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 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 in antipsychotics. A literature review must be made on various studies in order to pinpoint an accurate means of measuring adherence and to draw upon significant relationships between different patient factors and adherence.

Objective

Consequences of poor adherence with antipsychotics can lead to several detrimental outcomes, including exacerbations of symptoms, re-hospitalization, incarceration, and suicide. The objective of this study is to determine the variability and outcomes of adherence in best practices 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 Number	Authors	Article Title
1	Hana Pavlickova, Stephen A. Brenner, Stefan Priebe	The effect of financial incentives on adherence to antipsychotic depot medication: does it change over time?
2	Stefan Priebe, Ksenija Yeeles, Stephen Bremner, Christoph Lauber,	Effectiveness of financial incentives to improve adherence to maintenance treatment with antipsychotics: cluster randomized controlled trial
3	Steven C. Marcus, Jacqueline Zummo, Amy R. Pettit, Jeffrey Stoddard	Antipsychotic adherence and rehospitalization in schizophrenia patients receiving oral versus long-acting injectable antipsychotics following hospital discharge
4	Martha Sajatovic, Jennifer Levin, Luis F. Ramirez, David Y. Hahn	Prospective trial of customized adherence enhancement plus long-acting injectable antipsychotic medication in homeless or recently homeless individuals with schizophrenia or schizoaffective disorder
5	Nisha Wankoo, Subho Chakrabarti, Sandeep Grover	Adherence and continuation of treatment with first- and second-generation antipsychotics in schizophrenia
6	Kenneth L. Subotnik, Joseph Ventura, Denise Gretchen-Doorly, Gerhard S. Hellemann	The impact of second-generation antipsychotic adherence on positive and negative symptoms in recent-onset schizophrenia
7	Kristyna Vrbova, Dana Kamaradova, Klara Latalova, Marie Ociskova	Self-stigma and adherence to medication in patients with psychotic disorders—cross-sectional study
8	Christina Ullmann, PhD, Janis Kaehler, MA, Margret S.H. Harris, PhD, Julia Unser, MD,	Negative impact of self-stigmatization on attitude toward medication adherence in patients with psychosis
9	Steffen Moritz, Alexandra Hünsche, Tania M. Lincoln	Nonadherence to antipsychotics: The role of positive attitudes towards positive symptoms
10	Yoriko Kozuki, Karen G. Schepp	Visual-feedback therapy for antipsychotic medication adherence
11	Urvashi B. Patel, PhD, Quanhong Ni, MS, Carol Clayton, PhD, Peter Lam, Joseph Parks, MD	An attempt to improve antipsychotic medication adherence by feedback of medication possession ratio scores to prescribers
12	Kati Anneli Kannisto, Clive E Adams, Marita Koivunen, Jouko Katajisto	Feedback on SMS reminders to encourage adherence among patients taking antipsychotic medication: a cross-sectional survey nested within a randomised trial
13	Susanne Jaeger, Dr. rer.nat., Sabine Weibhaupt, Dipl.-Psych., Erich Flammer, Dipl.-Psych., Tilman Steinert, PRof. Dr.med.	Control beliefs, therapeutic relationship, and adherence in schizophrenia outpatients: a cross-sectional study
14	Paul N. Pfeiffer, MD, Dara Ganoczy, MPH, Marcia Valenstein, MD	Dosing frequency and adherence to antipsychotic medications
15	Alex Kopelowicz, MD, Roberto Zarate, PhD, Charles J. Wallace, PhD, Robert Paul Liberman, MD,	The ability of multifamily groups to improve treatment adherence in Mexican Americans with schizophrenia
16	Franck Jean Bayle, Arnaud Tessier, Sophie Bouju, David Misdrahi	Medication adherence in patients with psychotic disorders: an observational survey involving patients before they switch to long-acting injectable risperidone
17	Lan-Ting Lee, Kao Chin Chen, Wei Hung Chang, Po See Chen	Holistic consideration of patients with schizophrenia to improve medication adherence and outcomes
18	Christy Lai-Ming Hui, Venessa Wing-Yan Poon, Vivian Shuk-Kuen Kwok, Wing-Chung Chang, Sherry Kit-Wa Chan, Edwin Ho-Ming Lee, Eric Yu-Hai Chen	Prevalence and predictors of medication non-adherence among Chinese patients with first-episode psychosis
19	Jennifer Miller, Heidi Wehring, Robert P. McMahon, Bethany A. DiPaula, Raymond C. Love, Avodele Antoinette Morris, Heather Raley, Stephanie Feldman, Deanna L. Kelly	Urine testing for antipsychotics: a pilot trial for a method to determine detection levels
20	Sudeep Karve, Michael Markowitz, Dong-Jin Fu, Jean-Pierre Lindenmayer, Chi-Chuan Wang, Sean D. Candrilli, Larry Alphs	Assessing medication adherence and healthcare utilization and cost patterns among hospital-discharged patients with schizoaffective disorder
21	Iglika Vassileva, Vihra Milanova, Turan Asan	Predictors of medication non-adherence in Bulgarian outpatients with schizophrenia
22	Milan Grundmann, Ivana Kacirova, Romana Urinovska	Therapeutic drug monitoring of atypical antipsychotic drugs
23	Cecilia Brain, Katarina Allerby, Birgitta Sameby, Patrick Quinlan, Erik Joas, Ulla Karilampi, Eva, Lindström, Jonas Eberhard, Tom Burns, Margda Waern	Drug attitude and other predictors of medication adherence in schizophrenia: 12 months of electronic monitoring (MEMS) in the Swedish COAST-study
24	Nursen Yalcin-Siedentopf, MD, Fabienne Wartelsteiner, MD, Alexandra Kaufmann, MD; Falko Biedermann, MD, Monika Edlinger, MD, Georg Kemmler, PhD, Maria A. Rettenbacher, MD, Christian G. Widschwendter, MD, Geral Zernig, MD, W. Wolfgang Fleischhacker, MD, Alex Hofer, MD	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

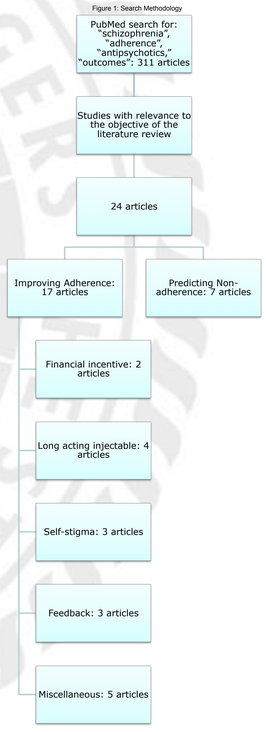

Table 1: Improving Adherence

	Article Number	Study design	Key findings	Positive or Negative Effect on Adherence?
Financial incentive	1	Cluster-randomized controlled trial	• Adherence was significantly higher in the intervention group than control group at the end of intervention (p=0.003) • There is no interaction effect between time and treatment group; the effect of financial incentives remains practically unaltered over a 1-year period • 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) • Although differences in clinical rated clinical improvement between the groups failed to reach statistical significance, patients in the intervention group had more favorable subjective 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	• A smaller percentage of patients receiving LAIs were nonadherent compared to patients receiving oral medications (P<0.001) • A smaller percentage of patients receiving LAIs had a 60-day continuous gap in medication compared to patients receiving 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) • Only patients receiving SGA LAIs and not FGA LAIs had a statistically significant reduction in odds of rehospitalization	• Positive
	4	Prospective, uncontrolled trial of	• Prospective, uncontrolled trial of customized adherence enhancement (CAE) plus long-acting injectable antipsychotic (LAI) using haloperidol decanoate in 30 homeless or recently homeless individuals with schizophrenia or schizoaffective disorder • Customized adherence enhancement included psychoeducation focused on medication, developing medication routines, communicating with providers about benefits and burdens of medications, and managing adherence in the context of substance abuse. • CAE-L appears to be associated with improved adherence, symptoms, and functioning in homeless or recently homeless individuals with schizophrenia or schizoaffective disorder • Individuals in this study reported missing 46%-57% of prescribed medication. Use of CAE-L was associated with good adherence to maintenance LAI (76% at 6 months) and dramatic improvement in oral prescribed drug adherence, which changed from missing approximately 46% of prescribed medication to 10% of prescribed medication at the end of the study.	• Positive
	5	Comparison of patients on FGA vs. SGA	• Patients on certain second-generation APs, notably olanzapine, are 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	• Bivariable analyses were done
			• The relationship between greater medication adherence and negative symptoms of schizophrenia are accounted for by the relationship of both variables with positive symptoms.
			• A reduction in positive symptoms can possibly mediate the impact of second-generation antipsychotic medication on suppression of negative symptoms
			• Higher levels of antipsychotic medication adherence were associated with:
			• Lower levels of two positive symptoms
			  ○ Lower levels of two forms of negative symptoms:
			  § Greater adherence to the second-generation oral antipsychotic medication, risperidone, was associated with lower levels of reality distortion (delusions and hallucinations), avolition-apathy, and alogia
			  § There is a possibility that initial adherence contributed to lower levels of alogia up to one year later
			• Significant correlations between antipsychotic medication adherence and negative symptoms become nonsignificant after controlling for reality distortion
			• The relationship between non-adherence and negative symptoms were correlated with low antipsychotic medication adherence should similarly be reconsidered in light of this potential mediation effect
				• 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 stigmaa, 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	• Study implies that reducing the extent of self-stigmatization, especially feeling of being alienated from society, could improve a negative attitude toward medication adherence in psychosis patients
			• Higher ROMI non-adherence scores were associated with ISMI subscales
			  ○ Alienation p < .001
			  ○ Stereotype endorsement p = .008
			  ○ Social withdrawal p = .017
			• Nonadherence scores were associated with gender
			  ○ Women have a more negative attitude toward medication adherence compared to men p = .013
			• Nonadherence scores were positively correlated with the number of reported side effects p < .05
			• Nonadherence scores negatively correlated with the SWN-K score p < .05
			  ○ What this means: Patients whom 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
				• Negative

	9	Survey
		.
			• Looks into what extent positive attitudes towards psychotic symptoms promote adherence
			• N = 91
			  ○ 22 reported nonadherent; 76 reported adherent
			• Results:
			  ○ 6.2 reasons for nonadherence reported:
			  ▪ Side effects - 71.4%; sudden subjective symptom improvement - 52.4%; forgetfulness - 33.3%; a positive aspect of psychosis - 27.3%
			  ○ 3.5 reasons for adherence
			  ▪ desire of a normal life - 74.6%; fear of psychotic symptoms 49.3%; symptoms were perceived as impairing - 43.3%; didn't want to be called crazy - 31.3%; family and friend advice - 20.9%
			  ○ Nonadherent patients were predominantly female (p = .01) and had high "BABS paranoia as survival strategy subscale" scores (p = .021)
			• Poor adherence is associated with ambivalence towards symptoms
			• Since patients attach meanings to their symptoms, it is important to address hopelessness and stigma in PTs in order to increase adherence. Increase in adherence can be improved from helping PTs feel validated and understood.
				• N/A

Feedback	10	N/A	• Adherence rates of the visual-feedback group slightly increased (P=0.026)
			  ○ Adherence rates for visual-feedback group increased
			  ○ Adherence rates for supportive counseling control group decreased
				• 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 • No significant difference between intervention and control groups in age or sex distribution • Intervention group had a significant increase in MPR between preintervention and intervention (p = .04) • After TAP intervention, MPR score in the intervention group was no longer statistically significant compared to the comparison group (p = .26)	• Positive
	12	Cross-sectional	• n=569 • 98% of participants on antipsychotic medication found the SMS reminders to encourage medication adherence and outpatient treatment easy to use and 87% felt that the SMS did not cause harm • Texts 1-6x/month	• Positive

Miscellaneous	13	Cross-sectional	• Expectations, beliefs, and attitudes play a prominent role in health behaviors
			  ○ This study explores whether or not Internal LoC is positively correlated with adherence
			• 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
			• Average score of modified D-STAR-P = 31.7
			  ○ 0 = worse possible therapeutic relationship
			  ○ 44 = best possible therapeutic relationship
			  ○ Therapeutic relationship was significantly correlated with adherence (r = .40)
			• 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)
			  ○ Powerful others HLC has an effect on medication adherence primarily via the relationship to the doctor
				• N/A

	14	Controlled trial	• There were no significant differences in MPRs between those receiving once-daily dosing and those receiving more than once-daily dosing • Adherence was measured by MPR (medication possession ratios) • Patients with decrease in dosing frequency had a significant increase in mean MPR when compared with PTs without a dosing frequency change (p <.001) • Patients with a dose frequency increase had a significant decrease in mean MPR compared to those without a frequency change (p <.001)	• Positive

	15	Controlled trial	• At the end of the 1-year treatment, MFG-adherence was associated with higher medication adherence than MFG-standard or treatment as usual only (P=0.003)
			  ○ MGA-A adherence vs MFG-S adherence
			  ▪ 4 months p = <.01; 8 months p = .03; 12 months p = .04; 18 months p = .01; NOT SIGNIFICANT AT 24 months p = .2
			• Also the 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 Nonadherence

Article Number	Study design	Key findings	Significant Predictors of Preidcting Nonadherence
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 • Don't overlook patients with less clinically severe symptoms • Not a controlled trial; data obtained from a larger cohort study which aimed to determine the effectiveness of the phase-specific early intervention program	• No hospitalization at baseline • Non-schizophrenia diagnosis
19	N/A	• Potential utility of the urine assay to help monitor adherence to antipsychotic medications • Not a controlled study • 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 schizoaffective disorder-related medications was highest during the 60-day period immediately following hospital discharge. • 62% of patients were non-adherent to their medications during the 60 day period before the admission while only 34.4% of patients were non-adherent to their medications during the 60 days period after the discharge. • Higher percentage of patients who adhered to their treatment during the 6-month post-index period than during the 6-month pre-index period (51% vs 37%).	• 60-day period post hospital discharge
21	Interview	• Three variables predictive for the medication adherence: 1) attitudes toward medication 2) severity of positive symptoms 3) ability to recognize psychotic symptoms • Assessed the level of adherence to the antipsychotic therapy, the socio-demographic factors and a number of clinical and social variables with possible impact on adherence levels in schizophrenia • 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 toward medication • High severity of 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 can provide tailor-made treatment for the specific needs of individual patients and can help in monitoring adherence	• Low levels of drug serum concentration

23	N/A	• Non adherence is defined as less than or equal to .80 of MEMS adherence scale (objective)
		• Low DAI-10 scores, higher positive symptom burden, poor function, side effects, and lack of insight predicted non-adherence
		• Global cognitive function was not significantly associated with global cognitive function
		• DAI-10 + PSP scores together proved as predictors of nonadherence
		  ○ negative DAI-10 score = non-adherence
		  ○ DAI-10 as a predictor of MEMS non-adherence: p = <.001
		  ○ PSP as a predictor of MEMS non-adherence: p = .007
			• Higher positive 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
		  ○ Only a small number of significant or trend level correlations
		  ○ All significant or near-significant tests yielded an inverse correlation indicating that higher ratios of observed vs expected plasma levels went along with a less positive drug attitude
		  ○ Role of side effects on view of the relation between attitude toward medication and ratio of observed vs expected plasma levels
		  ○ Negative correlation between DAI subscores and the ratio of observed vs expected plasma levels
		  ○ No significant associations between UKU items (sedation, weight, gain, extrapyramidal side effects, and sexual side effects) and the ratio of observed vs expected plasma levels
			• Negative attitude toward medication

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 schizo-affective disorders in addition to schizophrenic patients, despite our desire to look into strictly schizophrenic patients. Lastly, there is a potential for unforeseen 3rd variable impacting various results.

Conclusions

The PubMed search of articles regarding adherence on antipsychotics in schizophrenic 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 schizophrenic patients: financial incentive, use of long-acting injectables, self-stigma, use of feedback mechanism, and patient behaviors. Our analysis of the studies shows that the use of financial incentives, long-acting injectables, feedback mechanisms such as electronic monitoring medication cap 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 patient will stay nonadherent 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 multivariable dependent, 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. miket@pharmacy.rutgers.edu

Disclosure

No relationships to disclose