Neuropsychiatric Disease and Treatment

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ORIGINAL RESEARCH

Measurement of treatment adherence with antipsychotic agents in patients with schizophrenia

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This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment
30 September 2009
Number of times this article has been viewed

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Abstract: The importance of medication adherence in sustaining control of schizophrenic symptoms has generated a great deal of interest in comparing levels of treatment adherence with different antipsychotic agents. However, the bulk of the research has yielded results that are often inconsistent. In this prospective, observational study, we assessed the measurement properties of 3 commonly used, pharmacy-based measures of treatment adherence with antipsychotic agents in schizophrenia using data from the Veterans Health Administration during 2000 to 2005. Patients were selected if they were on antipsychotics and diagnosed with schizophrenia (N = 18,425). A gap of ≥30 days (with no filled index medication) was used to define discontinuation of treatment as well as medication "episodes," or the number of times a patient returned to the same index agent after discontinuation of treatment within a 1-year period. The study found that the 3 existing measures differed in their approaches in measuring treatment adherence, suggesting that studies using these different measures would generate different levels of treatment adherence across antipsychotic agents. Considering the measurement problems associated with each existing approach, we offered a new, medication episode-specific approach, which would provide a fairer comparison of the levels of treatment adherence across different antipsychotic agents.

Keywords: medication adherence, antipsychotic agents, schizophrenia

Introduction

Prior studies have demonstrated the efficacy and effectiveness of both typical (first-generation) and atypical (second-generation) antipsychotic agents in reducing schizophrenic symptoms.[1,2] However, the likelihood of sustaining control of schizophrenic symptoms depends on treatment adherence with antipsychotic agents by the patients.[3,4] The importance of sustained medication treatment in the management of schizophrenia, coupled with known differential side effects associated with typical and atypical antipsychotic agents,[5–8] has generated a lot of interest in the development of pharmacy-based measures to compare the levels of treatment adherence across different antipsychotic agents.[9–17]

In comparing treatment adherence with antipsychotic agents, there are 3 commonly used, pharmacy-based measures. Treatment persistence (TP) measures the length of time from the initiation of the index drug to the discontinuation of medication treatment as defined by a gap ≥30 days.[18] This measure considers only the first medication "episode," or the number of times a patient returned to the same index drug after discontinuation of medication treatment within 1 year, and does not take into account medication episodes beyond the first gap (or discontinuation of the medication). Medication possession

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ratio (MPR), on the other hand, measures the length of time or number of days on the index drug during a specified 1-year period.[19,20] Unlike TP, MPR takes into account all medication "episodes" of the same drug but ignores the size of the gaps between medication episodes." Finally, medication compliance also measures the length of time on the medication using all medication "episodes" during 1 year. But unlike MPR, this approach takes into account the size of the gaps, ie, using ≥30 days to define medication discontinuation.[21] Since patients who came back to the same antipsychotic agent for a second or third time within 1 year may represent more complicated cases, treatment persistence considering only the first medication episodes while excluding subsequent ones is likely to yield biased results disfavoring antipsychotic agents with more patients having ≥2 medication episodes. Similarly, while MPR and medication compliance incorporate all medication episodes within 1 year, these measures do not differentiate patients with one vs multiple medication episodes. Patients with different number of medication episodes may differ in the levels of treatment adherence with antipsychotic agents.

In this prospective, observational study, we used existing data from the Veterans Health Administration (VA), the largest integrated health care system in the United States, during fiscal years 2000 to 2005 to assess the extent to which different measurement properties associated with each of the 3 commonly used, pharmacy-based measures contributed to the inconsistent findings in the literature regarding the levels of treatment adherence with antipsychotic agents in schizophrenia. Considering that there are measurement problems associated with each of the existing 3 measures of treatment adherence, in this study, we also provided a new "episode-specific" approach to measuring treatment adherence that will provide a fairer comparison of the levels of treatment adherence across different antipsychotic agents.

Research design

The study used two existing databases from the Veterans Health Administration (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 US, with approximately 4.2 million enrollees and about 5% of the total US market share for hospital services. The VA administrative data consist of an outpatient file, which provides information system about all outpatient clinic visits in the VA, and an inpatient file, which provides medical information about all discharges from VA inpatient settings, including ICD-9-CM codes representing admitting and discharge diagnoses.[22] Pharmacy data came from the VA National Drug Formulary, which were automated uniformly throughout the VA system, and were 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 were entitled to medications at no charge or with a US$7.00 co-payment. 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 initial and refill prescriptions such as pharmacy chains.

Patients were selected into the study by the following steps. First, using VA pharmacy data from 10/1/2001 (October 1, 2001) through 3/31/2005 (March 31, 2005), we used a floating-date approach in identifying patients who "initiated" any of the eight selected antipsychotic agents, the most frequently prescribed agents in the VA. In other words, we selected patients with the first record of the index agent following at least 6 months with no record of the index agent. We also reserved 1 year following the initiation of the index agent for purposes of calculating treatment adherence. Therefore, during 10/1/2001 and 3/31/2005, patients could initiate any of the selected antipsychotic agents at any time between 4/1/2002 (the earliest possible dates for initiation due to the required prior 6-month clean period) and 4/1/2004 (the last possible dates for initiation due to the reserved 1 year for measuring treatment adherence). Second, to increase specificity, we further merged the pharmacy data with inpatient and outpatient data. Among the initiators of antipsychotic agents, we selected only those with ≥1 inpatient or ≥2 outpatient ICD-9-CM codes (≥7 days apart) of schizophrenia during 10/1/1999 to 9/30/2002.

All 3 existing measures of medication adherence were calculated across eight antipsychotic agents. MPR was simply measured by the length of time a patient was on any index drugs during the 1-year post-initiation period. Both treatment persistence and medication compliance were measured as the length of time a patient was continuously on any antipsychotic agents included in the study until a gap of ≥30 days with no filled index agent. In this study, a gap of ≥30 days

with no filled index agent was used to define discontinuation of treatment with the index drug as well as "medication episodes" or the number of times a patient had a medication record of the same index drug within a 1-year period.

Finally, we calculated a new medication episode-specific approach in which we not only incorporated all medication episodes, but also distinguished patients with a different number of medication episodes. More specifically, we measured treatment adherence with the index antipsychotic agent separately among patients with 1, 2, and 3 or more medication episodes. This medication episode-specific approach adjusted for the possible biases resulting from differential proportion of patients with multiple medication episodes across various antipsychotic agents.

Results

Patients eligible for the study were predominantly male (94.3%) and single (81.1%) with a mean age of 51.0 (SD = 10.7) (Table 1). They were more likely to be white (48.1%) and African-American (32.4%), with about 13% being "others" and 7% being Hispanics. Overall, the study subjects had a mean of 4.1 (SD = 2.4) comorbid conditions, with a mean of 2.2 (SD = 1.2) comorbid mental and 1.8 (SD = 1.9) comorbid medical conditions. In the 6 months prior to the initiation of the index drug, 52.9%, 42.9%, and 12.4%, had prior use of antidepressants, anxiolytics, and mood stabilizers, respectively, and as high as 96.3% of the study subjects had at least 1 psychiatric-related outpatient visit and about 32.3% had at least 1 psychiatric-related hospitalization.

Consistent with our earlier study findings,[23] a significant number of schizophrenia patients included in the study had ≥1 medication episodes within a specified 1-year study period (Table 2), suggesting that patients came back to the same index antipsychotic agent for a second or third or more times after a gap of ≥30 days with no index agent. Moreover, the proportion of patients with multiple medication episodes tended to vary across various antipsychotic agents, especially among the atypical antipsychotic agents. As reported in Table 2, the percentage of patients having 2 medication episodes ranged from 16.0% for olanzapine to 15.0% for risperidone, 14.5% for quetiapine, 10.5% for ziprasidone, and 8% for clozapine. Similarly, the percentage of patients having ≥3 medication episodes ranged from 4% for risperidone, 3.9% for olanzapine, 3.3% for quetiapine, and 2.6% for clozapine to 2.0% for ziprasidone. However, this pattern was not observed among the 3 typical agents, which had very similar percentages of patients with multiple medication records.

Table 1 Patient characteristics (N = 18,425)

Sociodemographic characteristics (2002)	**Mean + SD**	**%**
Age, years	51.0 ± 10.7	
Age groups, %:		
≤44		26.1
45–49		21.8
50–54		24.5
55–59		11.5
≥60		16.1
Male, %		94.3
Race, %		
White		48.1
Black		32.4
Hispanic		6.9
Others		12.7
Married, %		19.9
Clinical characteristics		
Number of comorbid conditions (2 years prior to initiation)		
Total (mean + SD)	4.04 ± 2.4	
Mental (mean ± SD)	2.23 ± 1.2	
Physical (mean ± SD)	1.82 ± 1.9	
Other clinical characteristics (6 months prior to initiation)		
Prior use of antidepressants, %		52.9
Prior use of mood stabilizers, %		12.4
Prior use of anxiolytics, %		42.9
Prior use of clozapine, %		2.4
% with at least one outpatient non-psychiatric visit		95.4
% with at least one outpatient psychiatric visit		96.3
% with at least one psychiatric hospitalization		32.3
% with at least one non-psychiatric hospitalization		15.9

Table 3 presents the results based on the 3 conventional approaches to measuring medication adherence. Treatment persistence, which took into account only the first medication episode, is highlighted by 3 shaded columns in Table 3. The results based on this measure indicated that patients who initiated atypical agents were generally more adherent than those who initiated typical agents as exemplified by longer days remained on the index drug following initiation until a gap of ≥30 days. Levels of treatment persistence also varied within each class of antipsychotic agents. Between 10/1/2002 and 3/31/2005, among the

Table 2 Number of patients with multiple medication episodes

Drug name	10/1/2002 to 3/31/2005						
	Total	1 Episode		2 Episodes		3 + Episodes	
	N	N	%	N	%	N	%
Atypical agents							
Clozapine	271	250	92.3	14	5.2	7	2.6
Olanzapine	5,412	4,337	80.1	865	16.0	210	3.9
Quetiapine	7,412	6,093	82.2	1,071	14.5	248	3.3
Risperidone	7,482	6,060	81.0	1,125	15.0	297	4.0
Ziprasidone	2,323	2,033	87.5	244	10.5	46	2.0
Typical agents							
Haloperidol	2,600	2,084	80.2	421	16.2	95	3.6
Perphenazine	414	255	80.2	51	16.0	12	3.8
Chlorpromazine	452	359	79.4	74	16.4	19	4.2

atypical agents, as expected, patients who initiated on clozapine were most adherent (255 days), followed by those initiated on quetiapine (186 days), ziprasidone (172 days), olanzapine (171 days), and risperidone (168 days). Among the typical agents, patients initiated on perphenazine were most adherent (169 days) and those initiated on haloperidol were least adherence (124 days). It is interesting to note that treatment persistence with perphenazine was equivalent to several atypical agents such as ziprasidone, olanzapine, and risperidone.

The last 2 columns of Table 3 also present the results based on the other 2 conventional approaches, MPR and treatment compliance, both of which used a gap of ≥30 days to define discontinuation of medication treatment and took into account all medication episodes. Compared to those calculated by treatment persistence, results with regard to the levels of treatment adherence with different antipsychotic agents based on MPR or treatment compliance were quite mixed. On the one hand, consistent with treatment persistence, both MPR and treatment compliance revealed that among the atypical agents, patients who initiated on clozapine were most adherent, whereas patients who were initiated on risperidone were least adherent; and among the typical agents, patients who initiated on perphenazine were most adherent and those initiated on haloperidol were least adherent. On the other hand, levels of treatment adherence with different antipsychotic agents tended to vary across the 3 existing measures. For instances, using treatment persistence, initiators of olanzapine and initiators of ziprasidone stayed on treatment for the same duration (151 days). However, using MPR, initiators of ziprasidone stayed on treatment significantly longer than initiators of olanzapine (269 vs 246 days; $P < 0.001$). Similarly, using MPR, initiators of ziprasidone remained on treatment slightly longer, but statistically non-significant, than initiators of quetiapine (269 vs 266 days). But, when medication compliance was used, initiators of quetiapine remained on treatment significantly longer than initiators of ziprasidone (191 vs 178 days; $P < 0.05$). Such a finding was also observed among the typical agents, in which initiators of chlorpromazine remained on medication treatment slightly longer than initiators of haloperidol (117 vs 110 days, $P < 0.05$) when measured by treatment persistence, but initiators of chlorpromazine remained on medication treatment significantly longer than initiators of haloperidol (234 vs 197 days, $P < 0.001$) when measured by MPR.

Results from Table 3 also revealed that among those with multiple medication episodes, the number of days patients remained on the index drug tended to be longer during the last medication episodes than during the initial medication episodes. For instance, among those with 2 medication episodes, patients remained on olanzapine for 68 days for the first episode, but 130 days for the second episode. Similarly, among those with 3 or more medication episodes, patients remained on olanzapine for 53 and 50 days, respectively, for the first and second episodes, but 96 days for the last episode. Furthermore, the differences in the number of days remaining on the index drug following initiation until a gap of ≥30 days across antipsychotic agents tended to vary across different medication episodes. As shown in Table 3, among patients with 1 medication episode, initiators of quetiapine had a significantly longer mean number of treatment days (186 days) than initiators of risperidone (168 days) ($P < 0.001$). However, among those with 2 or ≥3 medication episodes, initiators of quetiapine had shorter, though statistically non-significant, mean number of treatment days during the first medication episodes, but had significantly longer mean number of treatment days than initiators of risperidone during the last medication episodes.

These findings highlight the need to not only incorporate all medication episodes but also distinguish patients with single vs multiple medication episodes in measuring medication adherence. Considering that the number of patients with multiple medication episodes tended to vary across antipsychotic agents, coupled with the fact that number of days remaining on medication treatment tended to vary across antipsychotic agents when different medication episodes were used, we developed a new, episode-specific medication adherence measure. More specifically, we compared medication adherence across antipsychotic agents by

Table 3 Treatment persistence/medication compliance (using a gap of ≥30 days as discontinuation of medication) (10/1/2002 to 3/31/2005)

Drug name	1 Episode		2 Episodes			3 + Episodes			Treatment persistence	Medication possession ratio (MPR)	Medication compliance
	Mean ± SD	N	(1) Mean ± SD	(2) Mean ± SD	N	(1) Mean ± SD	(2) Mean ± SD	(3) Mean ± SD	N		
Atypicals											
Clozapine	255 ± 146	250	64 ± 65	170 ± 140	14	44 ± 49	46 ± 40	165 ± 166	6	240 ± 140	325 ± 252	254 ± 148
Olanzapine	171 ± 140	4,337	68 ± 57	130 ± 123	865	53 ± 39	50 ± 36	96 ± 97	179	151 ± 123	246 ± 228	176 ± 161
Quetiapine	186 ± 144	6,093	67 ± 55	143 ± 124	1,071	49 ± 36	50 ± 36	122 ± 113	218	165 ± 128	266 ± 315	191 ± 188
Risperidone	168 ± 140	6,060	69 ± 59	130 ± 122	1,125	53 ± 36	45 ± 31	94 ± 94	273	149 ± 124	241 ± 314	174 ± 165
Ziprasidone	172 ± 139	2,033	68 ± 58	154 ± 132	244	50 ± 37	43 ± 23	141 ± 123	42	151 ± 122	269 ± 113	178 ± 234
Typicals											
Haloperidol	124 ± 128	2,084	54 ± 49	117 ± 116	421	44 ± 36	37 ± 25	73 ± 75	79	110 ± 112	197 ± 114	133 ± 168
Perphenazine	169 ± 136	255	69 ± 54	151 ± 137	51	61 ± 47	51 ± 20	51 ± 27	12	149 ± 119	239 ± 246	177 ± 165
Chlorpromazine	131 ± 126	359	59 ± 49	132 ± 127	74	65 ± 51	50 ± 44	80 ± 91	18	117 ± 110	234 ± 283	143 ± 170

Note: See text for explanation of shading.

stratifying on the number of medication episodes. As shown in Table 4, results based on this new approach reveal one general finding, ie, number of days remaining on medication treatment across different antipsychotics tended to vary across different medication episodes. Among the 3 typical agents, initiators of chlorpromazine had better medication adherence than initiators of haloperidol, but such differences appeared to be trivial and non-significant among those with 1 medication episode (131 vs 124 days), moderate among those with 2 medication episodes (191 vs 171 days; $P < 0.05$), but strong among those with ≥3 medication episodes (195 vs 154 days; $P < 0.001$). Among the 5 atypical agents, initiators of olanzapine tended to stay significantly longer on treatment than initiators of risperidone among those with ≥3 medication episodes (199 vs 192 days, $P < 0.01$), but such a difference between the 2 agents was trivial and non-significant among those with 1 medication episode (171 vs 168 days) or 2 medication episodes (198 vs 199 days). Similarly, compared to initiators of quetiapine, initiators of ziprasidone had poorer treatment adherence among those with 1 medication episode (172 vs 186 days; $P < 0.001$), but better treatment adherence among those with 2 medication episodes (222 vs 210 days; $P < 0.01$).

Discussion and conclusions

Although a number of studies have found that poor adherence to medication treatment is quite common among many patients with schizophrenia,[9–11,13,15,16] the results for the levels of treatment adherence across the antipsychotic agents have been mixed. For instance, some studies indicated that the use of atypical antipsychotic agents was associated with significantly less medication switching than the use of typical antipsychotic agents,[4] and that only about 11% of the 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.[24] 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[25] Other studies reported that there were no statistically significant differences between levels of medication adherence to typical and atypical antipsychotic agents,[12,26] with about 44% and 48% of patients with schizophrenia continuing to refill their prescriptions for atypical and typical antipsychotic agents, respectively.[3]

In this study, we assessed the measurementproperties of the 3 commonly used, pharmacy-based measures of treatment adherence and found that each measure differed in

Table 4 Medication episode-specific treatment adherence (using a gap of ≥30 days as discontinuation of medication)

Drug name	10/1/2002 to 3/31/2005					
	1 Episode		2 Episodes		3 + Episodes	
	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N
Atypical agents						
Clozapine	255 ± 146	250	234 ± 205	14	255 ± 255	6
Olanzapine	171 ± 140	4,337	198 ± 180	865	199 ± 172	179
Quetiapine	186 ± 144	6,093	210 ± 179	1,071	221 ± 185	218
Risperidone	168 ± 140	6,060	199 ± 181	1,125	192 ± 161	273
Ziprasidone	172 ± 139	2,033	222 ± 190	244	184 ± 183	42
Typical agents						
Haloperidol	124 ± 128	2,084	171 ± 165	421	154 ± 136	79
Perphenazine	169 ± 136	255	220 ± 191	51	163 ± 153	12
Chlorpromazine	131 ± 126	359	191 ± 176	74	195 ± 186	18

its approach, which might have contributed to the inconsistent findings across antipsychotic agents. The results of the study revealed 3 findings. First, as high as 24% of the patients with schizophrenia had 2 or more medication episodes and percentage patients with 2 or more medication episodes tended to vary across different antipsychotic agents. Because multiple medication episodes can either be attributed to patients making more switches among antipsychotic agents or simply being less adherent to medication treatment, patients with more medication episodes may therefore have more severe symptoms of schizophrenia. Second, mean number of days remaining on medication treatment across patients with ≥2 medication episodes revealed that levels of medication adherence were universally lower at the initial episode(s), but much higher at the last episodes. This finding seems to indicate that the reason why patients having more medication episodes is largely due to switching among antipsychotic agents and not due to being less adherent to medication treatment. Patients with more severe symptoms are more likely to try several different antipsychotics before settling on the antipsychotic agent that they feel comfortable with. Third, number of days remaining on the medication treatment tended to vary across antipsychotic agents as well as across medication episodes. These findings highlight the measurement problems associated with conventional approach to measuring medication adherence. On the one hand, treatment persistence used only the first medication episode, which combined the single prescription for patients who had one prescription with the first episodes among patients who had two or three medication episodes. This approach excluded the second episode among patients with two medication episodes and the second and last episodes among those with three medication episodes. This inclusion and exclusion criteria associated with treatment persistence are problematic and the results based on the approach are likely to be biased. On the other hand, although medication compliance took into account all medication episodes, this approach had one drawback, that is, by lumping together patients with different numbers of medication episodes, one would not be able to capture the differences in medication adherence between patients with one medication episode and those with multiple medication episodes. This approach very much resembled the MPR, another commonly used measure of compliance with medication treatment.[19,20] While medication compliance considers the size of the gap, ie, ≥30 days, to define discontinuation of medication treatment, MPR does not take into account the size of the gap in defining discontinuation of medication treatment.

Recognizing that patients with 1 medication episode may be different from those with 2 or 3 medication episodes, we proposed an alternative approach in measuring medication adherence, ie, an episode-specific approach. This approach enabled us to distinguish patients with 1 medication episode from those with 2 or 3 medication episodes in terms of medication adherence. As discussed earlier, patients with multiple medication episodes may represent more complicated cases of schizophrenia. By comparing episode-specific medication adherence, our new approach provides a fair comparison of medication adherence across antipsychotic agents by avoiding the potential bias against those antipsychotic agents having more patients with multiple medication episodes, who present with more severe symptoms of schizophrenia and are more likely to switch back and forth among antipsychotic agents.

It is important to note two limitations of the study. First, the study included predominantly male patients from the VA health care services. Patterns of medication adherence to various antipsychotic agents observed in the present study may not be generalizable to female patients. Second, due to the observational nature of study, ie, without randomized assignment, the results of the study may 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 the 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 antipsychotic agents that tend to benefit the patients. Since poor medication adherence contributed to an estimated 40% relapses,[27] levels of medication adherence have become increasingly important in prescription choices among different antipsychotic agents. However, considering the inappropriateness of the conventional approach in measuring medication adherence 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,[28] dose of treatment, and stage of illness will influence levels of treatment adherence. Future research should also assess the impact of poor treatment adherence on a wide spectrum of patient outcomes.[29] A more comprehensive assessment using appropriate analytic methods should provide physicians with a better knowledge about treatment adherence associated with different antipsychotic agents and help them make prescription choices that will ultimately improve the care of schizophrenia.

Acknowledgments

This project was supported in part by the Center for the Assessment of Pharmaceutical Practices (CAPP) at Boston University School of Public Health, Center for Health Quality, Outcomes, and Economic Research at Bedford VA Medical Center, and an unrestricted educational grant from Eli Lilly and Company. The views expressed in this paper are those of the authors and do not reflect those of the funding institutions.

Disclosures

The authors declare no conflicts of interest.

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