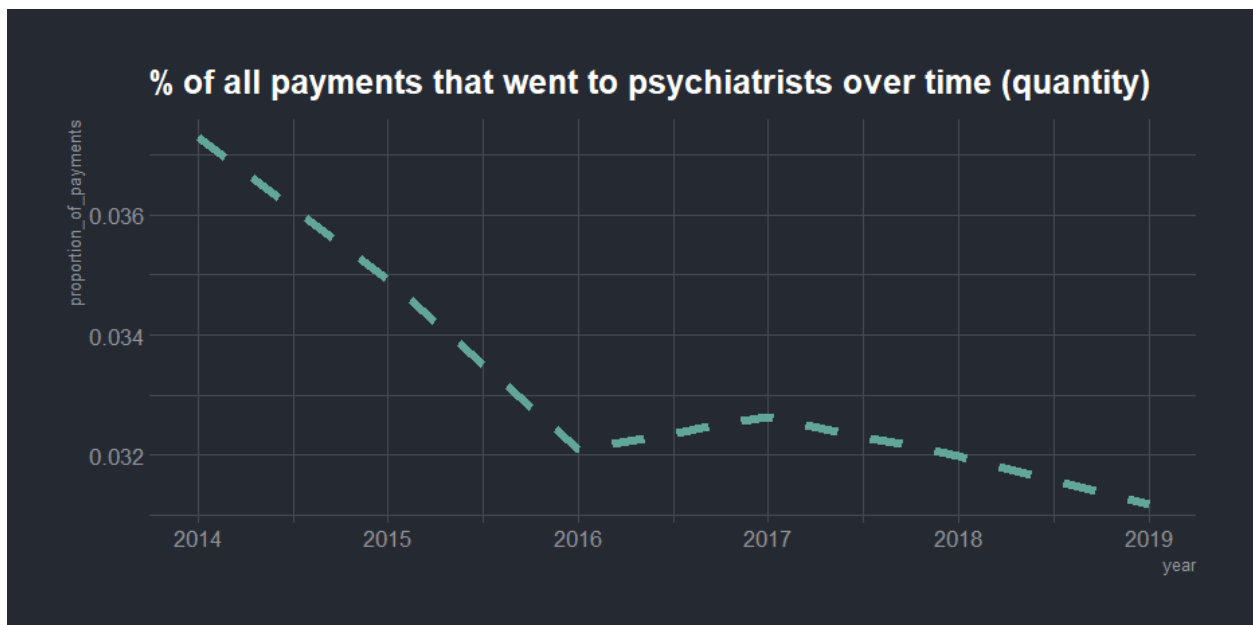
Figure 2**Figure 3**

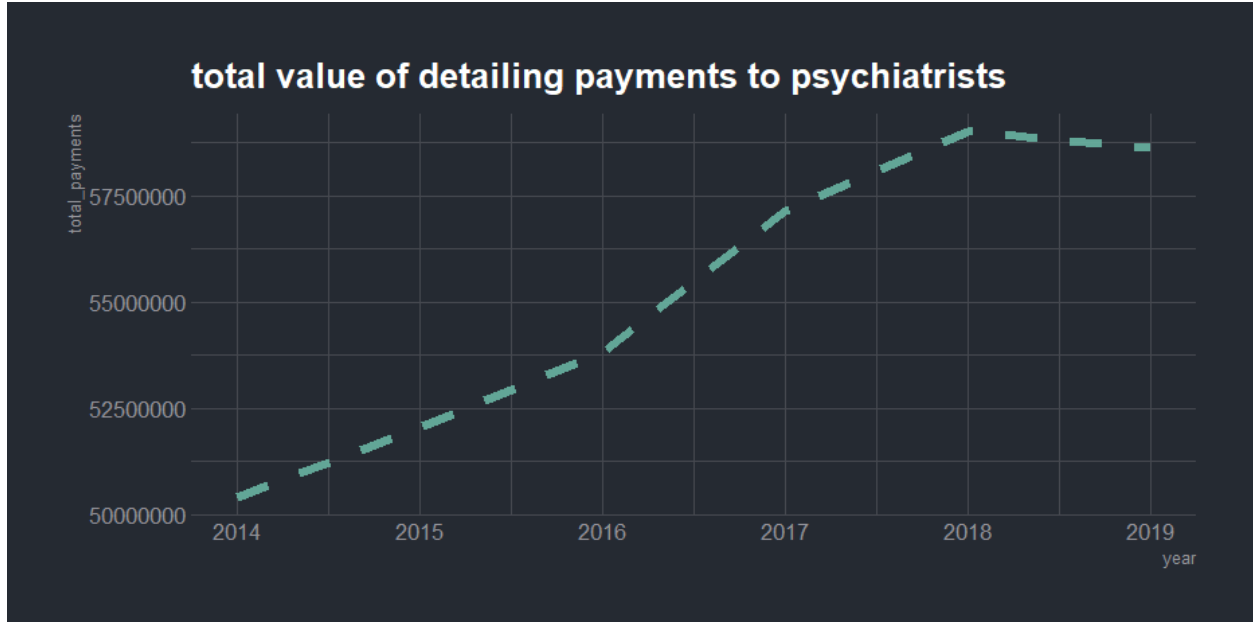
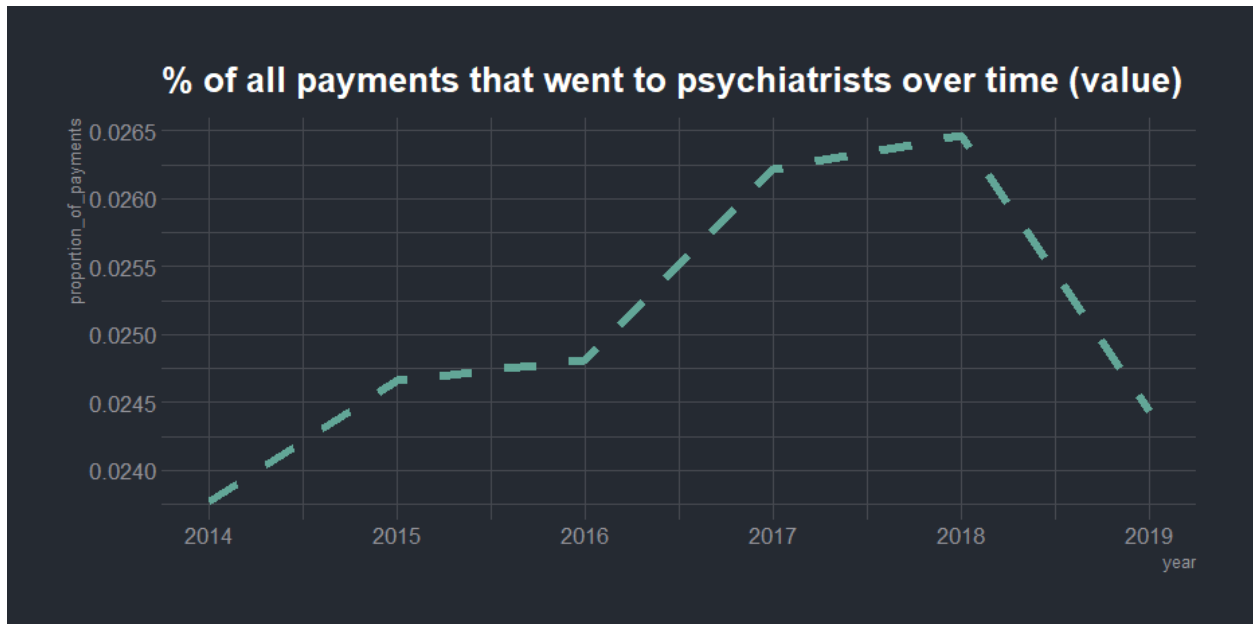
Figure 4**Figure 5**

Figure 6

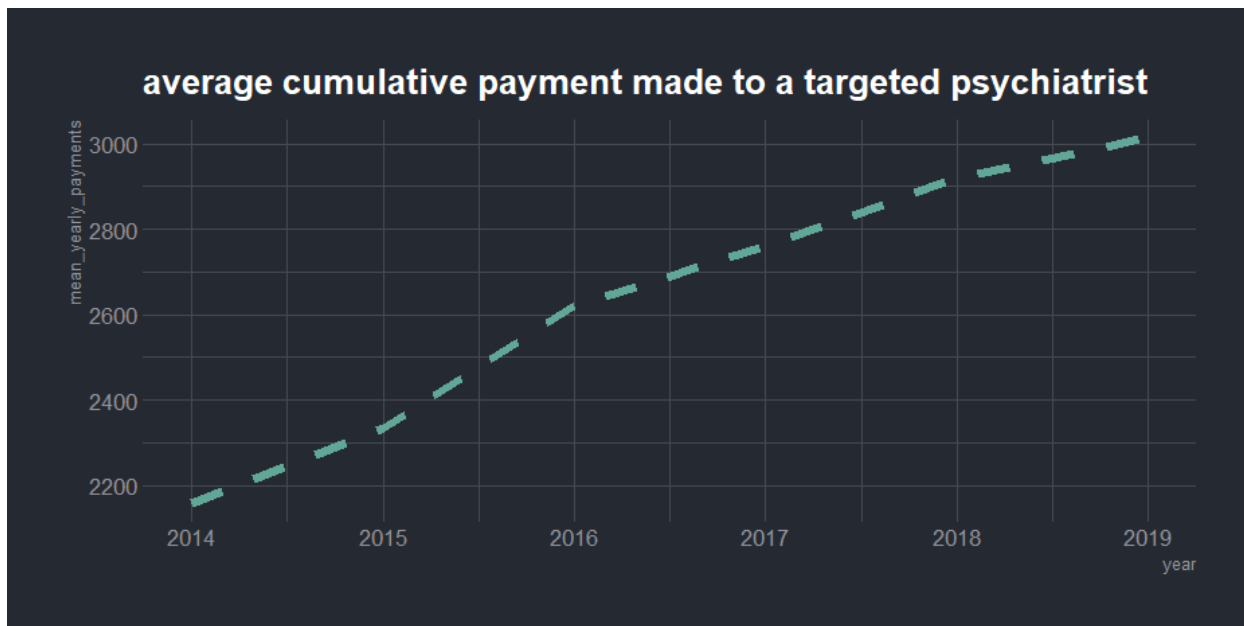


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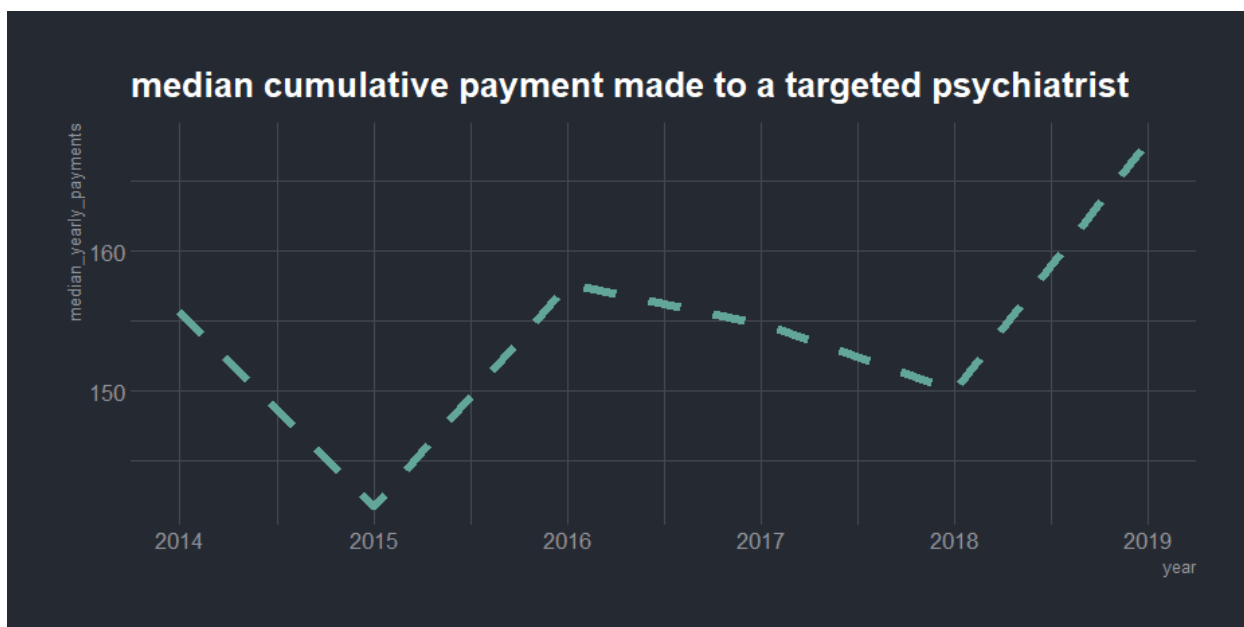


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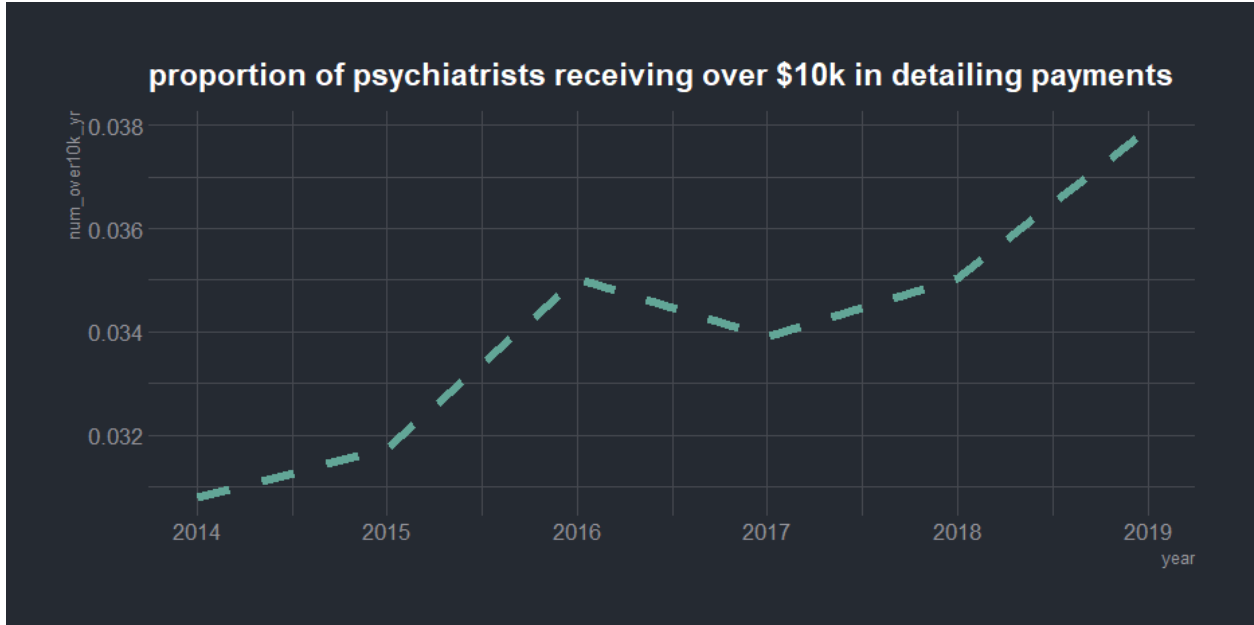


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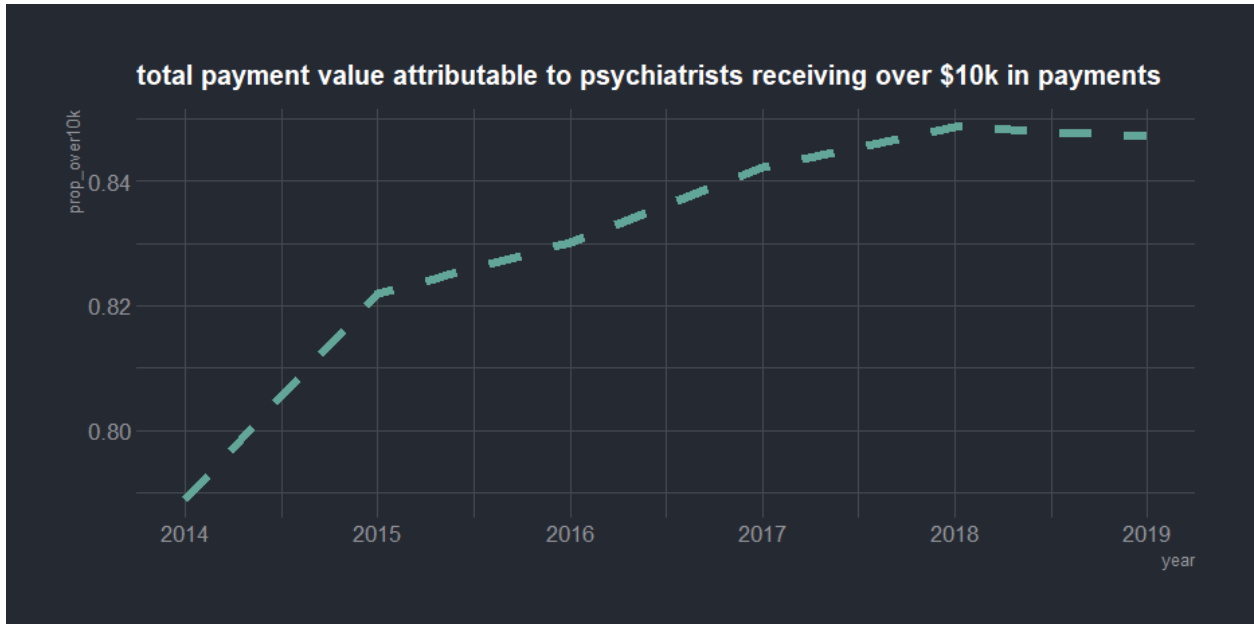


Figure 10



Figure 11

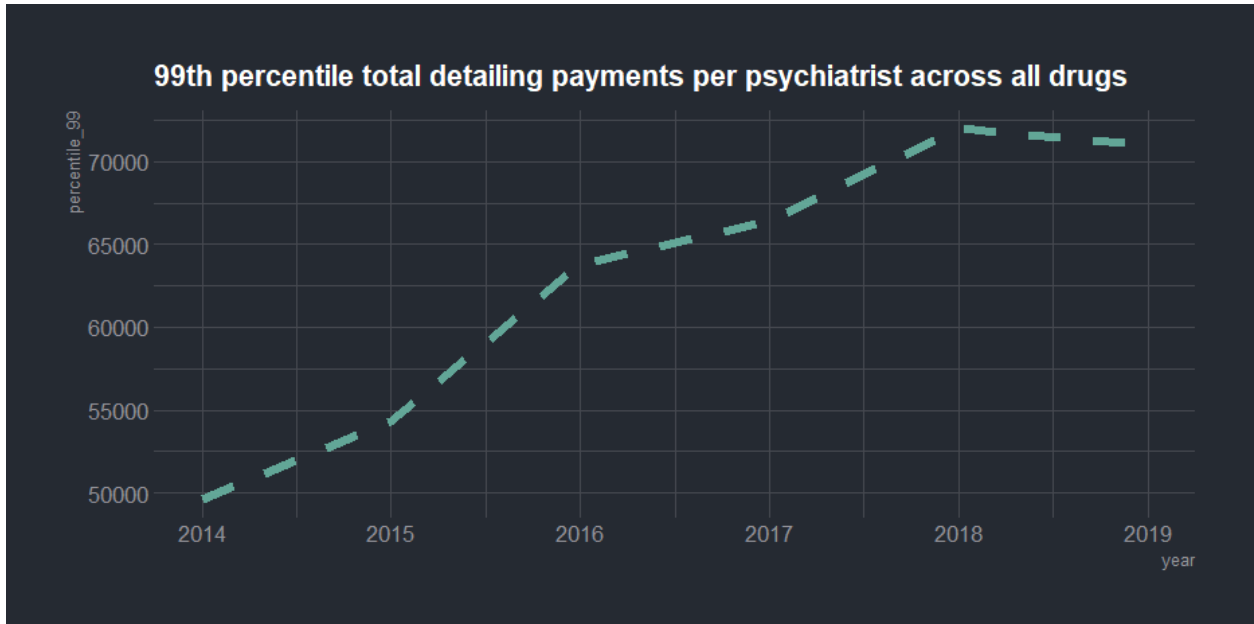


Figure 12

