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ASSOCIATION BETWEEN ADHERENCE AND PERSISTENCE WITH ANTIPSYCHOTICS AND OUTCOMES AMONG MEDICAID PATIENTS WITH SCHIZOPHRENIA

J. Panish,[1] S. Karve,[2] S. Candrilli,[2] R. Dirani[1]

[1]Ortho-McNeil Janssen Scientific Affairs, LLC, Titusville, NJ, USA; [2]RTI Health Solutions, Research Triangle Park, NC, USA

ABSTRACT

Background: Patients with schizophrenia often do not take medication as prescribed, which may increase relapse risk, often leading to rehospitalization and higher use of other health care services.

Purpose: To examine adherence and persistence rates among patients with schizophrenia experiencing ≥2 relapses who were treated with second-generation oral antipsychotics (SGOAs).

Methods: Using a multistate Medicaid database, adult (18-64 years) patients were identified with a diagnosis of schizophrenia and evidence of ≥2 relapses (ie, inpatient admission or emergency department visit with primary or secondary diagnosis of schizophrenia, depression, dementia, or other psychosis) within 1 year after SGOA therapy was initiated. A dichotomous measure of persistence was used, in which patients with therapy interruption (SGOA refill gap of >60 days) or discontinuation were categorized as nonpersistent, and patients with continuous SGOA use (ie, refill gap ≤60 days) were categorized as persistent. Adherence to SGOA therapy was measured using the medication possession ratio (MPR), calculated as patients' cumulative exposure to SGOAs during the 12-month period after SGOA initiation, divided by 365 days, and was stratified as adherent (MPR ≥ 0.80) and nonadherent (MPR < 0.80). Association between adherence to and persistence with SGOA treatment and psychiatric-related relapses was assessed using a series of negative binomial and Poisson regression models. No adjustment was made for multiplicity.

Results: The study cohort consisted of 3714 patients with mean age of 42.6 years (SD 11.63); 56% were female and 48% were black. Overall, 45% of patients were adherent to and 50% persistent with medication. Compared with older patients (mean age ~43.5 years) and patients of other racial groups (ie, white, Hispanic, and other), younger (mean age ~42.0 years) and black patients were significantly less likely to be adherent and persistent with SGOA therapy ($P < 0.001$ for each comparison). Fewer relapses on average were noted in adherent vs nonadherent patients (3.85 vs 4.13; $P < 0.001$) and in persistent vs nonpersistent patients (3.80 vs 4.21; $P < 0.001$). Patients who were adherent (incidence rate ratio [IRR] = 0.90; 95%CI = 0.86-0.94; $P < 0.001$) or persistent (IRR = 0.88; 95%CI = 0.84-0.92; $P < 0.001$) had significantly lower rates of psychiatric-related relapses compared with nonadherent and nonpersistent patients, respectively.

Conclusion: This analysis reinforces the need for improving treatment adherence and persistence among patients with schizophrenia, which may lower the rate of psychiatric-related relapse. Future research is needed to assess whether newer antipsychotic therapies with less-frequent dosing may improve adherence among patients with schizophrenia therapy.

BACKGROUND

- Schizophrenia is a complex psychiatric disorder characterized by distorted perceptions of reality, with an annual US prevalence of 1.1%[1]
- Primary pharmacologic treatment includes use of
  - First-generation antipsychotics (eg, haloperidol, chlorpromazine)
  - Second-generation antipsychotics (eg, paliperidone, olanzapine, aripiprazole)
- Adherence to pharmacologic treatment aids in lowering relapse rate[2]
- Medication adherence among patients with schizophrenia ranges from 20% to 89%[3]
- Antipsychotic nonadherence is associated with higher health care resource use and increased risk of schizophrenia relapse[4]
- Antipsychotic nonadherence accounts for ~30% of rehospitalizations[5]

STUDY OBJECTIVE

- This study examined adherence and persistence rates among patients with schizophrenia experiencing ≥2 relapse events (ie, psychiatric-related hospitalization and emergency department [ED] visits) and estimated all-cause and schizophrenia-related health care use after second-generation oral antipsychotic (SGOA) initiation

METHODS

Data source: Thomson Reuters MarketScan Medicaid Multistate database

- Data elements included details on inpatient, outpatient, and long-term services and outpatient prescription drug use (service-level claims including diagnosis codes, costs, and prescription information available)
  - Study period: January 1, 2004, to December 31, 2008
  - Demographic and plan enrollment information, including age, sex, race/ethnicity, aid category, and mental health substance abuse coverage
  - All data linked by unique encrypted enrollee identifiers
    - ~26 million Medicaid enrollees from 11 states

Inclusion and exclusion criteria

- Inclusion criteria
  - One prescription for an SGOA during the period January 1, 2005, to December 31, 2007
    - SGOAs include aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone
  - Index date: date of first SGOA prescription filled during this period
  - Two diagnosis claims for schizophrenia (ie, International Classification of Diseases, 9th revision, Clinical Modification [ICD-9-CM] code 295.xx) during 12 months before the index date
  - Two psychiatric-related relapse events during the 12 months after the index date
    - Defined as an inpatient admission or ED visit with a diagnosis related to a psychiatric condition, including schizophrenia, depression, anxiety, other psychoses, or dementia
  - Patients aged ≥18 years at the index date
  - Continuous Medicaid enrollment in the 12 months before and 12 months after the SGOA index date
- Exclusion criteria
  - Patients aged ≥65 years at any point during the observation period
  - Patients listed as dual beneficiaries (ie, both Medicare and Medicaid coverage)

Study measures

Covariates

- Patient characteristics included age, sex, race/ethnicity, health plan (ie, fee-for-service, capitated), mental health substance abuse coverage, reason for Medicaid eligibility
- Comorbidity burden assessed using the Charlson Comorbidity Index (CCI) for the following study periods:
  - Preindex date (ie, CCI score for the 12-month period before the index SGOA prescription)
  - Postindex date (ie, CCI score for the 12-month period after the index SGOA prescription)
  - Preindex and postindex date (ie, CCI score for the 12 months before and the 12 months after the index SGOA prescription)
- Medication use patterns assessed during the 12-month postindex date period
  - Average number of SGOA prescriptions obtained
  - Total number of SGOA therapy days
  - Average number of days per SGOA prescription (ie, prescription length)
  - Average SGOA daily dose
  - Total cost of SGOA prescriptions obtained
  - Average SGOA pill burden
  - SGOA dose escalation and time to dose escalation
  - SGOA monotherapy vs polypharmacy
    - Defined as the use of multiple SGOAs at initiation or at least 60 days of concomitant use of 2 SGOAs during the 12-month postindex date period
    - Average number of SGOAs observed after the date of the second psychiatric-related relapse event

Primary independent variables

- Antipsychotic therapy adherence and persistence were considered the primary independent variables for this study
- Adherence to SGOA assessed using the medication possession ratio (MPR)
  - Sum of days' supply in observation period ÷ (365 – days hospitalized during observation period)
  - Adherent: MPR >80%; nonadherent: MPR <80%
- *Persistence with SGOA* defined as
  - Category 1: *continuous use*, defined as patients continuing the index SGOA or switching to a different SGOA within the permissible gap of ≤60 days
  - Category 2: *therapy interruption*, defined as refill gap >60 days with subsequent reinitiation with index or other SGOA
  - Category 3: *therapy discontinuation*, defined as refill gap >60 days without subsequent reinitiation of therapy
  - Patients in category 1 classified as "persistent," patients in categories 2 and 3 classified as "nonpersistent"[6]

OUTCOME MEASURES

- Psychiatric-related relapse events
- All-cause and schizophrenia-related health care use assessed for the following service categories (all outcomes assessed during the 12-month period after the index SGOA date):
  - Hospital inpatient
  - Hospital outpatient
  - Physician office
  - ED
  - Pharmacy
  - Ancillary care
  - Total nonpharmacy medical
  - Total medical (ie, including pharmacy)

STATISTICAL ANALYSES

- Analyses carried out using SAS® version 9.1.3 (Cary, NC, USA)
- All variables analyzed descriptively
  - Means, standard deviations (SDs), medians, range, frequency distributions
  - Univariate differences between adherent and nonadherent and persistent and nonpersistent patients tested using the following tests:
    - Chi-square or Fisher exact test for categorical variables (eg, sex, race/ethnicity)
    - Student *t* test for continuous variables (eg, age, CCI score)
    - Multiplicity was not adjusted for
- Multivariable analyses conducted to assess differences in outcome measures between adherent and nonadherent patients and between persistent and nonpersistent patients after adjusting for baseline demographic and clinical characteristics
- Covariates included in the multivariable models
  - Age, sex, race/ethnicity, health plan, eligibility status, dose escalation, polypharmacy, mental health substance abuse coverage, CCI score, and indicator for adherence or persistence
- Types of models estimated dependent on outcome
  - Poisson/negative binomial models: for count data outcomes (eg, number of physician office visits)
  - Logistic regression: for dichotomous outcomes (eg, had a schizophrenia-related office visit)

RESULTS

- A sample attrition table is shown in **Table 1**

Table 1. Sequence of Steps

Attrition Steps	N
Patients with ≥1 SGOA claim during January 1, 2005, through December 31, 2007	64,835
Patients with ≥2 schizophrenia diagnosis claims during the 12-month preindex date period	30,038
Patients with ≥2 psychiatric-related inpatient or ED diagnosis claims during the 12-month postindex date period	11,897
Patients with ≥2 schizophrenia diagnosis claims and ≥2 psychiatric-related diagnosis claims	5510
Patients with continuous Medicaid enrollment (along with drug coverage) during the 12-month preindex and the 12-month postindex date periods	3901
Excluding patients aged <18 years or ≥65 years at the index date	3725
Excluding patients with Medicare eligibility at any time during the 12-month preindex and the 12-month postindex date periods	3717
Excluding patients with missing quantity dispensed information (final sample size)	**3714**

SGOA therapy adherence and persistence

- SGOA therapy adherence, mean (SD)
  - Study cohort: 0.66 (0.30)
  - Among adherent patients: 0.94 (0.06)
  - Among nonadherent patients: 0.43 (0.22)
  - Overall: 45% adherent to SGOA therapy
- SGOA therapy persistence
  - 50% of patients were persistent with SGOA therapy
  - 23% had ≥1 SGOA therapy interruption
  - 27% discontinued SGOA therapy

Demographic characteristics

- Study cohort age, mean (SD): 42.62 (11.63) years
  - Adherent (mean 43.44 years) vs nonadherent (mean 41.94 years; $P < 0.001$)
  - Persistent (43.50 years) vs nonpersistent (41.74 years; $P < 0.001$)
- Blacks were less likely than whites to be adherent to ($P < 0.001$) and persistent with ($P < 0.001$) SGOA therapy
- 96% of patients had "blind/disabled individual" as basis for Medicaid eligibility
- 97% of patients had mental health substance coverage
- On average, significantly higher comorbidity burden among adherent and persistent patients than among nonadherent (2.08 vs 1.73; $P < 0.001$) and nonpersistent (2.04 vs 1.74; $P < 0.001$) patients

SGOA use patterns

- Mean number of SGOA prescriptions
  - Overall, mean (SD): 12.02 (9.07)
  - Adherent, mean 18.46, vs nonadherent, mean 6.74 ($P < 0.001$)
  - Persistent, mean 17.54, vs nonpersistent, mean 6.51 ($P < 0.001$)
- Mean SGOA therapy duration
  - Overall, mean (SD): 230.48 (107.73) days
  - Adherent, mean 328.98, vs nonadherent, mean 149.74 days ($P < 0.001$)
  - Persistent, mean 320.65, vs nonpersistent, mean 140.41 days ($P < 0.001$)
- Patients receiving monotherapy
  - 84.91% of nonadherent patients vs 53.20% of adherent patients ($P < 0.001$)
  - 84.93% of nonpersistent patients vs 56.30% of persistent patients ($P < 0.001$)

Psychiatric-related relapse events

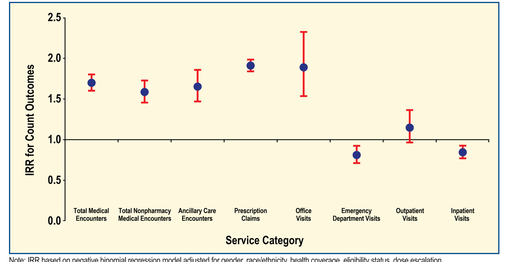
- Mean number of psychiatric-related relapse events
  - Overall, mean (SD): 4.01 (3.34)
  - Adherent, mean 3.85, vs nonadherent, mean 4.13 ($P < 0.001$)
  - Persistent, mean 3.80, vs nonpersistent, mean 4.21 ($P < 0.001$)
- Risk-adjusted rate of psychiatric-related relapse events was 10% lower among adherent patients than among nonadherent patients
  - Incidence rate ratio (IRR) = 0.90; 95% confidence interval (CI) = 0.86-0.94; $P < 0.001$
- Risk-adjusted rate of psychiatric-related relapse events was 12% lower among persistent patients than nonpersistent patients
  - IRR = 0.88; 95% CI = 0.84-0.92; $P < 0.001$

Unadjusted health care use

- Significantly smaller proportion of adherent and persistent patients had a schizophrenia-related ED visit during the 12-month postindex date period
  - Adherent vs nonadherent patients: 29.65% vs 35.13%; $P < 0.001$
  - Persistent vs nonpersistent patients: 30.44% vs 34.88%; $P = 0.004$

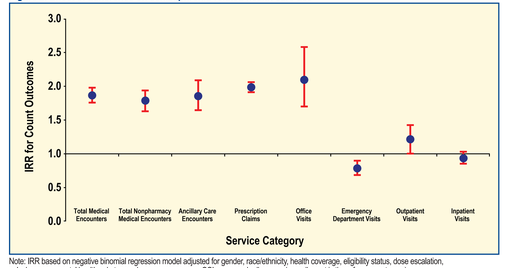
Covariate-adjusted health care use (Figures 1-4)

Figure 1. Effect of persistence on schizophrenia-related health care use



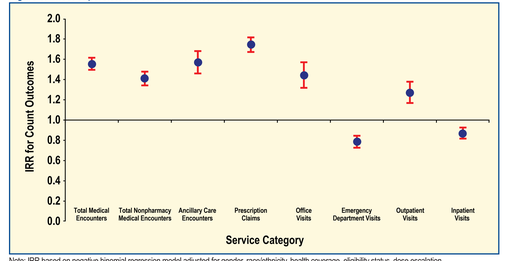
Note: IRR based on negative binomial regression model adjusted for gender, race/ethnicity, health coverage, eligibility status, dose escalation, polypharmacy, mental health substance abuse coverage, age, CCI score, and persistence (nonpersistent is the reference category).

Figure 2. Effect of adherence on schizophrenia-related health care use



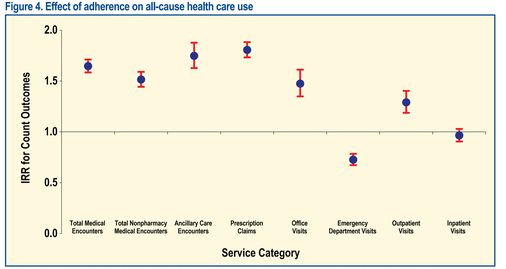
Note: IRR based on negative binomial regression model adjusted for gender, race/ethnicity, health coverage, eligibility status, dose escalation, polypharmacy, mental health substance abuse coverage, age, CCI score, and adherence (nonadherent is the reference category).

Figure 3. Effect of persistence on all-cause health care use



Note: IRR based on negative binomial regression model adjusted for gender, race/ethnicity, health coverage, eligibility status, dose escalation, polypharmacy, mental health substance abuse coverage, age, CCI score, and persistence (nonpersistent is the reference category).

Figure 4. Effect of adherence on all-cause health care use



Note: IRR based on negative binomial regression model adjusted for gender, race/ethnicity, health coverage, eligibility status, dose escalation, polypharmacy, mental health substance abuse coverage, age, CCI score, and adherence (nonadherent is the reference category).

LIMITATIONS

- Observation of a prescription claim assumed complete ingestion of the medication obtained
- Inaccuracy in diagnosis coding (ICD-9-CM codes) may lead to misidentification of patients as having schizophrenia
- Lack of data on factors related to medication adherence and outcome measures (eg, illness severity, medication side effects)
- Findings may not be generalizable to individuals enrolled in other federal (eg, Medicare) or commercial health plans

CONCLUSIONS

- ~45% of patients were adherent to SGOA therapy and ~50% of patients were persistent with SGOA therapy
- The psychiatric-related relapse rate was significantly lower among patients adherent to and persistent with SGOA therapy
- Significantly lower rates of all-cause and schizophrenia-related inpatient admissions and ED visits were observed among patients adherent to and persistent with SGOA therapy
- Significantly lower rates of all-cause and schizophrenia-related inpatient admissions were observed among patients persistent with SGOA therapy
- This analysis reinforces the need for improving treatment adherence and persistence among patients with schizophrenia, which may lower the rate of psychiatric-related relapse
- Future research is needed to assess whether newer antipsychotics with less-frequent dosing may improve adherence among patients receiving schizophrenia therapy

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Disclosures

J. Panish and R. Dirani are employees of Ortho-McNeil Janssen Scientific Affairs, LLC, and Johnson & Johnson stockholders.

S. Karve and S. Candrilli are employees of RTI Health Solutions.

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ABSTRACT

Background: Patients with schizophrenia often do not take medication as prescribed, which may increase relapse risk, often leading to rehospitalization and higher use of other health care services.

Purpose: To examine adherence and persistence rates among patients with schizophrenia experiencing ≥2 relapses who were treated with second-generation oral antipsychotics (SGOAs).

Methods: Using a multistate Medicaid database, adult (18-64 years) patients were identified with a diagnosis of schizophrenia and evidence of ≥2 relapses (ie, inpatient admission or emergency department visit with primary or secondary diagnosis of schizophrenia, depression, dementia, or other psychosis) within 1 year after SGOA therapy was initiated. A dichotomous measure of persistence was used, in which patients with therapy interruption (SGOA refill gap of >60 days) or discontinuation were categorized as nonpersistent, and patients with continuous SGOA use (ie, refill gap ≤60 days) were categorized as persistent. Adherence to SGOA therapy was measured using the medication possession ratio (MPR), calculated as patients' cumulative exposure to SGOAs during the 12-month period after SGOA initiation, divided by 365 days, and was stratified as adherent (MPR ≥ 0.80) and nonadherent (MPR < 0.80). Association between adherence to and persistence with SGOA treatment and psychiatric-related relapses was assessed using a series of negative binomial and Poisson regression models. No adjustment was made for multiplicity.

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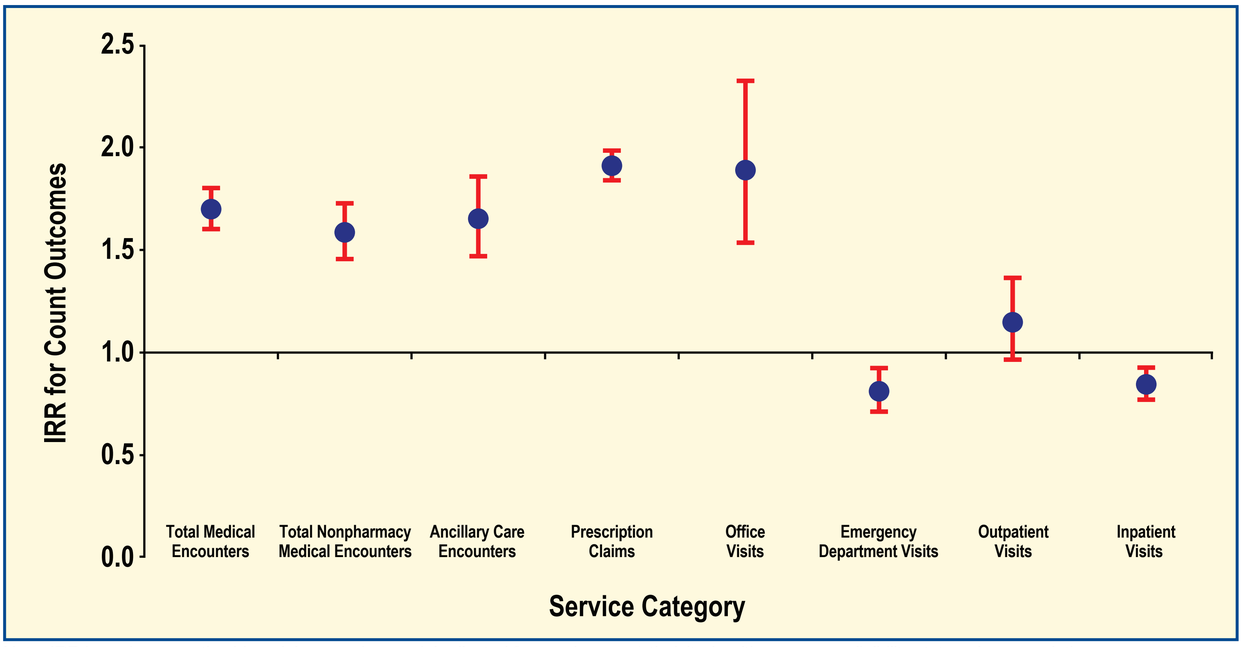
- Mean number of psychiatric-related relapse events
  - Overall, mean (SD): 4.01 (3.34)
  - Adherent, mean 3.85, vs nonadherent, mean 4.13 ($P < 0.001$)
  - Persistent, mean 3.80, vs nonpersistent, mean 4.21 ($P < 0.001$)
- Risk-adjusted rate of psychiatric-related relapse events was 10% lower among adherent patients than among nonadherent patients
  - Incidence rate ratio (IRR) = 0.90; 95% confidence interval (CI) = 0.86-0.94; $P < 0.001$
- Risk-adjusted rate of psychiatric-related relapse events was 12% lower among persistent patients than nonpersistent patients
  - IRR = 0.88; 95% CI = 0.84-0.92; $P < 0.001$

Unadjusted health care use

- Significantly smaller proportion of adherent and persistent patients had a schizophrenia-related ED visit during the 12-month postindex date period
  - Adherent vs nonadherent patients: 29.65% vs 35.13%; $P < 0.001$
  - Persistent vs nonpersistent patients: 30.44% vs 34.88%; $P = 0.004$

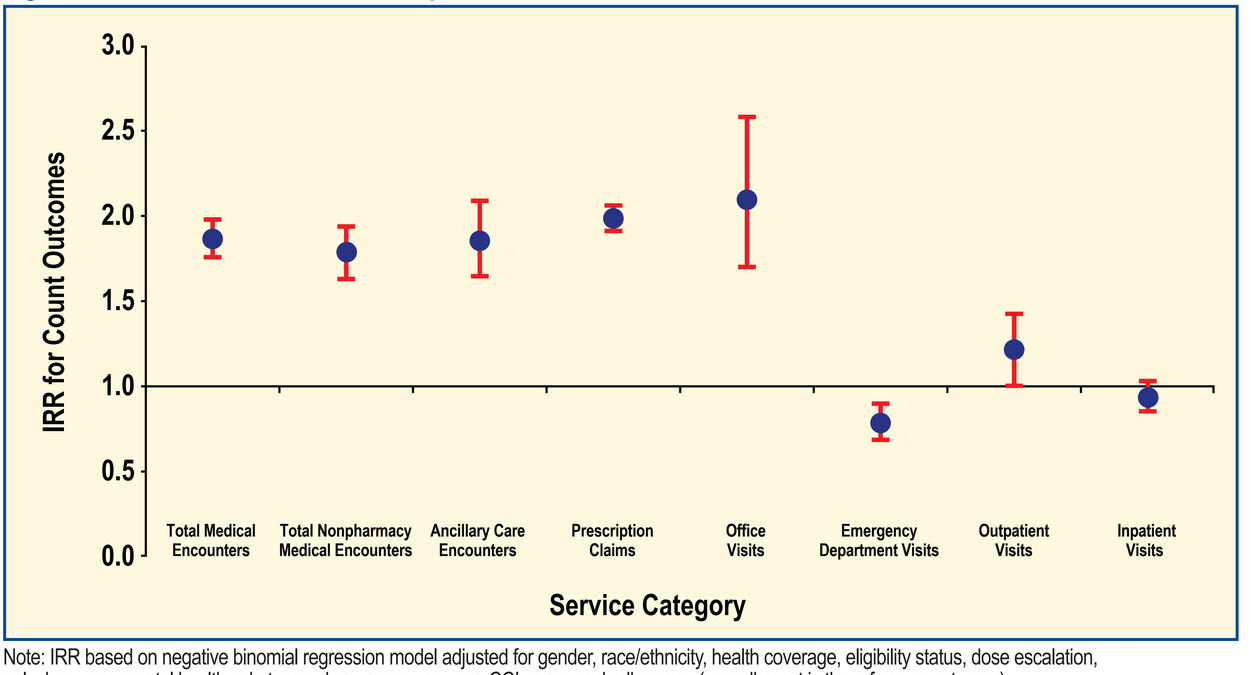
Covariate-adjusted health care use (Figures 1-4)

Figure 1. Effect of persistence on schizophrenia-related health care use



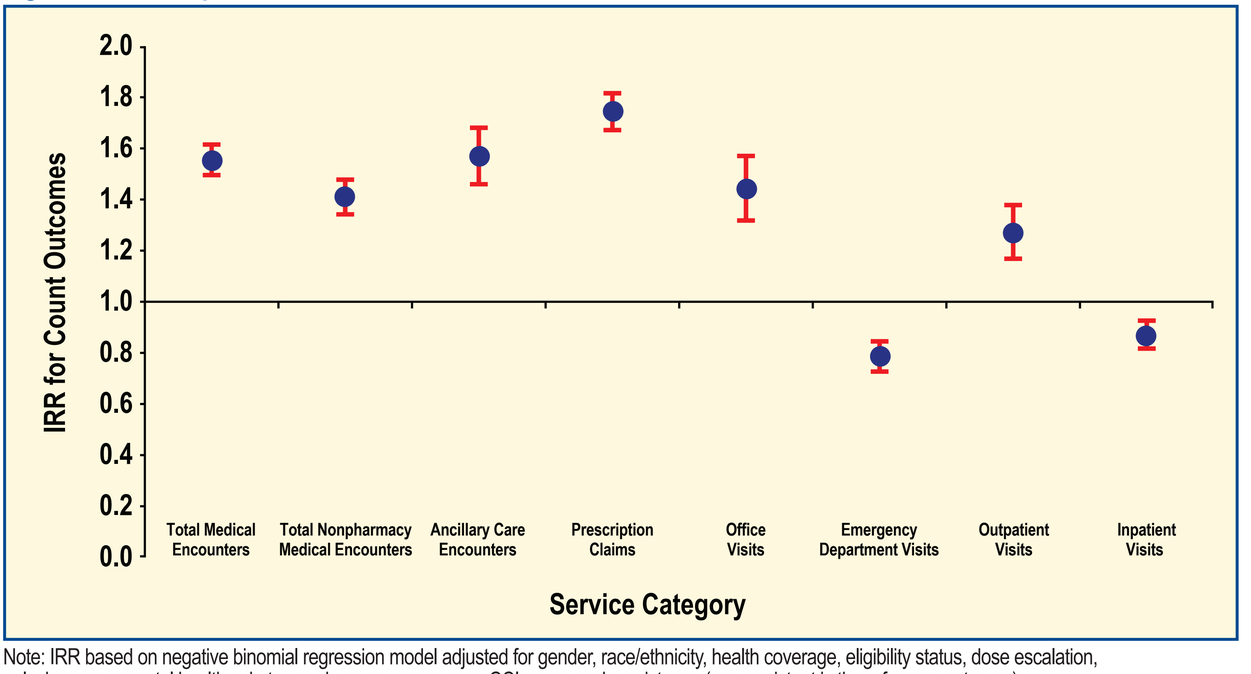
Note: IRR based on negative binomial regression model adjusted for gender, race/ethnicity, health coverage, eligibility status, dose escalation, polypharmacy, mental health substance abuse coverage, age, CCI score, and persistence (nonpersistent is the reference category).

Figure 2. Effect of adherence on schizophrenia-related health care use



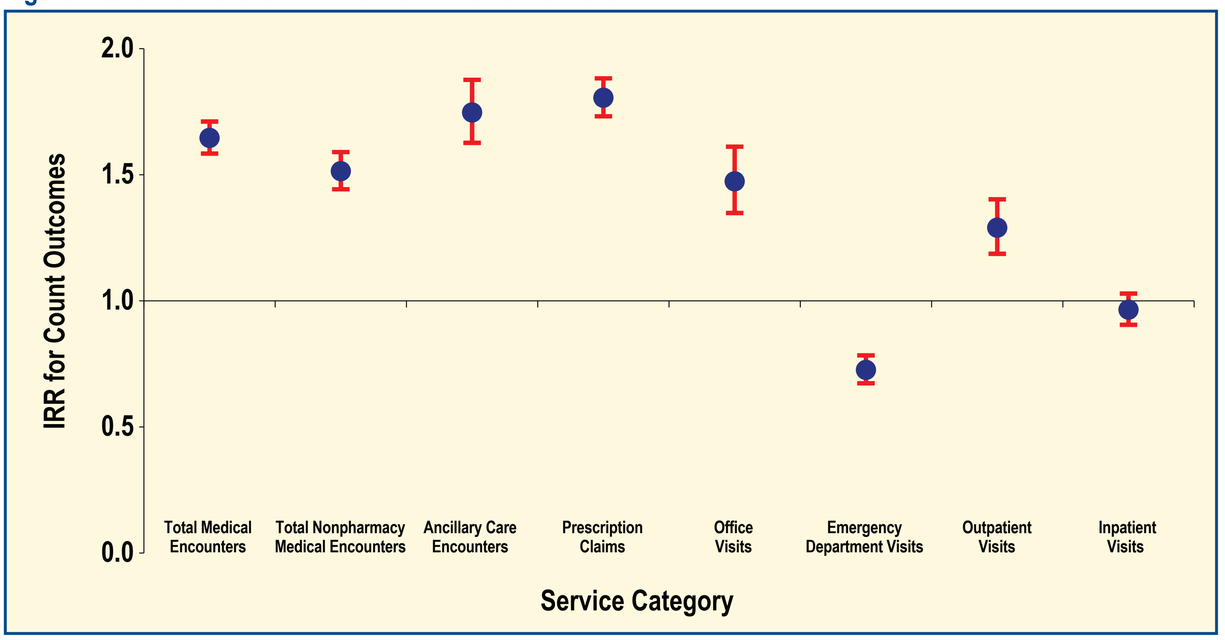
Note: IRR based on negative binomial regression model adjusted for gender, race/ethnicity, health coverage, eligibility status, dose escalation, polypharmacy, mental health substance abuse coverage, age, CCI score, and adherence (nonadherent is the reference category).

Figure 3. Effect of persistence on all-cause health care use



Note: IRR based on negative binomial regression model adjusted for gender, race/ethnicity, health coverage, eligibility status, dose escalation, polypharmacy, mental health substance abuse coverage, age, CCI score, and persistence (nonpersistent is the reference category).

Figure 4. Effect of adherence on all-cause health care use



Note: IRR based on negative binomial regression model adjusted for gender, race/ethnicity, health coverage, eligibility status, dose escalation, polypharmacy, mental health substance abuse coverage, age, CCI score, and adherence (nonadherent is the reference category).

LIMITATIONS

- Observation of a prescription claim assumed complete ingestion of the medication obtained
- Inaccuracy in diagnosis coding (ICD-9-CM codes) may lead to misidentification of patients as having schizophrenia
- Lack of data on factors related to medication adherence and outcome measures (eg, illness severity, medication side effects)
- Findings may not be generalizable to individuals enrolled in other federal (eg, Medicare) or commercial health plans

CONCLUSIONS

- ~45% of patients were adherent to SGOA therapy and ~50% of patients were persistent with SGOA therapy
- The psychiatric-related relapse rate was significantly lower among patients adherent to and persistent with SGOA therapy
- Significantly lower rates of all-cause and schizophrenia-related inpatient admissions and ED visits were observed among patients adherent to and persistent with SGOA therapy
- Significantly lower rates of all-cause and schizophrenia-related inpatient admissions were observed among patients persistent with SGOA therapy
- This analysis reinforces the need for improving treatment adherence and persistence among patients with schizophrenia, which may lower the rate of psychiatric-related relapse
- Future research is needed to assess whether newer antipsychotics with less-frequent dosing may improve adherence among patients receiving schizophrenia therapy

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