Prespecification of Analyses for Commercial Insurance Effects of Quetiapine Letters

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Version 1.0

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History

Version	Date	Notes
1.0	December 28, 2018	Initial pre-analysis plan.

1 Introduction

We describe an analysis plan for a study on the commercial insurance prescribing 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 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 prescribing by original study prescribers for patients covered by commercial insurance. Notably, the letters were sent by CMS, not commercial insurers, and only described prescribing that was covered by Medicare Part D.

The analyses will make use of commercial claims data from the Health Care Cost Institute (HCCI) for the years 2013-2016. The Medicare claims of the original study prescribers was 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.[1] Prescribing is defined as the total "days supply" of quetiapine attributed to the prescriber.

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

2 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.

2.1 Commercial prescribing regression

The first set of analyses in this study considers physician-level prescribing. This yields a regression of the form:

$$y_i = \alpha + \beta * treat_i + X_i\Gamma + \varepsilon_i$$

Where *i* indexes physicians, y_i is the outcome (e.g. days of the prescription drug supplied), $treat_i$ is an indicator for physician *i* being in the treatment group, and X_i is the set of physician controls (lagged values of the outcome and various risk adjustment measures). β, the effect of the treatment on the outcome, is the coefficient of interest.

The next set of analyses considers baseline patients of the prescribers. The patient level regressions will be of the form:

$$y_j = \alpha + \beta * treat_{i(j)} + X_{i(j)}\Gamma + Z_j\Theta + e_j$$

Where *j* indexes patients, $i(j)$ is patient *j*'s physician, y_j is the outcome (e.g. days of prescription drug received), $treat_{i(j)}$ is an indicator for the patient's physician being in the treatment group, $X_{i(j)}$ is the set of controls for characteristics of the patient's physician, and Z_j is the set of controls for characteristics about the patient. β, the effect of the treatment on the outcome, is the coefficient of interest.

2.2 Controls

Since the treatment was randomized without stratification, regressions analyzing original study participants will produce unbiased estimates of the coefficients of interest even without controls. However, controls can raise power by reducing the variance of the error term.

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.

2.2.1 No controls

Due to the randomization no controls are needed to eliminate confounding concerns, so the first specification will include no controls at all.

2.2.2 Lagged outcome controls

This specification will control a the lagged measure of the outcome (before the letters were sent) for the subject: the value during the year prior to the intervention. In the patient level specifications, we will include the lagged value of the physician outcome as well.

This specification will be the baseline reported in main tables.

2.2.3 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.

For physician-level regressions, we will use the following candidates: specialty from NPPES (indicators for primary taxonomy of internal medicine, family medicine, general practice, psychiatry, or other; indicator for secondary taxonomy of psychiatry); and measures of average patient characteristics during the year prior to the intervention, average patient age (at midpoint of age bands) and share of patients who are female.

In patient-level specifications we will, in addition, include more candidate controls about the patient. These controls will include age band-gender interactions, indicators for each condition described in the table in section 3.4, and an indicator for being a member without data for the full historical period (the 2 years prior to the intervention start).

2.3 Outcome duration

The outcome duration will be April 21, 2015 through December 31, 2016, inclusive, unless otherwise noted.

3 Prescriber level analyses

In this section we look at the effect of the letter on prescriber-level behavior. In presenting the primary and secondary outcomes, we will only include prescribing to commercially insured patients under age 65.

To provide points of comparison to the commercial insurance effects, we may calculate the same outcomes looking at Medicare beneficiaries. For these analyses, we will use Medicare Advantage claims data from HCCI (which we already have access to) or Medicare claims data from ResDAC (which we hope to gain access to in the future).

3.1 Total Quetiapine prescribing

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

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

- Total quetiapine claims
- Total quetiapine cost
- Total quetiapine grams supplied

We will also look for effects on the extensive margin (i.e. number of beneficiaries with any quetiapine) and intensive margin (i.e. average daily dose conditional on any receipt):

- Unique members receiving quetiapine in the 2015 post-intervention period
- Average daily dose in milligrams among members receiving quetiapine in the 2015 post-intervention period
- Unique members receiving quetiapine in 2016
- Average daily dose in milligrams among members receiving quetiapine in 2016

3.2 New vs. continuing prescribing

Quetiapine prescriptions may have refills, allowing patients to continue receiving the drug even if their physician has begun limiting prescribing. We will therefore look at whether we can detect effects on new vs. continuing prescriptions with the following secondary outcomes:

- Initial quetiapine fills (i.e. the first fill for a patient attributed to that prescriber, after at least a year of no fills for that patient attributed to the prescriber)
- Continuing quetiapine fills (i.e. fills that are not initial fills by the above definition)

3.3 Prescribing by patient age

To build suggestive evidence on whether physicians changed prescribing to patients who were close to Medicare age, we will split patients by their age band code (0-17, 18-24, 25-34,

35-44, 45-54, 55-64). Then, we will study as outcomes the days supplied of quetiapine to patients in each age band.

When/if we calculate these outcomes for Medicare prescribing as a point of comparison, we will use the following age categories: under 55, 55-64, 65-74, 75-84, 85+.

3.4 Prescribing by likely appropriateness

There is increasing concern among policymakers that many recipients of quetiapine are low-value candidates for the drug. Thus we will test whether prescribers respond to the letters by reducing prescribing to patients who appear to be low-value, intermediate, or guideline-concordant candidates for the drug.

Using historical diagnoses, we will split patients into four mutually exclusive and exhaustive categories:

1. **Guideline-concordant** patients have diagnoses for which quetiapine is approved by the FDA for treatment.
2. **Intermediate evidence** patients have diagnoses that are not FDA approved for quetiapine treatment, but systematic reviews suggest that quetiapine still may be appropriate.
3. **Low-value** patients have diagnoses for which, according to systematic reviews, quetiapine is unlikely to be an effective treatment.
4. **Unknown** evidence patients are those with any other diagnoses, or those without diagnosis histories.

Then, we will study as outcomes the days supplied of quetiapine to patients in each category.

Categorization of adult (age 18+) population	
Group	**Diagnoses**
Guideline-concordant	Any of the following: • Bipolar disorder • Schizophrenia • Major depression
Intermediate evidence	No guideline-concordant diagnoses *and* any of the following: • Generalized anxiety disorder • Depression (excluding major depression) • Obsessive-compulsive disorder • Personality disorder
Low-value	No guideline-concordant nor intermediate evidence diagnoses *and* any of the following: • Insomnia • Post-traumatic stress disorder • Eating disorder • Alcohol use disorder

	• Dementia/Alzheimer's disease
Unknown	All remaining patients

These classifications are based on current FDA labeling for quetiapine (Seroquel and Seroquel XR), a systematic review on off-label prescribing by the Agency for Healthcare Research and Quality (Maglione et al. 2011), and an expert panel analysis of off-label prescribing (Painter et al. 2017). Diagnoses will be identified from all inpatient, outpatient, and professional claims incurred during the two year period immediately prior to the intervention.

3.5 Effects by *ex ante* prescribing volume

The letters may affect physicians at different points in the prescribing distribution differently. To test this, we split the physicians into quartiles based on their total quetiapine days supplied during the 9-month pre-intervention period. We analyze effect heterogeneity by quartile by running separate regressions for each of the four groups.

3.6 Prescribing of other psychiatric drugs

Physicians are told that their quetiapine prescribing is being monitored, which may induce them to substitute their prescriptions toward other substances with related indications. To test for substitution, we will look at the days supplied of related antipsychotics:

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

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 Patient level analyses

We will explore whether the letters induce commercially insured patients to change their receipt of prescriptions and other health care utilization. To do so we will construct a baseline cohort of commercially insured patients and track the evolution of their utilization after their physicians receive the letters.

To provide points of comparison to the commercial insurance effects, we may calculate the same outcomes by constructing a baseline cohort of Medicare beneficiaries. For these analyses, we will use Medicare Advantage claims data from HCCI (which we already have access to) or Medicare claims data from ResDAC (which we hope to gain access to in the future).

4.1 Definition of patient cohort

In a patient-level regression, it is important that we analyze a set of beneficiaries defined based on pre-letter criteria. This is because the letter may change the composition of a prescriber's patients — a contemporaneously defined set of patients could differ in unobservables between treatment and control.

We will define the patient cohorts as patients who had a quetiapine fill from an original study participant during the one year pre-intervention period. Some patients may be traced to multiple physicians in the sample. We will drop such patients from the analyses.

Unless otherwise stated, all patient-level outcomes will count total health care utilization, not only utilization due to the patient's baseline prescriber.

4.2 Quetiapine receipt

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

We will study as additional outcomes other measures of quetiapine receipt:

- Total quetiapine claims
- Total quetiapine cost
- Total quetiapine grams received

4.2.1 Receipt by Source

Then, we will calculate days received from the following mutually exclusive and exhaustive sources:

- The baseline prescriber to which the patient was attributed
- All non-psychiatric prescribers (excluding the baseline prescriber)
- All psychiatric prescribers (excluding the baseline prescriber)

4.2.2 Discontinuation and Dose Reduction

We will also consider the following alternative measures of quetiapine receipt:

- Discontinuation, defined as having no quetiapine fills during the final quarter of 2016
- Dose reduction, defined as having a lower quetiapine dose (milligrams per day) during the final quarter of 2016 than in the quarter immediately prior to the intervention

4.3 Receipt of other psychiatric drugs

Patients may substitute away from quetiapine toward other drugs with related indications. To test for substitution, we will look at the days received of related antipsychotics:

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

Patients may also switch to other psychiatric medications, and we will analyze the days received of the following classes of drugs:

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

4.4 Health care utilization

We will also consider whether the letters have an effect on patients' health outcomes. Depending on which types of patients are affected by the letters, the marginal quetiapine prescription could be used for drug abuse or for legitimate treatment of psychiatric disorders. The effects on health outcomes are thus ambiguous.

We will consider a variety of outcomes related to mental health:

- Any ED encounter
- ED encounter for substance use disorder
- ED encounter for mental health reasons
- Any inpatient stay
- Inpatient stay for substance use disorder
- Inpatient stay for mental health reasons
- Outpatient psychiatrist encounter
- Outpatient psychologist encounter
- Disenrolled

To identify substance use disorder and mental health encounters, we will classify each encounter's principal diagnosis code according to the Healthcare Cost and Utilization Project Clinical Classifications Software (CCS) single-level index. Substance use disorder encounters will be identified as those with a principal diagnosis code in CCS categories 660 (alcohol-related disorders) or 661 (substance-related disorders). Mental health encounters will be identified as those with a principal diagnosis code in CCS categories 650-652, 655-659, 662, 663, or 670 (Heslin et al. 2015).

4.5 Receipt by likely quetiapine appropriateness groups

We will classify patients into unknown evidence, low-value, intermediate evidence, guideline-concordant candidates for quetiapine using the methodology described in section 3.4. Then, for each group we will study quetiapine receipt (as described in section 4.2), receipt of other drugs (as described in section 4.3), and health care utilization (as described in section 4.4).

5 References

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

Maglione, Margaret, Alicia Ruelaz Maher, Jianhui Hu, Zhen Wang, Roberta Shanman, Paul G. Shekelle, Beth Roth, Lara Hilton, Marika J. Suttorp, Brett A. Ewing, Aneesa Motala, and Tanja Perry, 2011. "Off-Label Use of Atypical Antipsychotics: An Update", AHRQ Comparative Effectiveness Reviews. Agency for Healthcare Research and Quality, Rockville (MD).

Painter, Jacob T., Richard Owen, Kathy L. Henderson, Mark S. Bauer, Dinesh Mittal, and Teresa J. Hudson, 2017. "Analysis of the Appropriateness of Off-Label Antipsychotic Use for Mental Health Indications in a Veteran Population." *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 37, 438–446. doi:10.1002/phar.1910

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*. 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/