Methodological Considerations in Estimating Adherence and Persistence for a Long-Acting Injectable Medication

Elizabeth J. Campagna, MS, PSTAT; Erik Muser, PharmD, MPH; Joseph Parks, MD; and Elaine H. Morrato, DrPH, MPH

ABSTRACT

BACKGROUND: Measures of medication adherence and persistence are important for researchers and policymakers to assess quality of care. Lack of adherence has been associated with adverse outcomes and higher costs of care. Long-acting medication formulations, including injectable forms, have been proposed as interventions to increase adherence and in turn improve health outcomes and costs. Standard measures of adherence/persistence were developed for orally administered medications. Methods for assessing adherence/persistence of long-acting injectable dose forms are understudied.

OBJECTIVE: To compare the consistency between standard measures of adherence/persistence versus proposed variations that consider the data quality and injectable administration method for a long-acting injectable second-generation antipsychotic (SGA) using an orally administered SGA as the reference.

METHODS: Standard adherence/persistence measures were designed for oral tablet formulations, in particular accounting for accumulation of pills caused by early refills. To address this limitation and the accuracy of the days supply field for long-acting injectable SGAs in pharmacy claims, 2 alternatives are proposed. The first approach calculates days supply using the labeled dosing schedule for the given injectable. The second approach builds on the first and sets days supply to the minimum of the time between injections and the time frame according to the labeled dosing schedule. Administrative health care claims data from the Missouri Medicaid system were analyzed to compare adherence/persistence measures between formulations. Common adherence/persistence measures, including medication possession ratio (MPR) and proportion of days covered (PDC), were evaluated in this study. The analysis cohorts comprised 195 adult patients with schizophrenia who initiated a long-acting injectable SGA (LA-SGA) and 369 patients initiating an oral SGA (O-SGA) from August 1, 2009, through April 30, 2010. Chi-squared tests, the Kruskal-Wallis test, and Kaplan-Meier curves were used to compare adherence/persistence measures between cohorts.

RESULTS: Days supply was most frequently recorded as 30 days for O-SGA and 28 days for LA-SGA. Time between claim fills was most commonly 28 days for both cohorts. Using the LA-SGA pharmacy claims data, MPR was 0.91 and did not vary significantly from MPR of O-SGA (0.90; test statistic = 0.29, $P = 0.590$). When applying the labeled dosing schedule to compute days supply, the LA-SGA MPR rose to 0.97 and varied significantly from MPR of O-SGA (test statistic = 9.60, $P = 0.002$). Additionally controlling for the inability for excess medication accumulation, MPR for LA-SGA dropped to 0.86, which varied significantly from MPR of O-SGA (test statistic = 4.01, $P = 0.045$). PDC varied from 0.55 to 0.61 for LA-SGA but was consistently significantly different from the 0.37 PDC value of O-SGA ($P < 0.05$ for each comparison).

CONCLUSIONS: Standard medication adherence/persistence measures yielded different conclusions when comparing a LA-SGA and an O-SGA, depending on the measure and underlying assumption for days supply. Adherence/persistence measures that address pharmacological differences in terms of formulation and duration of therapeutic drug levels between medications may be necessary and are particularly important as more injectable antipsychotic medications are approved in the United States. Therefore, payers and investigators should consider sensitivity analysis using different adherence/persistence definitions when making product comparisons to ensure confidence in conclusions.

J Manag Care Pharm. 2014;20(7):756-66

What is already known about this subject

- Lack of adherence has been associated with adverse outcomes and higher costs of care.
- Medication adherence and persistence definitions vary extensively in published literature yet are critical to researchers, payers, and policy decision makers. Moreover, drug adherence and persistence measures were designed for tablet formulations. Standard methods for measuring adherence and persistence using pharmacy claims data do not consider the unique characteristics of long-acting injectable formulations relative to oral formulations.
- Nonadherence with antipsychotic treatment is estimated to account for approximately 40% of all relapses in schizophrenia. Long-acting antipsychotic medication formulations, including injectable forms, have been proposed as interventions to help increase adherence and in turn improve health outcomes and costs. Adherence and persistence rates using administrative claims data for injectable long-acting antipsychotics compared with oral formulations are understudied.

What this study adds

- This study examines the consistency between standard measures of adherence and persistence relative to measures that take into consideration the unique characteristics of long-acting injectables relative to oral formulations. A case example is given using Medicaid claims data for paliperidone palmitate, a long-acting injectable second-generation antipsychotic (SGA), and aripiprazole, the most commonly used oral SGA in the dataset.

What this study adds *(continued)*

- In this analysis, estimates of medication possession ratio (MPR) varied from 0.86 to 0.97 and for proportion of days covered (PDC) from 0.55 to 0.61 for the long-acting injectable SGA cohort, depending on assumptions made. These results relative to oral SGA were not consistently significantly different for MPR (0.90) but were for PDC (0.37).
- Standard medication adherence and persistence measures yield varying conclusions when comparing a long-acting injectable SGA and an oral SGA medication. Adherence and persistence measures that address pharmacological differences in terms of formulation and duration of therapeutic drug levels between medications are necessary. Until then, investigators should consider sensitivity analysis using different adherence and persistence definitions when making product comparisons to ensure confidence in conclusions.

Measures of medication adherence and persistence are becoming increasingly valuable, since lack of adherence has been associated with adverse outcomes and higher costs of care.[1-5] Medication adherence/persistence is also an important component in the calculation of indicators used by policymakers to assess quality of care and to determine pay and performance goals, such as with the Healthcare Effectiveness Data and Information Set.[6] Adherence/persistence terminology, definitions, and methods of measurements vary extensively in published literature.[7,8] Andrade et al. (2006) advise that the choice of measures be determined by the advantages and limitations of the measures relative to the goal of the study.[7] In regards to pharmacy data, the most common measures currently used are medication possession ratio (MPR) and proportion of days covered (PDC).[3]

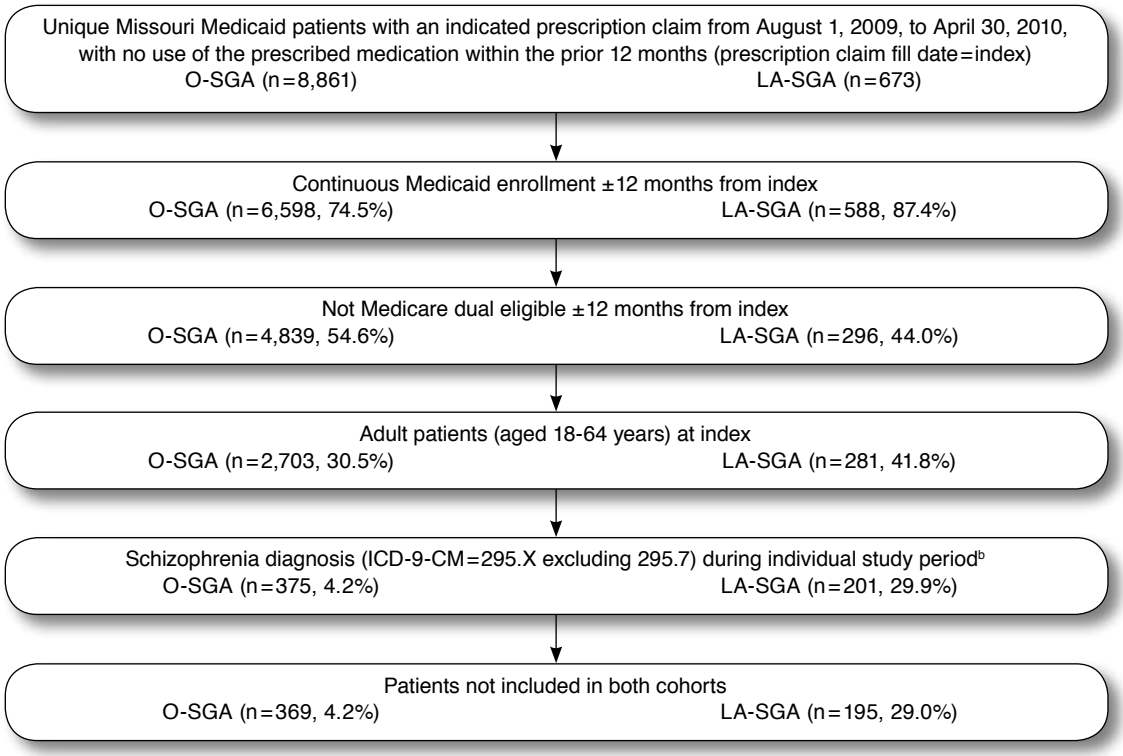
For comparability between studies and to avoid misperception, organizations and researchers should measure adherence/persistence in a consistent manner. Several entities have proposed standard terms and methods with the overarching goal of adopting a consistent framework for research.[9] Based on 3 years of international review and discussion, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Medication Compliance and Persistence Work Group published terminology and definitions related to adherence (synonymously referred to as *compliance* by ISPOR) and persistence in 2007.[10] The goal of this work was to provide guidance regarding the terms *compliance* and *persistence* as well as information on how to apply these measures for use in research. *Compliance* was defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen." *Persistence* was defined as "the duration of time from initiation to discontinuation of therapy." Measures of compliance cited by ISPOR include MPR and continuous measure of medication gaps (CMG). Measures of persistence include PDC and number of days to discontinuation.[11] The Pharmacy Quality Alliance, as well as the National Quality Forum, endorse PDC as the preferred method for medication adherence—their calculation of PDC is consistent with that of ISPOR.[12]

Low medication adherence is common in psychiatric patients for such reasons as disagreeable side effects, stigma, or inconvenience.[13] Antipsychotic medications are commonly required for chronic use, and nonadherence can lead to severe consequences, including relapse, hospitalization and, for some patients, an increased risk of death.[13] Gilmer et al. (2004) have reported that schizophrenic patients considered nonadherent are 2.5 times more likely to have a psychiatric hospitalization than those considered adherent.[1] Small changes in adherence/persistence have been shown to have significant impact on hospitalization.[2] Nonadherence with antipsychotic treatment is estimated to account for approximately 40% of all relapses in schizophrenia.[14-16] The odds of hospitalization for schizophrenia decrease by almost 20% for every 10% increase in MPR.[17] Long-acting (sustained or controlled release) antipsychotic medication formulations, including injectable forms, have been proposed as interventions to increase adherence/persistence and in turn improve health outcomes and costs. Longer antipsychotic half-life in and of itself has been shown to have an association with decreased hospitalization.[18] These formulations may improve safety, effectiveness, and tolerability from more predictable and continuous blood levels of medication over an extended period of time.[13] Compared with oral medication, the more sustained plasma concentrations of long-acting injectable antipsychotics may provide a wider window of opportunity to re-establish treatment without symptom recurrence or relapse.[19] The American Psychiatric Association practice guidelines recommend the use of long-acting injectable antipsychotics for schizophrenia patients with a history of recurrent relapse related to nonadherence.[20] Initial medication cost, which may be greater for long-acting injectable formulations, may potentially be offset by savings in physician, hospital, and lab costs.[21]

Adherence/persistence measures were designed for oral tablet formulations. With regards to antipsychotics in particular, MPR, PDC, and gap in therapy are common measures.[2,22] To our knowledge, there are no standard methods for measuring adherence/persistence in long-acting injectable formulations.

The purpose of this article was to compare consistency between standard measures of adherence/persistence with proposed variations that consider the data quality and injectable administration method for a long-acting injectable second-generation antipsychotic (SGA). An orally administered SGA served as the reference among schizophrenic adults enrolled in Missouri Medicaid. As the focus is on methodology, rather than on patient adherence/persistence, a single oral and a single

FIGURE 1 Case Example Cohort Selection[a]



[a]*In this study, O-SGA was represented by aripiprazole, and LA-SGA was represented by paliperidone palmitate.*

[b]*Baseline diagnoses of those without a diagnosis of schizophrenia during the study period (O-SGA, n=2,328, LA-SGA, n=80): 90.9% (n=2,115) and 86.3% (n=69) mood disorder; 60.9% (n=1,418) and 57.5% (n=46) anxiety disorder; 22.3% (n=518) and 45.0% (n=36) substance-related disorder; 12.7% (n=295) and 18.8% (n=15) alcohol-related disorders; 12.3% (n=287) and 17.5% (n=14) personality disorder; 11.7% (n=273) and 15.0% (n=12) suicide and intentional self-inflicted injury; 9.8% (n=227) and 31.3% (n=25) attention deficit hyperactivity disorder, conduct, disruptive behavior disorders; 6.3% (n=147) and 1.3% (n=1) adjustment disorder; 4.6% (n=107) and 37.5% (n=30) schizoaffective disorder; 3.7% (n=85) and 13.8% (n=11) developmental disorders; 2.8% (n=64) and 6.3% (n=5) delirium, dementia, and amnestic, and other cognitive disorders; 2.3% (n=54) and 2.5% (n=2) impulse control disorders, not elsewhere classified; 1.1% (n=26) and 5.0% (n=4) disorders usually diagnosed in infancy, childhood, or adolescence.*

O-SGA=oral second-generation antipsychotic; LA-SGA=long-acting injectable second-generation antipsychotic; ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification.

long-acting injectable medication were selected for ease of evaluation rather than looking at the entire medication class. The case examples used were paliperidone palmitate, a long-acting injectable SGA (LA-SGA), and aripiprazole, an oral SGA (O-SGA). Paliperidone palmitate was selected because it was the newest LA-SGA on the market at the time of this study. Aripiprazole was selected because it was the most commonly prescribed O-SGA in the Missouri Medicaid data at the time of this study.

Methods

Source Population

Administrative health care claims data from the Missouri Medicaid system were analyzed for 195 patients who initiated paliperidone palmitate, dosed once monthly and approved for the treatment of schizophrenia,[23] and for 369 patients initiating aripiprazole, from August 1, 2009, through April 30, 2010. Treatment of schizophrenia with aripiprazole is once a day.[24] Cohort inclusion criteria are outlined in Figure 1. To keep the focus on the therapeutic administration method rather than on a particular medication, paliperidone palmitate will be referred to as LA-SGA and aripiprazole as O-SGA.

Cohort Selection

The study population included adults (18-64 years of age) diagnosed with schizophrenia (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] 295.X, excluding 295.7). Dates of Medicaid and Medicare eligibility were provided with the claims data. Patients with at least 12 months of continuous Medicaid eligibility before and after medication initiation were eligible for the analysis. Patients

dually eligible for Medicaid and Medicare were excluded as Medicare claims data were not available. Prescriptions for the index medication were not allowed during the 12 month pre-period; however, use of other antipsychotic medications did not affect eligibility.

Key Variables

Medicaid pharmacy claims include fill date and days supply among other variables. Fill date represents the date the prescription was filled. Diagnoses were available from Medicaid inpatient and outpatient medical claims. Mental health is described using 13 predefined categories based on ICD-9-CM codes from the Clinical Classifications Software (CCS). Baseline is defined as the 12 months preceding medication initiation. Follow-up for each patient is 12 months following medication initiation, though medication use may cease before this time.

Persistence Measures

Terminology and definitions used reflect those from ISPOR Medication Compliance and Persistence Special Interest Group.[10,11] PDC is the number of days with medication available divided by the number of days in a specified time interval. If excess medication is received or refills are made early, the excess is applied towards subsequent absences of medication. The denominator for PDC is typically a clinically meaningful number of days that is the same for all intervals and patients (365 days in our study). PDC may be reported as dichotomous, referring to a patient as persistent when PDC > 0.80.[9]

$$PDC = \frac{Number\ of\ days\ during\ year\ when\ medication\ was\ available}{365}$$

Gaps are defined as the number of days during which a patient is without medication. Gaps are adjusted for oversupplies obtained during previous prescription intervals; this adjustment reduces the duration of treatment gaps. Maximum allowable gap may be summarized as a continuous outcome or categorical.[9] This study evaluated maximum gap as continuous, categorical, and at 2 cut-points: maximum gap exceeding (a) 7 days and (b) 3 days for O-SGA or 37 days for LA-SGA.[2,17] The 3/37-day gap definition was chosen based on average product half-life as a proxy for duration of therapeutic drug levels.[19] From a clinical perspective, LA-SGA continues to have therapeutic drug levels for a much longer duration following the last dose administered than is seen with O-SGA. Use of half-life as a proxy for the duration of therapeutic drug levels attempts to correct for this difference between LA-SGA and O-SGA. For patients with only an index fill, gap is defined as 365 days minus the days supply of the index fill.

$$Gap = [Fill\ date\ (i+1)] - [Fill\ date\ (i) + Days\ supply\ (i)] + Oversupply\ of\ previous\ Rx\ intervals$$

Discontinuation is defined by the first gap exceeding a predefined threshold. Time to discontinuation is computed as the count of days from the index prescription date to the final dispensing date prior to discontinuation plus the days supply of the final fill and any remaining oversupply.

Adherence Measures

Measures of adherence, MPR and CMG, require at least 2 fill dates; patients with an index fill only are excluded. MPR may also be referred to as the continuous measures of adherence.

MPR is calculated by summing the number of days supply for all fills and dividing by the number of days between the first fill and the last fill plus the days supply of the last fill. MPR may also be calculated excluding the days supply of the last refill from both the numerator and denominator. The denominator is truncated at the length of the study period, and values greater than 1.0 are generally truncated at 1.0. MPR may also be reported as dichotomous, referring to a patient as adherent when MPR > 0.80. This cut-point corresponds to a grace period between fills of approximately 7 days, assuming 30-day fills.[9]

$$MPR = \frac{\sum_{i=1}^{n} Days\ supply\ i}{[Last\ Rx\ date - Index\ Rx\ date] + Days\ supply\ of\ last\ Rx}$$

CMG is a ratio of the days in which a patient is without medication (gaps) to the observation period. Gaps can be negative (early fill) as well as positive (late fill). CMG requires addition of the positive and negative gaps, adjusting for oversupplies obtained during previous prescription intervals. The observation period is measured by days between the first and last fills. Negative values are set to zero.

$$CMG = \frac{\sum_{i=1}^{n-1} Gap\ between\ fill\ (i)\ and\ Fill\ (i+1)}{[Last\ Rx\ date - Index\ Rx\ date]}$$

Long-Acting Injection Considerations

The methods just described, designed for use with oral tablet/capsule formulations, present several challenges when applied to a long-acting injectable formulation. Specifically, accuracy of the days supply field is questionable,[25] and unlike tablets, which may be stockpiled if refilled early, an injection is not generally considered to last any longer if it is received sooner than expected. Overinflation of the days supply field in the data would bias individuals to being adherent or persistent when in fact they may not be. Erroneously accounting for early injections as a potential stockpile will again lead to overestimation of adherence and persistence. Adherence/persistence were evaluated for LA-SGA using 4 approaches: (1) Data as Received, (2) Derived Days = 30 days, (3) Derived Days = 28 days, and (4) Covered Days. The Derived Days approach addresses the potential inaccuracy of the days supply field. Covered Days builds on the Derived Days approach and removes the possibility of stockpiling.

TABLE 1 Demographic Characteristics, Environmental Setting, and Mental Health Diagnoses for Patients on O-SGA and LA-SGA

	O-SGA[a] (Case Example: Aripiprazole, N = 369)	LA-SGA[a] (Case Example: Paliperidone Palmitate, N = 195)	Test Statistic	*P* Value
Demographic characteristics				
Male	44.4 (164)	54.4 (106)	5.03	0.025
Age in years	38.0 [12.4]	37.9 [12.2]	-0.09	0.927
Race/ethnicity			14.56	<0.001
White	65.3 (241)	50.3 (98)		
Black/African American	31.4 (116)	47.7 (93)		
Other/unable to determine	3.3 (12)	2.1 (4)		
Environmental settings				
Received care at a community mental health center[b]	60.2 (222)	86.2 (168)	40.40	<0.001
Case management within 12 months prior to index	36.6 (135)	66.2 (129)	44.80	<0.001
Resided in an urban area[c]	73.4 (271)	77.4 (151)	1.08	0.299
Baseline mental health diagnoses (CCS)				
Number of mental health diagnoses	4.0 [2.0]	3.4 [1.9]	-3.70	<0.001
Schizophrenia and other psychotic disorders	85.6 (316)	95.4 (186)	12.39	<0.001
Mood disorder	81.8 (302)	64.1 (125)	21.83	<0.001
Anxiety disorder	59.6 (220)	43.1 (84)	14.05	<0.001
Substance-related disorder	37.7 (139)	33.8 (66)	0.81	0.369
Suicide or intentional self-inflicted injury	28.5 (105)	17.4 (34)	8.34	0.004
Personality disorder	28.2 (104)	18.5 (36)	6.46	0.011
Alcohol-related disorder	24.9 (92)	22.1 (43)	0.58	0.446
ADHD, conduct, disruptive behavior disorders	14.9 (55)	13.3 (26)	0.26	0.613
Developmental disorders	13.8 (51)	15.4 (30)	0.25	0.615
Delirium, dementia, amnestic, and other cognitive disorders	9.5 (35)	4.1 (8)	5.25	0.022
Adjustment disorder	7.6 (28)	3.1 (6)	4.58	0.032
Impulse control disorders, NEC	4.9 (18)	3.1 (6)	1.02	0.314
Disorders usually diagnosed in infancy, childhood, or adolescence	2.4 (9)	2.1 (4)	NA	0.999

[a]Reported values are given as % (n) or as mean [standard deviation]. Test statistics and associated P values are from Student's t-test when comparing means and otherwise from Pearson's chi-squared test of association or Fisher's exact test (test statistic listed as NA). Percentages may not total 100 due to rounding.

[b]Care received between August 2008 and April 2011.

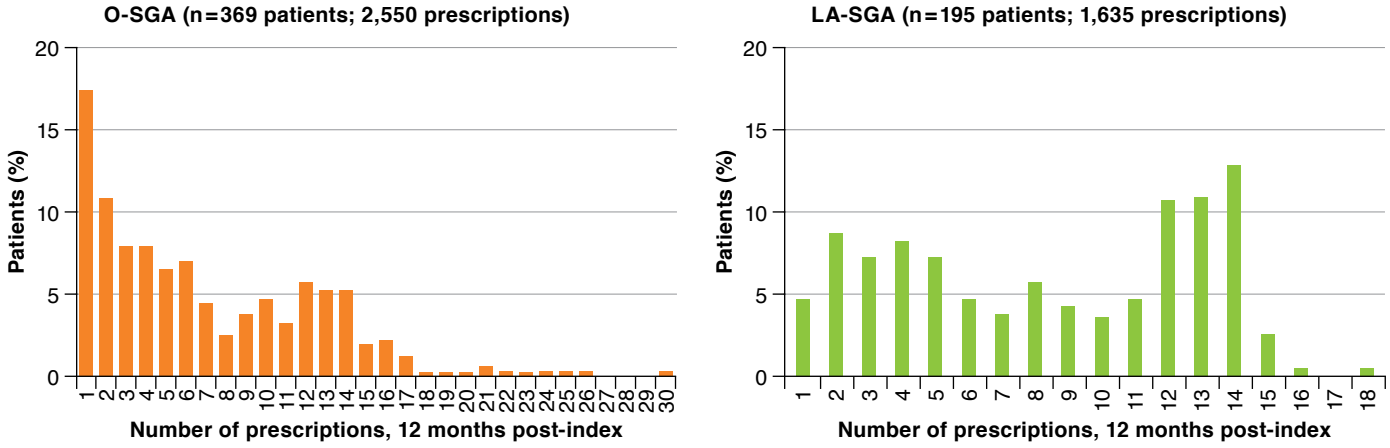
[c]County with greater than 50% of the population residing in an urban area.

ADHD = attention deficit hyperactivity disorder; CCS = Clinical Classifications Software; LA-SGA = long-acting injectable second-generation antipsychotic; NA = not applicable; NEC = not elsewhere classified; O-SGA = oral second-generation antipsychotic.

A proposed alternative approach to using days supply as recorded is to derive this measure using the labeled dosing schedule. Per the prescribing information for paliperidone palmitate, the second injection is to be given 7 ± 2 days after the first injection. Subsequent injections are to be given monthly ± 7 days.[23] When a gap between injections of greater than 6 weeks occurs, the injection timing schedule begins as though the patient was never on the medication. Using the labeled dosing schedule in lieu of days supply, an alternative approach was proposed that we called Derived Days, initially set to 30 days for all fills. If the first injection following the index is filled within less than 10 days, Derived Days is set to 7. Any injection following a gap of > 6 weeks since the previous injection is also set to 7 days. Since the prescribing information specifies "monthly," not specifically 30 days, a sensitivity comparison was performed using 28 days. Thirty days mirrors the oral definition of monthly, whereas 28 days may be more likely in real-world settings, since patients may have appointments scheduled on a weekly rather than monthly basis.

LA-SGA is received in a medical setting (including home health settings) and injected by a health care professional to ensure that the drug enters into the blood. Unlike pills, which may accumulate if refilled early, an injectable medication does not generally last any longer if it is received sooner than expected. Many adherence/persistence measures accommodate for early refills, taking into account excess medication that may be on hand. To account for this lack of excess in an injectable, a derived variable, Covered Days, is used rather than days supply. Covered Days is first defined as Derived Days using 30 days and then goes further to limit the coverage of each fill to

FIGURE 2 Per Patient Distribution of Prescriptions Claims



LA-SGA = long-acting injectable second-generation antipsychotic; O-SGA = oral second-generation antipsychotic.

the time between prescription claim dispense dates when less than the Derived Days value.

Statistical Analysis

Descriptive statistics were calculated to summarize patient characteristics for both cohorts. Student's t-test, Pearson's chi-squared test of association, and Fisher's exact test were used to compare cohort characteristics. Chi-squared tests and the Kruskal-Wallis test were used to compare adherence/persistence measures between cohorts. As suggested in prior publications, Kaplan-Meier curves were used to visualize time to discontinuation.[26,27] No adjustments were made for multiplicity or for differences in baseline characteristics between cohorts. All reported *P* values are from 2-sided hypothesis tests, and statistical significance was defined at the 0.05 level. Statistical analysis software (SAS 9.4, Cary, NC) was used for all analyses.

Results

The O-SGA and LA-SGA cohorts appeared comparable in regards to age at medication initiation (38.0 years vs. 37.9 years; t-statistic = -0.09, $P = 0.927$) and urbanicity (73.4% vs. 77.4%; $\chi^2 = 1.08$, $P = 0.299$). Patients initiating on O-SGA versus LA-SGA were more often female (55.6% vs. 45.6%; $\chi^2 = 5.03$, $P = 0.025$) and white (65.3% vs. 50.3%; $\chi^2 = 14.56$, $P < 0.001$). On average, O-SGA patients fall into more CCS mental health categories than LA-SGA patients (4.0 vs. 3.4; t-statistic = -3.70, $P < 0.001$); are less likely to receive care at a community mental health center (60.2% vs. 86.2%; $\chi^2 = 40.40$, $P < 0.001$); and less likely to receive case management (36.6% vs. 66.2%; $\chi^2 = 44.80$ $P < 0.001$). Baseline characteristics are highlighted in Table 1.

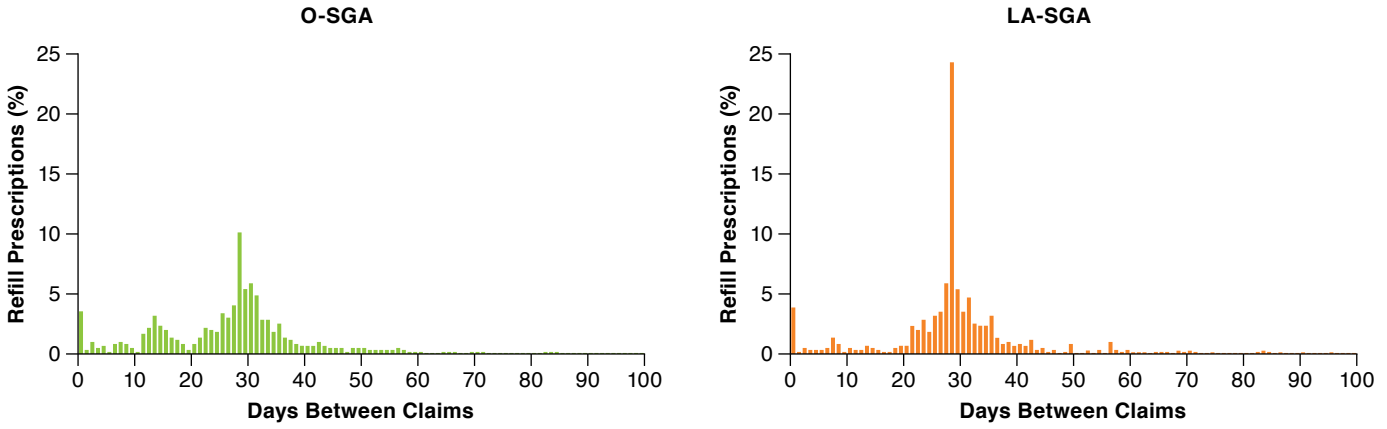
In the 12 months following drug initiation, the typical O-SGA user filled 7 prescriptions (interquartile range [IQR] 2-11) compared with LA-SGA users who filled 9 (IQR 4-13). Of O-SGA users, 17.3% (n = 64) had only 1 fill compared with 4.6% (n = 9) of LA-SGA users (Figure 2). Days supply was most frequently recorded as 30 days for O-SGA and 28 days for LA-SGA. Time between claim fills was most commonly 28 days for both cohorts (Figure 3).

Comparisons of adherence/persistence measures are provided in Table 2. Using the data as they were received for LA-SGA, MPR was 0.91 and did not vary significantly from MPR of O-SGA (0.90; test statistic = 0.29, $P = 0.590$). When applying the labeled dosing schedule (Derived Days = 30 days) to compute days supply, the MPR rose to 0.97 and varied significantly from MPR of O-SGA (test statistic = 9.6, $P = 0.002$). Additionally controlling for the inability of medication accumulation (Covered Days), MPR for LA-SGA fell to 0.86, which varied significantly from MPR of O-SGA (test statistic = 4.01, $P = 0.045$). MPR as dichotomous and CMG varied significantly between O-SGA and LA-SGA only when using the Derived Days = 30 days approach.

PDC varied from 0.55 to 0.61 for LA-SGA but was consistently significantly different from the 0.37 PDC value of O-SGA ($P < 0.05$). With the exception of Covered Days, dichotomous PDC estimates were also significantly different between LA-SGA and O-SGA.

The maximum gap in therapy observed in O-SGA versus LA-SGA patients was consistently significantly different, regardless of approach. No significant differences were observed between O-SGA and any LA-SGA estimate when defining discontinuation as a gap in therapy greater than 7 days. Significant variation was present when allowable gap thresholds were defined as up to 3 days for O-SGA versus up to 37 days for LA-SGA with the exception of the Covered Days approach.

FIGURE 3 Time Between Claims[a]



[a]*Days between claims > 100 are excluded: O-SGA, n = 62/2,181 (2.8%); LA-SGA, n = 20/1,440 (1.4%).*
LA-SGA = long-acting injectable second-generation antipsychotic; O-SGA = oral second-generation antipsychotic.

Time to discontinuation is presented in Figures 4A and 4B. Allowing gaps of up to 7 days, median time to discontinuation was 223 days for O-SGA and 155-165 days for LA-SGA. Persistent rate at 180 days ranged from 18.0% to 32.8% for LA-SGA and was 17.1% for O-SGA. Allowing gaps of up to 3 days for O-SGA and 37 days for LA-SGA, median time to discontinuation was 15 days for O-SGA and 112-150 days for LA-SGA. Regardless of the approach used in estimating time to discontinuation for LA-SGA, the results were significantly different than O-SGA ($P < 0.05$).

Discussion

Care must be taken to explain and understand assumptions of adherence/persistence measures prior to interpretation and comparison. Policymakers commonly use unadjusted adherence/persistence rates, and we wanted to provide information relevant to that decision-making context. The results highlight the sensitivity of standard medication adherence/persistence measures when assessing an injectable medication. With use of long-acting injectable antipsychotic medications increasing, policymakers should understand and acknowledge their variance with respect to research and policy related to adherence/persistence measures. As of the beginning of 2013, 6 long-acting injectable antipsychotics were approved and available in the United States.

MPR, for example, is very sensitive to variations in the days supply field. Using the Data as Received, one might conclude that there is no significant difference in adherence between O-SGA and LA-SGA. Applying the labeled dosing schedule and accounting for unavailable oversupply changes the conclusion. The constant denominator of PDC makes this measure more stable than MPR.

In regards to therapeutic drug levels, a gap of 1 day (or even 7 days) is not necessarily equivalent between a daily and long-acting injectable medication. Using half-life as a proxy for duration of therapeutic drug levels, 14.9% of O-SGA users were persistent at 180 days compared with 34.9%-44.1% of LA-SGA users.

In this case example, Derived Days = 28 days yields similar results to the Data as Received. This similarity suggests that if patients are indeed receiving the medication on a 28-day schedule, the days supply field as entered may be quite accurate. These inferences are not generalizable beyond this case example.

Examination of multiple scenarios is necessary to gain a solid understanding of the data as is knowledge of actual drug administration dates. Current discussions of adherence/persistence measures focus on defining taxonomy, as there are similar methods with varying perspectives and interpretations.[28] Emphasis is placed on how to efficiently, effectively, and accurately make these measurements.[29] Existing literature acknowledges that long-acting medication may improve adherence/persistence but does not address methods to measure and compare with other formulations.

Limitations

This study focused on comparing methodology and not patient populations. Our sample was limited to those with schizophrenia so as to reflect the labeled use of paliperidone palmitate and control for confounding by indication; however, those receiving a long-acting injectable may be inherently different from those starting an oral medication for the same indication. Unobserved variables may cause unbalance between the O-SGA and LA-SGA cohorts and affect differences observed

TABLE 2 Summary of Adherence and Persistence Measures

	O-SGA[a] (Case Example: Aripiprazole)	LA-SGA[a] (Case Example: Paliperidone Palmitate)											
		Data as Received	Test Stat	*P* Value	Derived Days = 28 Days	Test Stat	*P* Value	Derived Days = 30 Days	Test Stat	*P* Value	Covered Days	Test Stat	*P* Value
Adherence[b]													
MPR	0.90 (0.67-1.00)	0.91 (0.76-1.00)	0.29	0.590	0.92 (0.73-1.00)	0.78	0.376	0.97 (0.77-1.00)	9.60	0.002	0.86 (0.68-0.97)	4.01	0.045
MPR > 0.8	61.6 (188)	68.0 (121)	1.96	0.162	66.9 (119)	1.32	0.251	73.0 (130)	6.49	0.011	60.1 (107)	0.11	0.740
CMG	0.12 (0.00-0.42)	0.11 (0.00-0.28)	0.47	0.493	0.09 (0.00-0.29)	1.26	0.261	0.03 (0.00-0.25)	10.62	0.001	0.15 (0.04-0.35)	2.63	0.105
Persistence													
PDC	0.37 (0.12-0.82)	0.59 (0.19-0.92)	9.09	0.003	0.58 (0.25-0.90)	12.09	< 0.001	0.61 (0.27-0.96)	19.74	< 0.001	0.55 (0.21-0.82)	4.24	0.039
PDC > 0.8	25.2 (93)	36.4 (71)	7.77	0.005	35.4 (69)	6.46	0.011	37.9 (74)	9.94	0.002	27.2 (53)	0.26	0.610
Max gap, days	233 (80-320)	155 (45-295)	10.2	0.001	162 (50-274)	15.88	< 0.001	148 (35-268)	22.99	< 0.001	165 (64-290)	8.04	0.005
No gap	7.3 (27)	5.1 (10)			5.1 (10)			10.3 (20)			2.1 (4)		
1-10	3.5 (13)	6.2 (12)	7.47	0.058	4.1 (8)	3.71	0.295	5.1 (10)	7.56	0.056	5.1 (10)	7.48	0.058
11-30	4.3 (16)	8.7 (17)			7.7 (15)			8.7 (17)			4.1 (8)		
> 30	84.8 (313)	80.0 (156)			83.1 (162)			75.9 (148)			88.7 (173)		
> 7	90.2 (333)	89.2 (174)	0.14	0.704	91.3 (178)	0.16	0.688	85.1 (166)	3.27	0.070	94.4 (184)	2.83	0.093
> 3/37[c]	91.1 (336)	77.4 (151)	20.08	< 0.001	81.5 (159)	10.77	0.001	72.3 (141)	34.38	< 0.001	86.7 (169)	2.63	0.105

[a]*Reported values are given as median (interquartile range) or % (n). MPR includes last fill and is truncated at 1.0. Derived Days computes days supply for LA-SGA using the labeled dosing schedule; the labeled dosing schedule of "monthly" was evaluated at both 28 days and 30 days. Covered Days computes days supply as the minimum of time between prescription claims and the Derived Days (= 30 days) value. Test statistics and associated P values are from the Kruskal-Wallis test or Pearson's chi-squared test of association (LA-SGA vs. O-SGA). Percentages may not total 100 due to rounding.*

[b]*Includes patients with at least 2 fills: O-SGA (n = 305), LA-SGA (n = 178).*

[c]*Gap is evaluated at 3 days for O-SGA and 37 days for LA-SGA based on average product half-life as a proxy for duration of therapeutic drug levels.*

CMG = continuous measure of medication gaps; LA-SGA = long-acting injectable second-generation antipsychotic; Max = maximum; MPR = medication possession ratio; O-SGA = oral second-generation antipsychotic; PDC = proportion of days covered; Stat = statistic.

in adherence/persistence. Injectable formulations may be given to patients with a poor history of adherence caused by more serious illness. Therapy, in particular assertive community treatment programs and other intensive case management models, may be associated with higher medication adherence and persistence.[30] Controlling for known patient factors is encouraged if one is interested in predicting adherence/persistence.[26]

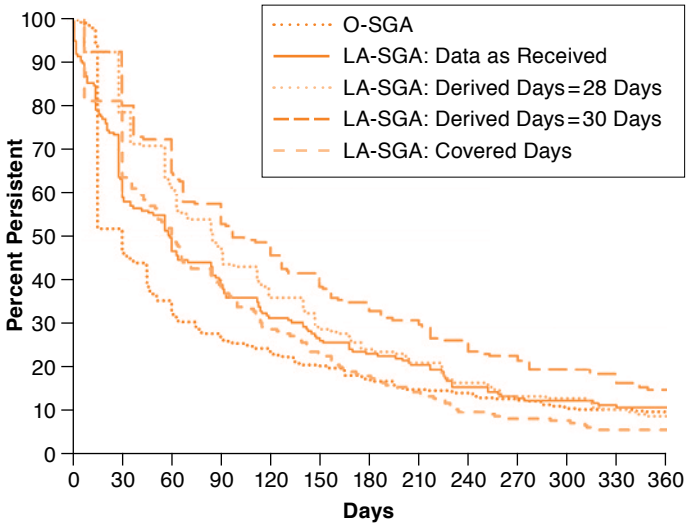
The main challenge in making comparisons between long-acting injectable and oral formulations lies in having multiple adherence/persistence measures and in accurately computing days with medication coverage. Adherence reflects a patient's behavior within the prescribed interval or episode of treatment, whereas persistence looks at a set interval of time, for example, 1 year. Adherence does not imply persistence. Therefore, it is important to use the appropriate measure for the hypothesis of interest and to interpret correctly.

MPR and other adherence measures are limited in that they include only patients with at least 1 refill claim; patients with only an index claim are excluded. In our study, 17.3% of O-SGA patients and 4.6% of LA-SGA patients had only an index claim. In most datasets, including ours, there is not a way to assess the frequency of prescriptions that are written and never filled.

Categorizing or dichotomizing continuous variables can simplify results but reduces the use of the available information. When possible, all information should be used. MPR of 80% corresponds to a gap of approximately 7 days, but this cut-point has limited scientific justification.[29] This cut-point should be adjusted to reflect the clinically appropriate grace period in medication. The grace period may not be the same across all medications. For our study, half-life was used to determine an appropriate gap threshold for each medication. A gap of 7 days for O-SGA versus LA-SGA could have much more serious consequences from an efficacy standpoint. Policymakers need to understand how measures are derived prior to applying them.

Computing covered days of an injection is not without assumptions. Monthly dosing is left open to interpretation, with sources citing 28-30 days.[19,23] This 2-day discrepancy can lead to conflicting conclusions. For example, when assuming 28-day dosing, 81.5% of patients have a gap greater than 37 days versus 72.3% when assuming a 30-day dosing schedule. Adding to this complexity, the package insert for paliperidone palmitate specifies a 7-day grace period. Applying this grace period, injections given up to 37 days apart (approximately equal to the half-life) are considered adherent. These

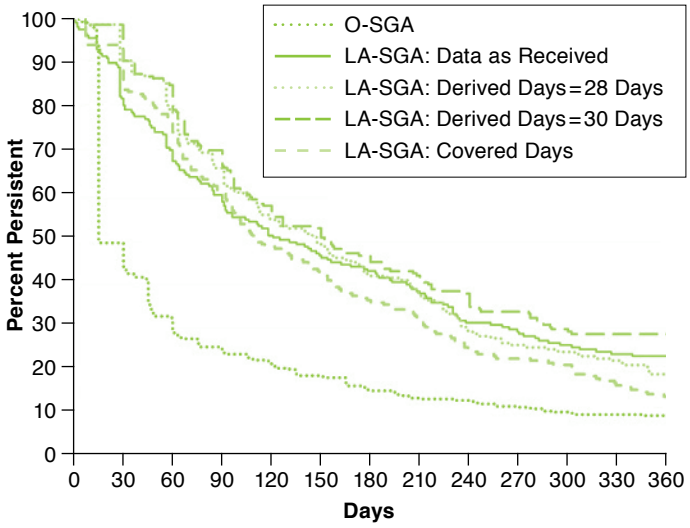
FIGURE 4A Time to Discontinuation, Allowing for a 7-Day Treatment Gap[a]



[a]*Persistence rates at 180 days post-index: 17.1% O-SGA versus 23.1% LA-SGA Data as Received ($\chi^2=2.97$, $P=0.08$); 24.1% LA-SGA Derived Days=28 days ($\chi^2=4.02$, $P=0.045$); 32.8% LA-SGA Derived Days=30 days ($\chi^2=18.13$, $P<0.001$); and 18.0% LA-SGA Covered Days ($\chi^2=0.07$, $P=0.794$). At the end of the study period, persistence rates were 9.8% O-SGA versus 10.8% LA-SGA Data as Received ($\chi^2=0.14$, $P=0.704$); 8.7% LA-SGA Derived Days=28 days ($\chi^2=0.16$, $P=0.688$); 14.9% LA-SGA Derived Days=30 days ($\chi^2=3.27$, $P=0.070$); and 5.6% LA-SGA Covered Days ($\chi^2=2.83$, $P=0.093$). Discontinuation was defined by the first gap in therapy exceeding 7 days. Time to discontinuation was computed as the count of days from the index prescription to the date of the final dispensing prior to exceeding the gap threshold plus the days supply of the final fill and any remaining oversupply. All patients were followed for 1 year from index.*

LA-SGA=long-acting injectable second-generation antipsychotic; O-SGA=oral second-generation antipsychotic.

FIGURE 4B Time to Discontinuation, Allowing for a 3- or 37-Day Treatment Gap[a]



[a]*Persistence rates at 180 days post-index: 14.9% O-SGA versus 42.1% LA-SGA Data as Received ($\chi^2=51.1$, $P<0.001$); 41.0% LA-SGA Derived Days=28 days ($\chi^2=47.81$, $P<0.001$); 44.1% LA-SGA Derived Days=30 days ($\chi^2=58.01$, $P<0.001$); and 34.9% LA-SGA Covered Days ($\chi^2=29.83$, $P<0.001$). At the end of the study period, persistence rates were 8.9% O-SGA versus 22.6% LA-SGA Data as Received ($\chi^2=20.08$, $P<0.001$); 18.5% LA-SGA Derived Days=28 days ($\chi^2=10.77$, $P=0.001$); 27.7% LA-SGA Derived Days=30 days ($\chi^2=34.38$, $P<0.001$); and 13.3% LA-SGA Covered Days ($\chi^2=2.63$, $P=0.105$). Discontinuation was defined by the first gap in therapy exceeding 3 days O-SGA or 37 days LA-SGA. Time to discontinuation was computed as the count of days from the index prescription to the date of the final dispensing prior to exceeding the gap threshold plus the days supply of the final fill and any remaining oversupply. All patients were followed for 1 year from index.*

LA-SGA=long-acting injectable second-generation antipsychotic; O-SGA=oral second-generation antipsychotic.

additional 7 days increase adherence/persistence measures from the Derived Days and Days Covered calculation considerably. Using a set dosing schedule rather than the days supply field eliminates potential inaccuracies from the days supply variable; however, varying the interpretation of "monthly" may lead to inconsistent results. Using actual days between prescription claims, with a maximum of 30 days in place of days supply, may help control for this inaccuracy; however, prescription dispense dates may not correspond with actual date of drug administration by a health care professional in all cases. Just as with prescriptions for oral medications, prescriptions for long-acting injectable antipsychotics may be picked up by the patient, a caregiver, a health care worker, or their office staff days in advance of the planned administration date. A specific administration code for paliperidone palmitate injection (J2426) was not introduced until 2011. We did examine the use of generic administration codes for injection but found only 2 instances where these codes were recorded in the claims data. Traditional measures of adherence/persistence allow for early fills to carry forward. Injectable formulations do not have an inherent oversupply if received early. The method of using actual days between prescription claims for injectable medications (with a given threshold) additionally removes the possibility of oversupply being carried forward. However, this method makes the assumption that fill date is equal to the administration date, which may not always be the case, since prescriptions are frequently picked up or delivered prior to the date that they start being used. Long-acting injectable antipsychotics are not routinely administered at the dispensing pharmacy. Bias from this assumption can over- or underinflate estimates and will vary by patient.

Another limitation, regardless of whether adherence/persistence measures are compared between similar or different formulations, is the assumption of prescription data as a proxy for actual ingestion/injection. A prescription fill does not guarantee a pill is taken or an injection is given starting on the fill date or ever. A study by Demyttenaere et al. (2001) found

that many patients (with depression) take their medication irregularly, alternating between taking too many pills on some days and too few pills on other days.[31] Also, in claims data we are unable to assess medication received from promotions/samples. Additionally, pill splitting, which is gaining popularity as health care costs rise, is undocumented. We cannot assume that pharmacy records are accurate.[5] Depending on the study size and on whether adherence is the primary outcome, the cost of other adherence collection techniques such as electronic monitoring should be weighed against the needed precision.[5]

Conclusions

Standard medication adherence and persistence measures yield different conclusions when comparing a long-acting injectable and oral antipsychotic medication. Adherence and persistence measures that address pharmacological differences in terms of formulation and duration of therapeutic levels between medications are necessary and are particularly important as more injectable antipsychotic medications are approved in the United States. Further research that applies these and alternative methods is needed. Until then, investigators should consider sensitivity analyses using different adherence and persistance definitions when making product comparisons to ensure confidence in conclusions.

Authors

ELIZABETH J. CAMPAGNA, MS, PSTAT, is Biostatistician, Colorado Health Outcomes Program, University of Colorado Anschutz Medical Campus; ELAINE H. MORRATO, DrPH, MPH, is Clinical Investigator, Colorado Health Outcomes Program, University of Colorado Anschutz Medical Campus, Aurora, Colorado, and Associate Professor, Health Systems Management and Policy, Colorado School of Public Health, Aurora, Colorado. ERIK MUSER, PharmD, MPH, is Associate Director, Translational Science, Health Economics & Outcomes Research, Janssen Scientific Affairs, LLC, Titusville, New Jersey, and JOSEPH PARKS, MD, is Distinguished Professor of Science, Missouri Institute of Mental Health, St. Louis, Missouri.

AUTHOR CORRESPONDENCE: Elizabeth J. Campagna, MS, PSTAT, Colorado Health Outcomes Program, University of Colorado Anschutz Medical Campus, 13199 E. Montview Blvd., Ste. 300, MS F443, Aurora, CO 80045. Tel.: 303.724.0382; Fax: 303.724.1839; E-mail: Elizabeth.Campagna@ucdenver.edu.

DISCLOSURES

This study was funded by Janssen Scientific Affairs, which employs Muser. Study concept and design were developed primarily by Campagna and Morrato. Most of the data were collected by Parks with help from Campagna, and all authors participated in data interpretation. First draft of the article was primarily written by Campagna with help from Morrato, and all authors worked on the revision.

REFERENCES

1. Gilmer TP, Dolder CR, Lacro JP, et al. Adherence to treatment with antipsychotic medication and health care costs among Medicaid beneficiaries with schizophrenia. *Am J Psychiatry*. 2004;161(4):692-99.

2. Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. *Psychiatr Serv*. 2004;55(8):886-91.

3. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation*. 2009;119(23):3028-35.

4. Roebuck MC, Liberman JN, Gemmill-Toyama M, Brennan TA. Medication adherence leads to lower health care use and costs despite increased drug spending. *Health Aff (Millwood)*. 2011;30(1):91-99.

5. Sajatovic M, Velligan DI, Weiden PJ, Valenstein MA, Ogedegbe G. Measurement of psychiatric treatment adherence. *J Psychosom Res*. 2010;69(6):591-99.

6. National Committee for Quality Assurance. HEDIS & Performance Measurement. Available at: http://www.ncqa.org/HEDISQualityMeasurement.aspx. Accessed February 25, 2014.

7. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf*. 2006;15(8):565-74.

8. Caetano PA, Lam JM, Morgan SG. Toward a standard definition and measurement of persistence with drug therapy: examples from research on statin and antihypertensive utilization. *Clin Ther*. 2006;28(9):1411-24.

9. Sikka R, Xia F, Aubert RE. Estimating medication persistency using administrative claims data. *Am J Manag Care*. 2005;11(7):449-57.

10. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. *Value Health*. 2008;11(1):44-47.

11. Peterson AM, Nau DP, Cramer JA, Benner J, Gwadry-Sridhar F, Nichol M. A checklist for medication compliance and persistence studies using retrospective databases. *Value Health*. 2007;10(1):3-12.

12. Nau DP. Proportion of days covered (PDC) as a preferred method of measuring medication adherence. Pharmacy Quality Alliance. Available at: http://ep.yimg.com/ty/cdn/epill/pdcmpr.pdf. Accessed February 25, 2014.

13. Siegel SJ. Extended release drug delivery strategies in psychiatry: theory to practice. *Psychiatry (Edgmont)*. 2005;2(6):22-31.

14. Weiden PJ, Mott T, Curcio N. Recognition and management of neuroleptic noncompliance. In: Shriqui CL, Nasrallah HA, eds. *Contemporary Issues in the Treatment of Schizophrenia*. Arlington, VA: American Psychiatric Press; 1995:411-34.

15. Kane JM. Problems of compliance in the outpatient treatment of schizophrenia. *J Clin Psychiatry*. 1983;44(6 Pt. 2):3-6.

16. Weiden PJ, Zygmunt A. Medication noncompliance in schizophrenia: part I, assessment. *J Prac Psych Behav Health*. 1997;3:106-10.

17. Kozma CM, Weiden PJ. Partial compliance with antipsychotics increases mental health hospitalizations in schizophrenic patients: analysis of a national managed care database. *Am Health Drug Benefits*. 2009;2(1):31-38.

18. Broder MS, Bates JA, Jing Y, Hebden T, Forbes RA, Chang E. Association between second-generation antipsychotic medication half-life and hospitalization in the community treatment of adult schizophrenia. *J Med Econ*. 2012;15(1):105-11.

19. Samtani MN, Sheehan JJ, Fu DJ, Remmerie B, Sliwa JK, Alphs L. Management of antipsychotic treatment discontinuation and interruptions using model-based simulations. *Clin Pharmacol*. 2012;4:25-40.

20. American Psychiatric Association. *Practice Guideline for the Treatment of Patients with Schizophrenia*. 2nd ed. Washington, DC: American Psychiatric Association; 2009.

21. Cramer MP, Saks SR. Translating safety, efficacy and compliance into economic value for controlled release dosage forms. *Pharmacoeconomics*. 1994;5(6):482-504.

22. Sleath B, Domino ME, Wiley-Exley E, Martin B, Richards S, Carey T. Antidepressant and antipsychotic use and adherence among Medicaid youths: differences by race. *Community Ment Health J.* 2010;46(3):265-72.

23. Invega Sustenna (paliperidone palmitate) extended-release injectable suspension, for intramuscular use. Janssen Pharmaceuticals. January 9, 2014. Available at: http://www.invegasustenna.com/important-product-information. Accessed February 26, 2014.

24. ABILIFY (aripiprazole) dosing. Bristol-Myers Squibb, Otsuka America Pharmaceutical, Inc. April 2011. Available at: http://www.abilify.com/pdf/dosing-guide.pdf. Accessed February 26, 2014.

25. Kozma CM, Durham M, Durkin M, Dickson M, Howe A. PMH84 validity of administrative claims data for calculating adherence measures for long-acting injectable (Lai) antipsychotic therapies. *Value Health.* 2012;15(4):A97.

26. Yeaw J, Benner JS, Walt JG, Sian S, Smith DB. Comparing adherence and persistence across 6 chronic medication classes. *J Manag Care Pharm.* 2009;15(9):728-40. Available at: http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=8250.

27. Sikirica V, Pliszka SR, Betts KA, et al. Comparative treatment patterns, resource utilization, and costs in stimulant-treated children with ADHD who require subsequent pharmacotherapy with atypical antipsychotics versus non-antipsychotics. *J Manag Care Pharm.* 2012;18(9):676-89. Available at: http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=15872.

28. Vrijens B, De Geest S, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol.* 2012;73(5):691-705.

29. Steiner JF. Rethinking adherence. *Ann Intern Med.* 2012;157(8):580-85.

30. Valenstein M, McCarthy JF, Ganoczy D, et al. Assertive community treatment in veterans affairs settings: impact on adherence to antipsychotic medication. *Psychiatr Serv.* 2013;64(5):445-51.

31. Demyttenaere K, Mesters P, Boulanger B, et al. Adherence to treatment regimen in depressed patients treated with amitriptyline or fluoxetine. *J Affect Disord.* 2001;65(3):243-52.