Comparative Effectiveness of Adaptive Pharmacotherapy Strategies for Schizophrenia

Protocol prepared by: T. Scott Stroup, MD, MPH, Tobias Gerhard, PhD, Mark Olfson, MD, MPH, Chacku Mathai, Melanie Wall, PhD, Zhiqiang Tan, PhD

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Background

Schizophrenia is a serious mental disorder that has a lifetime population risk approaching 1%.[1] In the U.S., schizophrenia affects approximately 2.4 million individuals.[2] It typically begins in early adulthood and is a major cause of disability.[3] Age-specific all-cause mortality rates in schizophrenia are more than 3 times greater than in the general population.[4] Outcomes of schizophrenia are variable, ranging from slight to severe disability. For affected individuals and their families, schizophrenia can be devastating. Many people with schizophrenia have substantial social and functional impairments that contribute to high rates of homelessness, unemployment, disability, and incarceration.[5,6] Globally, schizophrenia is the 5th leading cause of years lost to disability for men and 6th leading cause for women.[3]

Antipsychotic medications are a cornerstone of schizophrenia treatment.[7] However, because most people with schizophrenia respond only partially or not at all to an antipsychotic medication,[8] these medications are changed frequently and combined or different classes of psychotropic medication are added.[9,10] Preliminary analyses of national Medicaid data from 2001-2005 revealed that in the year before starting a new antipsychotic, most patients with schizophrenia fill a prescription for an antidepressant (67.3%), a benzodiazepine (53.2%), or a mood stabilizer (55.8%). The FDA has not approved any of these classes of drugs to treat schizophrenia, although strong evidence supports their use for the conditions for which they have been approved. Evidence is scare for effectiveness of these medications in people with schizophrenia.[11]

This investigation will address key patient-centered questions about medication strategies for individuals with schizophrenia who face common clinical situations, for example:

- "I have schizophrenia and take an antipsychotic drug but still have symptoms that interfere with my daily life."
- "I have schizophrenia and take an antipsychotic drug but often feel depressed."

In these scenarios, a doctor may recommend a medication change. Patients want to know: "What are my options? Which will best keep me out of the hospital so that I can keep my housing and job? Which will help me to lead a long life? Which choice will help me avoid the emergency room? I'm worried about side effects—which option will help me avoid serious heart problems? Or diabetes?"

A physician working with an individual with schizophrenia might have the following questions:

- What is the best medication to recommend for a person with schizophrenia who is not feeling better with just an antipsychotic?
- What is the best medication to recommend for this person who has now developed depression? Or anxiety? Or manic symptoms?

This will be the largest study of treatments for schizophrenia ever conducted. By conducting rigorous analyses using 10 years of national Medicaid data, the study will provide information to help make personalized treatment choices that fit an individual's clinical situation and preferences with the goal of achieving outcomes that matter to the patient.

Goal

More than half of individuals diagnosed with schizophrenia have an incomplete response to a prescribed antipsychotic medication.[10] In spite of the high proportion of patients who experience an incomplete response, little is known about the comparative effectiveness of treatment options that are commonly used in this situation. The proposed research question "For patients with schizophrenia who have persistent, emergent or recurrent psychiatric symptoms in spite of antipsychotic treatment, what are the medication treatment options and what are their comparative benefits and risks?" thus has considerable public health importance is relevant to a large proportion of the approximately 3 million individuals with schizophrenia in the U.S. specifically, the project seeks to achieve the following aims:

1. Within five clinically important schizophrenia subgroups, compare the effectiveness and safety of alternative medication strategies beyond antipsychotic monotherapy.

2. Within the five subgroups, explore whether the comparative effectiveness and safety of alternative treatment strategies varies according to patient age and presence of a substance use disorder.

3. Conduct instrumental variable and sensitivity analyses to examine the robustness of the treatment effectiveness results that are based on propensity score methods.

The project will yield unbiased, generalizable, and patient-centered information on the comparative effectiveness and safety of alternative medication strategies for patients with schizophrenia who have an incomplete response to

standard antipsychotic monotherapy. New information will be generated regarding the comparative effectiveness and safety of commonly used but poorly understood second-line medication treatment strategies. We will compare the effectiveness of these medication treatment strategies for schizophrenia in five subgroups based on presenting symptoms and syndromes that lead to initiation of a new psychotropic strategy: 1) schizoaffective, 2) depressive, 3) anxiety, 4) manic, and 5) uncomplicated schizophrenia.

The project is designed to address critical knowledge gaps in the comparative effectiveness of pharmacological management of patients with schizophrenia, broadly conceived to include the diagnoses of schizophrenia, early course schizophrenia (schizophreniform disorder), and schizoaffective disorder. Schizoaffective disorder, a subtype of schizophrenia characterized by psychotic symptoms and persistent mood symptoms, is often diagnosed in the Medicaid population.[12] The pharmacologic treatment of schizoaffective disorder has not been extensively studied in controlled trials,[13] though treatment for schizoaffective disorder shows patterns that are distinct from other schizophrenia subgroups.[12] Symptoms of anxiety,[14] depression,[15] and mania[16] also commonly occur in adults with schizophrenia. Nevertheless, clinical trials of standard pharmacological treatments for anxiety, depression, and mania routinely exclude patients with schizophrenia and related psychotic disorders. As a result, little is known about the comparative effectiveness of medication options for treating schizoaffective disorder, anxiety, depression, and mania in schizophrenia.[17]

There is little evidence on pharmacologic treatments in schizophrenia other than antipsychotics. The first step in medication treatment for schizophrenia is generally a single antipsychotic.[11,18,19] However, most patients with schizophrenia have an incomplete response to antipsychotic monotherapy. Switching antipsychotics is a common strategy for breakthrough symptoms, but the evidence suggests switching is more likely to affect side effects than to reduce core symptoms.[20,21] The one medicine consistently shown to often work when others do not is clozapine, which has an indication for both treatment-resistant schizophrenia and for reducing persistent suicidal behaviors[11] but is rarely prescribed.[22] Support for adding a second antipsychotic agent, though common in clinical practice,[23] is largely confined to case reports and open-label trials[24,25] rather than double- blind clinical trials.[26] The evidence for adding agents from different psychotropic classes is summarized in Table 1.

Current practice patterns vary widely. In our preliminary analyses, we found wide variation in prescribing of different classes of psychotropic medications to patients with schizophrenia in the year prior to initiation of a new antipsychotic medication, providing additional evidence regarding uncertainty of these treatment strategies. Across states, rates varied by 2 to 3 fold. Specifically, the initiation of benzodiazepines varied from 9.2% (Kentucky) to 29.7% (Vermont); antidepressants from 19.8% (Vermont) to 48.3% (Oklahoma); and mood stabilizers from 6.6% (North Dakota) to 18.9% (Texas). Such variation underscores deficiencies in widely accepted clinical evidence concerning these important treatment decisions.

There is no professional consensus on treatments for important subgroups with schizophrenia. Schizophrenia treatment guidelines and algorithms[11,18,19] have concluded that there is little evidence to guide selection of pharmacologic strategies for schizophrenia beyond the initial recommendation for antipsychotic monotherapy and then for clozapine for people with treatment-resistant illness.

Although there is limited information on the clinical comparisons we propose to study, recent evidence from a Finnish observational study of psychotropic polypharmacy in schizophrenia, which used methods that are similar to those that we propose, found substantial effect sizes.[27] In that study, for example, there was a significant increase in mortality associated with adjunctive benzodiazepine use compared to antipsychotic monotherapy and adjunctive antidepressant use was associated with markedly reduced risk of suicide

Despite the widespread use of various combinations of classes of psychotropic medicines in schizophrenia, their comparative safety and effectiveness have not been established. By determining which options are most effective in achieving desired outcomes in specific clinical situations, this project will promote personalized, evidence-based medicine and has the potential to reduce wasteful or harmful medication management approaches. By helping doctors and patients find effective treatments earlier than by simple trial and error, this project has the potential to reduce the potential harms and inconvenience of failed medication trials, adverse effects, and unnecessary hospitalizations.

Protocol Details

Overview of study design

The study is a retrospective cohort study of adults with schizophrenia that will compare outcomes of new users of alternative psychotropic medication strategies using 10 years of Medicaid data. The primary comparative effectiveness analyses will focus on subgroups of patients with schizophrenia facing common clinical situations.

Data source and cohort identification

The data source will be national (45-state) Medicaid Analytic Extracts data (2001-2010). The cohort will consist of adults who are 18 to 64 years old and diagnosed with schizophrenia who initiate a new psychotropic medication after a period of stable antipsychotic treatment. Individuals who are 65 or older because will be excluded because they also have Medicare and receive pharmacy benefits through Medicare Part D.

Schizophrenia will be defined as ≥2 outpatient claims or ≥1 inpatient claim for schizophrenia [ICD-9-CM: 295] during 365 days of consecutive Medicaid enrollment immediately prior to the index date.[28] Stable antipsychotic monotherapy will be defined by filled prescriptions for only one second-generation antipsychotic (excluding clozapine), and no other psychotropics, for ≥ 90 days immediately preceding the start of the index medication (t0). After the ≥90 days of stable treatment with a single second-generation antipsychotic, study patients will have had a change in therapy defined as (1) addition of a second antipsychotic or (2) addition of a different psychotropic drug class (antidepressant, mood stabilizer, or benzodiazepine). To ensure the patients are in active treatment there must be an active supply of antipsychotic medication on t0.

The eligibility criteria select a cohort of individuals that are likely to have schizophrenia,[28] have received antipsychotic monotherapy prior to the index date, and are still experiencing problems for which a new psychotropic medication strategy was initiated. A 1-year period of eligibility prior to follow-up initiation ensures sufficient time to collect service use related covariates to characterize cohort members.

Patients with stable clozapine monotherapy will be excluded because clozapine is largely reserved for the most severely ill patients. Patients who implement more than one change in therapy at the index date (e.g., addition of a mood stabilizer and an antidepressant) will also be excluded.

Subgroups

From the base study population described above, 5 clinical subgroups will be defined based on the presence of psychiatric diagnoses during the 30 days prior to and inclusive of the treatment change under study (index date) and who have this same diagnostic code from more than one provider to increase the validity of the diagnostic groups. The subgroups will be defined by codes to capture 1) uncomplicated schizophrenia (with schizophrenia codes from at least 2 different providers and without any diagnoses that would qualify them for the other subgroups during the 365 days prior to the index date), 2) schizoaffective disorder (ICD-9: 295.7) as the most recent schizophrenia-spectrum diagnosis, 3) depressive (ICD-9: 293.83, 296.2, 296.3. 296.9, 298.0, 300.4, 311), 4) manic (296.0, 296.4-296.8), and 5) anxiety (293.84, 300.00-300.02, 300.09, 300.20-300.23, 300.29, 300.3, 300.7, 308.0-308.9, 309.21, 309.81, 312.39, 313.0, 313.21, 313.23). These subgroups are defined to reflect the reason for the change in treatment.

Comparators

Pharmacological treatment options for patients with schizophrenia who are nonresponsive to antipsychotic monotherapy will include (1) initiation of a second antipsychotic, (2) initiation of an antidepressant, (3) initiation of a mood stabilizer and (4) initiation of a benzodiazepine.

Within each clinical subgroup, treatment options may be refined by exclusions at the drug class or individual agent level. For example, antidepressants are generally not considered treatment alternatives in patients presenting with mania, but could reasonably be considered for patients in the remaining four schizophrenia subgroups: depression, anxiety, schizoaffective disorder, and uncomplicated schizophrenia. Unless it is not considered a reasonable treatment option for a specific subgroup, initiation of a new antipsychotic will serve as the reference category because it is a frequently recommended approach to improving treatment response[29] and is a common treatment strategy across all of the clinical subgroups under study. A survey on the prescribing behaviors of clinicians who prescribe psychotropic medications for individuals with schizophrenia will inform these choices.

Outcomes of interest

Primary

The primary effectiveness outcome will be time to psychiatric hospitalization.

Secondary

We will also investigate time to index treatment discontinuation, time to introduction of another psychotropic medication, psychiatric emergency department visits, all-cause hospitalization, and death.

We will investigate adverse effects of medications including incidence of major cardiovascular events and diabetes mellitus.

Outcomes	
Death	Date of death will be defined by the Social Security Death Master File.
Psychiatric Hospitalization	Hospital claims will define inpatient admissions with a first listed mental disorder diagnosis (ICD-9:290-310). High levels of agreement between diagnoses in inpatient medical records and inpatient claims have been reported for several mental disorder groups, including schizophrenia (100.0%), major mood disorders (98.7%), alcohol dependence (97.8%), and drug dependence (96.4%).[30]
Psychiatric ED Visits	Emergency department claims are a reliable source of diagnostic information in relation to medical records [31,32] and a valid source of illness severity information.[33] Emergency department visits in which the first listed diagnosis is a mental disorder (ICD-9-CM: 290-319) will be defined as emergency department mental health visits.
Self-Injurious Behavior	Deliberate self-harm will be defined by an E-code of E950-E958, excluding late effects of deliberate self-harm (E959), on any inpatient, emergency department, or outpatient claim. High positive predictive values have been reported.[34]
Diabetes Mellitus	One or more claims with a physician diagnosis of diabetes will define diabetes mellitus. Using self-reported diabetes status as the criterion standard, ≥1 physician claim with any diagnosis of diabetes or a diabetes complication (ICD-9 codes: 295.00-2950.93, 357.2, 362.0-362.02, 366.41) has acceptable sensitivity (68.5%) and specificity (96.9%), and (kappa=0.76).[35] Sensitivity of 90% and specificity of 93% with self-reported diabetes.[104]
Cardiovascular Events:	Acute myocardial infarction (AMI) (ICD-9-CM: 410) or stroke (430-438, except 435) will be defined by daignostic codes on inpatient claims of ≥3 days in duration.[36-39] With this AMI definition 75% met criteria for definite or probable AMI on independent review of cardiac biomarkers, electrocardiograms, presenting symptoms, and medical history, and an additional 12% had a suspected AMI.[36-39]

Approach to confounding

Physicians make treatment choices in light of available clinical information and as a result there is a risk of confounding by clinical indication for the treatments under study. Our design minimizes confounding by indication by focusing on diagnostic subgroups. To further reduce confounding, we will control for a broad range of potentially relevant factors from claims histories. These factors will be identified in the 365-day period before drug initiation and used to calculate propensity scores. In addition we will conduct sensitivity analyses to estimate the extent of unmeasured confounding necessary to fully explain our observed findings and we will conduct instrumental variable analyses if a suitable instrument is identified.

Follow-up and censoring

Follow-up will begin at the date of new treatment initiation (t0 or index date) and will end after 365 days regardless of changes in pharmacotherapy (intent-to-treat approach). We will also conduct secondary analyses using a 180-day follow-up period and an as-treated specification.. In the as-treated approach, follow-up will end at discontinuation of the new treatment (>10 days without drug) or addition of another psychotropic agent (antipsychotic, mood stabilizer, antidepressant, or benzodiazepine). All analyses will be censored at loss of Medicaid (because that is the data source) with one exception—in intent-to-treat mortality analyses, follow-up will not be censored at loss of Medicaid because date of death data comes from the Social Security Master File, not Medicaid.

Analysis plan

AIM 1 Comparative Effectiveness: Main Effects: Within five clinically important schizophrenia subgroups, compare the effectiveness and safety of alternative medication strategies beyond antipsychotic monotherapy.

We will construct Cox models to estimate effects of the study treatments. We will first examine unadjusted treatment effects and then will conduct analyses using basic adjustment for demographic factors. Then we will construct Cox models using weighted propensity scores. Follow-up time will be censored at discontinuation or change of second drugs, death, or loss of Medicaid.

Propensity score estimation and application

Propensity score methods involve two steps: estimation of the propensity scores and application of the propensity score.[40] Estimation of the propensity scores involves decisions about which covariates to include in the prediction model of the propensity scores and what form the model should take. We will use expert opinion to select the variables to include in the propensity score. To estimate the propensity scores we will first use logistic regression including all baseline predictors occurring prior to treatment assignment.[41] In addition, we will augment our analysis with another non-parametric method for building the propensity score model such as a generalized boosting algorithm implemented with regression trees.[42] We will assess the sensitivity of our results to the choice of the propensity score model.

For the application of the propensity scores, we will use weighting by the odds to estimate the average treatment effect on the treated sample and weighting by the inverse probability of treatment weights to estimate the average treatment effect in the population.[40]

We will examine the covariate balance using standardized differences in covariate means across the treatment groups after weighting, and address any significant imbalances.

AIM 2 Heterogeneity of Treatment Effects: Within the five subgroups, explore whether the comparative effectiveness and safety of alternative treatment strategies varies according to patient age and presence of a substance use disorder.

We will use similar Cox model techniques for the HTE analyses. First we will assess interaction of age and substance use variables with treatment. If such interactions are found, we will then perform analyses examining alternative treatment strategies stratified by age group or substance use.

The rationale for investigating patient age as a moderator of antipsychotic treatment effects follows from evidence that individuals early in the course of psychosis may respond differently to medications than people with more chronic illness. The rationale for investigating comorbid diagnosis of a substance use disorder as a moderator of treatment effects follows from evidence that people diagnosed with schizophrenia and comorbid substance use disorders respond more poorly to antipsychotic medications than those without comorbid substance use disorders.

AIM 3 Instrumental Variable and Other Sensitivity Analyses

Instrumental variable analyses

We will also seek to use instrumental variable analyses to control for unobservable confounders. First, we will try to identify a feasible instrument and, if one is identified, we will apply it to our analyses. Instruments to be considered includes zip code, county, or state of patient residence; and, if there are significant time trends in the use of medications, year of prescription. We will also consider the prescribing patterns of prescribers but are concerned that this data may not be reliably available in the data.

If the candidate instrument meets the following basic criteria, we will integrate it into our statistical analyses: 1) the instrument is associated with use of the treatment; 2) the instrument does not cause the outcomes except through its relationship with the treatment (known as exclusion restriction); and 3) the instrument is not confounded with the outcomes (known as independence assumption).

We will evaluate the plausibility of exclusion restriction by examining whether a candidate instrumental variable is related to potentially hazardous co-prescriptions, and study whether the independence assumption needs to be made conditionally on observed patient characteristics.. We will employ methods rigorously developed for causal inference using instrumental variables, such as instrumental variable propensity score methods or near-far matching. These methods are applicable to various types of outcomes and to situations where the instrument is related to observed patient characteristics. These methods involve construction of instrument groups that, by weighting or matching, are similar in terms of observed covariates but differ in the instrument values. With these methods, treatment effects can be estimated by difference-in-difference, i.e., the ratio of the average outcome difference over the average treatment difference between the instrument groups. A complication of instrumental variable analysis is that the causal estimands inferred are in general distinct from the average treatment effects, overall or on the treated samples, as in the intention-to-treat analysis. We will perform bounding and sensitivity analyses to investigate the relationship between the instrumental variable estimates and intention-to-treat estimates and examine its implications for the interpretation of the final results.

Sensitivity Analyses

We will conduct sensitivity analyses to confirm findings from the primary analyses and to examine their generalizability. In addition to the primary 360-day intention-to-treat analyses we will conduct 180-day intention-to-treat analyses and as-treated analyses. Another sensitivity analysis will examine subgroups of people with depression, anxiety, or mania diagnoses that are listed by more than one provider.

Quantitative Sensitivity Analyses for Unmeasured Confounders. Because the observed relative risk is a closed- form function of the balance of confounders among exposure groups, the strength of the confounder, and the prevalence of the confounder, it is possible to estimate the extent of unmeasured and thus unadjusted confounding necessary to fully explain the observed findings, i.e., would move the observed relative risk to statistical insignificance (the null).

To quantify how strong unmeasured confounding would have to be to explain the observed effect sizes among our comparison groups,[44] ,we will use the array approach to understand how the strength of unmeasured confounders with known associations with our outcomes, such as BMI and risk of diabetes,[3] and the confounder imbalance among study groups might affect the observed relative risk.

Sample size

Table 5 presents sample size estimates for national 2001-2010 Medicaid data based on our preliminary analyses. For example, we expect that the following treatments with corresponding numbers will be options for the depression symptom subgroup: second antipsychotic (n = 2,192), mood stabilizer (n = 1,296), antidepressant (n = 4,646), and benzodiazepine (n =1,199). We will then, for example, compare 2,192 patient episodes with a second antipsychotic to 2,192 propensity-score matched patient episodes that were treated with an antidepressant. The 1:1 matching method uses a nearest neighbor algorithm.[45,46] As recommended for observational studies, we will use a caliper width of 0.2 of the standard deviation of the logit of the propensity score to ensure appropriate matching.[36]

Our power analysis is based on two-sided (alpha = .05) tests for differences in proportions between treatment groups, which depend upon the sample size of each group and the probability of the outcome. To demonstrate power, we conservatively use the expected number of distinct patients rather than episodes (distinct patients equal approximately 70% of the episodes in Table 5). Final statistical analyses of individual episodes will have greater power (i.e., be able to detect even smaller percent differences) and will incorporate random effects to account for patients who contribute more than one episode.[45,46]

Table 5: Estimated sample sizes of selected schizophrenia treatment episodes (2001-2010)

	Uncomplicated Schizophrenia	Schizoaffective Disorder	Depression	Mania	Anxiety
Second Antipsychotic	27,005	6,393	2,192	1,580	611
Mood Stabilizer	9,954	4,734	1,296	2,107	NA
Antidepressant	25,061	9,692	4,646	,NA	1,110
Benzodiazepine	12,248	3,681	1,199	840	1,099

We demonstrate the smallest detectable differences in proportions with >80% power for three examples. For example, in the depression group, 1534 distinct patients per group (70% of 2,192) distinct patients per group (antidepressant vs. second antipsychotic) will provide at least 80% power to detect a difference of 5.0% in the rate of hospital admission in 1 year of follow-up. Also within the depression group, the smallest treatment group (839 distinct patients of 1,199 initiating episodes of benzodiazepines), will provide at least 80% power to detect differences of 6.8% between the reference and the comparator group. In the smallest group overall (611 episodes in anxiety patients starting mood stabilizers), there is still >80% power to detect differences as small as 10.0% in their outcomes compared to those with anxiety in the comparator group. Because of the larger sample sizes, all comparisons in the uncomplicated schizophrenia and schizoaffective disorder groups will have power much greater than 80% to detect a 4% difference in proportions.

These large sample sizes permit identification of statistically significant differences of small magnitude, not all of which may have substantial clinical and policy importance. We will work with our patient, clinical, and policy stakeholders to interpret the meaning of the magnitude of observed treatment effects. The ability to detect small differences (Aim 1) will enable detection of clinically meaningful treatment heterogeneity (Aim 2).

Limitations

National Medicaid data offer exceedingly large, reliable and widely used sources of information for comparative outcomes research. Although the data do not include some self- reported, recovery-oriented outcomes that might be available in prospective studies, outcomes available in our data such as avoidance of serious medical illnesses, premature death, and the need for psychiatric emergency services and hospitalization are valued by patients as important near-term outcomes that help make long-term recovery possible.

The analytic plans for Aims 1 and 2 involve only Medicaid financed patients, which is the dominant source of payment for individuals diagnosed with schizophrenia in the U.S.[47] We will not be able to evaluate the comparative effectiveness of common pharmacological strategies in the relatively small patient population with private insurance. Similarly, we will not be able to study the comparative effectiveness of medication treatment strategies in uninsured patients. Yet the results of the proposed analysis will represent the experiences of most patients treated for schizophrenia in the United States including substantial representation of important groups, such as ethnic/racial minorities who are usually underrepresented in schizophrenia outcomes research, and patients with significant medical and mental health comorbidities who are often systematically excluded from such research.

Potential confounding is a concern in all observational comparative effectiveness research. We address potential confounding by treatment indication by restricting our analyses to second-line treatment strategies and comparable schizophrenia subgroups to create situations where the magnitude of potential confounding is expected to be limited due to a lack of strong evidence supporting one treatment option over others. The clinical diagnoses in claims data have the strong advantage of being the basis of real-world decision-making. In addition, propensity score methods will be used to minimize residual confounding from a large number of measured demographic and clinical patient characteristics.

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Appendices:

Appendiz 1: Exclusion Diagnoses

Appendix 2: Variables included in propensity scores

Appendix 1: Exclusion Diagnoses (Contraindications for clozapine, other antipsychotics, or life threatening)

Diagnosis	ICD-9-CM Codes*
Narrow angle glaucoma	365.02
Myocarditis	422.x, 391.2x, 398.0x
Neutrophil disorders	288.00-288.04, 288.09, 288.1x
Malignant neoplasms	140-205
Epilepsy, seizure disorders	345.xx
Alzheimer's and other cerebral degenerations	331.xx

* x indicates inclusion of any 5th digit if available for a diagnosis code.
xx indicates inclusion of any 4th and 5th digits if available for a diagnosis code.

Appendix 2: Variables included in the Propensity Score

Demographics
Gender
Male
Female
Age group
18-21
22-25
26-29
30-33
34-37
38-41
42-45
46-49
50-53
54-57
58-61
62-64
Race/Ethnicity
White, non-Hispanic
Black, non-Hispanic
Hispanic
Other
Medicaid Eligibility
Disability
Low income
Other
AP treatment Initiation year
2002
2003
2004
2005
2006
2007

2008
2009

Diagnostic History, past year	ICD-9-CM Codes*
Depression	293.83, 296.2x, 296.3x, 296.9x, 298.0x, 300.4x, 311.xx
Anxiety	293.84, 300.0x, 300.2x, 300.3x, 308.3x, 309.21, 309.81, 313.0x, 313.2x, 313.89
Bipolar	296.xx (not 296.2x or 296.3x or 296.9x)
Substance use disorder	291.xx, 292.xx, 303.xx, 304.xx
Moderate/severe mental retardation	318.xx
HIV	042, 043, 044, 079.53, V08
Neoplasms	140.xx-239.xx (Exclude people with malignant neoplasms 140.xx-205.xx)
Diabetes	250.xx
Obesity	270.xx
Hyperlipidemia	272.0x-272.4x, 272.7x, 272.9x
White blood cell diseases	288.xx,289.xx (exclude neutrophil d/o 288.00-288.04, 288.09, 288.1x)
Anemia	280.xx–285.xx
Drug-related dyskinesia	333.85
Hypertension	401.xx-405.xx
Ischemic heart disease	410.xx-414.xx
Pulmonary circulation diseases	415.xx-417.xx
Cardiac dysrhythmias	427.xx
Heart failure	428.xx
Cerebrovascular disease	430.xx-438.xx
Acute bronchitis and bronchiolitis	466.xx
Chronic bronchitis	491.xx
Pneumonia	480.xx-486.xx
Emphysema	492.xx
Asthma	493.xx
Appendicitis	540.xx–543.xx
Noninfectious enteritis and colitis	555.xx–558.xx
Diverticula of intestine	562.xx
Intestinal obstruction	560.xx
Chronic liver disease and cirrhosis	571.xx
Acute & chronic pancreatitis	577.0x, 577.1x
Cholelithiasis	574.xx
Acute kidney failure	584.xx
Chronic kidney failure	585.xx

Kidney infections	590.xx
Cellulitis and abscess	681.xx–682.xx
Osteoarthrosis and allied disorders	715.xx
Intervertebral disc disorder	722.xx
Fractures, all sites	800.xx–829.xx
Fracture of neck of femur	820.xx
Poisoning by psychotropic medication	969.xx
Poisonings	960.xx–989.xx
Suicide and self-inflicted injury	E950-959
Intracranial injury	815.xx-854.xx
Severe cardiovascular diseases	401.0x-404.9x, 410.xx-416.xx, 425.xx-437.xx, 440.xx-447.xx
Schizophreniform	295.4x
Schizoaffective	295.7x

* x indicates inclusion of any 5th digit if available for a diagnosis code.
xx indicates inclusion of any 4th and 5th digits if available for a diagnosis code.

Medication history, past year	Drug class
Psychotropic medication	
Antidepressants	SSRI/SNRI/mirtazapine, TCA and heterocyclic compounds, MAOI, trazodone-related antidepressants, bupropion
Mood Stabilizer	lithium, primary anticonvulsant, secondary anticonvulsant
ADHD medication	psychostimulants, alpha-agonists
Anxiolytic/hypnotics	benzodiazepines, GABA agonists, other newer or older anxiolytic/hypnotic
Other psychiatric medication	modafinil, oxybate, phendimetrazine, benzphetamine
OB/GYN medication	oral contraceptives, other contraception, medroxyprogesterone
Metabolic and related medication	lipid-lowering drugs, hypothyroid treatment, antithyroid agents, anorexiants
Cardiovascular medication	thiazide diuretic, ACE inhibitor/ARBs, other anti-hypertensives, other cardiovascular drugs
Respiratory/allergy medication	non-sedating antihistamines, other antihistamines, Corticosteroids, other Asthma medications, Smoking cessation
Gastrointestinal medication	histamine 2 receptor antagonists, proton-pump inhibitors, other prescription dyspepsia, Antacids, anti H pylori, phenothiazine antiemetics, Ulcerative colitis treatment
Neurologic/musculoskeletal medication	migraine treatment/prevention, NSAID, includes coxibs, narcotic analgesic, Non-narcotic analgesic (acetaminophen), Cyclobenzaprine, other skeletal muscle relaxants, other rheumatologic
Antibiotics	
Diabetic medication	
Hyperlipidemia medication	
Severe cardiovascular medication	

Health care services, past year

Mental Health Emergency Service

Outpatient visits for Schizophrenia (0-9, 10-29, 30-49, ≥50)

Hospital admissions for psychiatric illness (1, 2, 3,≥4)

Psychotherapy

Psychosocial Service contacts

CPT Codes for Psychotherapy or Psychosocial Service Contacts

Services	CPT Codes
Psychotherapy	90804-90829, 90841-90847, 90849, 90853, 90855, 90857, 90875, 90876
Psychosocial Service Contacts	H0036, H2000, H2010, H2011, H2012, H2014, H2017