Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/cegh

Original Article

Factors associated with adherence over time to antipsychotic drug treatment

Andre Ngamini Ngui^{a,b,*}, Helen-Maria Vasiliadis^{a,c}, Raymond Tempier^d

^a Hôpital Charles LeMoine Research Centre Longueuil, QC, Canada

^b Centre de réadaptation en dépendance de Montréal – Institut Universitaire, Canada

^c Department of Community Health Sciences, Université de Sherbrooke, QC, Canada

^d Department of Psychiatry, University of Ottawa, Ontario, Canada

ARTICLE INFO

Article history:

Received 12 September 2013

Accepted 6 November 2013

Available online 20 November 2013

Keywords:

Antipsychotic

Adherence/Non-adherence

Longitudinal study

Administrative databases

Pharmacoepidemiology

ABSTRACT

Background: Previous studies have used cross-sectional designs to assess factors associated with adherence to antipsychotics giving little information about patients' adherence over time.

Objective: The purpose of this study was to examine antipsychotic adherence over four 6-month periods at the aggregate and individual level in a large cohort of patients.

Methods: We identified 8595 patients who received an antipsychotic prescription between January 2000 and December 31st 2003 with a clearance period of three months. We used the medication possession ratio (MPR) to assess adherence. We examined whether patients had consistently good adherence (MPRs greater or equal to 0.8 in all 4-periods), consistently poor adherence (MPRs less than 0.8 in all periods), or inconsistent adherence. General estimating equations analysis (GEE) was used to assess factors associated with adherence over time.

Results: The cross-sectional prevalence of good adherence was highest at six-month but decreased at twelve-month and remained relatively stable at 27% overall. The overall proportion of consistently good adherence was 12.6% (95% CI = 11.88–13.28). About 13.71% of women and 11.01% of men were consistently good adherent. Factors associated with adherence among men are not always the same among women.

Conclusion: Adherence to medication is a core component of recovery from illness. Clinicians and medication prescribers should identify factors on which it is important to focus to enhance adherence.

Copyright © 2013, INDIACLEN. Publishing Services by Reed Elsevier India Pvt Ltd. All rights reserved.

1. Introduction

Antipsychotic medications are commonly prescribed for specific psychiatric disorders such as schizophrenia or bipolar disorder that are associated with psychotic symptoms.¹

Although second-generation antipsychotics are increasingly replacing typical agents in many countries including Canada,² studies consistently show that antipsychotic therapy tends to be eclipsed by high rates of non-adherence.³ Non-adherence to antipsychotic medication is consistently reported in cross-sectional studies. Cramer et al (1998) found non-adherence

* Corresponding author. 950 Louvain E, Montreal, QC H2M 2E8, Canada. Tel.: +1 514 385 1232.

E-mail addresses: ngaminuingui@gmail.com, nguiandre@yahoo.fr (A.N. Ngui).

2213-3984/\$ – see front matter Copyright © 2013, INDIACLEN. Publishing Services by Reed Elsevier India Pvt Ltd. All rights reserved.
<http://dx.doi.org/10.1016/j.cegh.2013.11.001>

rates ranging from 24% to 90%⁴ while in their systematic review, Lacro et al (2002) found non adherence rates ranging from 20% to 89% with an average rate of 50%.⁵ In general, the consensus among researchers is that the median rate of non-adherence to antipsychotics is approximately 40%.⁶ It has been previously reported that approximately 40% of patients with schizophrenia⁶ and up to 48% of those with bipolar disorder⁷ poorly adhere to their antipsychotics. Whatever the diagnosis, failing to adhere to antipsychotic treatments at any point of time may have serious social and clinical impacts. For instance, in a prospective study of over 6700 patients with schizophrenia treated with antipsychotic medications, non-adherence was related with poor functional outcomes, persistence of symptoms, increased risk of relapse and inpatient stays as well as number of suicide attempts.⁸ The consequences of non-adherence to antipsychotic treatments can also be devastating for patients and their family in terms of personal suffering and reduced quality of life as well as for society in general due to direct costs to the healthcare system due to resource consumption by frequent hospitalizations, and indirect costs such as loss of income and increased mortality.⁹

Previous studies have reported a number of patient and clinical-related factors associated with antipsychotic medication adherence. Among individual characteristics, non-adherence has been associated with lower education, substance abuse, poor insight negative attitude towards medications, a history of non-adherence, and inadequate discharge plan and poor therapeutic alliance with healthcare providers.^{5,10} Clinical conditions such as the presence of chronic medical conditions have also been associated with low adherence to antipsychotics.¹¹ Few authors have also showed gender differences on adherence to treatment with antipsychotics where females are less adherent.^{12,13} However, no study so far has assessed gender specific models of adherence.

Although there are considerable studies on factors associated with adherence to antipsychotics, less is known about adherence over time. Many studies have been carried in clinical settings using cross-sectional designs. There is no guarantee that patients who are identified as non-adherent in cross-sectional studies will remain non-adherent year after year or whether those with good adherence during the first year following the diagnosis of their illness will remain adherent in the long-run.

The aim of this study was to examine factors associated with adherence to antipsychotic medication and to describe longitudinal patterns of adherence in a general population of antipsychotic users within a public managed healthcare system in Saskatchewan (Canada). We also assess gender specific factors associated with adherence in males and females separately. In this study, adherence is defined as the extent to which patients take their medications as prescribed by their healthcare provider.

2. Data and methods

2.1. Data

Data used in this study came from linked databases maintained by Saskatchewan Health, which include health and

pharmaceutical services use and person registry and vital statistics information for registered residents.

The Saskatchewan Prescription Drug Plan provides coverage to eligible Saskatchewan residents (91%) for outpatient drugs which are listed in the Saskatchewan Formulary. Each prescription record includes information both on the physician prescriber and the patient. The Hospital Services data hold information collected from all hospitals in the province and include all acute care in-patient separations, day surgeries, and in-patient psychiatric separations on patients treated in general hospitals. The records include some of the following information: health services number, sex, year and month of birth, residence, most responsible diagnosis, other diagnoses, principal treatment, admission and discharge dates, length of stay, etc. For confidentiality purposes, each resident is given a unique health services number, which allows for record linkage between the databases.

2.1.1. Study population

All individuals aged 14 years and older, residing in the province of Saskatchewan, registered with Saskatchewan Health who were taking an antipsychotic medication were included in the study.

Study index date was January 1st 2000 or later with a clearance period of three months. That is, members of the cohort who had taken an antipsychotic in the past three months proceeding January 1st were excluded. The study population included subjects taking an antipsychotic medication between January 1st 2000 and December 31st 2003 with two years of follow-up data available. Those who died or exited the province within a 2 years follow-up period were excluded. The full study period was therefore between January 1st 2000 and December 31st 2005. All subjects were prospectively followed for two years (24 months) and adherence to antipsychotics was evaluated every six months. Previous studies showed that assessing adherence to antipsychotic at six months gave significant results for intervention.^{14–16} Patients who died before the end of the two years follow-up period were excluded from the analyses.

2.1.2. Outcome measures

The primary dependent variable was antipsychotic adherence using medication possession ratios (MPRs).¹⁷ The MPR was calculated as the ratio of the number days' supply of medication that a patient has received during the designated time period (six months) divided by the number of days' supply he needed to receive his prescribed dose continuously during the entire period (i.e. 6 months × 30 days).¹⁴

$$\text{MPR} = \frac{\text{Number of days supply of antipsychotic}}{\text{Number of days supply needed}}$$

Sixteen antipsychotics were identified in the present study and can be grouped into two categories: Typical or traditional antipsychotics (Chlorpromazine, Flupenthixol, Fluphenazine, Fluspirilene, Haloperidol, Loxapine, Mesoridazine, Pericyazine, Perphenazine, Pimozide, Pipothiazine, Prochlorperazine, Thioridazine, Thiothixene, Trifluoperazine and Zuclopenthixol) and atypical or Second-generation antipsychotics drugs (Clozapine, Olanzapine, Quetiapine and Risperidone).

2.1.3. Adherence categories

Cross-sectional adherence: We first categorized antipsychotic users according to their adherence during each 6-month study period. Users with MPRs <0.8 during a specific calculation period were considered to have poor adherence during that period, while users with MPRs ≥ 0.8 were considered to have good adherence during the period.¹⁸

Adherence over time: we also categorized individuals by their pattern of adherence over the four observation periods. Persons with MPRs ≥ 0.8 in all four observation periods were considered to have consistently good adherence, those with MPRs <0.8 in all four observation periods were considered to have consistently poor adherence, and those with MPRs ≥ 0.8 in some study periods but not all periods were considered to have inconsistent adherence. These three categories were used to document adherence to antipsychotic medication and facilitate interventions aiming to enhance adherence.

2.1.4. Covariates

Antipsychotic adherence was studied as a function of a number of socio-demographic and clinical variables. Socio-demographic variables included age, sex, marital status at baseline, place of residence (urban or rural) at baseline, the proportion of medication cost covered by the government, the type of antipsychotic used (typical or atypical), if the person had switched to another type of antipsychotic, the presence of a dispensed psychotropic drug during the same period as an antipsychotic (e.g. mood stabilizer, stimulant, antidepressant, sedative), type of physician who prescribed the antipsychotic and the length of hospitalization during the follow-up period and if the person was receiving welfare or social benefits at baseline or not.

2.1.5. Statistical analyses

Descriptive statistical analyses (means and frequencies) were used to describe the characteristics of the sample. For the variable “length of hospitalization”, we have used the Mann–Whitney test because it was a not normally distributed.¹⁹ Because of the correlated and clustered nature of our data, with observations nested within individuals over the four observation periods, generalized estimating equations (GEE) was the best approach to assess the predictors of consistently good adherence.²⁰ The empirical correlation matrix was used to fit the model. Analyses were completed using SAS 9.2® for windows. All statistical significance level was set at 0.05.

3. Results

Between January 1st 2000 and December 31st 2003, close to 13,150 persons were prescribed an antipsychotic in Saskatchewan and 4555 persons (34.64%) died before the end of the follow-up period i.e. two years. Data revealed that 2043 persons (44.57%) died within the first six-months, 3042 persons (66.36%) died within one year and 3629 patients (79.71%) died within 18-months of follow-up. The proportion of females was highest among those who died (59.9% females vs. 40.10% males; $p < 0.0001$). Further, those who died during the

study period were also older (72.45 ± 10.42 versus 49.71 ± 23.30 vs.; $p < 0.0001$).

3.1. Description of the sample and pattern of adherence over time

Table 1 outlines the demographic and clinical characteristics of the sample as a function of overall adherence to antipsychotic medication over time. Women represented about 57% of our sample; more than 55% were aged 45 years or more and 46% lived in an urban setting. An antipsychotic was prescribed by psychiatrists in 29% of cases whereas 47% of prescriptions were made by general physicians. The majority of patients (80%) received atypical antipsychotics and almost 10% of antipsychotic users changed their medication from typical to atypical whereas only 8% changed from atypical to typical antipsychotic during the study period. Table 1 also indicates that overall adherence over time is associated with older age (20%); being female (13%); being separated (13%); living in a rural region (13%); receiving welfare benefits (15%); and atypical antipsychotic use (13%). Complementary results (not shown in the tables) indicate that among the 3197 patients who were adherent at 6 months, the rate of non-adherence was 41% at 12 months, 45% at 18 months and 47% at 24 months.

During the 2-year period, the results showed that approximately half (52%) of antipsychotic users were consistently poor adherers to their medication and this was similar for both males and females (Table 2). When looking at gender differences, the results showed that women were more likely to be consistently good adherers (14% versus 11%; $p = 0.04$) and less likely to be consistently poor adherers (51% versus 55%, $p = 0.05$) to their medications than men (Table 2). When looking at adherence over the four 6-month periods (Fig. 1) the results showed a decrease of adherence from 37% in the first 6-months to 26% in the last 6-month period. Further, women had higher adherence rates over time than men.

The results of the multivariate GEE analyses (Table 3) showed that overall, amongst factors associated with good adherence to antipsychotics the following were important: older age, female gender, being married, living in an urban region, receiving welfare, proportion of drug cost covered by the government, using antidepressant, being prescribing antipsychotic by a psychiatrist, using typical antipsychotics and switching from atypical to typical antipsychotics.

The gender specific analyses of the determinants of adherence over time among men and women show that marital status, the use of a mood stabilizer and stimulant and length of stay in hospital were associated with adherence in men but not women. Region of residence, the use of an antidepressant and having being prescribed the antipsychotic by a general practitioner were associated with lower adherence in women.

4. Discussion

This study examined adherence rates to antipsychotic medications over a two-year period in a large population based sample in a public managed healthcare system providing

Table 1 – Description of the sample and pattern of adherence over time.

Patient characteristics	N	%	Adherence over time		p
			No (N = 7515)	Yes (N = 1080)	
Age group					<.0001
24 yrs and less	1593	18.53	93.85	6.15	
25 to 44 yrs	2080	24.20	93.22	6.78	
45 to 64 yrs	1720	20.01	90.06	9.94	
65 yrs and more	3201	37.25	79.08	20.92	
Gender					<.0001
Women	4945	57.53	86.29	13.71	
Men	3650	42.57	88.99	11.01	
Marital status at baseline					.0004
Single/divorced/separated/widowed	5312	61.80	85.45	13.55	
Married	3283	38.20	89.03	10.97	
Place of residence at baseline					.0004
Urban	4000	46.54	88.80	11.20	
Rural	4595	53.46	86.25	13.75	
Receiving welfare benefits at baseline					<.0001
Yes	5092	59.24	84.33	15.67	
No	3502	40.76	89.57	10.43	
Using mood stabilizer					<.0001
Yes	5190	60.38	89.66	10.34	
No	3405	39.62	85.97	14.03	
Using antidepressant					.001
Yes	5523	64.26	88.30	11.70	
No	3072	35.74	85.87	14.13	
Using stimulant					<.0001
Yes	681	7.92	92.66	7.34	
No	7914	92.08	86.99	13.01	
Using sedative					.53
Yes	299	3.48	88.63	11.37	
No	8296	96.52	87.39	12.61	
Type of physician who prescribed antipsychotic					<.0001
Psychiatrist only	2536	29.51	93.10	6.90	
General practitioner (GP) only	4057	47.20	84.45	15.55	
Other	2002	23.29	86.31	13.69	
Change in type of antipsychotic during the follow up					<.0001
From Typical to Atypical	915	10.65	91.91	8.09	
From Atypical to Typical	728	8.47	85.44	14.56	
No change	6952	80.88	87.05	12.95	
Proportion of the medication cost covered by the government (Mean $\pm$ SD)		49.25 $\pm$ 42.13	47.64 $\pm$ 42.48	60.45 $\pm$ 37.73	<.0001
Type of antipsychotic use at baseline					<.0001
Traditional (Typical)	1714	19.91	96.39	3.61	
Second-generation (Atypical)	6881	80.06	85.15	13.85	
Length of hospitalization (in days) (Mean $\pm$ SD)		32.53 $\pm$ 59.67	32.28 $\pm$ 59.31	47.64 $\pm$ 42.48	.31

gender specific information on determinants that may be useful to clinicians in identifying patients who might benefit from improved adherence rates. Choosing a cut-off point of adherence at 0.8 was important to compare the findings of the

present studies with those of previous studies. It has been shown that an MPR of 0.80 is indicative of good adherence.¹⁸

The results also showed that the use of second-generation (atypical) antipsychotics was significantly associated with

Table 2 – Proportion of adherence to antipsychotic medication by sex and by type of adherence.

	Type of adherence	Consistently poor adherence	Inconsistent adherence	Consistently good adherence
Overall	Prevalence	52.51%	34.93%	12.57%
	95% CI	51.45–53.56	33.93–35.94	11.88–13.28
Women	Prevalence	50.66%	35.63%	13.71%
	95% CI	49.26–52.05	34.31–36.98	12.78–14.70
Men	Prevalence	55.01%	33.97%	11.02%
	95% CI	53.40–56.62	32.45–35.53	10.04–12.07

Fig. 1 – Proportion (%) of adherence to antipsychotic medication by sex and by time of measure.

better adherence overall and in both men and women. Results from previous studies have also shown improved compliance with second-generation antipsychotics as compared to conventional drugs.^{3,21} In a previous large study ($n = 7864$) on a MEDICAID population with schizophrenia, Eaddy et al (2005) found that those treated with second-generation antipsychotics had a slightly higher adherence than those in using typical drugs.²² In previous studies, this has been explained by the fewer side effects found with second-generation antipsychotics.^{3,23}

The findings of this study showed a number of socio-demographic and clinical factors associated with adherence. The association between age and adherence found in our study is consistent with the literature. One previous study on adherence among individuals with bipolar disorder also showed that older adults were more likely to adhere to their antipsychotic medications as compared to their younger counterparts.²⁴ The authors suggest that the older group may represent a survivor cohort characterized by long-term adherers.²⁴ Others have suggested that younger individuals may not fully understand the severity of their illness and the need of treatment follow-up. In fact, recent studies have shown that younger individuals are less likely to attend outpatient consultations and more likely to abandon their psychiatric therapy.²⁵ As seen in the literature, marital status of being married was also associated with good adherence over time as compared to those who were not. An earlier study of the determinants of 6-month adherence in first-episode psychosis patients showed the importance of family social support and also showed that non-adherent patients were more likely to be single.²⁶

When looking at system factors, the contribution of the government to the cost of the medication was also significantly associated with good adherence over time. This finding is similar to a large population based study on the association between drug copayments and adherence to statin treatment in patients with cardiovascular disease, which also showed that high copayments were barriers to statin adherence.²⁷ The results underline the importance of government co-payments for vulnerable populations and lower socio-economic groups.

We also found that use of mood stabilizer was associated with better adherence over time in males, whereas in females,

the use of antidepressants decreased the likelihood of adherence to antipsychotics over time. Further, medication switches from atypical to typical antipsychotics were associated with decreased adherence. The interpretation of these results should be made with caution. More qualitative data are needed to understand the effects of these psychotropic drugs on symptoms and consequently on adherence to treatment regimens and finally adherence to pharmacotherapy. For instance, receiving medications with fewer side effects may also improve adherence.

Our findings showed a significant difference in adherence among men and women ($p < 0.0001$). We noted that 13.71% of women and 11.01% of men were consistently good adherent. This difference may be explained by the sexual dysfunction, which influence men more than women taking antipsychotic.²⁸

By providing evidence that factors associated with adherence to antipsychotic drugs may vary over time, the current analyses address some of the limitations of previous studies, which studied adherence over a short period of time. The most important limitation of our study is the omission of several important risk factors that may influence adherence, particularly therapeutic alliance, patients' attitudes toward the illness and medication, substance abuse and the delay between illness diagnosis and initiation to antipsychotic medication. It is also difficult to confirm if a prescription delivered was actually consumed. However, most prescriptions were refills and this may be an indication of medication intake. Although a drug dispensed is not synonymous with drug consumption, studies have shown good concordance ($\kappa = 0.70$) between claims data and self-reported use of psychotropic drugs.²⁹ It is also important to note that in Saskatchewan, reliable coding of mental health diagnoses is problematic given that an important number of physicians are on salary and not paid on a fee for service basis. We could therefore not conclude on adherence levels with respect to different diagnoses. Also, factors which may have diminished adherence such as side effects were not present in the database. Another limitation of the data is that the presence of mental disorders is not reliably measured in the dataset and therefore we could not control for the persistence or severity of symptoms throughout the study period.

Finally, although administrative data are primarily collected to serve administrative purposes, they are valuable research tools. They permitted in this study to assess longitudinal determinants of adherence to antipsychotics in a large population sample. Using the MPR to measure adherence is one of the main strengths of this study. This method has advantage to be a direct measure of adherence because of the use of prescription claims data.^{11,18} Another important strength is that our data cover the entire province and not only a single hospital or a single city. The methodological approach is another important strength of the present study. Using GEE analyses, we were able to compare temporal trends of adherence to antipsychotic medication.

5. Conclusions

The current study is unique since it examines adherence in the general population prospectively over two years and

Table 3 – Factors associated with consistently good adherence to antipsychotic fitted by the GEE.

Variable	Overall		Women		Men	
	OR	95% CI	OR	95% CI	OR	95% CI
Age group						
24 yrs and less	1		1		1	
25–44 yrs	1.24	1.08–1.43*	1.41	1.15–1.74*	1.14	0.93–1.39
45–64 yrs	1.77	1.53–2.05**	2.04	1.65–2.51**	1.59	1.28–1.97**
65 yrs and more	3.67	3.18–4.23**	4.52	3.72–5.50**	2.94	2.33–3.70**
Gender						
Women	1		–	–	–	–
Men	0.92	0.84–0.99*				
Marital status at baseline						
Single/divorced/separated/widowed	1		1		1	
Married	1.23	1.13–1.35**	1.09	0.97–1.22	1.37	1.18–1.60**
Place of residence at baseline						
Urban	1		1		1	
Rural	0.89	0.83–0.97*	0.89	0.81–0.99*	0.89	0.79–1.01
Receiving welfare benefits at baseline						
No	1		1		1	
Yes	0.90	0.82–0.99*	.91	0.80–1.03	.91	0.79–1.06
Using mood stabilizer						
Yes	1.08		1.04		1.18	
No	1	0.99–1.18*	1	0.93–1.17	1	1.03–1.35*
Using antidepressant						
Yes	0.87		0.85		0.94	
No	1	0.81–0.96*	1	0.76–0.96*	1	0.83–1.07
Using stimulant						
Yes	1.16		1.00		1.20	
No	1	1.0–1.36	1	0.75–1.33	1	0.98–1.46
Using sedative						
Yes	0.86	0.70	0.85	0.65	0.88	
No	1	0.70	1	0.65	1	0.61–1.25
Type of physician who prescribed antipsychotic						
Psychiatrist only	1.79		1.86		1.73	
General practitioner (GP) only	0.92	1.62–1.98**	0.83	1.63–2.14**	1.04	1.48–2.02**
Other	1	0.82–1.02	1	0.71–0.96*	1	0.88–1.22
Change in type of antipsychotic during the follow up						
From Typical to Atypical	1.09		1.10		1.05	
From Atypical to Typical	.48	0.95–1.24	0.44	0.92–1.31	.60	0.85–1.30
No change	1	0.41–0.58**	1	0.35–0.55**	1	0.44–0.78*
Proportion of the medication cost covered by the government	1.01	1.00–1.01**	1.01	1.00–1.01**	1.01	1.00–1.01**
Type of antipsychotic use at baseline						
Atypical	1		1		1	
Typical	5.13	4.23–6.16**	5.36	4.23–6.79**	4.72	3.54–6.30**
Length of hospitalization	1.00	0.99–1.00	0.99	0.99–1.00	1.00	1.00–1.01*

** $p < 0.0001$.* $p < 0.05$.

focuses on adherence factors. Ongoing adherence with antipsychotic medications is an important issue if patients' outcomes are to be optimized. We acknowledge that developing interventions that improve patient adherence remains challenging. The findings of this study distinctly contribute to the adherence literature to antipsychotic medications. Having documented the influence of different factors on adherence over time, we hope this research will encourage physicians and policymakers to take measures to increase patients' awareness of the need to use antipsychotic medications in order to fully attain their benefits. We also saw the importance of government co-payments of medications on adherence rates. Research needs to move forward to understand how to help patients to improve their adherence and to assist healthcare professionals in supporting them. There is a

consensus that tailored interventions are essential. In addition, it is important to understand adherence behaviours over time in order to recognize specific periods during a person's life when adherence is more difficult to achieve. Further studies are however needed to assess the influence of the neighbourhood context and the physician therapeutic alliance on medication adherence over time.

Conflicts of interest

The authors acknowledge the contribution of the Canadian Foundation for Innovation Grant to the collection of the data for this project. None of the authors received salaries, consultation fees or any reimbursement from this foundation,

nor held any shares in this organization. The authors declare that they have no conflict of interests.

Acknowledgements

This study was based, in part, on de-identified data provided by the Saskatchewan Ministry of Health. The interpretations and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Ministry of Health.

REFERENCES

- Byerly MJ, Nakonezny PA, Lescouffair E. Antipsychotic medication adherence in schizophrenia. *Psychiatr Clin North Am*. 2007;30(3):437–452.
- Horn M, Procyshyn RM, Warburton WP, et al. Prescribing second-generation antipsychotic medications: practice guidelines for general practitioners. *BC Med J*. 2012;54(2):75–82.
- Voruganti LP, Baker LK, Awad G. New generation antipsychotic drugs and compliance behaviour. *Curr Opin Psychiatry*. 2008;21:133–139.
- Cramer J, Rosenheck P. Compliance with medication regimens for mental and physical disorders. *Psychiatr Serv*. 1998;49:196–201.
- Lacro J, Dunn L, Dolder C, Leckband S, Jeste D. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. *J Clin Psychiatry*. 2002;63:892–909.
- Valenstein M, Ganoczy D, McCarthy J, Kim M, Lee T, Blow F. Antipsychotic adherence over time among patients receiving treatment for schizophrenia: a retrospective review. *J Clin Psychiatry*. 2006;67:1542–1550.
- Gianfrancesco F, Sajatovic M, Rajagopalan K, Wang R. Antipsychotic treatment adherence and associated mental health care use among individuals with bipolar disorder. *Clin Ther*. 2008;30(7):1358–1374.
- Novick D, Haro JM, Suarez D, Perez V, Dittmann RW, Haddad PM. Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. *Psychiatry Res*. 2010;176(2–3):109–113.
- Barkhof E, Meijer CJ, de Sonnevile LMJ, Linszen DH, de Haan L. Interventions to improve adherence to antipsychotic medication in patients with schizophrenia – A review of the past decade. *Eur Psychiatry*. 2012;27(1):9–18.
- Hunt GE, Bergen J, Bashir M. Medication compliance and comorbid substance abuse in schizophrenia: impact on community survival 4 years after a relapse. *Schizophrenia Res*. 2002;54(3):253–264.
- Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation*. 2009;119(23):3028–3035.
- Castberg I, Westin AA, Spigset O. Does level of care, sex, age, or choice of drug influence adherence to treatment with antipsychotics? *J Clin Psychopharmacol*. 2009;29(5):415–420. <http://dx.doi.org/10.1097/JCP.0b013e3181b2fced>.
- Seeman MV. Gender differences in the prescribing of antipsychotic drugs. *Am J Psychiatry*. 2004;161:1324–1333.
- Valenstein M, Kavanagh J, Lee T, et al. Using a pharmacy-based intervention to improve antipsychotic adherence among patients with serious mental illness. *Schizophr Bull*. 2011;37(4):727–736.
- Kamali M, Kelly L, Gervin M, Browne S, Larkin C, O'Callaghan E. Psychopharmacology: insight and comorbid substance misuse and medication compliance among patients with schizophrenia. *Psychiatr Serv*. 2001;52:161–163.
- Kamali M, Kelly BD, Clarke M, et al. A prospective evaluation of adherence to medication in first episode schizophrenia. *Eur Psychiatry*. 2006;21(1):29–33.
- Sajatovic M, Velligan DI, Weiden PJ, Valenstein MA, Ogedegbe G. Measurement of psychiatric treatment adherence. *J Psychosomatic Res*. 2010;69(6):591–599.
- Cantrell CR, Eaddy MT, Shah MB, Regan TS, Sokol MC. Methods for evaluating patient adherence to antidepressant therapy: a real-world comparison of adherence and economic outcomes. *Med Care*. 2006;44(4):300–303.
- Katz MH. *Study Design and Statistical Analysis: A Practical Guide for Clinicians*. UK: Cambridge. 2006:188.
- Edwardes MD, Forrester JE. Statistical analysis of correlated data using generalized estimating equations: an orientation. Hanley JA, Negassa A, eds. *Am J Epidemiol*. 2003;157(4):364–375.
- Al-Zakwani IS, Barron JJ, Bullano MF, Arcona S, Drury CJ, Cockerham TR. Analysis of healthcare utilization patterns and adherence in patients receiving typical and atypical antipsychotic medications. *Curr Med Res Opin*. 2003;19(7):619–626.
- Eaddy M, Grogg A, Locklear J. Assessment of compliance with antipsychotic treatment and resource utilization in a medicaid population. *Clin Ther*. 2005;27(2):263–272.
- Sajatovic M, Valenstein M, Blow F, Ganoczy D, Ignacio R. Treatment adherence with antipsychotic medications in bipolar disorder. *Bipolar Disord*. 2006;8(3):232–241.
- Sajatovic M, Blow F-C, Kales H-C, Valenstein M, Ganoczy D, Ignacio R- V. Age comparison of treatment adherence with antipsychotic medications among individuals with bipolar disorder. *Int J Geriatr Psychiatry*. 2007;22(10):992–998.
- Mitchell AJ, Selmes T. Why don't patients attend their appointments? Maintaining engagement with psychiatric services. *Adv Psychiatr Treat*. 2007;13(6):423–434.
- Rabinovitch M, Bécharé-Evans L, Schmitz N, Joobor R, Malla A. Early predictors of nonadherence to antipsychotic therapy in first-episode psychosis. *Can J Psychiatry*. 2009;54(1):28–35.
- Ye X, Gross CR, Schommer J, Cline R, St. Peter WL. Association between copayment and adherence to statin treatment initiated after coronary heart disease hospitalization: a longitudinal, retrospective, cohort study. *Clin Ther*. 2007;29(12):2748–2757.
- Smith SM, O'Keane V, Murray R. Sexual dysfunction in patients taking conventional antipsychotic medication. *Br J Psychiatry*. 2002;181(1):49–55.
- Saunders K, Simon G, Bush T, Grothaus LG. Assessing the feasibility of using computerized pharmacy refill data to monitor antidepressant treatment on a population basis: a comparison of automated and self-report data. *J Clin Epidemiol*. 1998;51(10):883–890.