Prespecification of Analyses for Peer Effects of Quetiapine Letters

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Version 1.0

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History

Version	Date	Notes
1.0	December 4, 2018	Initial pre-analysis plan.

1 Introduction

We describe an analysis plan for a study on the peer effects of informative letters that were sent to high-volume prescribers of quetiapine (branded Seroquel and Seroquel XR) in Medicare Part D. We may perform additional analyses in the course of the study; when analyses were not pre-specified in this document we will make note of that fact.

This study is a follow-up analysis of a previous randomized controlled trial (Sacarny et al 2018). In the original study, CMS identified 5,055 high-volume primary care prescribers of quetiapine. The prescribers were enrolled at a 1:1 ratio to a placebo arm (2,528 prescribers) or a treatment arm (2,527 prescribers). The placebo arm was sent a letter describing an unrelated Medicare regulation and later a correction letter. The treatment arm was sent three letters, each spaced approximately 3 months apart, stating that their prescribing of quetiapine was high relative to peers[1] and that it was under review by CMS. Letters to both groups were initially sent on April 20, 2015.

This follow-up analysis considers whether the intervention altered Medicare prescribing by peers of the original study participants. Peers are defined as either members of the same group practice as the original study prescribers or as those who share patients with original study prescribers.

The analyses will make use of public use aggregated Medicare claims data. The Medicare claims of the original study prescribers were already studied in Sacarny et al. (2018). At the time of writing, we have seen the Medicare claims data of the peers of the original study prescribers, but we have kept the treatment status of the original study participants blinded in these analyses.

The **primary outcome** of the study is the effect of the letters on the prescribing of quetiapine over the approximately 21 months following the initial sending of the letters.[2] Prescribing is defined as the total "days supply" of quetiapine attributed to the prescriber. See section 4.1 for more details.

Our analyses use public use Medicare Part D files provided by CMS for the years 2013-2016; Physician Compare group practice data archived immediately prior to the intervention (April 3, 2015); National Plan and Provider Enumeration System (NPPES) data archived prior to the intervention where available (March 2015, 2014, and 2013) and post-intervention data (March 2016 and 2017) for records that are missing in earlier files; and CMS Physician Shared Patient Patterns data for 2014.

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[1] In the letters, peers were defined as other quetiapine prescribers in the same state. For this study, our concept of peer effects uses a different definition of "peer" – other prescribers who share membership in a practice with or have referral relationships with original study participants.

[2] Specifically, we will look at outcomes through end-of-year 2016, an outcome duration of 20.5 months.

2 Identification of Prescriber Peers

The unit of analysis for peer effects is the peer prescriber of original study participants. In this section we outline how we will identify peers. We consider approaches using both the CMS Physician Compare data and the CMS Physician Shared Patient Patterns data.

2.1 Physicians in the Same Provider Groups

Our first set of peers will be other physicians in the same provider groups as the original study participants. To identify these peers, we will use the CMS Physician Compare dataset. The data is sourced from the Medicare enrollment file (Provider Enrollment, Chain, and Ownership System, or PECOS) and shows the groups to which providers reassign their Medicare payments.

2.2 Physicians Connected by Shared Patients

Our second set of peers will be physicians who share patients with the original study participants. To identify these peers, we will use the 2014 CMS Physician Shared Patient Patterns 30-day file, a pairwise-NPI-level dataset that indicates the number of patients shared between any two NPIs.

2.3 Peer Group Definitions

Using the aforementioned data sources, we will study all outcomes using the following peer group definitions:

Peer Group 1: Physicians who were in the same practice group as original study participants
Peer Group 2: Physicians who shared patients with original study participants

Preliminary summary statistics about the original study participants as well as the two peer groups can be found in Table 1.

2.3.1 Restrictions

To more accurately identify physicians who work together, we will only consider a physician a peer of an original study participant if the following conditions are all met:

- Is in the same practice ZIP code as the original study participant, according to the NPPES
- Prescribed any quetiapine in 2014
- Was not an original study participant

Table 1: Preliminary Summary Statistics about Original Participants and Peers

	(1)		(2)	(3)
	Original Study		Peers, by peer group definition	
	Prescribers		Same Practice	Shared Patients
Primary Taxonomy		Primary Taxonomy		
General Practice	0.046	General Practice	0.004	0.010
Family Medicine	0.478	Family Medicine	0.378	0.355
Internal Medicine	0.470	Internal Medicine	0.356	0.297
Psychiatry	0.001	Psychiatry	0.080	0.070
Other	0.005	Other	0.182	0.269
Any Psychiatry	0.003	Any Psychiatry	0.084	0.074
Days Supplied of Antipsychotics		Days Supplied of Antipsychotics		
Quetiapine	4,109 (3,634)	Quetiapine	1,574 (2,150)	2,164 (3,607)
Other Atypical	3,491 (5,413)	Other Atypical	1,746 (4,477)	2,823 (7,627)
Typical	498 (1,250)	Typical	249 (1,032)	478 (2,008)
Peers in Same Practice Sample		Peers in Original Study		
Total	2.0 (4.3)	Total	1.4 (0.8)	1.3 (0.8)
Peers=0	0.545	Peers=0	0.000	0.000
Peers=1	0.142	Peers=1	0.759	0.779
Peers=2	0.084	Peers=2	0.165	0.157
Peers=3	0.053	Peers=3	0.049	0.039
Peers=4+	0.176	Peers=4+	0.027	0.026
Peers in Shared Patients Sample				
Total	2.4 (3.3)			
Peers=0	0.372			
Peers=1	0.176			
Peers=2	0.128			
Peers=3	0.084			
Peers=4+	0.239			
N	5,055	N	7,563	8,989

All statistics are means; standard deviations in parentheses. Taxonomy derived from NPPES file. Days supply of antipsychotics derived from 2015-2016 CMS Part D public use data. 'Same Practice' peers identified from CMS provider enrollment data as represented in the Physician Compare public use file. 'Shared Patients' peers identified from CMS shared patient data. See text for more details.

3 Overview

In this section we lay out our regression specifications, including functional form and the sets of statistical controls that will be used in the analyses.

3.1 Peer effects regression

Here we consider the prescribing behavior of the peers of the original study prescribers (we call the unit of analysis the "peer analysis subjects"). These physician level regressions will be of the form:

$$y_i = \alpha + \beta \mathrm{I}(t_{-i} > 0) + \kappa_{s_{-i}} + X_i \Gamma + \varepsilon_i$$

Where *i* indexes peer analysis subjects and *-i* indicates that the variable aggregates over the "peers" of the subjects, e.g. original study participants connected to the subject. y_i is the outcome (e.g. days of the prescription drug supplied); t_{-i} is a measure of the intensity of treatment for subject *i*, the number of subject *i*'s peers who were assigned to the treatment group; s_{-i} is the total number of subject *i*'s peers in the original study, making $\kappa_{s_{-i}}$ fixed effects for each value of this variable; and X_i is the set of controls. β, the effect of having at least one peer assigned to treatment on the outcome, is the coefficient of interest.

3.2 Controls

Since the treatment was randomized without stratification, regressions analyzing original study participants would produce unbiased estimates of the coefficients of interest even without controls. However, controls can raise power by reducing unexplained variation. Regressions analyzing peer effects will require additional controls to yield unbiased estimates, described above.

We pre-specify two sets of controls and also note the potential use of machine learning to define a richer set of controls without overfitting.

3.2.1 Basic controls

One specification will include only the minimal controls needed to eliminate confounding. The treatment measure of interest for a peer analysis subject is an indicator for whether any of her peers were assigned to the treatment group. This indicator will be correlated with the total number of peers that the subject has, which is potentially associated with her total prescribing volume and characteristics of her patients, confounding the estimate of the treatment effect.

Therefore we include fixed effects for the number of peers in the original study ($\kappa_{s_{-i}}$). Conditional on this count, the number of peers assigned to treatment is random due to the randomization of the original study, and so is any function of that number.

3.2.2 Basic controls + lagged outcome controls

In addition to the controls in 3.2.1, this specification will control for the lagged measure of the outcome (before the letters were sent) for the subject, as represented by the 2014 value of the outcome in public use Medicare data. This specification will be the baseline reported in main tables.

3.2.3 Potential machine learning approach

We will explore using machine learning to define a richer set of controls without overfitting. Here we provide the candidate control variables for potential selection by the machine learning algorithm: specialty from NPPES (indicators for primary taxonomy of internal medicine, family medicine, general practice, psychiatry, or other; indicator for secondary taxonomy of psychiatry); and risk-adjustment measures from the 2014 CMS Part D prescriber summary public use file, average patient age, average patient HCC risk score, total number of patients, number of patients over age 65, number of patients who are female, number of patients who are white, and number of patients who are dually eligible.

3.3 Inference

We will use randomization inference for all hypothesis tests. We will calculate the p-values of all test statistics by drawing 1,000 random assignments of original study prescribers to treatment/control arms and by then estimating the distribution of the statistics over these assignments.

3.4 Outcome duration

The outcome duration will be April 21, 2015 through December 31, 2016, inclusive, unless otherwise noted. Since we draw outcomes from Medicare public use files that have only annual measures, when only calendar year data is available, we add together the calendar year 2015 and 2016 measures. Due to the randomization, prescription drug supply and other outcomes during the 2015 pre-intervention period is expected to be uncorrelated with treatment assignment for the original study physicians and to be uncorrelated with conditional treatment intensity for the peer analysis subjects.

4 Outcomes

We now outline the peer effects outcomes we will study using data from the Medicare public use files, which include aggregated, annual physician-level prescribing information on 100% of patients enrolled in Medicare Part D.

4.1 Quetiapine prescribing

Our first analysis will look at the effect of the letters on overall quetiapine prescribing behavior. The **primary outcome** will be days supplied of quetiapine.

We will also study as secondary outcomes other measures of quetiapine prescribing:

- Total quetiapine claims
- Total quetiapine cost
- Unique beneficiaries receiving quetiapine in 2015
- Unique beneficiaries receiving quetiapine in 2016

4.2 Prescribing of other antipsychotics and total antipsychotic prescribing

We will analyze other measures of antipsychotic prescribing as secondary outcomes. Specifically, we will consider as outcomes the days supplied of the sets of antipsychotics:

- First-generation antipsychotics
- Other "atypical" antipsychotics besides quetiapine
- All first-generation and atypical antipsychotics including quetiapine

We also observe both the total number of dispensing events for antipsychotic medications as well as the number of unique beneficiaries with claims for antipsychotic drugs. Thus, we can distinguish between the two margins of response: whether prescribers took patients off antipsychotic medication entirely (the extensive margin) or if physicians reduced total antipsychotic prescribing across the board without halting any patient's prescribing entirely (the intensive margin). To that end, we will study as outcomes:

- Total antipsychotic claims
- Total antipsychotic cost
- Unique beneficiaries receiving antipsychotics in 2015
- Unique beneficiaries receiving antipsychotics in 2016

Due to limitations in Medicare public use data, unique antipsychotic beneficiary counts will only include beneficiaries age 65 and up.

4.3 Prescribing of other psychiatric medications

Prescribers may also substitute their patients to other psychiatric medications, and we analyze the days supplied of the following classes of drugs:

- Benzodiazepines indicated for insomnia
- Benzodiazepines not indicated for insomnia
- Non-benzodiazepine insomnia drugs
- Antidepressants

4.4 Alternative measures of intensity of connection

The magnitude of the peer effect may depend on the intensity of the connection between the peer and the original study participant. That is, peers who are more intensively connected to an original study participant (by e.g. sharing more patients) may react more strongly to the letter intervention than physicians who are less connected.

We explore several alternative measures of connection intensity. To do so, we redefine t_{-i} as the intensity of connection to original study participants in the treatment group and s_{-i} as the intensity of connection to all original study participants. Because s_{-i} will now take on many values, it will no longer be possible to control for it as fixed effects. Instead, we will control for s_{-i} with polynomials with the degree chosen by the AIC criterion. The alternative measures are:

- Total number of shared patients received from and sent to original study participants
- The original measures of treatment and total connection, as described in section 3.1, scaled by the subject's network degree d_i (i.e. the number of peers of the subject): $\tilde{t}_{-i} = t_{-i}/d_i, \tilde{s}_{-i} = s_{-i}/d_i$

4.5 Alternative functional forms of treatment effect

The baseline model estimates the effect of having at least one peer assigned to treatment. Here we explore alternative functional forms of the treatment effect.

The first alternative is to allow a linear effect of treatment:

$$y_i = \alpha + \beta t_{-i} + \kappa_{s_{-i}} + X_i\Gamma + \varepsilon_i$$

The second alternative is to allow flexible effects by including fixed effects for the treatment variable:

$$y_i = \alpha + \sum_k \beta_k \mathrm{I}(t_{-i} = k) + \kappa_{s_{-i}} + X_i\Gamma + \varepsilon_i$$

We will also estimate these fixed effects by subgroup according to the total number of ties to original study participants s_{-i}:

$$y_i = \alpha + \sum_l \sum_{k \le l} \beta_k^l \mathrm{I}(s_{-i} = l \wedge t_{-i} = k) + \kappa_{s_{-i}} + X_i\Gamma + \varepsilon_i$$

5 References

Heslin, Kevin C, Elixhauser, Anne, Steiner, Claudia A. *Hospitalizations Involving Mental and Substance Use Disorders Among Adults, 2012*. Rockville, MD: Agency for Healthcare Research and Quality; 2015.

Sacarny, Adam, Michael L. Barnett, Jackson Le, Frank Tetkoski, David Yokum, Shantanu Agrawal, 2018. "Effect of Peer Comparison Letters for High-Volume Primary Care Prescribers of Quetiapine in Older and Disabled Adults: A Randomized Clinical Trial." *JAMA Psychiatry*. 2018;75(10):1003–1011. doi:10.1001/jamapsychiatry.2018.1867

6 Appendix: Drug Categories

Below is a list of each drug used in our analysis, by generic name.

Antipsychotics‡			**Benzodiazepines****		**Non-Benzodiazepine Insomnia††**
First-Gen	**Atypical**	**Antidepressants§**	**Insomnia‡‡**	**Not for Insomnia**	
Chlorpromazine	Aripiprazole	Amitriptyline	Estazolam	Alprazolam	Doxepin
Fluphenazine	Asenapine	Amoxapine	Flurazepam	Chlordiazepoxide	Eszopiclone
Haloperidol	Brexiprazole	Bupropion	Quazepam	Clobazam	Ramelteon
Loxapine	Cariprazine	Citalopram	Temazepam	Clonazepam	Suvorexant
Molindone	Clozapine	Clomipramine	Triazolam	Clorazepate	Tasimelteon
Perphenazine	Iloperidone	Desipramine		Diazepam	Zaleplon
Pimozide	Lurasidone	Desvenlafaxine		Flunitrazepam	Zolpidem
Thioridazine	Olanzapine	Doxepin		Halazepam	
Thiothixene	Paliperidone	Duloxetine		Lorazepam	
Trifluoperazine	Pimavanserin	Escitalopram		Midazolam	
	Risperidone	Fluoxetine		Oxazepam	
	Ziprasidone	Fluvoxamine		Prazepam	
		Imipramine			
		Isocarboxazid			
		Maprotiline			
		Milnacipran			
		Mirtazapine			
		Nefazodone			
		Nortriptyline			
		Paroxetine			
		Phenelzine			
		Protriptyline			
		Selegiline			
		Sertraline			
		Tranylcypromine			
		Trazodone			
		Trimipramine			
		Venlafaxine			
		Vilazodone			

‡ Includes all antipsychotics used in the 2016 CMS data: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/Part-D-Prescriber.html

§ From: https://www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/Medicaid-Integrity-Education/Pharmacy-Education-Materials/Downloads/ad-adult-dosingchart.pdf

** From: https://www.cdc.gov/drugoverdose/resources/data.html

†† Non-benzodiazepine, non-barbituate prescription sleep aids according to: https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm101557.htm

‡‡ Benzodiazepines with FDA indications for insomnia according to: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4730295/