An alternative approach to measuring treatment persistence with antipsychotic agents among patients with schizophrenia in the Veterans Health Administration

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Abstract: Prior studies have demonstrated the importance of treatment persistence with antipsychotic agents in sustaining control of schizophrenic symptoms. However, the conventional approach in measuring treatment persistence tended to use only the first prescription episode even though some patients received multiple prescriptions (or multiple treatment episodes) of the same medication within one year following the initiation of the index drug. In this study, we used data from the Veterans Health Administration in the United States to assess the extent to which patients received multiple prescriptions. The study found that about a quarter of the patients had two or more treatment episodes and that levels of treatment persistence tended to vary across treatment episodes. Based on these results, we offered an alternative approach in which we calculated treatment persistence with typical and atypical antipsychotic agents separately for patients with one, two, or three treatment episodes. Considering that patients with different number of treatment episodes might differ in disease profiles, this treatment episode-specific approach offered a fair comparison of the levels of treatment persistence across patients with different number of treatment episodes. Future research needs to extend the analyses beyond two antipsychotic classes to individual antipsychotic agents. A more comprehensive assessment using appropriate analytic methods should help physicians make prescription choices that will ultimately improve the care of patients with schizophrenia.

Keywords: treatment persistence (or discontinuation), treatment episode, antipsychotic agents, schizophrenia

Introduction

Prior studies have demonstrated the efficacy and effectiveness of both typical (1st generation) and atypical (2nd generation) antipsychotic agents in reducing schizophrenic symptoms (Purdon et al 2000; Hirsch et al 2002; Kane et al 2002). However, the likelihood of sustaining control of schizophrenic symptoms depends on the persistence of treatment (Vanelli et al 2001; Menzin et al 2003). The importance of sustained treatment in the clinical management of schizophrenia, coupled with known differential side effects associated with typical and atypical antipsychotic agents (Kane 1996; Allison et al 1999; Leucht et al 1999; Leslie and Rosenheck 2001), has generated a lot of interest in comparing treatment persistence across antipsychotic agents (APA 1997; Lehman and Steinwachs 1998; VA 1998; Valenstein et al 2002; Docherty et al 2003; Lehman et al 2004; Lieberman et al 2005; Ren et al 2006).

In assessing treatment persistence across different antipsychotic agents, prior studies have indicated that although antipsychotic agents significantly reduce the symptoms of schizophrenia, poor treatment persistence is quite common among many patients with schizophrenia (APA 1997; Lehman and Steinwachs 1998; VA 1998;

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Valenstein et al 2002; Lehman et al 2004; Lieberman et al 2005). One study indicated that about 60%–79% of patients with schizophrenia who participated in the study discontinued pharmacologic treatment within a few months (Tafesse et al 2003). Another study reported that about 50% of patients with schizophrenia did not take their prescribed medications as directed (Lacro et al 2002). Similarly, studies using data from the Veterans Health Administration (VA) revealed that about 50% of the patients with schizophrenia who were discharged from hospitals did not remain in treatment over time (VA 2002). These findings were recently corroborated by the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) trial, which reported that as many as 74% of the patients discontinued medication treatment before the 18th month following the start of the CATIE trial (Lieberman et al 2005).

Poor treatment persistence of antipsychotic agents has been well documented to result in poor patient outcomes (Ayuso-Gutierrez and Vega 1997; Svarstaad et al 2001; Menzin et al 2003; Lehman et al 2004). Using California Medicaid (MediCal) prescription and medical claims data, Tafesse and colleagues examined the relationship between treatment persistence of antipsychotic medications and hospitalization among patients with schizophrenia (Tafesse et al 2003). The study yielded results indicating that patients with poor treatment persistence were 1.5 times more likely to be readmitted compared to patients with better treatment persistence. This result was also reported in a study by Grogg and colleagues, in which they found that patients with low adherence were 49% more likely to have an inpatient hospitalization when compared with compliant patients (Grogg et al 2002).

Recognizing the importance of treatment persistence in controlling symptoms of schizophrenia, a number of studies have compared levels of treatment persistence across different antipsychotic agents (Cramer and Rosenheck 1999; Dixon et al 1999; Vanelli et al 2001; Dolder et al 2002; Zhu et al 2003; Ren et al 2006). However, the results of these studies tend to be mixed. For instance, some studies indicated that the use of atypical antipsychotic agents was associated with significantly less treatment switching than the use of typical antipsychotic agents (Menzin et al 2003), and that only about 11% of patients with schizophrenia who were receiving typical antipsychotic agents achieved uninterrupted therapy, with a mean duration of 142 days over a year, or 39% of days covered (McCombs et al 1999). Another study based on the VA database, however, reported that treatment persistence with atypical antipsychotic agents was only modestly better than that with typical antipsychotic agents (Cramer and Rosenheck 1999). Other studies reported that there were no statistically significant differences in the levels of treatment persistence of either typical or atypical antipsychotic agents (Citrome and Volavska 2002; Dolder et al 2002), with about 44% and 48% of patients with schizophrenia continued to refill their prescriptions for atypical and typical antipsychotic agents, respectively (Vanelli et al 2001).

The existing body of literature focusing on the comparisons among antipsychotic agents with regard to treatment persistence remains largely problematic. In most of the studies, treatment persistence or time to "discontinuation" or "switching" to another antipsychotic agent is often calculated in terms of mean number of days from first "initiation" to first discontinuation or a first gap of ≥15 or ≥30 days (Haynes 2001). This measurement of treatment persistence does not take into account the number of days from second or third "initiation" to second or third discontinuation of treatment (or treatment episodes beyond the first prescription). Because patients who switch back to the same antipsychotic agent for a second or third time within a year may represent more complicated cases, treatment persistence using only the first treatment episode while excluding subsequent treatment episodes during a specified study period may yield biased results. Thus, in this present study, we offered an alternative approach, which included patients with multiple prescriptions of the same antipsychotic agent within a year following the initiation of the index drug. We also compared levels of treatment persistence, using conventional and our alternative approach, between typical and atypical antipsychotic agents.

Methods

The study used two existing databases from the VA: (1) pharmacy data from the VA National Pharmacy Benefits Management Program (PBM) and (2) VA national administrative data. The VA is the largest integrated health care system in the United States, with approximately 4.2 million enrollees and about 5% of the total US market share for hospital services. The VA administrative data consist of outpatient files, which provide information system about all outpatient clinic visits in the VA, and inpatient files, which provide medical information about all discharges from VA inpatient settings, including ICD-9-CM codes representing admitting and discharge diagnoses (Lamoreaux 1996). We identified patients with schizophrenia using the 295.xx ICD-9-CM codes from the outpatient and inpatient files. To increase specificity of the ICD-9-CM codes for schizophrenia, the study further identified patients with ≥1 inpatient or ≥2

outpatient ICD-9-CM codes (≥7 days apart) of schizophrenia. This approach has been shown to increase specificity without sacrificing sensitivity (Leslie and Rosenheck 2001).

Pharmacy data came from the VA National Drug Formulary, which are automated uniformly throughout the VA system, and are updated monthly. The national pharmacy data consist of extensive prescription information for all VA patients who obtain their prescriptions in the VA system. This centralized database provides comprehensive prescription information: medication class, dose, dates of issues, fills, refills, and dispenses, quantity of pills dispensed, and number of days of medication dispensed. At the time of the study, the veterans enrolled in the VA are entitled to medications with a US $7.00 co-payment arrangement. The economic incentive for veterans is almost always to obtain medications through VA medical centers rather than from other systems of care. This system allows for tracking almost all antipsychotic medications, whereas in other civilian systems this might be extremely difficult given multiple sources for obtaining initial and refill prescriptions such as pharmacy chains. Using the pharmacy data for VA fiscal years (FY) 2000, 2001, 2002, 2003, and 2004, we defined "initiation" using a 6-month "clean" period in which a patient was not on the target drug prior to initiation. More specifically, patients were initiated on the target drug at any point of time within one year provided that they had not been on the target drug for 6 months prior to initiation. We reserved one year following the initiation to calculate treatment persistence. Based on this definition of initiation, we created two non-overlapping periods using a floating date approach: 10/1/1999–3/31/2002 and 10/1/2002–3/31/2005.

Treatment persistence was measured as the length of time where a patient was continuously on any antipsychotic agents included in the study until discontinuation of treatment or until the first gap of ≥15 days without the target medication. We also conducted sensitivity analysis using a gap of ≥30 days as treatment discontinuation. Unlike the conventional approach, which included only the first treatment episode, in calculating treatment persistence, the alternative approach that we proposed in the study incorporated all treatment episodes by calculating treatment persistence separately among patients with one treatment episode, among patients with two treatment episodes, and among patients with three treatment episodes.

Since poor treatment persistence is associated with poor tolerability of the side-effects of the medications, we opted to compare typical versus atypical antipsychotic agents, which are known to differ in side-effect profiles (Allison et al 1999; Chakos et al 2002). For typical antipsychotic agents as a class, we selected three agents, representing high potency (haloperidol), medium potency (perphenazine), and low potency (chlorpromazine), whereas for atypical antipsychotic agents as a class, we included three most commonly prescribed agents during period 1: olanzapine, risperidone, and quetiapine, and we added ziprasidone during period 2. It is important to note that treatment persistence was measured at the individual drug level and then aggregated to the drug class level. For instance, for typical agents, if patient A switched from one typical to another typical, and patient B switched from one typical to one atypical, then treatment persistence was measured by taking the average of patient A's and B's length of time from the initiation date of the target drug to the date when the switch took place for the two patients, respectively.

Results

Based on the above-described procedures, we found that it was quite common for patients with schizophrenia to have multiple prescriptions of the same antipsychotic agent after discontinuation, defined either as a gap of ≥15 or ≥30 days, within one year following the initiation of the index drug. As shown in Table 1, between 10/1/1999 and 3/31/2002 when using a gap of ≥15 days to define treatment discontinuation, as many as 25% of the patients had multiple prescriptions of the same drug for both typical and atypical antipsychotic agents. This finding was corroborated by sensitivity analyses using both a gap of ≥30 days in defining treatment discontinuation as well as using data from period 2, or between 10/1/2002 and 3/31/2005. Based on these results, we opted to use the first three treatment episodes to calculate treatment persistence, which captured about 98% or 99% of the patients using ≥15 days or ≥30 days as treatment discontinuation, respectively.

Using conventional approach in calculating treatment persistence, we found that patients taking atypical agents were more compliant than patients taking typical agents as exemplified by the higher levels of treatment persistence (Table 2). During the period between 10/1/1999 and 3/31/2002, patients taking atypical agents remained on the index drug for 150 days (until there was a gap of ≥15 days) following initiation as compared to 107 days for those taking typical agents ($p < 0.001$). During the same period, patients taking atypical agents remained on the index drug for 174 days (until there was a gap of ≥30 days) compared with 122 days for those taking typical agents ($p < 0.001$). Sensitivity analyses using period 2 revealed similar results. However, levels of treat-

Table 1 Percentage of patients with different number of treatment episodes, by period and definition of treatment discontinuation

	10/1/1999–3/31/2002								10/1/2002–3/31/2005							
		Gap ≥15 days[a]				Gap ≥30 days[a]					Gap >15 days[a]				Gap >30 days[a]			
Drug class	N	# of episodes (%)				# of episodes (%)				N	# of episodes (%)				# of episodes (%)			
		1	2	3	4+	1	2	3	4+		1	2	3	4+	1	2	3	4+
Atypical agents	17,390	74.6	18.3	5.5	1.6	83.1	14.0	2.6	0.3	22,629	74.6	18.0	5.6	1.8	79.9	16.2	3.6	0.3
Typical agents	4,001	74.0	18.9	5.7	1.5	80.6	16.4	2.8	0.3	3,370	72.8	19.4	6.3	1.4	79.9	16.2	3.6	0.3

[a]Treatment persistence is defined as the # of days on the index drug(s) within one year following initiation until a gap of ≥15 or ≥30 days.

ment persistence with atypical agents saw a decline between the two study periods, whereas levels of treatment persistence with typical agents remained more or less the same. Despite this reduced gap between the two classes of drugs between period 1 and period 2, the differences in the levels of treatment persistence between typical and atypical antipsychotic agents remained significant ($p < 0.001$).

Tables 3 and 4 present treatment persistence in terms of mean number of days on the index drug among those with one prescription episode, as well as treatment persistence for each prescription episode among those with two or three prescription episodes, respectively. As revealed in Tables 3 and 4, the conventional approach in calculating treatment persistence included the prescription episode among patients with only one prescription episode, the first prescription episode among those with two prescription episodes, and the first prescription episode among those with three prescription episodes (shaded columns). Among patients with one prescription episode, initiators of atypical antipsychotic agents had significantly longer mean number of treatment days than initiators of typical antipsychotic agents ($p < 0.001$). However, the differences in the level of treatment persistence between the two classes of antipsychotic agents were trivial when using the first prescription episodes among patients with two or three prescription episodes. On the other hand, of the prescription episodes that are not included in the conventional approach in calculating treatment persistence, we found that initiators of atypical agents had significantly better treatment persistence than initiators of typical agents ($p < 0.001$). These findings, which were also observed when we analyzed data from period 2 as well as using ≥30 days in defining treatment discontinuation, suggest that the conventional approach tends to underestimate the gap in treatment persistence between the typical and atypical agents.

These findings highlight the need to incorporate all prescription episodes in the measurement of treatment persistence. The incorporation of all prescription episodes tended to represent routine clinical practices as a number of studies had indicated that switching across antipsychotic agents was quite common among patients with schizophrenia (Ren et al 2003, 2005a). As shown in Table 5 (see columns subtitled "all episodes"), we included all prescription episodes in the calculation of treatment persistence first by taking the sum of the number of days staying on the index drug for patients with two or three treatment episodes, and then by taking the average number of days staying on the index drug across the three patient groups, ie, those with one, two, or three treatment episodes. However, what we obtained from this approach was a measure that very much resembled the Medication Possession Ratio (MPR), a commonly used measure of patient adherence with medication treatment (Sclar et al 1991, 2001). This particular approach has one drawback, that is, by lumping together patients with different number of prescription episodes, one would not be able to capture the differences in treatment persistence between patients with one prescription episode and those with multiple prescription episodes. As discussed earlier, patients with multiple prescription episodes might represent more complicated cases of schizophrenia.

Table 2 Conventional approach to measuring treatment persistence, or mean number of days on the target drug following initiation, by period and definition of treatment discontinuation

	10/1/1999–3/31/2002			10/1/2002–3/31/2005		
Drug class		Gap ≥15 days	Gap ≥30 days		Gap ≥15 days	Gap ≥30 days
	N	Mean ± SD	Mean ± SD	N	Mean ± SD	Mean±SD
Atypical agents	17,094	150 ± 120	174 ± 128	22,429	135 ± 117	154 ± 125
Typical agents	3,933	107 ± 107	122 ± 115	3,324	110 ± 106	125 ± 116

T-tests of means indicate that all differences between typical and atypical agents are statistically significant at $p < 0.001$.

Table 3 Treatment persistence, by the number of treatment episodes and period (using a gap of ≥15 days as discontinuation of medications)

	Period 1 (10/1/1999–3/31/2002)								
Drug class	1 episode		2 episodes			3 episodes			
	Mean ± SD	N	(1) Mean ± SD	(2) Mean ± SD	N	(1) Mean ± SD	(2) Mean ± SD	(3) Mean ± SD	N
Atypical agents	179 ± 142	12,856	65 ± 57	147 ± 130	3,253	55 ± 45	49 ± 35	113 ± 110	985
Typical agents	125 ± 127	2,877	61 ± 54	106 ± 104	797	53 ± 40	44 ± 30	83 ± 82	257
	Period 2 (10/1/2002–3/31/2005)								
Drug class	1 episode		2 episodes			3 episodes			
	Mean ± SD	N	(1) Mean ± SD	(2) Mean ± SD	N	(1) Mean ± SD	(2) Mean ± SD	(3) Mean ± SD	N
Atypical agents	160 ± 139	16,684	64 ± 56	135 ± 125	4,416	53 ± 41	52 ± 37	117 ± 112	1,329
Typical agents	127 ± 124	2,469	63 ± 57	114 ± 112	659	51 ± 42	42 ± 31	104 ± 110	196

The conventional approach in calculating treatment persistence included the prescription episode among patients with only one prescription episode, the first prescription episode among those with two prescription episodes, and the first prescription episode among those with three prescription episodes (shaded columns).

To distinguish patients with one prescription from those with two or three prescriptions or treatment episodes, we offered an alternative approach, which was treatment episode-specific in which treatment persistence with typical and atypical antipsychotic agents was measured separately for patients with one, two, or three treatment episodes within one year following the initiation of the target drug. The results presented in Table 5 indicate that consistent with the conventional approach, patients who were initiated on atypical agents had better treatment persistence than those who were initiated on typical agents in all three comparison groups, ie, those with one prescription, those with two treatment episodes, and those with three treatment episodes. In addition, levels of treatment persistence exhibited variation for patients with one, two, or three prescriptions. Generally speaking, among patients with one prescription, initiators of typical agents tended to fare worst in the level of treatment persistence. This finding suggests that conventional approach in calculating treatment persistence tends to underestimate the gap between typical and atypical agents. Take study period 1 and treatment discontinuation using a gap of ≥15 days as an example. Using conventional approach, initiators of atypical agents stayed on the treatment 43 days longer than initiators of typical agents, whereas using our episode-specific approach among patients with one prescription, initiators of atypical agents remained on the treatment 54 days longer than initiators of typical agents. Similar findings were also observed using data from study period 2 and using a gap of ≥30 days as treatment discontinuation.

Discussions and conclusions

Over the past two decades, interest has increased in studies on treatment persistence with antipsychotic agents (Lehman and Steinwachs 1998; Valenstein et al 2002; Lehman et al 2004; Lieberman et al 2005; Ren et al 2006). A number of studies have reported that poor treatment persistence with antipsychotic agents is a common problem among patients with schizophrenia (Docherty et al 2003; Tafesse et al 2003), which results in relapse of schizophrenic symptoms, increased outpatient visits, hospital admissions, and

Table 4 Treatment persistence, by the number of treatment episodes and period (using a gap of >30 days as discontinuation of medications)

	Period 1 (10/1/1999–3/31/2002)								
Drug class	1 episode		2 episodes			3 episodes			
	Mean ± SD	N	(1) Mean ± SD	(2) Mean ± SD	N	(1) Mean ± SD	(2) Mean ± SD	(3) Mean ± SD	N
Atypical agents	197 ± 143	14,352	68 ± 57	151 ± 97	2,505	50 ± 38	51 ± 35	114 ± 111	480
Typical agents	139 ± 133	3,126	62 ± 53	113 ± 112	707	54 ± 38	42 ± 27	88 ± 88	156
	Period 2 (10/1/2002–3/31/2005)								
Drug class	1 episode		2 episodes			3 episodes			
	Mean ± SD	N	(1) Mean ± SD	(2) Mean ± SD	N	(1) Mean ± SD	(2) Mean ± SD	(3) Mean ± SD	N
Atypical agents	174 ± 141	18,523	67 ± 57	139 ± 126	3,305	51 ± 37	47 ± 32	114 ± 107	712
Typical agents	141 ± 130	2,698	61 ± 61	133 ± 127	546	57 ± 45	46 ± 30	68 ± 64	109

The conventional approach in calculating treatment persistence included the prescription episode among patients with only one prescription episode, the first prescription episode among those with two prescription episodes, and the first prescription episode among those with three prescription episodes (shaded columns).

Table 5 An alternative measure of treatment persistence, by treatment episodes, period, and definition of treatment discontinuation

	Period 1 (10/1/1999–3/31/2002)				**Period 2 (10/1/2002–3/31/2005)**			
	Gap ≥15 days as treatment discontinuation				Gap ≥15 days as treatment discontinuation			
	All episodes	Episode-specific			All episodes	Episode-specific		
Drug class		1 episode	2 episodes	3 episodes		1 episode	2 episodes	3 episodes
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Atypical agents	187 ± 153	179 ± 142	212 ± 187	217 ± 190	171 ± 150	\ ± 139	199 ± 181	222 ± 190
Typical agents	137 ± 135	125 ± 127	167 ± 158	180 ± 152	141 ± 136	127 ± 124	177 ± 169	197 ± 183
	Gap ≥30 days as treatment discontinuation				Gap ≥30 days as treatment discontinuation			
	All episodes	Episode-specific			All episodes	Episode-specific		
Drug class		1 episode	2 episodes	3 episodes		1 episode	2 episodes	3 episodes
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Atypical agents	201 ± 146	197 ± 143	219 ± 154	215 ± 184	180 ± 148	174 ± 141	206 ± 183	212 ± 176
Typical agents	147 ± 139	139 ± 133	175 ± 165	184 ± 153	151 ± 140	141 ± 130	194 ± 188	171 ± 139

T-tests of means indicate that all differences between typical and atypical agents are statistically significant at $p < 0.001$.

associated unnecessary medical expenses (Grogg et al 2002; Lacro et al. 2002; Docherty et al 2003; Tafesse et al 2003). Recognizing the importance of treatment persistence to the sustained control of the symptoms of schizophrenia, prior studies have compared treatment persistence between typical and atypical antipsychotic agents, but yielded inconsistent findings.

In this study, we offered an alternative approach to the measurement of treatment persistence. The justification for this alternative approach is based on the observation that as many as 25% of the patients included in the study had at least two prescriptions of the same agent within one year following the initiation of the target drug. A close examination of the episode-specific mean number of treatment days revealed that for patients with multiple prescriptions, levels of treatment persistence tended to be universally lower at the initial episode(s), but much higher at the last episodes. This finding has important implication for the conventional approach in measuring treatment persistence. On the one hand, the conventional approach used only the first prescription, which combined the single prescription for patients who had one prescription with the two first prescriptions for patients who had two or three treatment episodes, respectively. On the other hand, the conventional approach excluded two treatment episodes (the last episodes for patients with two or three prescriptions). Thus inclusion and exclusion criteria associated with the conventional approach are problematic and the results based on the approach are likely to be biased.

Recognizing that patients with one prescription might be different from those with two or three prescriptions, we advocated for an alternative approach in measuring treatment persistence, ie, the treatment episode-specific approach. This approach will enable us to distinguish patients with one prescription from those with two or three treatment episodes. As discussed earlier, patients with multiple treatment episodes might represent more complicated cases of schizophrenia. By comparing episode-specific treatment persistence, the alternative approach provided a fair comparison in treatment persistence across antipsychotic agents by avoiding the potential bias against those antipsychotic agents, which are more likely to be prescribed to patients who present with more severe mental diseases and therefore more likely to switch back and forth between medications.

It is important to note three limitations of the study. First, the study included predominantly male patients from the VA health care services where female representation is typically low. We do not know whether the patterns of treatment persistence across antipsychotic agents observed in the present study are unique to male patients. As such, the results may not be generalizable to female patients. It is possible that male and female patients may have different responses to antipsychotic agents in terms of efficacy or effectiveness as well as tolerability of side-effects, a subject that requires further research. Second, the study only included three typical antipsychotic agents, which may not be representative of the first generation of antipsychotic agents. More research is needed to extend to other typical agents, especially those that are most commonly prescribed. Similarly, future research needs to analyze atypical agents not only at the class level but also at the individual drug level. Finally, due to the nature of observational study, ie, without implementing the randomized assignment rules, the results of the study can be affected by selection biases. Despite the fact that observational studies represent the spectrum of routine medical practice better than randomized experiments, it is

important for future observational studies to use statistical techniques, such as propensity scores and sensitivity analyses, to minimize the confounding errors associated with observational studies.

Despite these limitations, the results of the study have important implications for the care of patients with schizophrenia. With several antipsychotic drugs available, physicians are increasingly confronted with many critical choices in selecting medications that tend to benefit the patients. Since poor treatment persistence contributed to an estimated 40% relapses (Weiden and Zygmund 1997), levels of treatment persistence have become an increasingly important factor in prescription choices by physicians of different antipsychotic agents. However, considering the inappropriateness of the conventional approach in measuring treatment persistence as well as the limitations of the present study, more research is needed to examine the extent to which adjunctive use of other agents, a common practice among patients with schizophrenia (Ren et al 2004), will influence levels of treatment persistence. Future research should also assess the impact of poor treatment persistence on a wide spectrum of patient outcomes (Ren et al 2005b). A more comprehensive assessment using appropriate analytic methods should provide physicians with a better knowledge about treatment persistence associated with different antipsychotic agents and help them make prescription choices that will ultimately improve the care of schizophrenia.

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