

These online materials include four sections. In Section 1, we consider an alternative estimand. In Section 2, we provide measures on our survey respondents and discuss implications of our low response rate. In Section 3, we include the questions from our survey. In Section 4, we discuss the role of measurement error in the assessment of preference; describe the other proxies of preference measured in the pilot study; and present results under each of these measurements.

Appendix 1: The Positive Strength of the Instrument Weighted Average Treatment Effect

Small et al. recently described identification results for the “positive strength of the instrument weighted average treatment effect” (PSIVWATE) using the standard IV estimator, and further described a bias formula for violations of monotonicity. We do not estimate this bias because, as Small et al. show, the PSIVWATE itself is not well-defined and thus neither is the bias of the standard IV estimator. The difficulty is that the PSIVWATE depends on the unmeasured confounders U that are chosen to explain confounding when, within some strata of U , the instrument is negatively correlated with the actual treatment. In general, we would not know what reasonable candidates are for U , and thus would not be able to proceed.

Small DS, Tan Z, Lorch SA, Brookhart A. Working paper: instrumental variable estimation when compliance is not deterministic: the stochastic monotonicity assumption. 2014. arXiv: 1407.7308.

Appendix 2: Pilot Study Survey Respondents

IMS Health provided data to identify physicians with a relevant medical specialty, active history of prescribing antipsychotic medications, and valid email address. Demographic and medical practice information was obtained from the AMA Physician Masterfile for physicians with primary medical specialties in family medicine, internal medicine, psychiatry, or a relevant variant or combination of these three specialties. This physician information was linked to Xponent prescription databases, which consists of prescription claims records processed from a sample of US retail pharmacies that includes more than half of all retail pharmacies in the US. We defined active prescribers as those who had written more than ten antipsychotic prescriptions between January 1 and December 31, 2011.

We identified 17,665 physicians who met our eligibility criteria and contacted a random subsample of 4,800. Physicians were twice emailed informing about the study, including a hyperlink to the online questionnaire. From email tracking embedded in the hyperlink, we know 96 (2%) clicked on the survey link. Fifty-three (1%) physicians completed the questionnaire. No identifying information was collected linking those who completed the questionnaire to their email address and thus to the AMA Physician Masterfile or IMS Health Xponent data sources.

Details of the demographic and medical practice characteristics for those contacted, those who clicked on the survey link, and those who completed the questionnaire are described in eTable 1. Because survey responses were confidential and not individually linked to the AMA Physician Masterfile or IMS Health Xponent data sources, we have limited information on the representativeness of the physicians who completed the survey, although we have some information on the representativeness of those who clicked on the survey link. Those who clicked on the survey appeared representative with respect to medical specialty, major professional activities, number of antipsychotic prescriptions written, sex, age, and region of practice. Based on survey responses, those who completed the survey appeared reasonably representative of medical specialty but perhaps more likely to be retired or semi-retired.

In particular, we cannot know whether the prescribing preferences and decisions of the respondents represent the prescribing preferences and decisions of the physicians who may have seen our hypothetical patients. To the extent that they are not representative, our assessments of local monotonicity violations and the bias in effect estimates would not be valid. However, any detection of a global monotonicity violation, even in a non-representative subsample, is valid. Similarly, any detection of disagreement between physicians implying multiple versions of the instrument is also valid under the assumption that those physicians could have seen that patient. As such, even though the respondents may not be representative, our survey results could be interpreted as valid *detection* of the issues described in this manuscript, although any inference about the *scope* of the problem (including bias assessment) may be skewed.

Appendix 3: Survey Questions

(page 1 of 8)

What year did you graduate from medical school? _____

What is your specialty? Please be specific about subspecialties as applicable. _____

On average, how many hours per week do you spend seeing patients?

- 0 hours
- 1 to 19 hours
- 20 or more hours

What percent of your time spent seeing patients is at an inpatient (vs. outpatient) facility?

- 0 to 49%
- 50 to 100%

What percent of your time spent seeing patients is at an academic (vs. non-academic) facility?

- 0 to 49%
- 50 to 100%

What percent of your patients are 65 years of age or older?

- 0 to 49%
- 50 to 100%

In the past year, approximately how many patients did you prescribe an antipsychotic agent?

- I did not prescribe any of my patients an antipsychotic medication
- 1 to 9 patients
- 10 to 19 patients
- 20 or more patients

(page 2 of 8)

On the next few pages we present five hypothetical patient scenarios. For each of these patients, your most likely treatment approach may or may not include prescribing an antipsychotic medication (possibly in addition to other medications). Please read these hypothetical case histories and select the course of action you would be most likely to take.

The information presented in these scenarios is necessarily less than you would glean and possibly search out were you face-to-face with the patient in question. We appreciate your effort to answer each question with your most likely decision given the information presented.

For the purposes of this survey, we have grouped antipsychotic medications into two classes: conventional (older, 1st generation) vs. atypical (newer, 2nd generation) medications. Note that your response does not necessarily imply which medication within the class you are considering. For your reference, we have included a list of medications that we consider belonging to each of these classes. We will include this list again on each relevant page.

Conventional: chlorpromazine, droperidol, fluphenazine, haloperidol, loxapine, perphenazine, pimozide, thiothixene, thioridazine, trifluoperazine

Atypical: aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone

(page 3 of 8)

Consider the following hypothetical patient, JD. In your most likely treatment approach, would you prescribe any antipsychotic medication? A 76 year-old male, JD, presents with worsening symptoms of dementia. He was first seen for dementia two years ago, but the symptoms date back at least five years before that. A full neurologic work-up was consistent with a diagnosis of Alzheimer's disease. In addition to his on-going difficulties with memory, organization, and navigating, he now is becoming easily agitated and occasionally manifests paranoid thoughts that are distressing to himself and his family. JD has a healthy weight (BMI=22). Other than what is noted here, he has no noteworthy family or personal medical history.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

In addition to the history provided above, you also learn one of the following. For each of these scenarios separately, consider your most likely treatment approach: would you prescribe any antipsychotic medication?

JD had a myocardial infarction less than a year ago.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

JD has diabetes.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

JD had a hip fracture less than a year ago.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

JD had a myocardial infarction and a hip fracture, both in this past year.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

(page 4 of 8)

Consider the following hypothetical patient, KS. In your most likely treatment approach, would you prescribe any antipsychotic medication? A 74 year-old female, KS, presents with new symptoms of her mood disorder. KS has had recurring dysthymic and depressive symptoms for the past 20 years, treated intermittently but successfully with SSRIs. More recently, she has expressed feeling frequently agitated, having difficulty concentrating, and extreme insomnia. She is concerned these symptoms are impeding her ability to care for her elderly husband. Appropriate evaluation has revealed no metabolic, endocrine, or neurologic source of these new symptoms. KS has a healthy weight (BMI=24). Other than what is noted here, she has no noteworthy family or personal medical history.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

In addition to the history provided above, you also learn one of the following. For each of these scenarios separately, consider your most likely treatment approach: would you prescribe any antipsychotic medication?

KS has high cholesterol, but no history of cardiac events.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

KS had a myocardial infarction two years ago.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

Three years ago, KS had supplemented her treatment for her mood disorder with aripiprazole, and experienced positive results. She discontinued aripiprazole about a year ago.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

Three years ago, KS had supplemented her treatment for her mood disorder with aripiprazole, but discontinued aripiprazole almost immediately.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

(page 5 of 8)

Consider the following hypothetical patient, HW. In your most likely treatment approach, would you prescribe any antipsychotic medication? A 76 year-old female, HW, with a diagnosis of schizophrenia, presents with a recurrence of psychotic symptoms. HW has had a 5-year remission of psychotic symptoms since her previous episode. She has been previously treated with both conventional and atypical antipsychotic medications. HW has diabetes (BMI=22), but otherwise has no noteworthy personal or family history.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

In addition to the history provided above, you also learn one of the following. For each of these scenarios separately, consider your most likely treatment approach: would you prescribe any antipsychotic medication?

HW was treated with olanzapine during her last psychotic episode; her symptoms remitted quickly but she did complain of sedative side effects.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

HW was treated with olanzapine during her last psychotic episode; her symptoms only remitted when the dose was escalated, at which point she experienced extreme metabolic side effects.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

HW was treated with haloperidol during her last psychotic episode; her symptoms remitted quickly, but she did complain of minor sedative and extrapyramidal side effects.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

HW was treated with haloperidol during her last psychotic episode; her symptoms only remitted when the dose was escalated, at which point she experienced extrapyramidal side effects including severe dystonia.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

(page 6 of 8)

Consider the following hypothetical patient, JW. In your most likely treatment approach, would you prescribe any antipsychotic medication? An 86 year-old female, JW, with a probable Alzheimer's diagnosis presents with new symptoms of hallucinations and paranoia. JW has exhibited escalating dementia symptoms for five years, and moved to a nursing home last year when she could no longer care for herself. Nursing home staff report she has become violent when agitated. Behavioral interventions and redirection have been tried, and have not succeeded in reducing her periods or severity of agitation. JW has a BMI of 18, and a family history of osteoporosis. Other than what is noted here, she has no noteworthy family or personal medical history.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

In addition to the history provided above, you also learn one of the following. For each of these scenarios separately, consider your most likely treatment approach: would you prescribe any antipsychotic medication?

JW had a hip fracture two years ago.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

JW has a family history of cardiac arrhythmias.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

JW has a cardiac arrhythmia.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

JW has a family history of cardiac arrhythmias, and had a hip fracture two years ago.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

(page 7 of 8)

Consider the following hypothetical patient, NM. In your most likely treatment approach, would you prescribe any antipsychotic medication? A 28 year-old male, NM, with a diagnosis of schizophrenia, presents with a new psychotic episode after a five-year remission from his first episode. During the first episode, NM was treated with risperidone for one year, and tapered gradually off with minimal withdrawal symptoms. NM is overweight (BMI=28), and has diabetes. Other than what is noted here, he has no noteworthy family or personal medical history.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

In addition to the history provided above, you also learn one of the following. For each of these scenarios separately, consider your most likely treatment approach: would you prescribe any antipsychotic medication?

NM is currently unemployed and uninsured (he was on his parents' insurance during his first episode).

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

NM is currently employed and has comprehensive health insurance.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

NM was a healthy weight (BMI=24); his weight gain and onset of diabetes were concurrent with his first treated episode.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

Although he chose to stay on the medication at the time, NM had experienced extreme akathisia and dystonia when treated with risperidone.

- Yes, I would prescribe a conventional antipsychotic medication
- Yes, I would prescribe an atypical antipsychotic medication
- No, I would not prescribe an antipsychotic medication

(page 8 of 8)

Generally, when you are considering prescribing an antipsychotic medication to a patient for the first time, do you choose conventional or atypical antipsychotic medications?

- I generally choose to prescribe conventional antipsychotic medications
- I generally choose to prescribe atypical antipsychotic medications

When you are newly prescribing an antipsychotic medication to a patient, do you choose an atypical antipsychotic medication 0%, 10%, ..., 90%, or 100% of the time?

- 0%
- 10%
- 20%
- 30%
- 40%
- 50%
- 60%
- 70%
- 80%
- 90%
- 100%

Consider the last real patient for whom you newly prescribed an antipsychotic medication. Without revealing any private health information, what type of antipsychotic medication did you prescribe to this patient?

- A conventional antipsychotic medication
- An atypical antipsychotic medication

Appendix 4: Measurement of Preference

Throughout the main text we assume that physician's preference can be and is measured without error. Implicitly, this means we viewed preference as causally related to treatment decisions, i.e., intervening on preference could affect treatment. However, we do not directly observe physicians preferences but rather measure it through proxies such as the prescription given to the prior patient. The standard IV estimator identifies LATE-like effects when the measured instrument is non-causal, as described by Hernan and Robins¹⁰ for both binary and continuous preference. We focus on the LATE and thus ignored the issue of measurement error in order to underscore our main finding: compliance types are ill-defined.

We also presented results from our pilot study based on only one measure of preference. The pilot study included five proxies in total:

- Prior Patient Preference: self-report of the class of antipsychotic (atypical versus conventional) prescribed to their most recent patient beginning antipsychotic
- Continuous Practice-Based Preference: self-report of the proportion of atypical (versus conventional) antipsychotic newly prescribed to patients prescribed an antipsychotic
- General Preference: self-reported "general preference" for atypical versus conventional antipsychotic when considering a new antipsychotic prescription for a patient
- Unconditional Empirical Preference: the proportion of atypical (versus conventional) antipsychotic prescribed to the hypothetical patients presented in our scenarios (for whom the physician prescribed an antipsychotic)
- Conditional Empirical Preference: for a given vignette, the proportion of atypical (versus conventional) antipsychotic prescribed to the hypothetical patients within that vignette (for whom the physician prescribed an antipsychotic)

The first measure approximates the commonly used preference proxy in prior IV studies. Other commonly used preference proxies include dichotomized versions of our continuous practice-based preference, e.g., comparing physicians who prescribe atypical antipsychotic 90% or more of the time versus less than 90% of the time.

A benefit of the empirical preference measure is that it is not directly a function of the type of patients seen by each physician. Preference measures based on real prescribing history, however, are functions of the physicians' true preference levels and the types of patients seen by each physician. In our pilot study, proxies based on prescribing history correlated reasonably with one another, but modestly with empirical preference. In other words, how a physician treated their prior patient was associated with how they treated other previous patients, but was only weakly associated with how they treated a new (hypothetical) set of patients. This suggests that proposed instruments based on prescribing history may in practice be confounded (eFigure 1). For previous discussion of this possible confounding, see Hernán and Robins,¹⁰ Davies et al.,² and Swanson and Hernán.³

Results based on each of the proxies are presented in eTables 3-4 and eFigure 2. The distribution of these proxies across physicians is presented in eTable 3. A summary of global monotonicity violations by preference proxy are presented in eTable 4. In eFigure 2, we present the distribution of compliance types for each of the hypothetical patients.

eTable 1. Characteristics of Physicians Who Were Contacted, Clicked on the Survey Link, and Responded to Survey

	Physicians Contacted (N=4800)	Clicked on Survey Link (N=96)	Responded to Survey (N=53)¹
Primary Specialty, N (%) ²			
Family Medicine	432 (9)	5 (5)	4 (8)
Internal Medicine	373 (8)	2 (2)	0 (0)
Psychiatry	3997 (83)	89 (93)	47 (89)
Unknown	0 (0)	0 (0)	2 (4)
Major Professional Activity, N (%)			
Office-Based Practice	3629 (76)	68 (71)	NA
Hospital Staff	374 (8)	9 (9)	NA
Inactive ³	597 (12)	16 (17)	NA
Other/Unknown	200 (4)	3 (3)	NA
Antipsychotic Medication Prescriptions Written in 2011, Median N (IQR)	214 (65-705)	258 (88-804)	NA
Gender, N (%)			
Female	879 (18)	20 (21)	NA
Male	3901 (81)	76 (79)	NA
Unknown	20 (0)	0 (0)	NA
Age in Years, Median (IQR)	66 (61-72)	67 (63-74)	66 (60-72)
Region, N (%)			
Midwest	893 (19)	18 (19)	NA
Northeast	1193 (25)	29 (30)	NA
South	1344 (28)	22 (23)	NA
West	983 (20)	19 (20)	NA
Unknown	387 (8)	8 (8)	NA

1. No identifying data were collected in the survey, and thus we are unable to link survey responses to the information in the AMA Physician Masterfile or IMS Health Xponent data sources. Physicians who responded to the survey self-reported their primary specialty. We further used their self-reported year graduating from medical school to impute their age (assuming an average age when graduating medical school of 26 years). We did not directly measure major professional activity in the survey, but qualitative assessments of physicians' responses to questions about their practice (e.g., time spent seeing patients in an inpatient versus outpatient facility) suggested a similar distribution of professional activities to the full eligible sample. No suitable proxies for the remaining covariates in the table were assessed in the survey.
2. Primary specialty may sum to more than 100% as physicians may have a dual primary specialty (e.g., family medicine and psychiatry) on record. The specialty listed for the physicians contacted reflect their specialty prior to defining the eligible sample, while the specialty listed for the physicians who clicked on the survey were collected from an updated AMA report after the survey was implemented. While two physicians who responded to the survey did not provide their primary specialty, it is known that they specialized in family medicine, internal medicine, or psychiatry, given our eligibility criteria.
3. Physicians may have been retired or semi-retired at the time of survey collection (August-November 2013). However, by our eligibility criteria, we know all contacted physicians prescribed more than ten antipsychotic medication scripts in January-December of 2011.

eTable 2. Patient Characteristics in the Current Study and from Previous IV Studies of Antipsychotic Class and Mortality

	Current Study	Wang 2005	Schneeweiss 2007	Pratt 2010	Huybrechts 2011
Years of Data Collection	2013	1994-2003	1996-2004	2003-2006	2001-2005
% Female	75	81	63	42	75
Age, Mean or Median	78	83	80	83	83
% Dementia, Delirium, or Alzheimer's Disease	50	48; 15 ¹	12; 8 ¹	NA	76; 54 ¹
% Mood Disorder	25	31	22	NA	54 ²
% Psychotic Disorder	25	23	15	NA	15
% Cardiovascular Diseases (Examples)					
Cardiac Arrhythmia	5	1	0	NA	27
Myocardial Infarction	10	4	2	NA	7
% Diabetes	30	26	14	NA	NA
IV effect estimate, per 100 patients ³	NA	7.3 (2.0, 12.6)	4.2 (1.2, 7.3)	23.8 (17.6, 30.0)	8.8 (-1.3, 19.0)

1. Dementia; delirium

2. Depression only

3. Reported effect estimate using IV methods, comparing conventional to atypical antipsychotic medications with respect to risk of all-cause mortality (follow-up of 6-12 months). 95% confidence intervals appear in parentheses.

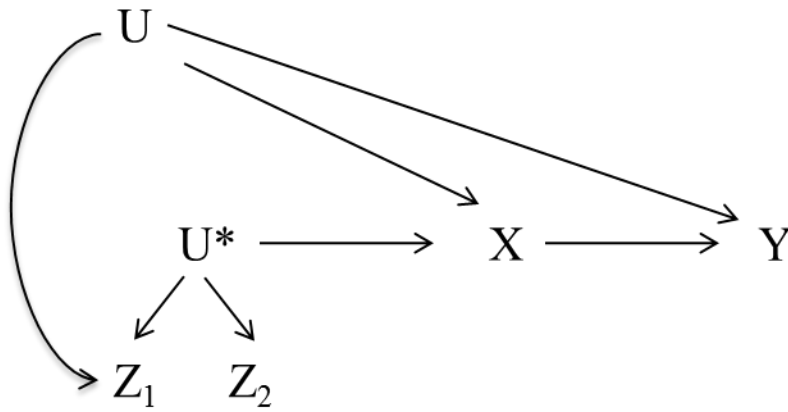
eTable 3. Proxy Measures of Overall Physician's Preference for Atypical (vs. Conventional) Antipsychotic Medication

Preference Measure	Physician Preferences, N (%)	
	All Physicians (N=53)	Psychiatrists Only (N=47)
Prior patient	47 (89)	43 (91)
'General' preference	50 (94)	46 (98)
Continuous preference in practice		
40%	1 (2)	1 (2)
50%	3 (6)	3 (6)
60%	2 (4)	1 (2)
70%	6 (11)	4 (9)
80%	10 (19)	8 (17)
90%	18 (34)	18 (38)
100%	13 (25)	12 (26)
Empirical preference from survey, median % (IQR)	80 (50, 100)	87 (50, 100)

eTable 4. Distribution of Global Monotonicity Violations across Hypothetical Patients by Measure of Preference

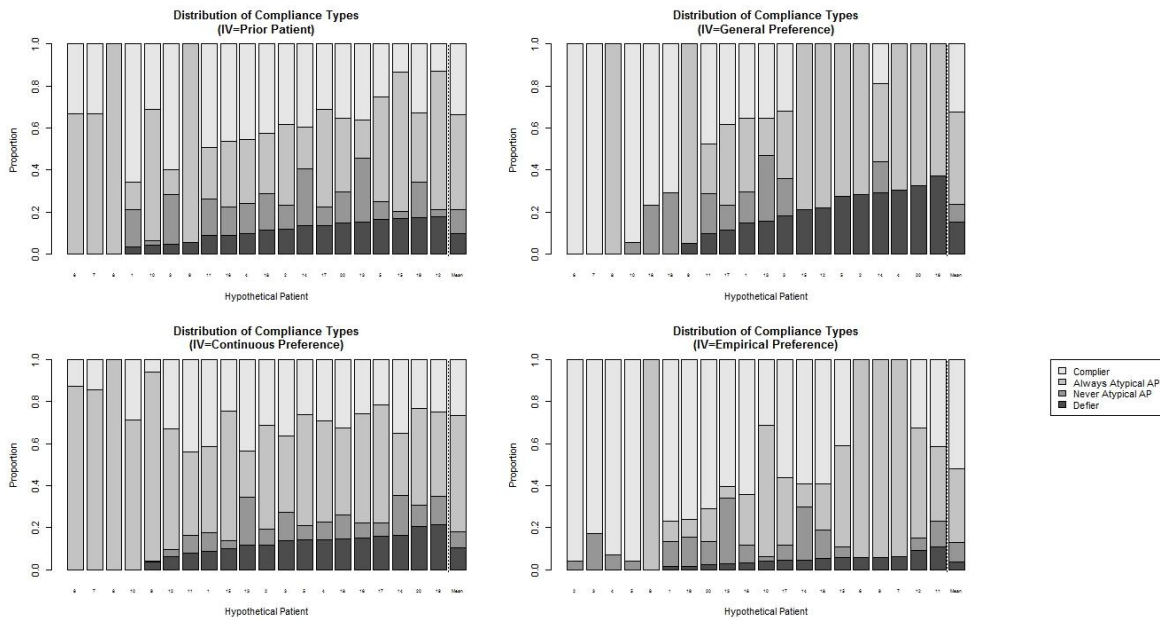
Preference Measure	Patients Exhibiting Global Monotonicity Violations, N (%)	
	All Physicians	Psychiatrists Only
Prior patient	17 (85)	16 (80)
General preference	14 (70)	14 (70)
Continuous preference in practice	19 (95)	19 (95)
Empirical preference overall	19 (95)	19 (95)
Empirical preference within vignette	11 (55)	11 (55)

eFigure 1. Causal Diagram Depicting Preference Proxies Defined Based on Prescribing History and Defined Empirically



U = unmeasured confounders; X = treatment (atypical vs. conventional antipsychotic medication); Y = outcome (mortality); U = true preference level; Z₁ = measured preference, defined by the class of antipsychotic prescribed by the physician to their prior patient newly prescribed an antipsychotic medication; Z₂ = measured preference, defined by the class of antipsychotic prescribed to a hypothetical patient chosen independent of their patient population

eFigure 2. Distribution of Compliance Types for Each of the N=20 Hypothetical Patients by the Distribution of Physician Preferences and Prescribing Decisions



1. Self-reported continuous preference was dichotomized at $\geq 80\%$ versus $< 80\%$ atypical Antipsychotic prescriptions. Empirical preference was dichotomized at $\geq 50\%$ versus $< 50\%$ atypical AP prescriptions.