Antipsychotic Adherence in Patients with Schizophrenia: Variability and Outcomes in Best Practices

Junga Joanne Kim, Pharm.D. Candidate., Prince-Harry Mangondato, Pharm.D. Candidate., Megan E Maroney, Pharm.D., BCPP, Michael Toscani, Pharm.D.

Background

Consequences of poor adherence with antipsychotics in patients with schizophrenia can lead to several detrimental outcomes, including exacerbations of symptoms, re-hospitalization, incarceration, and suicide. These outcomes can prove to be both costly and counterproductive to the overall efforts of any healthcare system. Studying adherence is difficult because it is often subjectively executed and variable in methodology. To be able to meaningfully address the problem of non-adherence, and come up with a way to improve adherence to antipsychotics, a literature review was conducted in order to pinpoint an accurate means of measuring adherence and to draw upon significant relationships between different patient factors and adherence.

Objective

The objective of this study is to determine the variability in outcomes of adherence and best practices to improve adherence to antipsychotic regimens in patients with schizophrenia.
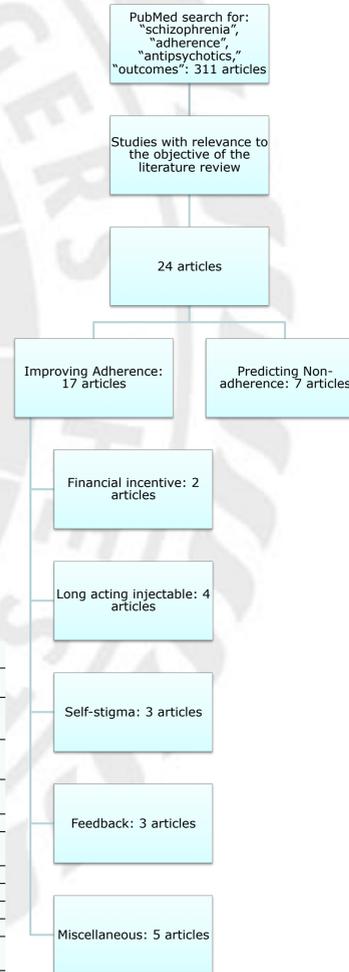
Methods

A PubMed search was conducted from 1995 to 2015, using the following medical subject headings: antipsychotics, adherence, schizophrenia, and outcomes. Each article was reviewed against a standard criteria for acceptance, such as determination of appropriateness and relevance to the objective. All articles were analyzed using descriptive statistics to capture information such as: study design, patient population, indications, comparative agents, adherence, intervention type, clinical outcomes, and cost. Outcomes (clinical, humanistic, satisfaction, and adherence) from these studies were analyzed to evaluate the variability of these measures used in the trials. Data were organized to focus on those interventions and practices that resulted in positive adherence and clinical outcomes.

Studies Used

Article	Authors	Article Title
1	Pavlickova H, et al.	The effect of financial incentives on adherence to antipsychotic depot medication: does it change over time?
2	Priebe S, et al.	Effectiveness of financial incentives to improve adherence to maintenance treatment with antipsychotics: cluster randomized controlled trial
3	Marcus SC, et al.	Antipsychotic adherence and rehospitalization in schizophrenia patients receiving oral versus long-acting injectable antipsychotics following hospital discharge
4	Sajatovic M, et al.	Prospective trial of customized adherence enhancement plus long-acting injectable antipsychotic medication in homeless or recently homeless individuals with schizophrenia or schizoaffective disorder
5	Warikoo N, et al.	Adherence and continuation of treatment with first- and second-generation antipsychotics in schizophrenia
6	Subotnik KL, et al.	The impact of second-generation antipsychotic adherence on positive and negative symptoms in recent-onset schizophrenia
7	Vrbova K, et al.	Self-stigma and adherence to medication in patients with psychotic disorders—cross-sectional study
8	Ullmann C, et al.	Negative impact of self-stigmatization on attitude toward medication adherence in patients with psychosis
9	Moritz S, et al.	Nonadherence to antipsychotics: The role of positive attitudes towards positive symptoms
10	Kozuki Y, Schepp KG	Visual-feedback therapy for antipsychotic medication adherence
11	Patel UB, et al.	An attempt to improve antipsychotic medication adherence by feedback of medication possession ratio scores to prescribers
12	Kannisto KA, et al.	Feedback on SMS reminders to encourage adherence among patients taking antipsychotic medication: a cross-sectional survey nested within a randomised trial
13	Jaeger S, et al.	Control beliefs, therapeutic relationship, and adherence in schizophrenia outpatients: a cross-sectional study
14	Pfeiffer PN, et al.	Dosing frequency and adherence to antipsychotic medications
15	Kopelowicz A, et al.	The ability of multifamily groups to improve treatment adherence in Mexican Americans with schizophrenia
16	Bayle FJ, et al.	Medication adherence in patients with psychotic disorders: an observational survey involving patients before they switch to long-acting injectable risperidone
17	Lee LT, et al.	Holistic consideration of patients with schizophrenia to improve medication adherence and outcomes
18	Hui CL, et al.	Prevalence and predictors of medication non-adherence among Chinese patients with first-episode psychosis
19	Miller J, et al.	Urine testing for antipsychotics: a pilot trial for a method to determine detection levels
20	Karve S, et al.	Assessing medication adherence and healthcare utilization and cost patterns among hospital-discharged patients with schizoaffective disorder
21	Vassileva I, et al.	Predictors of medication non-adherence in Bulgarian outpatients with schizophrenia
22	Grundmann M, et al.	Therapeutic drug monitoring of atypical antipsychotic drugs
23	Brain C, et al.	Drug attitude and other predictors of medication adherence in schizophrenia: 12 months of electronic monitoring (MEMS) in the Swedish COAST-study
24	Yalcin-Siedentopf N, et al.	Measuring adherence to medication in schizophrenia: the relationship between attitudes toward drug therapy and plasma levels of new-generation antipsychotics

Results

Figure 1: Search Methodology

PubMed search for: "schizophrenia", "adherence", "antipsychotics", "outcomes": 311 articles
→ Studies with relevance to the objective of the literature review
→ 24 articles
→ Improving Adherence: 17 articles | Predicting Non-adherence: 7 articles

Improving Adherence subgroups:
- Financial incentive: 2 articles
- Long acting injectable: 4 articles
- Self-stigma: 3 articles
- Feedback: 3 articles
- Miscellaneous: 5 articles

Table 1: Improving Adherence

	Article #	Study design	Key findings	Positive or Negative Effect on Adherence?
Financial incentive	1	Cluster-randomized controlled trial	• Adherence was significantly higher in the intervention than control group at the end of intervention (p=0.003) • Higher total amount of incentives was associated with a poorer adherence (P=0.023)	• Positive
	2	Cluster-randomized controlled trial	• Adherence was significantly higher in the intervention group than control group at the end of intervention (p=0.003) • Statistically significant but not clinically different in quality of life rating (P=0.002) • The number of admissions to hospital and adverse events were low in both groups and did not show substantial differences	• Positive
Long acting injectable	3	Retrospective cohort design	• Less patients on LAIs were non-adherent vs. patients on oral medications (P<0.001) • A smaller percentage of patients receiving LAIS were rehospitalized for schizophrenia compared to those receiving oral medications (P=0.01)	• Positive
	4	Prospective, uncontrolled trial	• Customized adherence enhancement (CAE) plus long-acting injectable antipsychotic (LAI) to patients • Use of CAE-L associated with improved adherence, symptoms, and functioning in schizophrenic patients • Use of CAE-L associated with good adherence to LAI (76% at 6 months)	• Positive
SGA vs. FGA	5	Comparison of patients on FGA vs. SGA	• Patients on certain second-generation antipsychotics more likely to continue with their treatment than those on first-generation APs. • Patients on olanzapine differed significantly from those on FGAs in terms of their mean compliance rating scale (CRS) and DAI-10 scores at 3 months as well as over the 6-month study-period.	• Positive
	6	N/A	• Higher levels of antipsychotic medication adherence were associated with lower levels of positive symptoms and lower levels of negative symptoms • Second-generation antipsychotics lower negative symptoms more than first-generation antipsychotics do	• Positive
Self-stigma	7	Cross-sectional study	• Significant negative correlation with current adherence to treatment and levels of self-stigma • ISMI is a scale of measurement of internalized stigma, which includes feelings of alienation and exclusion from society, rate of withdrawal from society, perception of how others have behaved toward them since they were diagnosed as mentally ill. • Adherence: negative correlation of -0.3653 with the total ISMI score (P<0.005)	• Negative
	8	N/A	• Reducing the extent of self-stigmatization, especially feeling of being alienated from society, could improve a negative attitude toward medication adherence • Patients who suffer from side effects due to antipsychotic medication and experience less well-being when being treated with antipsychotics are more likely to have negative attitude toward medication adherence • Non-adherence scores were positively correlated with the number of reported side effects p < .05	• Negative
	9	Survey .	• Reasons for non-adherence: side effects, sudden subjective symptom improvement, forgetfulness • Reasons for adherence: desire of a normal life, fear of psychotic symptoms, didn't want to be called crazy, family and friend advice • Poor adherence is associated with ambivalence towards symptoms • Since patients attach meaning to their symptoms, it is important to address hopelessness and stigma in patients in order to increase adherence. Increase in adherence can be improved from helping patients feel validated and understood.	• N/A
Feedback	10	N/A	• Adherence rates of the visual-feedback group slightly increased (P=0.026)	• Positive
	11	Controlled trial	• The intervention group, who was noticed when patients failed to refill essential prescriptions in a timely manner, had a significantly greater increase in MPR score between pre intervention and intervention periods (p <0.05)	• Positive
	12	Cross-sectional	• n=569 • 98% of participants on antipsychotic medication found the SMS reminders (1-6x/month) to encourage medication adherence and outpatient treatment easy to use and 87% felt that the SMS did not cause harm	• Positive
Misc	13	Cross-sectional	• The 'powerful others' dimension of the health locus of control can decrease medication adherence but is mediated by a strong relationship between therapist and patient • Self-report measures for the assessment of medication adherence, locus of control, and therapeutic relationship • MARS (mean score of self-rated medication adherence) = 7.4 = good adherence • Internal HLC (health locus of control) on adherence = not statistically significant • Direct effect of powerful others HLC on adherence = not statistically significant • Therapeutic relationship on adherence = significantly positively related (p <.05) • Indirect effect of powerful others HLC on adherence = significant (p < .05) o Powerful others HLC has an effect on medication adherence primarily via the relationship to the doctor	• N/A
	14	Controlled trial	• No significant differences in MPRs between those receiving once-daily dosing and those receiving more than once-daily dosing • Patients with decrease in dosing frequency had a significant increase in mean MPR vs. patients without a dosing frequency change (p <.001) • Patients with a dose frequency increase had a significant decrease in mean MPR vs. those without a frequency change (p <.001)	• Positive
	15	Controlled trial	• Multi-family groups (MFG-A) and multi-family standard group (MFG-S) convened in hour sessions twice monthly for 1 year, with more focus on medication on MFG-A group than MFG-S. • After 1 year, MFG-A was associated with higher medication adherence than MFG-S or treatment as usual only (P=0.003) • MFG-A had a longer time to first hospitalization (P=0.001) • MFG-adherence less likely to be hospitalized than those in MFG-standard (p = .04)	• Positive
	16	Cross-sectional, observational survey	• Therapeutic alliance (4PAS) was lower in "severely ill" or "among the most extremely ill" patients (P<0.001), and in those with a lack of insight (P<0.001) • Medication adherence, as evaluated in terms of the MAQ, was significantly associated with therapeutic alliance, as measured by 4PAS (P<0.0001) • Age <40 years was associated with "low" MAQ classification (P=0.0003)	• N/A
	17	N/A	• Evaluating the medication adherence of patients can be determined by two key domains, namely patients' behaviors (regularly visiting clinics or frequently approaching HCPs) and attitude/knowledge (a favorable response to his/her disease or understanding the nature of his/her disease) • Patient characteristics should be taken into account to design holistic and individualized treatment plans. • An algorithm that is suitable for treating patients with schizophrenia before applying traditional prescribing guidelines.	• N/A

Results (continued)

Table 2: Predicting Non-adherence

Article #	Study design	Key findings	Significant Predictors of Non-adherence
18	Large, cohort study	• Predictors for non-adherence year 1: no hospitalization at baseline (P=0.010) and non-schizophrenia diagnosis (P=0.032) • Predictors for non-adherence year 2: acute/subacute onset and older age of onset	• No hospitalization at baseline • Non-schizophrenia diagnosis
19	N/A	• Potential utility of the urine assay to help monitor adherence to antipsychotic medications • Urine sample for patients taking risperidone, quetiapine, olanzapine and/or haloperidol • Urine sample was able to detect all four antipsychotic medications and their metabolites	• Negative result in urine testing
20	Retrospective cohort study	• Adherence to medications highest during the 60-day period immediately following hospital discharge • 62% of patients non-adherent to medications during the 60 day pre-admission while 34.4% of patients non-adherent to medications during the 60 days period after the discharge	• 60-day period post hospital discharge
21	Interview	• Multiple regression analysis provided a three-step model where the total predicting value was 38.1% (P<0.001) • In the first step, attitudes towards medication were selected as the variable to predict the values of the MAQ (medication adherence questionnaire) (P<0.001) • In the second step, attitudes toward antipsychotic medication • In the third step, attitudes toward medication (P<0.001) and positive symptoms (P<0.001)	• Negative attitude • Severe positive symptom • Inability to recognize psychotic symptoms
22	N/A	• Therapeutic drug monitoring (TDM) involves measurement of drug serum concentrations followed by interpretation and good cooperation with the clinician • TDM provides tailor-made treatment for the specific needs of individual patients to help in monitoring adherence	• Low levels of drug serum concentration
23	N/A	• Low DAI-10 scores, higher positive symptom burden, poor function, side effects, and lack of insight predicted non-adherence • DAI-10 + PSP scores together proved as predictors of non-adherence o negative DAI-10 score = non-adherence o DAI-10 as a predictor of MEMS non-adherence: p = <.001 o PSP as a predictor of MEMS non-adherence: p = .007	• Higher negative symptom burden • Poor function • Presence of side effects to medication • Lack of insight
24	Controlled trial	• Association between DAI and ratio of observed vs expected plasma levels o Only a small number of significant or trend level correlations o No consistent correlation between patients' attitude toward drug therapy and the individual ratios observed vs. expected plasma levels of medication o No consistent correlation between subjective and objective measures of medication adherence	• N/A

Limitations

This literature review does not fully encompass the entirety of literature on antipsychotic adherence in patients with schizophrenia. With the perusal of multiple abstracts throughout the PubMed database, only 24 articles out of 311 available articles were analyzed and deemed fit for the scope of this literature review. Consequently, the use of PubMed as the only search engine used serves as a limitation since there are many other databases available. In addition, the amount of articles reviewed was also impacted by the fact that some full articles could not be accessed within our means. An additional limitation is that some of the studies included patients with a diagnosis of schizoaffective disorder, despite our desire to look into strictly patients with a schizophrenia diagnosis. Lastly, there is a potential for unforeseen confounding variables that may have impacted the results.

Conclusions

The PubMed search of articles regarding adherence on antipsychotics in patients with schizophrenia patients yielded a total of 311 studies. We decided that only 24 out of the 311 articles were applicable for this literature review based on a perusal of the abstracts. From the analysis of the 24 articles, we determined a list of variables that affect medication adherence in patients with schizophrenia: financial incentives, use of long-acting injectables, self-stigma, use of feedback mechanisms, and patient behaviors. Our analysis of the studies showed that the use of financial incentives, long-acting injectables and feedback mechanisms such as electronic monitoring medication caps helped improve adherence. However, the more self-stigma that the patient has, and the more negative attitudes that patients have towards their illness, the higher chance that the patient will become non-adherent to their medications. In order to prevent non-adherence, we reviewed articles that suggested methods to predict non-adherence in patients. Urine testing and therapeutic drug monitoring are some of the ways to predict non-adherence. Because adherence is dependent on multiple variables, the search for methods to improve adherence should be continued.

Author Contact Information

Junga Joanne Kim, Pharm.D. Candidate — rujoannekim@gmail.com
Prince-Harry Mangondato, Pharm.D. Candidate — ph.mangodato@gmail.com
Megan E. Maroney, Pharm.D., BCPP — mmaroney@pharmacy.rutgers.edu
Michael Toscani, Pharm.D. — mjket@pharmacy.rutgers.edu