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Incidence, predictors, healthcare utilization, and cost associated with antipsychotic polypharmacy in the Texas Medicaid population

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by

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Dissertation

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

The University of Texas at Austin

May 2014

Dedication

To mom and dad, my pillars of strength.

Acknowledgements

As I approach the end of my graduate program at The University of Texas at Austin, I am indebted to several people for their support and encouragement. I have been extremely fortunate to have Dr. Lawson as my supervisor. I cannot thank him enough for his continued guidance and encouragement, even during the toughest times of my graduate career. Without his mentorship and support I would not have been able to come this far. I would also like to thank all my committee members—Dr. Rascati, Dr. Barner, Dr. Richards, and Dr. Miller for their feedback and contribution to this project. I am grateful to Dr. Rascati for her support and guidance through my time at UT. Dr. Barner taught me attention to detail and to be very thorough. Dr. Richards has been a great friend and mentor; I thank her for her continued support. Dr. Miller helped me improve this project through his invaluable clinical expertise.

I would like to thank all the other faculty members in the Division of Health Outcomes and Pharmacy Practice, Drs. Brown, Ford, Shepherd, and Wilson who made graduate school an enriching experience for me. I had the pleasure of working with Renee Acosta during my time as a teaching assistant; I thank her for her support and encouragement. I am grateful to Mickie Shepherd and Stephanie Crouch for their help and support. I would also like to thank the staff in the College of Pharmacy, including Iris Jennings, Belinda Lehmkuhle, and Jay Hamman, and many others.

I am thankful to the wonderful graduate students in the Division of Health Outcomes and Pharmacy Practice. Hitesh Chandwani has always been a sounding board and a great friend. I would also like to thank Haesuk, Abiola, Ayo, Dawn, Julieta, Lung-I, Milli, and many others for their continued support.

I am grateful to my friends for their support. Divya Vasudevan has been a constant source of encouragement and has always helped me believe that I can overcome all the obstacles of graduate school. I would also like to thank Esha, Saloni, Rachita, and all my other friends for their love and support.

I owe my success to my family. Without the unwavering love and support of my parents (Bela and Rajiv Desai) and my brother (Parth Desai), this journey would not have been possible. I am grateful to my loving husband, Shaival Lakdawala. He has stood by my side through the highs and lows of graduate school and has always been my rock.

I would also like to thank my extended family for their continued love, support, and encouragement.

Incidence, predictors, healthcare utilization, and cost associated with antipsychotic polypharmacy in the Texas Medicaid population

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The University of Texas at Austin, 2014

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Antipsychotic medications are effective in the treatment of psychotic disorders. Monotherapy (MT) with antipsychotics is consistently recommended as the treatment of choice by several guidelines yet antipsychotic polypharmacy (APP) is widespread in clinical practice. The objectives of this study were to evaluate the incidence of APP, identify predictors of APP, and compare adherence, health resource utilization, and costs between patients on MT and APP using prescription and medication claims from Texas Medicaid (2006 to 2011).

Patients newly initiated on antipsychotics were followed for 12 months and categorized into the APP (exposure to two or more antipsychotics for a defined time interval) and MT (no evidence of APP during the study period) groups. This sample of patients was used to evaluate incidence and predictors of APP and compare medication adherence and persistence between the MT and APP groups using multiple, logistic, and Cox proportional hazards regressions. Patients in the MT and APP groups were then

matched based on their duration of exposure to antipsychotics and all-cause healthcare utilization and costs were compared using logistic and generalized linear models regression (negative binomial, Poisson, and gamma). Regression analyses for patients matched on duration of antipsychotic exposure accounted for the correlation between matched pairs.

The incidence of APP was 5.4%. Several demographic, clinical, physician, and prior utilization characteristics were associated with APP. Medication adherence and persistence were better in the APP group. Length of hospital stay and medical, drug, and total costs were higher for the APP group. Sensitivity analyses were conducted for psychiatric-related costs and varied overlap and gap periods. The results for most of the sensitivity analyses were similar to the base case.

Patients prescribed APP had higher medical, drug and total costs and also higher healthcare utilization i.e. increased drug costs were not offset by decreased medical costs. Long-term APP raises concern as state Medicaid agencies are allocating their limited resources to this expensive treatment which has very scarce data supporting its use. More effectiveness research on APP is needed to help provide prescription guidance to clinicians for patients who do not respond well to treatment with a single antipsychotic.

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1. INTRODUCTION

1.1. Problem statement

Webster's dictionary defines polypharmacy as the act of prescribing two or more drugs together to treat a single condition.[1] Fulton and Allen describe polypharmacy as the use of medications which are not clinically indicated.[2] Evidence-based medication (EBM) informs us about the clinical indications of medications based on safety and efficacy.[3] Prescribing more medications than clinically warranted is considered a questionable practice due to safety concerns. However, it is important to remember that pharmacotherapy is a complex field encompassing more than EBM suggestions of safety and efficacy.

Antipsychotic polypharmacy (APP) is the concomitant use of more than one antipsychotic medication. Clinical guidelines recommend monotherapy of antipsychotics as the preferred therapy.[4,5,6,7,8,9] Despite consistent monotherapy recommendations, the use of APP is widespread in clinical practice. The prevalence of APP varies depending on clinical settings. In

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1 Dictionary.com. Polypharmacy [online]. Available from URL: http://dictionary.reference.com/browse/polypharmacy. Accessed October 23, 2012.

2 Fulton MM, Allen ER. Polypharmacy in the elderly: a literature review. J Am Acad Nurse Pract 2005; 17 (4): 123-32.

3 Tranulis C, Skalli L, Lalonde P, et al. Benefits and risks of antipsychotic polypharmacy: an evidence-based review of the literature. Drug Saf 2008;31(1):7-20.

4 The expert consensus guideline series. Treatment of schizophrenia. J Clin Psychiatry 1999; 60 suppl 11:3-80.

5 National Institute for Clinical Excellence: Core interventions in the treatment and management of schizophrenia in adults in primary and secondary care. NICE Clinical Guideline 82; 2009.

6 Moore TA, Buchanan RW, Buckley PF, et al. The Texas medication algorithm project antipsychotic algorithm for schizophrenia: 2006 update. J Clin Psychiatry 2007;68(11):1751-62.

7 American Psychiatric Association: Practice guidelines for the treatment of patients with schizophrenia. In Am J Psychiatry Volume 161. 2nd ed. American Psychiatric Association; 2004:1-56.

8 Kreyenbuhl J, Buchanan RW, Dickerson FB, et al. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2009. Schizophr Bull 2010; 36(1):94-103.

9 The International Psychopharmacology Algorithm Project. IPAP schizophrenia algorithm. Available at: www.ipap.org/schiz. Assessed October 9, 2012.

inpatient settings the prevalence ranges from 8%[10] to as high as 68%[11] while studies conducted in outpatient settings show prevalence rates from 4%[12] to 26%.[13] According to a meta-analysis conducted by Gallego et al., the pooled prevalence of APP in North America between 1970 and 2009 was 16% (Interquartile range [IQR]=7.2%-24.4%). From 1980 to 2000, the prevalence of APP in North America increased by 34.0%, from 12.7% (IQR=4.5%–46%) to 17% (IQR=9.1%–23.0%).[14] Similar increases were noted in studies conducted using Medicaid databases. Clark et al.[15] noted an increase of 18.6 percentage points from 5.7% in 1995 to 24.3% in 1999 and Ganguly et al.[16] observed an increase of nine percentage points from 32.0% in 1998 to 41.0% in 2000.

Although the concomitant use of multiple antipsychotics is widespread, there is very limited evidence regarding the safety and efficacy of APP in controlled clinical trials. In fact, several potential hazards are associated with APP.[17] It could lead to increased adverse effects, decreased benefits of an atypical antipsychotic if it is combined with a typical antipsychotic (e.g., increased risk of extrapyramidal side effects along with the presence of metabolic side effects due to the atypical antipsychotics), and possible pharmacokinetic interactions. Studies have

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10 Dolder CR, McKinsey J. Antipsychotic polypharmacy among patients admitted to a geriatric psychiatry unit. J Psychiatr Pract 2011;17(5):368-74.

11 Divac N, Jasović-Gasić M, Samardzić R, et al. Antipsychotic polypharmacy at the University Psychiatric Hospital in Serbia. Pharmacoepidemiol Drug Saf 2007;16(11):1250-1.

12 Botts S, Hines H, Littrell R. Antipsychotic polypharmacy in the ambulatory care setting, 1993-2000. Psychiatr Serv 2003;54(8):1086.

13 Procyshyn RM, Honer WG, Wu TK, et al. Persistent antipsychotic polypharmacy and excessive dosing in the community psychiatric treatment setting: a review of medication profiles in 435 Canadian outpatients. J Clin Psychiatry 2010;71(5):566-73.

14 Gallego JA, Bonetti J, Zhang J, et al. Prevalence and correlates of antipsychotic polypharmacy: a systematic review and meta-regression of global and regional trends from the 1970s to 2009. Schizophr Res 2012; 138(1):18-28.

15 Clark RE, Bartels SJ, Mellman TA, et al. Recent trends in antipsychotic combination therapy of schizophrenia and schizoaffective disorder: implications for state mental health policy. Schizophr Bull 2002;28(1):75-84.

16 Ganguly R, Kotzan JA, Miller LS, et al. Prevalence, trends, and factors associated with antipsychotic polypharmacy among Medicaid-eligible schizophrenia patients, 1998-2000. J Clin Psychiatry 2004;65(10):1377-88.

17 Tranulis C, Skalli L, Lalonde P, et al. Benefits and risks of antipsychotic polypharmacy: an evidence-based review of the literature. Drug Saf 2008;31(1):7-20.

shown that APP is associated with higher healthcare resource utilization and costs. A study conducted using an employer claims database found that the mean total medical cost for APP patients was about $7,000 more than for those on antipsychotic monotherapy (MT).[18] The analysis controlled for patient characteristics and indicators of disease complexity. Gilmer et al. found that an increase of 9.3 percent points in APP over a five-year period was associated with an increase of almost two percent points in hospitalization rates.[19] In addition, complex medication regimens, such as those associated with APP, could also lead to a reduction in medication adherence.

Few studies in the US have used large databases, such as Medicaid, to estimate the prevalence of APP. Due to the debilitating nature of the diseases that antipsychotics are used to treat, it is possible that several antipsychotic users may be classified as disabled or have low incomes and hence, would be enrolled in state Medicaid programs. Most published studies are dated, with the most recent one by Constantine et al. examining the period from 2004-2006.[20] However, specific atypical antipsychotics, such as paliperdone (2007), iloperidone (2009), asenapine (2009), and lurasidone (2010) were approved more recently, i.e., after the most recent study that used a state Medicaid database to estimate the prevalence of APP was conducted. Therefore, research including these newer drugs is needed. In addition, no known study examining APP was conducted in Texas, a state with a higher than average prevalence of mental illness.[21]

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[18] Loosbrock DL, Zhao Z, Johnstone BM, et al. Antipsychotic medication use patterns and associated costs of care for individuals with schizophrenia. J Ment Health Policy Econ 2003;6(2):67-75.

[19] Gilmer TP, Dolder CR, Folsom DP, et al. Antipsychotic polypharmacy trends among Medicaid beneficiaries with schizophrenia in San Diego County, 1999-2004. Psychiatr Serv 2007;58(7):1007-10.

[20] Constantine RJ, Andel R, Tandon R. Trends in adult antipsychotic polypharmacy: progress and challenges in Florida's Medicaid program. Community Ment Health J 2010;46(6):523-30.

[21] Welsh KJ, Patel CB, Fernando RC, et al. Prevalence of bipolar disorder and schizophrenia in Houston Outreach Medicine, Education, and Social Services (HOMES) clinic patients: implications for student-managed clinics for

In view of the described gaps in the literature, this study aims to estimate the incidence, predictors, healthcare costs, and utilization associated with APP in the state of Texas.

underserved populations. Academic Medicine: Journal of the Association of American Medical Colleges 2012;87(5):656-61.

1.2. Significance

Antipsychotics have revolutionized the treatment of psychiatric illnesses since their initial availability in the 1950s. With the introduction of atypical antipsychotics (also called second-generation antipsychotics), the overall use of antipsychotic medications has increased tremendously. A statistical brief published by the Agency for Healthcare Research and Quality (AHRQ) using the Medical Expenditure Panel Survey (MEPS) showed that the total number of purchases of antipsychotics increased from 17.4 million in 1997 to 32.4 million in 2007, an increase of 86%.[22] Expenditures for prescription antipsychotics in an outpatient setting increased almost 5-fold from $1.7 billion to $7.4 billion during the same period. Another study conducted by Alexander et al. using data from the IMS Health National Diagnostic and Therapeutic Index showed that the number of antipsychotic-related outpatient visits increased from 6.2 million in 1995 to 16.7 million in 2006 and declined to 14.3 million in 2008.[23] Data on those patient visits where typical or atypical antipsychotic use was reported were used in the analyses. They estimated that in 2008, $60 million and $9.9 billion were spent on typical (also called first-generation antipsychotics) and atypical antipsychotics, respectively. The use of antipsychotics for Food and Drug Association (FDA)-approved indications increased from 4.4 million visits in 1995 to 9 million visits in 2008. The estimated cost for off-label use of antipsychotics in 2008 was $6 billion, of which $5.4 billion was for uses with uncertain evidence. A prescribing shift occurred from typical antipsychotics in 1995 (84% of all antipsychotic visits) to atypical antipsychotics by 2008 (93% of all antipsychotic visits). The proportion of all typical

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[22] Stagnitti, M. N. Trends in Antipsychotics Purchases and Expenses for the US Civilian Noninstitutionalized Population, 1997 and 2007. Statistical Brief #275. January 2010. Agency for Healthcare Research and Quality, Rockville, MD.
Available at: http://www.meps.ahrq.gov/mepsweb/data_files/publications/st275/stat275.pdf. Accessed April 3, 2014.

[23] Alexander GC, Gallagher SA, Mascola A, et al. Increasing off-label use of antipsychotic medications in the United States, 1995-2008. Pharmacoepidemiol Drug Saf 2011;20(2):177-84.

antipsychotics used for schizophrenia patients increased from 32% of typical treatment visits in 1995 to 48% in 2008. Over the same period, atypical agents use increased for bipolar affective disorder (10% of all atypical treatment visits to 34%) and depression (12% to 18%) while their use for schizophrenia (56% to 23%) declined.

It is likely that an increase in APP would have accompanied the increase in the use of antipsychotic medication. In addition to being associated with higher costs and questionable safety, some studies have shown that APP is associated with poorer patient outcomes.[24,25] Research is needed to update the 'real world' prevalence of APP in the outpatient setting to provide healthcare professionals and policy makers with current information about the magnitude of the problem. Identification of patient-related predictors of APP would help healthcare providers recognize patients most likely to be prescribed APP. This insight would enable them to take preemptive steps to ensure that APP is used only when all other feasible treatment options have failed. Estimates of healthcare utilization and costs associated with APP will illustrate the enormous financial burden associated with APP. This will help policy makers in developing direction for state mental health agencies and other entities for addressing the challenges associated with APP.

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[24] Anil Yagcioglu AE, Kivircik Akdede BB, Turgut TI, et al. A double-blind controlled study of adjunctive treatment with risperidone in schizophrenic patients partially responsive to clozapine:efficacy and safety. J Clin Psychiatry 2005;66(1):63–72.

[25] Honer WG, Thornton AE, Chen EY, et al. Clozapine alone versus clozapine and risperidone with refractory schizophrenia. N Engl J Med 2006;354(5):472–82.

2. LITERATURE REVIEW

2.1. Antipsychotics and their uses

2.1.1. ANTIPSYCHOTIC MEDICATIONS

Typical antipsychotics include chlorpromazine, fluphenazine, haloperidol, and perphenazine.[26] They are associated with a number of neurological side effects including movement disorders, which are often irreversible, and orthostatic hypotension. Atypical antipsychotics, the newer class of drugs, include aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. They are generally associated with less severe side effects compared to typical antipsychotics; however, they have side effects associated with metabolic disorder such as diabetes, high cholesterol, and weight gain. They are more effective in treating negative symptoms and improving cognitive functioning. *Table 1* provides a list of the generic and brand names of antipsychotics.

Antipsychotics are approved by the FDA for use in patients with schizophrenia and bipolar disorder.[27] Some antipsychotics are also prescribed for other diseases such as treatment resistant depression and others.[28] However, antipsychotics are widely used for off-label indications (indications not approved by the FDA) to treat various psychiatric conditions. While it is legal for doctors to prescribe medications off-label, it is not legal for manufacturers to actively promote such use. A study conducted on off-label use of antipsychotics found that the

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[26] Schizophrenia-Mayo Clinic Staff, Mayo Clinic. Available at: http://www.mayoclinic.com/health/schizophrenia/DS00196. Accessed October 15, 2010.

[27] Maglione M, Ruelaz Maher A, Hu J, Wang Z, Shanman R, Shekelle PG, Roth B, Hilton L, Suttorp MJ, Ewing BA, Motala A, Perry T. Off-Label use of atypical antipsychotics: An update. Comparative Effectiveness Review No. 43. (Prepared by the Southern California Evidence-based Practice Center under Contract No. HHSA290-2007-10062-1.) Rockville, MD: Agency for Healthcare Research and Quality. September 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed April 1, 2014.

[28] Christian R, Saavedra L, Gaynes BN, et al. Future Research Needs for First- and Second-Generation Antipsychotics for Children and Young Adults [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012 Feb. (Future Research Needs Papers, No. 13.) Appendix A, Tables of FDA-Approved Indications for First- and Second-Generation Antipsychotics.

most common indications included attention-deficit hyperactivity disorder (ADHD), anxiety, dementia in elderly patients, depression, eating disorders, insomnia, obsessive compulsive disorder, personality disorder, post-traumatic stress disorder (PTSD), substance use disorders, and Tourette's syndrome.

Table 1: Generic and brand names for antipsychotics

Generic Name	**Brand name**
Typical antipsychotics	
Chlorpromazine	Largactil, Thorazine
Fluphenazine	Prolixin
Haloperidol	Haldol
Loxapine	Loxitane
Molindone	Moban
Perphenazine	Trilafon
Pimozide	Orap
Thioridazine	Mellaril
Thiothixene	Navane
Trifluoperazine	Stelazine
Atypical antipsychotics	
Aripiprazole	Abilify
Asenapine	Saphris
Clozapine	Clozaril, FazaClo
Iloperidone	Fanapt
Lurasidone	Latuda
Olanzapine	Zyprexa, Zydis, Relprevv
Paliperidone	Invega
Quetiapine	Seroquel
Risperidone	Risperdal
Ziprasidone	Geodon

2.1.2. SCHIZOPHRENIA AND ASSOCIATED DISORDERS

Schizophrenia is a chronic debilitating disease characterized by perturbations of language, perception, thinking, social activity, affect, and volition.[29] It generally begins in late adolescence with a gradual onset and the outcomes may progress from social withdrawal and perceptual distortions to chronic delusions and hallucinations.

Patients may have positive symptoms, such as conceptual disorganization, delusions, or hallucinations or they may have negative symptoms such as loss of function, anhedonia, decreased emotional expression, impaired concentration, and diminished social engagement. For the diagnosis of schizophrenia to be confirmed, a patient must have at least two of these symptoms for one month and continuous symptoms for at least six months.

The four main subtypes of schizophrenia are catatonic, paranoid, disorganized, and residual. The patient may have symptoms for more than one type.

Catatonic schizophrenia: It is characterized by increase in motor activity, negativism, and imitation of speech and movement of others.

Disorganized schizophrenia: There is disorganization of speech and behavior which is accompanied by silly behavior.

Paranoid schizophrenia: Patients are preoccupied with a specific delusional system and do not show signs of disorganized schizophrenia.

Residual schizophrenia: It is characterized by negative symptoms in the absence of delusions, hallucinations, and increased motor activity.

[29] Reus VI. Mental Disorders. In: , Kasper D, Braunwald E, Hauser SL, Longo DL, Jameson JL, Fauci AS, eds. Harrison's Principles of Internal Medicine. 16th ed. New York: McGraw Hill; 2004.

In addition, there are two closely related disorders:

Schizophreniform disorders: Patients have the symptoms of schizophrenia but not for the duration that is required to confirm a schizophrenia diagnosis.

Schizoaffective disorders: Patients have the symptoms of schizophrenia and in addition have independent periods of mood disturbances.

Antipsychotic medications are the cornerstone of treatment for schizophrenia, both for acute and maintenance treatment. They are effective in the treatment of hallucinations, delusions, and thought disorders. As noted previously, there are two types of antipsychotics: typical and atypical. Typical antipsychotics act by blocking the dopamine D_2 receptors and atypical antipsychotics act on dopamine, serotonin, and other neurotransmitter systems.[30] Some antipsychotics may act within a few hours or days of therapy initiation, but full effect usually requires six weeks to several months of daily, therapeutic dosing.

[30] Psychiatric Medicine. In: Kasper D, Braunwald E, Fauci AS, eds. Harrison's Manual of Internal Medicine. 16th ed. New York: McGraw Hill; 2005:962-969.

2.1.3. BIPOLAR DISORDER

Bipolar disorder is characterized by very quick mood swings between periods of very good or very irritable mood and depression.[31] Bipolar disorder type I is characterized by at least one manic episode and periods of major depression. In bipolar disorder type II, people experience alternating periods of high energy and impulsiveness (called hypomania) and episodes of depression. Cyclothymia is a mild form of bipolar disorder where the patient alternates between hypomania and mild depression. Bipolar disorder strikes in adolescence or early adulthood and occurs equally in males and females. The lifetime prevalence of bipolar I disorder in community samples ranges between 0.4%-1.6%, while that of bipolar II disorder is about 0.5%, and lifetime prevalence of cyclothymic disorder is 0.4%-1%.[32]

Mood stabilizers are commonly used to treat bipolar disorder. Antipsychotics are also used for the condition. A systematic review conducted by Derry et al. found that antipsychotics are effective in the treatment of bipolar disorders.[33] Literature suggests faster onset of haloperidol compared to lithium or atypical antipsychotics. Efficacy has also been demonstrated by atypical antipsychotics such as aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone.[34]

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[31] US National Library of Medicine. Bipolar Disorder. Available at: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001924/. Accessed October 11, 2012.

[32] Mood Disorders. In: First MB ed. Diagnostic and Statistical Manual of Mental Disorders 4th ed. Washington (DC): American Psychiatric Association, 2000.

[33] Derry S, Moore RA. Atypical antipsychotics in bipolar disorder: systematic review of randomized trials. BMC Psychiatry 2007;7:40.

[34] Tohen M, Vieta E. Antipsychotic agents in the treatment of bipolar mania. Bipolar Disord 2009;11 Suppl 2:45-54.

2.2. Guidelines for use of antipsychotic medications

Several practice guidelines have been developed on the use of antipsychotics for the treatment of schizophrenia. These include the Expert Consensus Guidelines on the treatment of schizophrenia, the National Institute of Health and Clinical Excellence (NICE) guidelines, the Texas Medication Algorithm Project (TMAP), the American Psychiatry Association (APA) guidelines, the Patient Outcomes Research Team (PORT), and the International Psychopharmacology Algorithm Project.

According to the Expert Consensus Guidelines for the treatment of schizophrenia, patients with a first episode and predominantly positive or negative symptoms should be prescribed atypical antipsychotics.[35] The guidelines also recommend atypical antipsychotics for those who have episodes despite good compliance with typical antipsychotics. For patients non-compliant with oral medications, long-acting depot antipsychotics are recommended. For patients initiated on typical antipsychotics who experience inadequate response, the recommended treatment is switching to a newer atypical antipsychotic. If there is non-response with sequential trials to typical and newer atypical antipsychotics, the recommendation is raising the dose of the antipsychotic or switching to clozapine. The preferred methods of switching include cross-titration or overlap and taper; the preferred duration of switch is four to five weeks if the switch does not involve clozapine and seven to eight weeks if the switch does involve clozapine. Thus, polypharmacy with antipsychotics during switching is acceptable for up to eight weeks.

[35] The expert consensus guideline series. Treatment of schizophrenia. J Clin Psychiatry 1999; 60 suppl 11:3-80.

The NICE guidelines recommend that the choice of antipsychotic should be a combined decision of the patient and the physician.[36] NICE recommends starting at the lower end of the licensed range and then titrating upwards. Trials of medications at optimum doses must be carried out at least for four to six weeks. Avoid loading doses of the antipsychotics. As required prescriptions to antipsychotics may be made but the physician must take into account their effect on the total dose, efficacy, side effects, and adherence. Clozapine must be offered to patients whose illness does not respond to sequential trials of at least two antipsychotics (one of which must be a non-clozapine second-generation antipsychotic). If there is no response even after prescribing clozapine, consider adding a second antipsychotic to augment treatment with clozapine. An adequate trial of an augmentation may be from eight to 10 weeks. The selected antipsychotic must not compound the side effects of clozapine. Antipsychotic polypharmacy is not recommended except for a short period of time while switching medications.

According to the TMAP, atypicals are preferred as treatment for first-episode schizophrenia due to better tolerance.[37,38] In case of failure with one atypical antipsychotic, the algorithm recommends use of typical antipsychotics or other atypicals. Two failed trials of antipsychotics warrant the use of clozapine. The guideline recommends that long delays to initiation of clozapine should be avoided. Patients with persistent symptoms of suicide or violence or comorbid substance abuse disorder should be initiated on clozapine early. In case of partial response to clozapine, it should be combined with other atypical and typical antipsychotics. In case of clozapine refusal or non-response to polypharmacy with clozapine, the

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[36] National Institute for Clinical Excellence: Core interventions in the treatment and management of schizophrenia in adults in primary and secondary care. NICE Clinical Guideline 82; 2009.

[37] Miller AL, Hall CS, Buchanan RW, et al. The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2003 update. J Clin Psychiatry 2004; 65(4):500-8.

[38] Moore TA, Buchanan RW, Buckley PF, et al. The Texas medication algorithm project antipsychotic algorithm for schizophrenia: 2006 update. J Clin Psychiatry. 2007;68(11):1751-62.

use of monotherapy, probably a typical or atypical antipsychotic, before moving to non-clozapine polypharmacy is recommended. Combinations of antipsychotics are attempted only when all monotherapy has failed.

The APA guidelines recommend use of an atypical antipsychotic for first episode patients.[39] Atypical antipsychotics are also recommended for patients with a history of extrapyramidal side effects, prolactin elevation, weight gain, hyperglycemia, or hyperlipidemia. For those with persistent suicidal ideation or persistent hostility or aggressive behavior, the guidelines recommend clozapine. Long-acting injectable antipsychotics are recommended for those with poor adherence to oral antipsychotics.

The PORT recommends antipsychotics other than clozapine and olanzapine as first-line treatment for persons experiencing first-episode schizophrenia.[40] Patients with multi-episode schizophrenia must be offered continuous antipsychotic treatment to maintain symptom relief and reduce risk of relapse. PORT guidelines recommend the use of long-acting injectable antipsychotics when that is the preferred route of administration (in case of non-adherence with oral drugs). Clozapine should be offered to patients who continue to experience clinically significant positive symptoms after two adequate trials of antipsychotic agents. People with symptoms of hostility and suicide should also be treated with clozapine.

The International Psychopharmacology Algorithm Project recommends an initial trial of four to six weeks with an atypical antipsychotic (amisulpride, aripiprazole, quetiapine, risperidone, or ziprasidone) or if that is unavailable, with a typical antipsychotic.[41] If the trial is

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[39] Lehman AF, Lieberman JA, Dixon LB, et al. Practice guidelines for the treatment of patients with schizophrenia, second edition. Am J Psychiatry 2004;161:Suppl:1-56.

[40] Kreyenbuhl J, Buchanan RW, Dickerson FB, et al. The schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2009. Schizophr Bull 2010; 36(1):94-103.

[41] The International Psychopharmacology Algorithm Project. IPAP schizophrenia algorithm. Available at: www.ipap.org/schiz. Accessed October 9, 2012.

inadequate or it fails, the dose is adjusted. An adequate trial is one which continues for at least four to six weeks with the patient receiving the therapeutic dose for at least four weeks. If psychoses persist even after dose adjustment, then a four to six week trial of a second atypical antipsychotic (if available or a typical antipsychotic is if the atypical is unavailable) is carried out before moving the patient to clozapine. The choice of the second medication depends on the first one and the reasons for treatment failure other than lack of efficacy (such as side effects). If psychoses persist or the patient suffers from tardive dyskinesia or tardive dystonia despite an adequate trial, the patient is put on a six-month trial of clozapine up to 900 mg/day. If the symptoms continue to persist, the clozapine is optimized or augmented with electroconvulsive therapy or adjuvant medication.

All the guidelines recommend polypharmacy of antipsychotics only when all other monotherapy options have been unsuccessful. Also, apart from the Expert Consensus Guidelines for the treatment of schizophrenia, no other guidelines offer any guidance on the duration of polypharmacy. *Table 2* provides a summary of the guidelines.

Table 2: Summary of guidelines for antipsychotics[42]

	Expert Consensus Guidelines, 1999	National Institute of Health and Clinical Excellence, 2009	Texas Medication Algorithm Project, 2006	American Psychiatric Association, 2004	Patient Outcomes Research Team, 2004	International Psychopharmacology Algorithm Project, 2005
First episode	SGA	SGA, FGA	SGA	SGA	SGA, FGA	SGA
Second choice	SGA	SGA, FGA	SGA, FGA	SGA, FGA, Clozapine	SGA, FGA	SGA
Third choice	Clozapine	Clozapine	Clozapine	Clozapine	Clozapine	Clozapine
Fourth choice	Clozapine augmentation	Clozapine augmentation	Clozapine augmentation	Clozapine augmentation	-	Clozapine augmentation, SGA
Fifth choice	-	-	SGA, FGA	-	-	-
Sixth choice	-	-	Combinations	-	-	-

42 Moore TA, Covell NH, Essock SM, et al. Real-world antipsychotic treatment practices. Psychiatr Clin North Am 2007;30(3):401-16.

2.3. Antipsychotic prescribing trends

The use of antipsychotic medications in the general population increased tremendously in the mid-1990s due to the introduction of atypical antipsychotics. One reason for this increase in utilization is that atypical antipsychotics are associated with fewer side effects than typical antipsychotics. Another possible reason for widespread antipsychotic use was FDA approval of several atypical antipsychotics for conditions other than schizophrenia and bipolar disorder.

In a longitudinal analysis of national data to study antipsychotic prescribing in US nursing homes from 1996 to 2006, Castle et al. found that the use of antipsychotics increased from 16.4% in 1996 to 25.9% in 2006.[43] The authors found that controlling for facility, staffing, and resident factors, for-profit facilities were more likely than non-profit facilities to increase antipsychotic use and organizations which were chain facilities were less likely to increase antipsychotic use compared to independent facilities.

Several studies have been conducted using the National Ambulatory Medical Care Survey (NAMCS), a nationally representative ongoing survey of US office-based physicians, to determine antipsychotic usage trends. A study conducted by Daumit et al. used the NAMCS and the National Hospital Ambulatory Medical Care Survey from 1992 to 2000.[44] The authors found that for patients between 18 to 69 years of age, antipsychotic medications were prescribed or continued in 5,032 visits (only unweighted frequencies were reported in the study) and 33% of the visits involved prescription or continuation of an atypical antipsychotic over the eight-year study period. The percentage of visits with an atypical medication prescribed increased dramatically during the study period.

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[43] Castle NG, Hanlon JT, Handler SM. Results of a longitudinal analysis of national data to examine relationships between organizational market characteristics and changes in antipsychotic prescribing in US nursing homes from 1996 to 2006. Am J Geriatr Pharmacother 2009;7(3):14-50.

[44] Daumit GL, Crum RM, Guallar E, et al. Outpatient prescriptions for atypical antipsychotics for African Americans, Hispanics, and whites in the United States. Arch Gen Psychiatry 2003;60(2):121-8.

Sankaranarayanan et al. used the NAMCS 1996-2002 files. Over the eight-year study period, there were 47.7 million visits involving a mental health disorder and the mention of an antipsychotic.[45] There was an increase of 195% and 149% for atypical and combination antipsychotics, respectively, from 1996-1997 to 2002-2003 and a 71% decrease in the use of typical antipsychotics over the same period. Another study conducted by Aparasu et al. used 1998-2002 NAMCS data and reported a nearly two-fold increase in the number of antipsychotic-related visits from 4.6 million in 1998 to 8.6 million in 2002.[46] The proportion of visits associated with atypical antipsychotics rose from 40% to 84% and the number of visits associated with typicals declined.

NAMCS has also been used to study antipsychotic prescribing trends in children. Copper et al. analyzed data from 1995 to 2002 and found that there were 5,762,193 visits to healthcare providers where children were prescribed antipsychotics.[47] Antipsychotic prescribing frequency increased from 8.6 per 1,000 children in 1995-1996 to 39.4 per 1,000 children in 2001-2002. More than half the antipsychotics were prescribed for behavioral indications or affective disorders, indications for which antipsychotic use in children has not been thoroughly studied.

Comer and his colleagues used 1996-2007 NAMCS data to analyze the trends of outpatient visits with antipsychotic prescriptions in patients with anxiety disorder.[48] Over the 12-year study period, antipsychotic prescribing rose from 6.9% (1996-1999) to 14.5% (2004-2007)

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45 Sankaranarayanan J, Puumala SE. Antipsychotic use at adult ambulatory care visits by patients with mental health disorders in the United States, 1996-2003: national estimates and associated factors. Clin Ther 2007;29(4):723-41.

46 Aparasu RR, Bhatara V, Gupta S. U.S. national trends in the use of antipsychotics during office visits, 1998-2002. Ann Clin Psychiatry 2005;17(3):147-52.

47 Cooper WO, Arbogast PG, Ding H, et al. Trends in prescribing of antipsychotic medications for US children. Ambul Pediatr 2006;6(2):79-83.

48 Comer JS, Mojtabai R, Olfson M. National trends in the antipsychotic treatment of psychiatric outpatients with anxiety disorders. Am J Psychiatry 2011;168(10):1057-65.

among visits for anxiety disorders with no co-occurring diagnosis of an FDA-approved indication for antipsychotics and from 10.6% (1996-1999) to 21.3% (2004-2007) overall.

Yang et al. used the Veterans Affairs (VA) database from Texas (1997-2002) to evaluate antipsychotic medication utilization trends. They found that between 1997 and 2002 antipsychotic prescriptions changed from primarily typicals to primarily atypicals. Overall combination therapy increased slightly over time (4.3%), switching remained stable (14.1%), and monotherapy remained predominant (81.5%).[49] Weintraub et al. found that overall antipsychotic medication use between 2002 and 2008 in VA patients with Parkinson disease (PD).[50] However, while the number of prescriptions for risperidone and olanzapine decreased, prescriptions for quetiapine increased. In 2008, 50% of the patients with PD had an antipsychotic prescription and, for those treated with atypical antipsychotics, 66% used quetiapine. About 30% received high-potency antipsychotics (defined in this study as those antipsychotics associated with causing or worsening parkinsonism).

The IMS Health National Disease and Therapeutic Index was used to study trends in the use of second-generation antipsychotics from 1998 to 2008.[51] This study showed that the number of visits in which mood stabilizers and typical antipsychotics were prescribed declined and those in which atypical antipsychotics were prescribed increased by 42%.

Among non-dual eligible Medicaid beneficiaries in Texas, the number of patients with prescriptions for antipsychotics increased from 52,292 (2.5% of all beneficiaries) to 128,437

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[49] Yang M, Barner JC, Lawson KA, et al. Antipsychotic medication utilization trends among Texas veterans: 1997-2002. Ann Pharmacother 2008;42(9):1229-38.

[50] Weintraub D, Chen P, Ignacio RV, et al. Patterns and trends in antipsychotic prescribing for Parkinson disease psychosis. Arch Neurol 2011;68(7):899-904.

[51] Pillarella J, Higashi A, Alexander GC, et al. Trends in use of second-generation antipsychotics for treatment of bipolar disorder in the United States, 1998-2009. Psychiatr Serv 2012;63(1):83-6.

(3.8% of all beneficiaries) from 2001 to 2008.[52] This highlights the tremendous increase in the prescribing of antipsychotic medications in the past decade. This increase in prescribing of antipsychotic medications may have been accompanied by a simultaneous increase in the co-prescribing of multiple antipsychotics. The prevalence of antipsychotic polypharmacy will be discussed in greater detail in a later section.

[52] Medicaid Analytic eXtract (MAX) Rx Table Listing. Available at: http://www.cms.gov/Research-Statistics-Data-and-Systems/Computer-Data-and-Systems/MedicaidDataSourcesGenInfo/Medicaid-Analytic-eXtract-MAX-Rx-Table-Listing.html. Accessed March 15, 2014.

2.4. Benefits and risks of antipsychotic polypharmacy

Antipsychotic polypharmacy (APP) is the concurrent use of two or more antipsychotic medications. Although this practice is not supported by any established treatment guidelines, APP is prominent in routine clinical practice with rates varying from 4% to almost 65% depending on the setting, year, and methodology used to define and calculate APP.[53,54] The prevalence of APP will be discussed in more detail in the next section. This section describes the risks and benefits associated with APP and briefly discusses the published clinical evidence regarding the concurrent use of multiple antipsychotics.

The pharmacologic justification to use APP is to achieve better therapeutic activity by enhancing D_2 (dopamine) receptor blockade or antagonism of several receptors beyond the D_2 and 5-HT_2 (5-hydroxytryptamine) receptors based on the possibility that the other receptors may be relevant in the pathogenesis of positive and negative symptoms. Positron emission studies have shown that 60% to 80% D_2 occupancy is needed to achieve the optimal therapeutic response while avoiding extra-pyramidal symptoms (EPS).[55,56] Clozapine and quetiapine are too loosely bound to achieve D_2 occupancy more than 70% when administered alone, but when given in combination with a high-affinity D_2 blocker such as risperidone, the required D_2 blockade can be achieved while retaining the reduced risks of EPS.[57,58] A second antipsychotic

53 Botts S, Hines H, Littrell R. Antipsychotic polypharmacy in the ambulatory care setting, 1993-2000. Psychiatr Serv 2003;54(8):1086.

54 Gallego JA, Bonetti J, Zhang J, et al. Prevalence and correlates of antipsychotic polypharmacy: a systematic review and meta-regression of global and regional trends from the 1970s to 2009. Schizophr Res 2012; 138(1):18-28.

55 Kapur S, Seeman P. Antipsychotic agents differ in how fast they come off the dopamine D2 receptors. Implications for atypical antipsychotic action. J Psychiatry Neurosci 2000;25(2):161–6.

56 Nordstrom AL, Farde L,Wiesel FA, et al. Central D2-dopamine receptor occupancy in relation to antipsychotic drug effects: A double-blind PET study of schizophrenic patients. Biol Psychiatry 1993;33(4):227–35.

57 Freudenreich O, Goff DC. Antipsychotic combination therapy in schizophrenia: a review of efficacy and risk of current combinations. Acta Psychiatr Scand 2002;106(5):323-30.

may also be added to reduce adverse effects of the first. For example, apripiprazole is sometimes added to reduce plasma prolactin levels which have been elevated by the use of a potent D_2 receptor blocker.[59,60] APP may also be used while switching from one antipsychotic to another where a second antipsychotic is initiated while the first drug dosage is tapered until discontinuation. Often times a patient's symptoms appear to respond better when the antipsychotics are being co-administered which could lead to permanent polypharmacy.[61,62] It is important for the clinician to attempt discontinuation of the initial medication and use symptomatic treatments for side effects which may arise during return to monotherapy before deciding to use long-term polypharmacy. APP may also be used to manage particularly challenging symptoms. Efficacy towards aggressive behavior differs among atypical antipsychotics.[63] Another common reason for concomitant antipsychotic use is the use of the second antipsychotic "as needed" (pro re nata (prn)). Although this is prescribed for short-term use, since the "prn" prescriptions are discretionary, a small proportion of these cases may translate into long-term polypharmacy.[64]

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58 Kapur S, Zipursky RB, Remington G, et al. 5HT-2 and D2 receptor occupancy of olanzapine in schizophrenia: A PET investigation. Am J Psychiatry 1998;155(7):921–8.

59 Shim JC, Shim JG, Kelly DL, et al. Adjunctive therapy with a dopamine partial agonist, aripiprazole, for antipsychotic-induced hyperprolactinemia: a placebo controlled trial. Am J Psychiatry 2007; 164(9):1404-10.

60 Hoffer ZS, Roth RL, Matthew M. Evidence for the partial dopamine receptor agonist aripiprazole as first-line treatment of psychosis in patient with iatrogenic or tumorigenic hyperprolactinemia. Psychosomatics 2009; 50(4):317-24.

61 Stahl SM, Grady MM. A critical review of atypical antipsychotic utilization: Comparing monotherapy with polypharmacy and augmentation. Curr Med Chem 2004;11(3):313–27.

62 Stahl SM. Antipsychotic polypharmacy, Part 1: Therapeutic option or dirty little secret? J Clin Psychiatry 1999;60(7):425–6.

63 Eisen C, Shaner R, Unutzer J, et al. Datapoints: second-generation antipsychotic medication combinations for schizophrenia. Psychiatr Serv 2008;59(3):235.

64 Langan J, Shajahan P. Antipsychotic polypharmacy: review of mechanisms, mortality and management. The Psychiatrist 2010; 34:58-62.

There are several problems associated with APP. These include a potential risk of poor adherence due to complex medication regimens,[65] an increase in possible adverse effects due to drug interactions, and exposure of patients to high doses of antipsychotic drugs.[66,67] Concurrent antipsychotic use is a major contributor toward high-dose prescribing, although the therapeutic value of this is uncertain as there is no convincing evidence that higher than the licensed doses of antipsychotics are more advantageous in the treatment of acute episodes or treatment-resistant schizophrenia.[68] Combining typical and atypical antipsychotics increases the risk of adverse effects such as EPS and thus, the advantage of using an atypical may be lost.[69] Paton et al. noted that the proportions of patients prescribed anti-Parkinsonian drugs (to combat EPS) were almost the same in patients on typical antipsychotics and those on a combination of typical and atypical antipsychotics. Use of APP may also be associated with increased risk of metabolic diseases[70] and mortality.[71,72] APP is also associated with a high financial burden. Details on the economic impact of APP are discussed in a later section.

The clinical evidence on APP is limited to case studies and open-label studies with few randomized controlled trials. In a review, Patrick et al. (2005) searched PubMed from 1976 to

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65 Fenton WS, Blyler CR, Heinssen RK. Determinant of medication compliance in schizophrenia: empirical and clinical findings. Schizophr Bull 1997: 23(4):637-51.

66 Paton C, Barnes TR, Cavanagh MR, et al. High-dose and combination antipsychotic prescribing in acute adult wards in the UK: the challenges posed by p.r.n. prescribing. Br J Psychiatry. 2008;192(6):435-9.

67 Taylor D, Atkinson J, Fischetti C, et al. A prospective 6-month analysis of the naturalistic use of aripiprazole: factors predicting favorable outcome. Acta Psychiatr Scand 2007; 116(6):461-6.

68 Davis JM, Chen N. Dose response and dose equivalence of antipsychotics. J Clin Psychopharmacol 2004; 24(2):192-208.

69 Paton C, Lelliott P, Harrington M, et al. Patterns of antipsychotic and anticholinergic prescribing for hospital inpatients. J Psychopharmacol 2003;17(2):223-9.

70 Correll CU, Fredrickson AM, Kane JM, et al. Does antipsychotic polypharmacy increase the risk of metabolic syndrome? Schizophr Res 2007;89(1-3):91-100.

71 Weinmann S, Read J, Aderhold V. Influence of antipsychotics on mortality in schizophrenia: systematic review. Schizophr Res 2009;113(1):1-11.

72 Baandrup L, Gasse C, Jensen VD, et al. Antipsychotic polypharmacy and risk of death from natural causes in patients with schizophrenia: a population-based nested case-control study. J Clin Psychiatry 2010;71(2):103-8.

2002 to identify case series, clinical trials and reports that compared monotherapy and APP.[73] They found 52 studies, of which four were double-blind studies, 13 were open-label clinical trials, and 35 were case reports; only one open-label study and two case studies examined outcomes associated with monotherapy versus combination therapy in the same set of patients. The most frequently used combinations were clozapine with risperidone. More than half the studies (28 out of 52) involved treatment with atypical antipsychotics. Three quarters of the double-blind studies and 69% of the open-label trials found combination therapy more effective than monotherapy at alleviating symptoms and 13 out of the 35 case studies also reported overall positive symptoms. Patrick et al. concluded that although APP is not evidence based, there is no evidence against its use and recommended further research.

In the same year, Chan and Sweeting reviewed combinations of atypical antipsychotics other than clozapine and found four open-label studies, five case series, and 12 case reports which showed clinical effectiveness of combination therapy.[74] There were no randomized controlled trials. There were seven cases where combination therapy with aripiprazole led to deterioration of symptoms. There were three cases which demonstrated that combinations were associated with adverse effects.

More recently in 2008, Pandurangi and Dalkilic conducted a review and identified 75 studies on the use of combinations of atypical antipsychotics (including clozapine).[75] They identified the following combinations: clozapine + risperidone (26 reports, of which only four were randomized controlled trials—one showed symptom improvement in the combination

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[73] Patrick V, Levin E, Schleifer S. Antipsychotic polypharmacy: Is there evidence for its use? J Psychiatr Pract 2005;11(4):248–57.

[74] Chan J, Sweeting M. Combination therapy with non-clozapine atypical antipsychotic medication: A review of current evidence. J Psychopharmacol 2007;21(6):657–64.

[75] Pandurangi AK, Dalkilic A. Polypharmacy with second-generation antipsychotics: a review of evidence. J Psychiatr Pract 2008;14(6):345-67.

group, one showed no significant difference between the two groups, and two showed better symptom control in the monotherapy group), clozapine + sulpiride or amisulpride (five case studies, one double-blind placebo controlled trial (which showed improvement in the combination group), one single-blind randomized trial), clozapine + olanzapine (two case reports), clozapine + quetiapine (one case study and one case report), clozapine + ziprasidone (one open-label non-randomized study, one case study and three case reports), and clozapine + aripiprazole (one open-label non-randomized study, four case reports, and four case studies). Numerous case reports on combinations of atypical antipsychotics were found but there were no blinded or controlled randomized trials. Two open-label randomized trials were found. Potkins et al.[76] examined the combination of quetiapine and risperidone and Kotler et al.[77] studied olanzapine plus sulpiride. Of the eight randomized trials found, three trials supported use of a second atypical antipsychotic and one found selective improvement in disorganized thinking, two found no significant benefit of the combination, one found limited benefit involving improved mood symptoms, and one was a pharmacokinetic study that found that risperidone did not affect serum quetiapine levels.[78,79,80,81,82,83,84] There is widespread use of combination

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76 Potkin SG, Thyrum PT, Alva G, et al. The safety and pharmacokinetics of quetiapine when co-administered with haloperidol, risperidone, or thioridazine. J Clin Psychopharmacol 2002(2);22:121–30.

77 Kotler M, Strous RD, Reznik I, et al. Sulpiride augmentation of olanzapine in the management of treatment-resistant chronic schizophrenia: Evidence for improvement of mood symptomatology. Int Clin Psychopharmacol 2004;19(1):23–6.

78 Potkin SG, Thyrum PT, Alva G, et al. The safety and pharmacokinetics of quetiapine when co-administered with haloperidol, risperidone, or thioridazine. J Clin Psychopharmacol 2002(2);22:121–30.

79 Kotler M, Strous RD, Reznik I, et al. Sulpiride augmentation of olanzapine in the management of treatment-resistant chronic schizophrenia: Evidence for improvement of mood symptomatology. Int Clin Psychopharmacol 2004;19(1):23–6.

80 Shiloh R, Zemishlany Z, Aizenberg D, et al. Sulpiride augmentation in people with schizophrenia partially responsive to clozapine. A double blind, placebo-controlled study. Br J Psychiatry 1997;171:569–73.

81 Josiassen RC, Joseph A, Kohegyi E, et al. Clozapine augmented with risperidone in the treatment of schizophrenia: A randomized, double-blind, placebo-controlled trial. Am J Psychiatry 2005;162(1):130–6.

82 Anil Yagcioglu AE, Kivircik Akdede BB, Turgut TI, et al. A double blind controlled study of adjunctive treatment with risperidone in schizophrenic patients partially responsive to clozapine: Efficacy and safety. J Clin Psychiatry 2005;66(1):63–72.

therapy, but due to the duration and cost issues associated with undertaking large efficacy trials, it may be reasonable to focus on specific combinations; for example, those which are most frequently used.

Several meta-analyses have been conducted on antipsychotic combinations. Paton et al. included four trials and concluded that a long clinical trial of clozapine with atypical antipsychotics should be conducted.[85] Taylor and Smith[86] found marginal benefit of combination therapy (compared to placebo) based on 10 trials and Correll et al.[87] also reported a small effect in favor of combination therapy. Barbui et al.[88] evaluated 21 research articles and found weak evidence and modest to absent effect. A Cochrane review[89] of trials of clozapine with other antipsychotics did not find any evidence to modify existing recommendations.

A recent review of literature conducted by Lochmann van Bennekom et al. demonstrated that theories behind APP had only modest clinical and pre-clinical evidence.[90] Studies supporting the neurobiological effects of APP were lacking and the efficacy literature is limited to modest beneficial clinical evidence.

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83 Honer WG, Thornton AE, Chen EY, et al. Clozapine alone versus clozapine and risperidone with refractory schizophrenia. N Engl J Med 2006;354(5):472–82.

84 Freudenreich O, Henderson DC, Walsh JP, et al. Risperidone augmentation for schizophrenia partially responsive to clozapine: A double-blind, placebo-controlled trial. Schizophr Res 2007;92(1-3):90–4.

85 Paton C, Whittington C, Barnes TR. Augmentation with a second antipsychotic in patients with schizophrenia who partially respond to clozapine: a meta-analysis. J Clin Psychopharmacol 2007(2); 27:198–204.

86 Taylor DM, Smith L. Augmentation of clozapine with a second antipsychotic: a meta-analysis of randomized, placebo-controlled studies. Acta Psychiatr Scand 2009; 119(6):419–25.

87 Correll CU, Rummel-Kluge C, Corves C, et al. Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials. Schizophr Bull 2009; 35(2):443–57.

88 Barbui C, Signoretti A, Mule S, et al. Does the addition of a second antipsychotic drug improve clozapine treatment? Schizophr Bull 2009; 35(2):458–68.

89 Cipriani A, Boso M, Barbui C. Clozapine combined with different antipsychotic drugs for treatment resistant schizophrenia. Cochrane Database Syst Rev 2009;(3):CD006324.

90 Lochmann van Bennekom MW1, Gijsman HJ, Zitman FG. Antipsychotic polypharmacy in psychotic disorders: a critical review of neurobiology, efficacy, tolerability and cost effectiveness. J Psychopharmacol 2013;27(4):327-36.

The widespread use of antipsychotic polypharmacy is probably due to insufficient effects of monotherapy. It is important to conduct RCTs, naturalistic studies and head-to-head comparisons for the various combinations to inform clinical practice.[91]

[91] Zink M, Englisch S, Meyer-Lindenberg A. Polypharmacy in schizophrenia. Curr Opin Psychiatry 2010;23(2):103-11.

2.5. Prevalence of antipsychotic polypharmacy

Several guidelines, including the APA guidelines,[92] the schizophrenia PORT treatment recommendations,[93,94] the TMAP schizophrenia algorithms,[95] the NICE guidelines,[96] the Expert Consensus Guidelines for treatment of patients with schizophrenia,[97] and the International Psychopharmacology Algorithm Project[98] recognize antipsychotics as the cornerstone therapy for treatment of patients with schizophrenia, and have consistently recommended monotherapy as the treatment of choice.

Although none of the expert guidelines advocate polypharmacy of antipsychotics, the TMAP algorithm states that for some individual patients, a combination of antipsychotics might be optimal but there is no way to predict who might benefit and there are numerous possible antipsychotic combinations.[99] Thus, the algorithm does not recommend trials of combinations until clozapine has failed and it also guides the physician to be alert to improvement in patient status during the temporary medication overlap period while switching from one antipsychotic to another and consider return to the combination if none of the monotherapies are as effective as the combination. The Expert Consensus guidelines offer guidance on the duration of concomitant

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92 American Psychiatric Association: Practice guidelines for the treatment of patients with schizophrenia. In Am J Psychiatry Volume 161. 2nd ed. American Psychiatric Association; 2004:1-56.

93 Lieberman JA, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Eng J Med 2005; 353(12):1209–23.

94 Kreyenbuhl J, Buchanan RW, Dickerson FB, et al. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2009. Schizophr Bull 2010; 36(1):94-103.

95 Moore TA, Buchanan RW, Buckley PF, et al. The Texas medication algorithm project antipsychotic algorithm for schizophrenia: 2006 update. J Clin Psychiatry 2007;68(11):1751-62.

96 National Institute for Clinical Excellence: Core interventions in the treatment and management of schizophrenia in adults in primary and secondary care. NICE Clinical Guideline 82; 2009.

97 The expert consensus guideline series. Treatment of schizophrenia. J Clin Psychiatry 1999; 60 suppl 11:3-80.

98 The International Psychopharmacology Algorithm Project. IPAP schizophrenia algorithm. Available at: www.ipap.org/schiz. Accessed October 9, 2012.

99 Moore TA, Buchanan RW, Buckley PF, et al. The Texas medication algorithm project antipsychotic algorithm for schizophrenia: 2006 update. J Clin Psychiatry 2007;68(11):1751-62.

use of two antipsychotics at no longer than 8 weeks (60 days) while switching from one antipsychotic to another using the overlap and tapering or cross-titration method of switching.[100]

Only the Expert Consensus guidelines provide an operational definition for long-term antipsychotic polypharmacy. Different studies have used different definitions of polypharmacy and, thus, the prevalence of APP widely varies. The rates of APP also vary tremendously across different treatment settings.

Monotherapy is preferred as it is possible to document a patient's response to each medication, reduce the complexity of the treatment regimen, reduce the risk of adverse events, and make it easier to manage future symptoms.[101] In the case of polypharmacy, there is increased likelihood of pharmacokinetic and pharmacodynamic interactions and the 'atypical' nature of the antipsychotic is lost if it is combined with a typical antipsychotic.

Despite consistent recommendations for monotherapy, the use of combinations of antipsychotics is widespread. This is likely due to the introduction of several new atypical antipsychotics in the past two decades that have augmented the arsenal of typical antipsychotics that were already available.

A study by Leslie et al. estimated the prevalence of APP in a Veterans Affairs (VA) population with schizophrenia between June and September 1999 at 6.8%.[102] Another study used the National Psychosis Registry of the VA and examined long-term APP in patients with schizophrenia and schizoaffective disorder between 1999 and 2001.[103] The authors estimated that 9.5% of the patients had long-term APP, defined as receipt of two or more antipsychotics

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100 Moore TA, Buchanan RW, Buckley PF, et al. The Texas medication algorithm project antipsychotic algorithm for schizophrenia: 2006 update. J Clin Psychiatry 2007;68(11):1751-62.

101 Miller AL, Craig CS: Combination antipsychotics: pros, cons, and questions. Schizophr Bull 2002; 28(1):105-9.

102 Leslie DL, Rosenheck RA. Use of pharmacy data to assess quality of pharmacotherapy for schizophrenia in a national health care system: Individual and facility predictors. Med Care 2001;39(9):923-33.

103 Kreyenbuhl J, Valenstein M, McCarthy JF, et al. Long-term combination antipsychotic treatment in VA patients with schizophrenia. Schizophr Res 2006; 84(1):90–9.

concomitantly for at least 90 consecutive days during the study period. Weissman evaluated the extent of APP in the New York Metropolitan region VA among schizophrenia patients between 2000 and 2001 and noted an increase in APP from 15% to 17%.[104]

Ganguly et al. examined Medicaid-eligible schizophrenia patients from the states of California and Georgia between 1998 and 2000.[105] They found that 23% (Georgia: 18.1%, California: 29.3%) of the patients received long-term APP, defined as concomitant use of two or more antipsychotics for at least 61 days without a break period of 31 days or more. Non-clozapine polypharmacy was more prevalent than clozapine polypharmacy (19.4% vs. 2.5%). Within the non-clozapine polypharmacy group, atypical + typical was the most prevalent combination (15.7%), followed by atypical + atypical (3.9%), and finally typical + typical (2.8%). Gilmer and his colleagues used California Medicaid data from 1999 to 2004 to study trends in the prevalence of APP in patients with schizophrenia.[106] The monthly rate of second-generation APP increased from 3.3% in 1999 to 13.7% in 2004 and the rate of combination of first- and second-generation antipsychotics decreased from 10.8% in 1999 to 8.3% in 2004. The proportion of patients receiving APP for 12 months increased from 5.1% in 1999 to 14.4% in 2004.

Another study examined the prevalence of APP among fee-for-service (FFS) Medicaid beneficiaries in five states (California, Nebraska, Oregon, Utah and Wyoming) from 1998 to

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104 Weissman EM. Antipsychotic prescribing practices in the Veterans Healthcare Administration--New York metropolitan region. Schizophr Bull 2002;28(1):31-42.

105 Ganguly R, Kotzan JA, Miller LS, et al. Prevalence, trends, and factors associated with antipsychotic polypharmacy among Medicaid-eligible schizophrenia patients, 1998-2000. J Clin Psychiatry 2004;65(10):1377-88.

106 Gilmer TP, Dolder CR, Folsom DP, et al. Antipsychotic polypharmacy trends among Medicaid beneficiaries with schizophrenia in San Diego County, 1999-2004. Psychiatr Serv 2007;58(7):1007-10.

2003.[107] Polypharmacy was defined as the initiation of multiple antipsychotics or at least 60 consecutive days of concomitant antipsychotic medication overlapping the index medication. The overall prevalence of APP was 6.4% (3,534 patients). The highest rates of APP were observed in patients with a schizophrenia diagnosis, those having ten or more unique mental health diagnoses, those with clozapine as the index drug, and those with a recent mental health-related hospitalization.

More recently, Constantine et al. studied the trends of APP in the FFS population of Florida's Medicaid program between 2002 and 2006.[108] APP was defined as use of two or more antipsychotics for 60 consecutive days with no gap exceeding 15 days. The overall prevalence of APP was 21%. The prevalence showed an increasing trend until 2004 and a decreasing trend thereafter. The authors carried out a similar study of children (ages six to 12 years) and adolescents (ages 13 to 17 years) in the Florida Medicaid program over the same time period using the same definition for APP.[109] Seven percent of the children and 8% of the adolescents had APP and the mean length of the polypharmacy episode was 170 and 186 days for children and adolescents, respectively. Times to initiation of polypharmacy were 506 and 385 days for children and adolescents, respectively. Kogut et al. used Rhode Island Medicaid FFS claims to estimate the extent of APP in 2003. They found that 10.1% of the patients had at least two prescription fills for two different antipsychotic medications during the 90 days prior to the most recent prescription fill. Of the patients eligible for the study, eight percent used two atypical antipsychotics and 2.1% used one typical and one atypical antipsychotic. The highest rates of

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[107] Morrato EH, Dodd S, Oderda G, et al. Prevalence, utilization patterns, and predictors of antipsychotic polypharmacy: experience in a multistate Medicaid population, 1998-2003. Clin Ther 2007;29(1):183-95.

[108] Constantine RJ, Andel R, Tandon R. Trends in adult antipsychotic polypharmacy: progress and challenges in Florida's Medicaid program. Community Ment Health J 2010;46(6):523-30.

[109] Constantine RJ, Boaz T, Tandon R. Antipsychotic polypharmacy in the treatment of children and adolescents in the fee-for-service component of a large state Medicaid program. Clin Ther 2010;32(5):949-59.

polypharmacy were observed in males and in patients between 18 and 64 years of age.[110] Clark and his colleagues used prescription claims from New Hampshire Medicaid beneficiaries with schizophrenia or schizoaffective disorder between 1995 and 1999 and found that the proportion of patients treated with atypical antipsychotics grew from 43% in 1995 to 90% in 1999. Concurrent use of two or more antipsychotic medications increased from 5.7% in 1995 to 24.3% in 1999.[111]

Botts et al. used the National Ambulatory Medical Care Survey (NAMCS) 1993-2000, a multistage probability survey of visits to office-based physicians in the US, to estimate APP in ambulatory care.[112] Antipsychotics were reported in one percent of the visits and of these, four percent of the visits reported prescription of two antipsychotics. The APP rate increased over each two-year period. A study by Barbui et al. looked at the extent of polypharmacy among schizophrenia patients in four European countries (Croydon (UK), Verona (Italy), Amsterdam (Netherlands), and Leipzig (Germany)) and found that among the 375 patients, 13% persistently received polypharmacy.[113] APP was defined as use of two or more antipsychotics at baseline and follow-up of the study. A study conducted in British Columbia, Canada between October 2005 and October 2006 to determine the proportion of community mental health outpatients treated with persistent APP (two antipsychotics for at least 90 days) estimated the overall prevalence of

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110 Kogut SJ, Yam F, Dufresne R. Prescribing of antipsychotic medication in a Medicaid population: use of polytherapy and off-label dosages. J Manag Care Pharm 2005;11(1):17-24.

111 Clark RE, Bartels SJ, Mellman TA, et al. Recent trends in antipsychotic combination therapy of schizophrenia and schizoaffective disorder: implications for state mental health policy. Schizophr Bull 2002;28(1):75-84.

112 Botts S, Hines H, Littrell R. Antipsychotic polypharmacy in the ambulatory care setting, 1993-2000. Psychiatr Serv 2003;54(8):1086.

113 Barbui C, Nosè M, Mazzi MA, et al. Persistence with polypharmacy and excessive dosing in patients with schizophrenia treated in four European countries. Int Clin Psychopharmacol 2006;21(6):355-62.

APP at 25.7%.[114] The prevalence of persistent APP was highest for patients with schizoaffective disorder (33.7%), followed by schizophrenia (31.7%), psychosis not otherwise specified (20.0%), bipolar disorder (16.9%), and major depression (14.3%).

Several studies have also been conducted in inpatient settings to estimate the extent of APP. Jaffe et al. estimated the rate of APP among inpatients in a large state hospital in New York in 1999.[115] Co-prescribing (intentional co-prescribing of two antipsychotics for at least 28 days) occurred in 37.3% of the patients and 4.6% were treated with three or more antipsychotics. The mean length of a polypharmacy episode was 97 days. Another study conducted on inpatients in a hospital in Spain found that for the patients admitted in March 2011, the prevalence of APP was 47.1%. Twenty-four percent of the patients on APP were elderly people.[116] Quetiapine was the most highly prescribed drug (56.8%) in combinations. A study conducted over a 60-day surveillance period (between December 2000 to February 2001) among patients at the William R. Sharpe, Jr. Hospital found that of the 201 patients placed on scheduled antipsychotics, 85 (41%) were prescribed more than one antipsychotic concomitantly.[117] In a study conducted using inpatients admitted into the University Psychiatric Hospital in Serbia between 2002 and 2005, APP was observed in 67.7% of the hospitalizations. APP with two drugs was seen in 63.3% and that with three drugs was seen in 4.1% of the hospitalizations. APP was defined as concomitant

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[114] Procyshyn RM, Honer WG, Wu TK, et al. Persistent antipsychotic polypharmacy and excessive dosing in the community psychiatric treatment setting: a review of medication profiles in 435 Canadian outpatients. J Clin Psychiatry 2010;71(5):566-73.

[115] Jaffe AB, Levine J. Antipsychotic medication coprescribing in a large state hospital system. Pharmacoepidemiol Drug Saf 2003;12(1):41-8.

[116] López de Torre A, Lertxundi U, Hernández R, et al. Antipsychotic polypharmacy: a needle in a haystack? Gen Hosp Psychiatry 2012;34(4):423-32.

[117] Schumacher JE, Makela EH, Griffin HR. Multiple antipsychotic medication prescribing patterns. Ann Pharmacother 2003;37(7-8):951-5.

use of more than one antipsychotic for at least 28 days.[118] McCue et al. reviewed medical records of patients discharged from the Woodhull Medical and Mental Health Center between 1995 and 2000 and found that none of the patients were discharged on treatment with more than one antipsychotic in 1995, while 15.9% of the patients were in 2000.[119] Dolder et al. conducted a retrospective analysis of patients admitted to a geriatric facility in North Carolina between 2006 and 2010 and found that nearly 13% of the patients had APP at the time of admission and this was reduced to eight percent at the time of discharge.[120] Quetiapine was the drug which was most commonly involved with antipsychotic polypharmacy. An audit carried out at the Birch Hill Hospital, Lancashire found the prevalence of APP at 17.4%.[121]

Faries et al. used data from the U.S. Schizophrenia Care and Assessment Program (US-SCAP), a non-randomized, naturalistic, three-year prospective multi-center study conducted between July 1997 and September 2003.[122] Patients were enrolled from California, Colorado, Connecticut, Florida, Maryland, and North Carolina and were from different health care systems. On a daily basis, APP was defined as use of more than one antipsychotic medication. Substantial APP was defined as use of two or more antipsychotics concomitantly for at least 60 but less than 300 days and predominant APP was defined as use of two or more antipsychotics concomitantly for 300 or more days out of the year. Monotherapy, substantial monotherapy, and predominant monotherapy had similar definitions. During a one-year follow-up period, only a third of the

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118 Divac N, Jasović-Gasić M, Samardzić R, et al. Antipsychotic polypharmacy at the University Psychiatric Hospital in Serbia. Pharmacoepidemiol Drug Saf 2007;16(11):1250-1.

119 McCue RE, Waheed R, Urcuyo L. Polypharmacy in patients with schizophrenia. J Clin Psychiatry 2003;64(9):984-9.

120 Dolder CR, McKinsey J. Antipsychotic polypharmacy among patients admitted to a geriatric psychiatry unit. J Psychiatr Pract 2011;17(5):368-74.

121 Ranceva N, Ashraf W, Odelola D. Antipsychotic polypharmacy in outpatients at Birch Hill Hospital: incidence and adherence to guidelines. J Clin Pharmacol 2010;50(6):699-704.

122 Faries D, Ascher-Svanum H, Zhu B, et al. Antipsychotic monotherapy and polypharmacy in the naturalistic treatment of schizophrenia with atypical antipsychotics. BMC Psychiatry 2005;5:26.

patients were on predominant monotherapy. Almost 58% of the patients had at least one prolonged period of polypharmacy for 60 days or more. Patients averaged 195.5 days on monotherapy, 155.7 days on polypharmacy, and 13.9 days without antipsychotic therapy. Another one-year naturalistic study conducted in Japan between 2003 and 2004 by Ye et al. reported that of the 1,850 patients eligible for the study, 56.8% had APP (defined as concomitant use of two or more antipsychotics for at least 60 days) at some point during the one-year study period.[123]

Aggarwal et al. examined the concomitant use of oral antipsychotics in patients treated with long-acting intramuscular (LAI) antipsychotics for schizophrenia and schizoaffective disorder from the Connecticut Mental Health Center between July 1, 2009 and June 30, 2010.[124] Concomitancy was defined as simultaneous oral and LAI antipsychotic use at any time during the study period. Of the 124 patients on LAIs, 46% were prescribed a concomitant oral antipsychotic. This is contrary to the notion that LAIs are used as monotherapy in 'real-world' settings. Such concomitancy may represent a common practice of APP and should be investigated further.

Tungaraza et al. conducted a study that looked at the use of multiple antipsychotic medications in people living in the community under the community mental health team (CMHT) in the urban and rural parts of North East Wales between 2006 and 2007.[125] Psychotropic polypharmacy was widespread in this population with 67.3% taking more than one psychotropic drug. Of the 211 individuals examined, 82.5% were on a single antipsychotic, and

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123 Ye W, Ascher-Svanum H, Flynn JA, et al. Predictors of antipsychotic monotherapy with olanzapine during a 1-year naturalistic study of schizophrenia patients in Japan. Clinicoecon Outcomes Res 2012;4:13-9.

124 Aggarwal NK, Sernyak MJ, Rosenheck RA. Prevalence of concomitant oral antipsychotic drug use among patients treated with long-acting, intramuscular, antipsychotic medications. J Clin Psychopharmacol 2012;32(3):323-8.

125 Tungaraza TE, Gupta S, Jones J, et al. Polypharmacy and high-dose antipsychotic regimes in the community. The Psychiatrist 2010; 34(2):44-6.

17.5% were on two antipsychotics. In a two-phase national survey conducted between 2002 and 2003 in Italy to investigate characteristics of patients admitted to acute inpatient facilities, the extent of antipsychotic polypharmacy was found to be 32.6%.[126]

Despite recommendations of antipsychotic monotherapy by several expert guidelines, APP is widely practiced in various clinical settings. A meta-analysis of studies estimating the prevalence of APP between 1970 and 2009 found that the median prevalence of APP was 19.6%.[127] Another meta-analysis estimated the prevalence of APP among antipsychotic treated youth at 9.6 ±7.2% (5.9 ± 4.5% in child studies, 12.0 ± 7.9% in adolescent studies).[128]

Generally, the concurrent use of more than one antipsychotic varied over a very wide range, from as low as 4% to as high as almost 65%, depending on the population studied, the year when the study was conducted, the study method, definition of APP, the type of treatment site, and the duration of the study period.

Table 3 contains a summary of the studies that evaluated the prevalence of APP.

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126 Santone G, Bellantuono C, Rucci P, et al. Patient characteristics and process factors associated with antipsychotic polypharmacy in a nationwide sample of psychiatric inpatients in Italy. Pharmacoepidemiol Drug Saf. 2011;20(5):441-9.

127 Gallego JA, Bonetti J, Zhang J, et al. Prevalence and correlates of antipsychotic polypharmacy: a systematic review and meta-regression of global and regional trends from the 1970s to 2009. Schizophr Res 2012;138(1):18-28.

128 Toteja N1, Gallego JA, Saito E, et al. Prevalence and correlates of antipsychotic polypharmacy in children and adolescents receiving antipsychotic treatment. Int J Neuropsychopharmacol 2013; 14:1-11. [Epub ahead of print].

Table 3: Summary of studies that evaluated the prevalence of antipsychotic polypharmacy

Author	Year	Prevalence	Population	Definition of APP
US: Administrative data bases				
Leslie et al. (2001)	1999	6.8%	Veterans Affairs	Patients prescribed more than one antipsychotic during a one-week window
Clark et al. (2002)	1995-1999	5.7-24.3%	New Hampshire Medicaid beneficiaries	Using combination of antipsychotics for over nine months
Weissman (2002)	2000-2001	15-17%	New York metropolitan region Veterans Affairs	Co-prescription of two or more antipsychotics for at least two months
Botts et al. (2003)	1993-2000	4%	NAMCS	At least two antipsychotics prescribed at the office-based physician visit
Ganguly et al. (2004)	1998-2000	23%	California and Georgia Medicaid beneficiaries	Concomitant use of two or more antipsychotics for at least 61 days without a break period of 31 days or more
Faries et al. (2005)	July, 1997 and September, 2003	58%	Three-year prospective multi-center study with patients from California, Colorado, Connecticut, Florida, Maryland, and North Carolina and different healthcare systems	Use of two or more antipsychotics concomitantly for at least 60 but less than 300 days

Table 3: Summary of studies that evaluated the prevalence of antipsychotic polypharmacy (continued)

Author	Year	Prevalence	Population	Definition of APP
Kogut et al. (2005)	2003	10.1%	Fee-for-service Rhode Island Medicaid beneficiaries	At least two dispensings of two different antipsychotics during the 90 days prior to the most recent dispensing
Kreyenbuhl et al. (2006)	1999-2000	9.5%	Veterans Affairs	Receipt of two or more antipsychotics concomitantly for at least 90 consecutive days
Gilmer et al. (2007)	1999-2004	5.1-14.4%	California Medicaid beneficiaries	Receiving multiple second-generation medications
Morrato et al. (2007)	1998-2003	6.4%	California, Oregon, Utah, Nebraska, and Wyoming Medicaid beneficiaries	Initiation of multiple antipsychotics or at least 60 consecutive days of concomitant antipsychotic medication overlapping the index medication
Constantine et al. (2010)	2002-2006	21%	Fee-for-service Florida Medicaid beneficiaries	Use of two or more antipsychotics for greater than 60 consecutive days with no gap exceeding 15 days
Constantine et al. (2010)	2002-2006	6% (children), 8% (adolescents)	Fee-for-service Florida Medicaid beneficiaries, children and adolescents	Use of two or more antipsychotics for greater than 60 consecutive days with no gap exceeding 15 days

Table 3: Summary of studies that evaluated the prevalence of antipsychotic polypharmacy (continued)

Author	Year	Prevalence	Population	Definition of APP
Aggarwal et al. (2012)	July 1, 2009 and June 30, 2010	46% (oral + long acting antipsychotic)	Connecticut Mental Health Center	Simultaneous oral and long acting injectable antipsychotic use at any time during study period
Tungaraza et al. (2010)	2006 and 2007	17.5%	Community-dwellers under the community mental health team (CMHT) in the urban and rural North East Wales	Use of two antipsychotics
Ye et al. (2012)	2003-2004	56.8%	One-year naturalistic study conducted in Japan	Concomitant use of two or more antipsychotics for at least 60 days
US Hospitals				
Jaffe et al. (2003)	1999	37.3%	Large state hospital in New York	Intentional co-prescribing of two antipsychotics for at least 28 days
McCue et al. (2003)	1995-2000	0% in 1995, 15.9% in 2000	Woodhul Medical and Mental Health Center, New York, US	Receiving two or more antipsychotics at discharge
Schumacher et al. (2003)	December 2000 to February 2001	41%	William R. Sharpe, Jr. Hospital in West Virginia, US	Receipt of two or more scheduled antipsychotics concomitantly
Dolder et al. (2011)	2006-2010	13% at the time of admission, 8% at the time of discharge	Geriatric facility in North Carolina	Patients using multiple antipsychotics at admission and discharge
Barbui et al. (2006)		13%	UK, Italy, Netherlands, Germany	Use of two or more antipsychotics at baseline and follow-up of the study

Table 3: Summary of studies that evaluated the prevalence of antipsychotic polypharmacy (continued)

Author	Year	Prevalence	Population	Definition of APP
International hospitals				
Divac et al. (2007)	2002-2005	63.3%	University Psychiatric Hospital in Serbia	Concomitant use of more than one antipsychotic for at least 28 days
Procyshyn et al. (2010)	October 2005-October 2006	25.7%	British Columbia, Canada	Use of two antipsychotics for at least 90 days
Ranceva et al. (2010)	January-May 2008	17.4%	Birch Hill Hospital, Lancashire	Patients receiving more than one antipsychotic
Santone et al. (2011)	2002 and 2003	32.6%	Two-phase national survey conducted in Italy	At least two antipsychotics simultaneously prescribed during index admission
Lopez de Torre et al. (2012)	March 2011	47.1%	Inpatients in a Spanish hospital	Use of two antipsychotics for one week

2.6. Predictors of antipsychotic polypharmacy

It is important to identify characteristics of patients most likely to be prescribed APP so that this high-risk population can be monitored and their outcomes can be regularly evaluated. Several studies have attempted to identify this high-risk group of patients.

A study conducted using Medicaid-eligible enrollees from Georgia and California between 1998 and 2000 used a stepwise logistic regression procedure to determine if demographics, diagnostic-related comorbidities, drug classes, antipsychotics agent, and prior healthcare utilization were related to long-term APP.[129] Being eligible for California Medicaid, male gender, and belonging to the aid category (aged, blind, or disabled) were associated with increased likelihood of APP. Weight loss or malnutrition, diagnosis of epilepsy, other psychoses, and other mental disorders also predicted long-term concomitant use of multiple antipsychotics.

Exposure to medication for cancer, Parkinson's disease, and respiratory disorders were associated with increased likelihood of APP. Diagnosis for acquired immunodeficiency syndrome (AIDS), alcohol abuse, personality disorders, and use of drugs for cardiac conditions were associated with lower likelihood of APP. Psychiatric-related inpatient and outpatient visits in the 6-month period prior to the index claim, regular use of antipsychotics, and index dates in the fourth quarter were also positively associated with APP.

Morrato et al. used Medicaid data from five states (California, Nebraska, Oregon, Utah, and Wyoming) and reported the prevalence of APP at about six percent.[130] They found that the strongest predictor for antipsychotic polypharmacy was a schizophrenia diagnosis, with concomitant antipsychotic use being three times as likely in patients with such a diagnosis

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[129] Ganguly R, Kotzan JA, Miller LS, et al. Prevalence, trends, and factors associated with antipsychotic polypharmacy among Medicaid-eligible schizophrenia patients, 1998-2000. J Clin Psychiatry 2004;65(10):1377-88.
[130] Morrato EH, Dodd S, Oderda G, et al. Prevalence, utilization patterns, and predictors of antipsychotic polypharmacy: experience in a multistate Medicaid population, 1998-2003. Clin Ther 2007;29(1):183-95.

compared to those without any mental health diagnosis. In fact, the likelihood of polypharmacy increases with each additional diagnosis of a mental illness. Patients with mental health-related hospitalizations were more likely to have APP. Patients initiated on typical antipsychotics were more likely to have APP compared to those initiated on olanzapine and risperidone. With regards to demographic characteristics, males (compared to females), patients between 18 and 24 years of age (compared to those between 25 and 34 years of age), and Asians (compared to whites) were more likely to have APP.

Kreyenbuhl et al. examined the predictors of long-term APP among Veterans Affairs (VA) patients with schizophrenia or schizoaffective disorder in 2000.[131] The multivariate analyses carried out to identify the predictors of APP showed that younger, unmarried patients, those with a military service-related disability, and those with a schizophrenia diagnosis (compared to schizoaffective disorder) were more likely to be on multiple antipsychotics. African American patients were less likely to be on polypharmacy compared to whites. Patients with a depression or substance abuse diagnosis and those who had a higher co-morbidity burden as measured by the Charlson Comorbidity Index (CCI) were less likely to receive polypharmacy. Those who had a psychiatric hospitalization in the prior year or several outpatient mental health-related visits were also more likely to receive APP.

Biancosono et al. examined physicians' reasons for prescribing multiple antipsychotics by conducting a study on psychiatric patients discharged from an inpatient facility and receiving antipsychotic therapy during a six-year recruitment period from 1998 to 2003 in Italy.[132] They found that the factors which predicted APP were the Brief Psychiatric Rating Scale (BPRS) for

131 Kreyenbuhl JA, Valenstein M, McCarthy JF, et al. Long-term antipsychotic polypharmacy in the VA health system: patient characteristics and treatment patterns. Psychiatr Serv 2007;58(4):489-95.

132 Biancosino B, Barbui C, Marmai L, et al. Determinants of antipsychotic polypharmacy in psychiatric inpatients: a prospective study. Int Clin Psychopharmacol 2005;20(6):305-9.

positive symptoms, BPRS for manic/hostility, being employed, and presence of APP on admission. Antipsychotic polypharmacy at admission was the strongest predictor of polypharmacy at discharge. Another study conducted in Italy by Santone et al. reported that APP was associated with a schizophrenia diagnosis, poor insight into the patient's illness, and use of anti-Parkinsonism drugs.[133]

A study examining APP among children in the fee-for-service component of Florida Medicaid between 2002 and 2007 found that adolescents (13-17 years) were more likely to receive polypharmacy compared to children (six to 12 years).[134] Patients whose ethnicity was classified as 'other' were more likely to receive concomitant multiple antipsychotics compared to whites. Patients with a diagnosis of psychotic disorders were more likely to receive polypharmacy (compared to bipolar I disorder) and those with a diagnosis of major depressive disorder, other bipolar/mood disorder, ADHD, behavioral disorder, and anxiety/adjustment disorder were less likely to receive APP (compared to bipolar I disorder).

In a prospective, observational study conducted on Japanese patients with schizophrenia between 2003 and 2004, stepwise logistic regression was used to identify predictors of antipsychotic monotherapy as compared to polypharmacy.[135] The authors noted that older age, shorter duration of schizophrenia, outpatient status, presence of comorbid medical conditions, lower body mass index, no prior anticholinergic use, no prior mood stabilizer use, and switching from a previous antipsychotic were all associated with increased odds of antipsychotic monotherapy. Another study conducted in China found that younger age, number of

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133 Santone G, Bellantuono C, Rucci P, et al. Patient characteristics and process factors associated with antipsychotic polypharmacy in a nationwide sample of psychiatric inpatients in Italy. Pharmacoepidemiol Drug Saf 2011;20(5):441-9.

134 Constantine RJ, Boaz T, Tandon R. Antipsychotic polypharmacy in the treatment of children and adolescents in the fee-for-service component of a large state Medicaid program. Clin Ther 2010;32(5):949-59.

135 Ye W, Ascher-Svanum H, Flynn JA, et al. Predictors of antipsychotic monotherapy with olanzapine during a 1-year naturalistic study of schizophrenia patients in Japan. Clinicoecon Outcomes Res 2012;4:13-9.

hospitalizations, site of study (Hong Kong vs. Beijing), and use of depot antipsychotics were all significantly associated with APP.[136]

Dolder et al. conducted a retrospective analysis to study the patterns of use of antipsychotics among patients in a geriatric psychiatry unit in North Carolina between 2006 and 2010.[137] Patients with severe mental illness or dementia plus a mental illness were more likely to receive polypharmacy compared to those with dementia alone. Also those residing in a facility were more likely to receive multiple antipsychotics compared to those living at home.

Gallego et al. conducted a meta-analysis of all the studies that estimated the prevalence of APP.[138] They carried out a meta-regression to identify predictors of polypharmacy and found that inpatient status, typical antipsychotic use, and a schizophrenia diagnosis independently predicted APP.

Based on a review of existing literature, Correll et al. found that APP was associated with patients, illness and treatment factors which pointed towards greater disease severity and chronicity. However, there were certain provider characteristics at play which suggested that some of the APP may be unfounded.[139]

Table 4 contains a list of potential factors associated with APP. This table has been adapted from an article published by Ganguly et al.[140]

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136 Xiang YT, Weng YZ, Leung CM, et al. Clinical and social determinants of antipsychotic polypharmacy for Chinese patients with schizophrenia. Pharmacopsychiatry 2007;40(2):47-52.

137 Dolder CR, McKinsey J. Antipsychotic polypharmacy among patients admitted to a geriatric psychiatry unit. J Psychiatr Pract 2011;17(5):368-74.

138 Gallego JA, Bonetti J, Zhang J, et al. Prevalence and correlates of antipsychotic polypharmacy: a systematic review and meta-regression of global and regional trends from the 1970s to 2009. Schizophr Res 2012;138(1):18-28.

139 Correll CU, Gallego JA. Antipsychotic polypharmacy: a comprehensive evaluation of relevant correlates of a long-standing clinical practice. Psychiatr Clin North Am 2012;35(3):661-81.

140 Ganguly R, Kotzan JA, Miller LS, et al. Prevalence, trends, and factors associated with antipsychotic polypharmacy among Medicaid-eligible schizophrenia patients, 1998-2000. J Clin Psychiatry 2004;65(10):1377-88.

Table 4: Potential factors associated with antipsychotic polypharmacy (Adapted from 134)

Diagnostic-related comorbidities	**Demographics**
Congestive heart failure	Age
Myocardial infarction	Gender
Cardiac arrhythmias	Race
Valvular disease	**Eligibility categories**
Peripheral vascular disease	Aid category (aged, blind, disabled)
Hypertension	**Drug class**
Hemiplegia/paraplegia	4 cardiac drug classes (antiarrhythmic + inotropic + vasopressor, ACE inhibitors, antianginal agents, loop diuretics)
Epilepsy	Parkinson's disease drugs
Other neurologic disorders	Peripheral vascular disorder drugs
Chronic pulmonary disease	Hypertension drugs
Asthma	3 respiratory drug classes (adrenergic bronchodilators + asthma vasopressors + combinations, methylxanthines, inhalers + leukotrienes + combinations)
Tuberculosis	Insulins
Diabetes, uncomplicated	Oral hypoglycemic
Diabetes, complicated	Cancer drugs
Thyroid disorder	3 Epilepsy drug classes (hydantoin + succinimide + oxazolidinedione, barbiturates + certain benzodiazepines, miscellaneous anticonvulsants [valproic acid and derivatives, carbamazepine and derivatives, gabapentin, lamotrigine, tiagabine, topiramate, levetiracetam])
Renal failure and chronic disease	Glaucoma drugs
Liver disease	Gout drugs
Peptic ulcer disease	Hyperlipidemia, hypercholesterolemia drugs
Acquired immunodeficiency syndrome	Thyroid disorder drugs
Metastatic solid tumor	Menopause drugs (hormone replacement therapy)
Any malignancy	Allergy drugs
Rheumatoid arthritis/collagen vascular disease	Anxiety drugs
Coagulopathy	Pain (terminal) drugs, narcotics, analgesics
Obesity	Depression drugs
Weight loss/malnutrition	Dementia/Alzheimer's drugs
Fluid and electrolyte disorder	Tuberculosis drugs

Table 4: Potential factors associated with antipsychotic polypharmacy (Adapted from 134)

(continued)

Diagnostic-related comorbidities	**Drug class**
Anemia	Rheumatologic drugs/Crohn's disease drugs/ulcerative colitis drugs
Sickle cell anemia	Migraine drugs
Drug abuse	ESRD/transplant drugs
Alcohol abuse	Mean number of drugs classes per patient
Bipolar and manic depressive illness	Antipsychotic agents: Atypicals, typicals
Other psychoses/mixed psychoses	Mood stabilizers: Lithium
Other mental disorders	**Prior healthcare utilization**
Personality disorders	Mental health cost in prior period
Depression or schizoaffective disorder	Number of psychiatric outpatient visits, physician specialty
Cerebrovascular disease	Psychiatric inpatient episode, latest inpatient days, cumulative inpatient days
Alzheimer's disease	**Date variables**
Non-Alzheimer's dementia	Quarter in which episode started
Non-head trauma	Year in which episode started
Head trauma	
Drug overdose	
Ophthalmologic disease	
Anxiety states	
Number of comorbidities per patient	

2.7. Adherence to antipsychotics

Medication adherence is extremely important in psychiatry, especially for chronic conditions. Non-adherence rates of 40% to 60% have been reported for antipsychotics, 18% to 56% for mood stabilizers, and 30% to 97% (median 63%) for antidepressants.[141,142,143] These poor adherence rates, in part, explain the difference between the efficacy seen during clinical trials and effectiveness seen during routine clinical practice.[144]

Several studies have shown poor adherence to antipsychotic medications. In a three-year prospective, naturalistic study conducted among patients with schizophrenia between 1997 and 2003, adherence was measured using medication possession ratio (MPR) and persistence was measured as time to all-cause medication discontinuation (first medication gap of more than 30 days). Only 59% of the patients were deemed adherent (MPR>0.8). A greater proportion of atypical antipsychotic users were adherent (59.4%) compared to the typical antipsychotic users (34.5%). Persistence was significantly shorter for the typical antipsychotics group (173.9 days) compared to the atypical antipsychotics group (260.7 days).[145]

Mullins et al. conducted a study in adult Maryland Medicaid patients with schizophrenia and measured discontinuation of antipsychotic agents using refill patterns. At one-year follow-up, 90.4% of the patients had discontinued their antipsychotic medications. The discontinuation rates did not differ significantly for patients on aripiprazole, olanzapine, risperidone, or

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141 Scott J, Pope M. Nonadherence with mood stabilizers: prevalence and predictors. J Clin Psychiatry 2002; 63(5):384–90.

142 Zygmunt A, Olfson M, Boyer CA, Mechanic D. Interventions to improve medication adherence in schizophrenia. Am J Psychiatry 2002; 159(10):1653–64.

143 Pampallona S, Bollini P, Tibaldi G, Kupelnick B, Munnizza C. Patient adherence in the treatment of depression. Br J Psychiatry 2002; 180:104–9.

144 Patel MX, David AS. Medication adherence: predictive factors and enhancement strategies. Psychiatry 2007; 6(9):357-61.

145 Ascher-Svanum H, Zhu B, Faries DE, et al. Adherence and persistence to typical and atypical antipsychotics in the naturalistic treatment of patients with schizophrenia. Patient Prefer Adherence 2008;2:67-77.

ziprasidone but were significantly higher for those on quetiapine.[146] Another retrospective database study was conducted on Quebec Drug Plan beneficiaries who were initiated on antipsychotics between 2000 and 2007. Patients initiated on quetiapine had a high risk of discontinuation compared to olanzapine initiators. Risperidone, clozapine, and polytherapy users had a lower risk of discontinuation compared to olanzapine users. Those who discontinued were not likely to return to treatment and those who did return to treatment had a high likelihood of discontinuing again.[147]

Some studies have been conducted to compare adherence to antipsychotics and time to discontinuation of medication in patients on monotherapy and those on APP. Between December 2004 and March 2008, 15 sites in the National Institute of Mental Health's Schizophrenia Trials Network and five sites in Connecticut's public mental health system recruited adult patients who had a diagnosis of schizophrenia or schizoaffective disorder and were using two antipsychotics.[148] Patients were randomly assigned to stay on polypharmacy or switch to monotherapy. Kaplan Meier and Cox proportional hazards analyses were carried out to determine time to discontinuation of therapy. The primary outcome was all-cause medication discontinuation. Of the 114 patients studied, 56 remained on polypharmacy and 58 switched to monotherapy. By month six, 86% of those on polypharmacy were still taking their assigned medication while 69% of those on monotherapy were still taking their assigned medication. However, two-thirds of the patients were successful in switching to monotherapy. They had no difference in symptom control compared to the polypharmacy group and the switch to

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146 Mullins CD, Obeidat NA, Cuffel BJ, et al. Risk of discontinuation of atypical antipsychotic agents in the treatment of schizophrenia. Schizophr Res 2008;98(1-3):8-15.

147 Moisan J, Grégoire JP. Patterns of discontinuation of atypical antipsychotics in the province of Québec: A retrospective prescription claims database analysis. Clin Ther 2010;32 Suppl 1:S21-31.

148 Essock SM, Schooler NR, Stroup TS, et al. Effectiveness of switching from antipsychotic polypharmacy to monotherapy. Am J Psychiatry 2011;168(7):702-8.

monotherapy resulted in weight loss. In the polypharmacy group, discontinuing one of the two antipsychotics lead to treatment discontinuation of all medications more quickly than when both medications were continued. In fact, another study by Hori et al. showed that if schizophrenia patients on APP switched to MT, it lead to improvements in attention, daily living and work skills.[149]

In a retrospective cohort study conducted in Medicaid enrollees from California, Nebraska, Oregon, Utah, and Wyoming between 1998 and 2003, the authors compared medication adherence (measured using MPR) and persistence to antipsychotic medications between the polypharmacy and monotherapy groups.[150] Each group was further divided into two categories based on whether the patients had concomitant psychotropic therapy or not. The polypharmacy group had higher adherence (0.82 for the no concomitant psychotropic therapy group, 0.83 for the concomitant psychotropic therapy group) compared to the monotherapy group (0.75 for both with and without psychotropic therapy groups). The persistence was also higher in the polypharmacy groups compared to the monotherapy groups (251, 283, 214, and 273 days for the polypharmacy groups with and without psychotropic therapy and monotherapy groups with and without psychotropic therapy, respectively).

A study by Katona et al. used data collected from the Hungarian National Health Insurance Fund's database to assess the time to all-cause medication discontinuation in patients on antipsychotic monotherapy either staying on monotherapy or switching to polypharmacy (two or more antipsychotics).[151] All-cause discontinuation showed superiority for the monotherapy

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[149] Hori H, Yoshimura R, Katsuki A, et al. Switching to antipsychotic monotherapy can improve attention and processing speed, and social activity in chronic schizophrenia patients. J Psychiatr Res 2013;47(12):1843-8.
[150] Morrato EH, Dodd S, Oderda G, et al. Prevalence, utilization patterns, and predictors of antipsychotic polypharmacy: experience in a multistate Medicaid population, 1998-2003. Clin Ther 2007;29(1):183-95.
[151] Katona L, Czobor P, Bitter I. Real-world effectiveness of antipsychotic monotherapy vs. polypharmacy in schizophrenia: To switch or to combine? A nationwide study in Hungary. Schizophr Res 2014;152(1):246-54.

group for most second generation antipsychotics (both oral and depot). For first generation antipsychotics, there was no difference between the monotherapy and polypharmacy group for the orals while the polypharmacy group showed superiority for the depot antipsychotics. For discontinuation due to mortality and hospitalizations, an advantage was noted in the polypharmacy group.

Although adherence to antipsychotic therapy is poor, it was observed that those on more than one antipsychotic had better adherence than those on a single antipsychotic medication. It has been well established that multiple antipsychotics lead to an increased likelihood of adverse events and drug interactions and are also associated with significantly higher costs than monotherapy.[152] Combining an atypical antipsychotic with a typical antipsychotic makes it lose its 'atypical' nature and the patient is as likely to suffer from extrapyramidal symptoms including tardive dyskinesia as those on typical antipsychotics.[153] Studies have demonstrated that patients are more likely to be adherent to simple medication regimens rather than complex regimens.[154,155] Despite these factors, studies comparing monotherapy and polypharmacy of antipsychotics have found better adherence rates in the polypharmacy group.

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152 Miller AL, Craig CS. Combination antipsychotics: pros, cons, and questions. Schizophr Bull 2002; 28(1):105-9.

153 Canales PL, Olsen J, Miller AL et al. Role of antipsychotic polypharmacotherapy in the treatment of schizophrenia. CNS Drugs 1999;12(3):179-88.

154 Chen A. Noncompliance in community psychiatry: A review of clinical interventions. Hospital and Community Psychiatry 1991;42(3):282-7.

155 Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353(5):487-97.

2.8. Factors affecting adherence to antipsychotics

Regular use of antipsychotic medications is the cornerstone of treatment for psychotic disorders as it helps prevent relapse of the disease. Several studies have been conducted to identify predictors of non-adherence among antipsychotic users. The literature on factors predicting non-adherence is vast; this literature review is focused on studies that were considered to be relevant to the current study.

Valenstein et al. reported that in a cohort of VA patients with schizophrenia or schizoaffective disorder between October 1998 and September 1999, about 40% of the patients receiving one antipsychotic and 38% receiving two antipsychotics had an MPR < 0.8, indicating poor adherence.[156] The patient factors predicting poor adherence included African American ethnicity and young age. Those with poor adherence were less likely to have ever received high antipsychotic doses. Patients on atypical antipsychotics were more likely to be poorly adherent than those on typical antipsychotics (41.5% vs. 37.8%).

Another study conducted by Valenstein et al. used data from VA patients with schizophrenia between 2000 and 2003.[157] The authors examined whether the patients had consistently good adherence (MPR≥0.8 in all four years), consistently poor adherence (MPR<0.8 in all four years), or inconsistent adherence. The authors found that 36% to 37% of the patients had poor adherence in each year. About 18% were consistently poorly adherent and 43% were inconsistently adherent. Patients who were younger, non-white, had a substance abuse diagnosis, had a psychiatric-related hospitalization, or predominantly used typical antipsychotics were more likely to have consistently poor adherence.

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[156] Valenstein M, Blow FC, Copeland LA, et al. Poor antipsychotic adherence among patients with schizophrenia: medication and patient factors. Schizophr Bull 2004;30(2):255-64.

[157] Valenstein M, Ganoczy D, McCarthy JF, et al. Antipsychotic adherence over time among patients receiving treatment for schizophrenia: a retrospective review. J Clin Psychiatry 2006;67(10):1542-50.

Sajatovic et al. used VA data from 2003 and evaluated adherence to antipsychotic medications among patients with bipolar disorder.[158] They found that about 45% of patients received antipsychotic medications for bipolar disorder and these patients were more likely to be younger and have comorbid substance abuse or post-traumatic stress disorder compared to those not receiving antipsychotics. A little less than half the patients (48.1%) were partially adherent ($0.5 < MPR < 0.8$) (21.2%) or non-adherent ($MPR \leq 0.5$) (26.9%) and 51.9% were adherent ($MPR \geq 0.8$). The mean MPR was 0.76 and the median duration of treatment was 240 days. Factors associated with non-adherence included younger age, minority ethnicity, comorbid substance abuse disorder, and homelessness.

Between 2004 and 2006 Kreyenbuhl et al. evaluated the time to discontinuation among VA patients with schizophrenia.[159] The median time to discontinuation differed by antipsychotic and ranged from a minimum of 95 days for haloperidol to a maximum of 164 days for chlorpromazine. Eighty-four percent of the patients discontinued their index antipsychotic during the follow-up period. The factors associated with greater risk of discontinuation included younger age, non-white ethnicity, homelessness, comorbid substance abuse disorder, prior (three months before index antipsychotic drug was started) hospitalization, and use of another antipsychotic at the time of discontinuation of the index medication (switching).

A study was conducted using community-dwelling Medicaid beneficiaries from Florida with schizophrenia between 1999 and 2000.[160] The patients were divided into four categories depending on their adherence: maximal adherence (75-100%), moderate adherence (50-74.9%),

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158 Sajatovic M, Valenstein M, Blow FC, et al. Treatment adherence with antipsychotic medications in bipolar disorder. Bipolar Disord 2006;8(3):232-41.

159 Kreyenbuhl J, Slade EP, Medoff DR, et al. Time to discontinuation of first- and second-generation antipsychotic medications in the treatment of schizophrenia. Schizophr Res 2011;131(1-3):127-32.

160 Becker MA, Young MS, Ochshorn E, et al. The relationship of antipsychotic medication class and adherence with treatment outcomes and costs for Florida Medicaid beneficiaries with schizophrenia. Adm Policy Ment Health 2007;34(3):307-14.

limited adherence (25-49.9%), and negligible adherence (0-24.9%); the proportions of patients in each class were 64%, 12.4%, 18.8%, and 4.9%, respectively. Logistic regression analysis was carried out to identify factors predicting adherence. Being male, older or middle aged, white, and without co-occurring substance abuse was associated with high adherence rates.

Another study conducted using Florida Medicaid beneficiaries with schizophrenia between 2004 and 2005 found that the mean adherence (measured as MPR) and medication persistence were 0.79 and 94.1%, respectively.[161] Persistence was defined as the number of days between the first and last antipsychotic prescription divided by the number of days remaining in the follow-up period after the first antipsychotic prescription was filled. The proportions of patients with an MPR between 0.8 and 1, 0.5 to less than 0.8, and less than 0.5 were 66%, 20%, and 14%, respectively. The predictors of poor adherence included new initiation of treatment, younger age, substance abuse disorder, use of a mood stabilizer, antidepressant, anxiolytic, or anticholinergic, and use of long-acting first-generation antipsychotics.

It has been consistently seen across several studies using administrative claims data that certain factors such as younger age, ethnic minorities, psychiatric-related comorbidities, inpatient hospitalizations, and concurrent use of other psychotropic medications are associated with poor adherence to antipsychotic medications. It is important to identify patients poorly adherent to antipsychotics and monitor them carefully as poor adherence is associated with more hospitalizations and higher costs.

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161 Lang K, Meyers JL, Korn JR, et al. Medication adherence and hospitalization among patients with schizophrenia treated with antipsychotics. Psychiatr Serv 2010;61(12):1239-47.

2.9. Healthcare utilization in antipsychotic users

This section contains an overview of healthcare utilization in antipsychotic users. There is very limited literature that specifically compares the healthcare utilization in people on antipsychotic monotherapy and polypharmacy. Therefore, studies that have examined healthcare utilization in antipsychotic users are briefly discussed.

APP has been associated with increased rates of hospitalizations. Gilmer et al. found that among San Diego county Medicaid beneficiaries with schizophrenia, the proportion of patients using APP for 12 months increased from 3.3% in 1999 to 13.7% in 2004, and the proportion of those using APP who were hospitalized increased from 7.2% to 9.0% during the same period.[162] Sajatovic et al. examined gender differences in clinical characteristics and hospital resource utilization among older people with schizophrenia or schizoaffective disorder in an acute care state hospital between January and December 1998. There were no gender differences with respect to length of stay, type and amount of prescribed antipsychotics, and use of seclusion facilities in the hospital. This was based on observation of 66 individuals.[163] Katona et al. used the data from the Hungarian National Health Insurance Fund's database and found that medication discontinuation due to a hospitalization or death was lesser in patients with antipsychotic polypharmacy (using two antipsychotics) as compared to those with monotherapy.[164]

Adult patients with schizophrenia from California Medicaid (1998-2001) were used to compare the resource utilization between patients who continued on their index medication,

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[162] Gilmer TP, Dolder CR, Folsom DP, et al. Antipsychotic polypharmacy trends among Medicaid beneficiaries with schizophrenia in San Diego County, 1999-2004. Psychiatr Serv 2007;58(7):1007-10.

[163] Sajatovic M, Sultana D, Bingham CR, et al. Gender related differences in clinical characteristics and hospital based resource utilization among older adults with schizophrenia. Int J Geriatr Psychiatry 2002;17(6):542-8.

[164] Katona L, Czobor P, Bitter I. Real-world effectiveness of antipsychotic monotherapy vs. polypharmacy in schizophrenia: To switch or to combine? A nationwide study in Hungary. Schizophr Res 2014;152(1):246-54.

switched medications, and abandoned medications. The use of psychiatric and non-psychiatric emergency services was higher for the switchers as compared to the continuers. The same trend was observed for inpatient hospitalizations, non-psychiatric physician visits or outpatient hospital visits, and use of other outpatient psychiatric or non-psychiatric services. Healthcare resource utilization was seen to be higher for switchers compared to the continuers.[165]

Al-Zakwani et al. examined pharmacy and medical reimbursement data from a southeastern US health plan to compare the healthcare utilization between atypical and typical antipsychotic users. After adjusting for baseline characteristics, time of therapy, and medication adherence (measured as MPR), the patients using atypical antipsychotics experienced fewer inpatient hopitalizations, emergency department visits, and physician office visits compared to the typical antipsychotic users.[166]

Chen et al. compared utilization patterns in schizophrenia patients with and without exposure to mood stabilizers using Georgia Medicaid enrollees between 1999 and 2001. The groups were matched using propensity scores controlling for demographic factors, comorbidities, prior utilization, and prescriber specialty. Patients on both antipsychotics and mood stabilizers were on therapy for a longer period of time and incurred higher drug costs compared to those on antipsychotics only, but there was no significant difference in total healthcare expenditures, hospitalizations, emergency department visits, and nursing home visits between the two groups.[167]

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165 Noordsy DL, Phillips GA, Ball DE, et al. Antipsychotic adherence, switching, and health care service utilization among Medicaid recipients with schizophrenia. Patient Prefer Adherence 2010;4:263-71.

166 Al-Zakwani IS, Barron JJ, Bullano MF, et al. Analysis of healthcare utilization patterns and adherence in patients receiving typical and atypical antipsychotic medications. Curr Med Res Opin 2003;19(7):619-26.

167 Chen H, Kennedy WK, Dorfman JH, et al. The effect of adjunctive mood stabilizers on antipsychotic utilization patterns and health resource utilization for Medicaid enrollees with schizophrenia. Curr Med Res Opin 2007;23(6):1351-65.

Iasevoli et al. conducted a study among psychotic inpatients in an Italian hospital.[168] Patients were categorized into the two (or more) and one antipsychotic groups. After four weeks of treatment it was observed that both groups significantly improved in global psychopathology, but the improvement was better in the MT vs. the APP group. This study assessed clinical outcomes but did not look at any utilization outcomes between the two groups.

[168] Iasevoli F, Buonaguro EF, Marconi M, et al. Efficacy and clinical determinants of antipsychotic polypharmacy in psychotic patients experiencing an acute relapse and admitted to hospital stay: results from a cross-sectional and a subsequent longitudinal pilot study. ISRN Pharmacol 2014;2014:762127. doi: 10.1155/2014/762127.

2.10. Cost of antipsychotic polypharmacy

Potentially appropriate uses of APP include using it in acute care settings where immediate response is required or while switching from one antipsychotic to another. A more controversial use is the long-term maintenance of a patient on more than one antipsychotic due to partial or non-response to monotherapy. In theory, all antipsychotics are able to control positive symptoms of psychosis by blocking D_2 dopamine receptors.[169] Atypical antipsychotics do this by completely blocking the D_2 receptors in the limbic area, which controls the psychosis, while incompletely blocking the D_2 receptors in the extrapyramidal area, which prevents the motor side effects.[170] The extrapyramidal receptors can be completely blocked by giving a typical antipsychotic in addition to the atypical or by increasing the dosage of the atypical antipsychotic. Since it is not possible to block more than 100% of the D_2 receptors that control psychosis, further addition of drugs might block the wrong D_2 receptors (those causing extrapyramidal side effects) giving the same clinical effect as a typical antipsychotic but costing almost 20 times as much as typical monotherapy.[171]

Loosbrock et al. examined the medication use patterns for the calendar year 1997 using the IMS Health LifeLink employer claims database which contains information from indemnity and Preferred Provider Organizations for almost 1.6 million employees, dependents, and retirees.[172] Patients with schizophrenia were identified using ICD-9 codes. Patients were classified into one of the following five categories: (1) no treatment—patients taking no

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169 Stahl SM. Essential Pharmacology, 2nd ed. New York, NY: Cambridge University Press; 2000.

170 Meltzer HY. Mechanism of action of atypical antipsychotics. In: Davis KL, Chamey D, Nemeroff CL, et al., eds. Neuropsychopharmacology: The Fifth Generation of Progress. Philadelphia, PA: Lippincott, Williams and Wilkins;2002.

171 Drug Utilization Review Board of California Medicaid Program. Department of Health Services, Medi-Cal Division. Sacremento, CA. 2001.

172 Loosbrock DL, Zhao Z, Johnstone BM, et al. Antipsychotic medication use patterns and associated costs of care for individuals with schizophrenia. J Ment Health Policy Econ 2003;6(2):67-75.

antipsychotics; (2) monotherapy—patients taking a single antipsychotic; (3) switch—patients who discontinued their prescribed antipsychotic and got a prescription for another one; (4) augment—continued with initially prescribed antipsychotic and had at least one additional antipsychotic medication; and (5) concomitant use—patients who were on concomitant use of more than one antipsychotic at the start of the observation period. The mean cost per patient was $11,042. Of the total cost, 63% was attributable to institutional costs which included inpatient, outpatient, and other institutional costs, and 23% was attributable to outpatient medication costs. Atypical antipsychotics represented eight percent of the total costs or a third of the outpatient medication costs. After controlling for all other factors, compared to monotherapy, all other groups were associated with higher total costs (total costs included medication costs and institutional costs). Mean total costs were $4,244 higher in the augmented group compared to the monotherapy group when all other factors were controlled for. Those in the concomitant use group had $7,109 higher mean total costs compared to the monotherapy group.

Zhu and colleagues used data from the US Schizophrenia Care Assessment Program (US-SCAP) a large, nonrandomized, naturalistic, three-year prospective, multi-site study conducted between July 1997 and September 2003.[173] Participants were enrolled from diverse healthcare systems in six states: California, Colorado, Connecticut, Florida, Maryland, and North Carolina. Patients with schizophrenia initiating on olanzapine, risperidone, and quetiapine were included in the study. The total cost differed by the medication and was highest for quetiapine, followed by risperidone and then olanzapine. The one-year post period cost for other antipsychotics was also higher in the group that initiated on quetiapine ($3,439) compared to risperidone ($1,936) and olanzapine ($1,530). Thus, the total cost for all antipsychotics was the highest for quetiapine

[173] Zhu B, Ascher-Svanum H, Faries DE, et al. Cost of antipsychotic polypharmacy in the treatment of schizophrenia. BMC Psychiatry 2008;8:19.

initiators, followed by ripseridone and olanzapine. The mean cost of a concomitant atypical (typical) antipsychotic was $7.44 ($1.26) per day for quetiapine initiators, $3.15 ($1.15) for risperidone initiators, and $2.02 ($1.79) for olanzapine initiators. Thus, the practice of APP adds substantial cost to the antipsychotic medication and may even double the cost of the medication.

Stahl et al. analyzed California Medicaid data between May 1, 1999 and August 31, 2000 to assess the antipsychotic usage patterns among patients initiating on risperidone, olanzapine, or quetiapine.[174] The patient population was divided into three categories: (1) patients who received only one second-generation antipsychotic (SGA) in the 16-month study period; (2) those who received more than one SGA for not more than 59 days out of any 75-day period concomitantly; and (3) those who received more than one of the three drugs simultaneously for at least 60 days out any 75-day period. The total number of patients receiving one of the three SGAs for 60 days out of any 75-day period during the study period was 116,114. The total expenditure for Medi-Cal beneficiaries receiving an SGA was $309,644,640. Those in the first group (N=91,969) accounted for $219,123,216 (70.8%), those in the second group (N=19,350) accounted for $54,380,659 (17.6%), and the third group (N=4,795) accounted for $36,134,508 (11.7%). The mean costs per patient for groups one, two, and three were $2,382, $2,810, and $7,536, respectively. Thus, the cost per patient on polypharmacy was more than 3 times that for a patient on monotherapy.

Valuck et al. conducted a retrospective cohort study of Medicaid-eligible antipsychotic users from five western state Medicaid programs—California, Nebraska, Oregon, Utah, and Wyoming—between 1998 and 2003.[175] Patients were classified as receiving polypharmacy or

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[174] Stahl SM, Grady MM. High-cost use of second-generation antipsychotics under California's Medicaid program. Psychiatr Serv 2006;57(1):127-9.

[175] Valuck RJ, Morrato EH, Dodd S, et al. How expensive is antipsychotic polypharmacy? Experience from five US state Medicaid programs. Curr Med Res Opin 2007;23(10):2567-76.

not based on the pattern of antipsychotic medication prescriptions in the year following the index antipsychotic drug claim. Polypharmacy was defined as more than one antipsychotic for at least 60 days during the 365-day period following the index antipsychotic drug claim. The monotherapy group included patients who did not have any APP during the one-year study period. The final cohort included 55,383 patients with APP. Over the five-year study period, the median drug expenditure increased and the non-drug expenditure decreased. Patients who initiated on typical antipsychotics had higher non-drug costs compared to drug costs while the trend was reversed for those initiating on atypical antipsychotics. The difference in adjusted drug costs between monotherapy and polypharmacy differed by state; polypharmacy cost $2,079 more in California, $1,991 more in Oregon and $1,716 more in Utah. When patients had APP and concomitant non-antipsychotic psychotropic therapy, the adjusted differences compared to monotherapy were $3,486, $7,058, $2,801 for California, Oregon, and Utah, respectively. The differences in the non-drug costs were much smaller for both comparisons. The sample size of the number of enrollees from Nebraska and Wyoming was too small to be included in this analysis. For those on polypharmacy, drug costs represented 70% to 80% of the costs while for those on monotherapy, drug costs represented about 58% of the costs. APP was associated with a 2-fold increase in the likelihood of being a high-cost patient (top 20% of the adjusted total healthcare costs). The likelihood of being in the high-cost group increased with an increase in the number of mental health comorbidities and better adherence. This was consistent for all states used in the analysis of high costs (California, Oregon, and Utah). For patients in California (which had the largest sample size), individuals were more likely to be in the high-cost group if they had diabetes, dyslipidemia, hypertension, APP alone or in combination with other psychotropic medications.

Trends in the use of antipsychotic medications between 1999 and 2004 in California Medicaid beneficiaries with schizophrenia were analyzed by Gilmer et al. [176] They divided the patients into four groups for each month that the patient was enrolled in Medi-Cal: first-generation antipsychotic (FGA) medication only, SGA medication only, a FGA and a SGA, and multiple SGA medications. There were 15,962 unique Medi-Cal beneficiaries with schizophrenia who had prescription fills for antipsychotics between 1999 and 2004. For the full sample, the annual antipsychotic medication cost per patient increased from $4,148 in 1999 to $5,231 in 2004, which was a 27% increase. The per patient cost of FGA monotherapy decreased from $117 in 1999 to $53 in 2004, that of SGA monotherapy increased from $2,982 to $3,269, the cost of the FGA and SGA combination group decreased only slightly from $670 in 1999 to $567 in 2004, but an increase of $983 was seen in the SGA polypharmacy group with the costs increasing from $359 to $1,342.

More recently, Bandup et al. conducted a study using data from adult schizophrenia patients in two psychiatric referral centers in Denmark on January 1, 2008 and January 1, 2009.[177] The study population consisted of 736 patients. The total healthcare costs for the polypharmacy group was higher than that for the monotherapy group. This difference was attributed to consumption of psychiatric services including inpatient and outpatient services. The polypharmacy patients had an excess of seven to nine inpatient days and six to nine outpatient contacts compared with the monotherapy group. The average cost for an individual in the polypharmacy group was 25% and 17% higher than monotherapy before and after adjusting for

[176] Gilmer TP, Dolder CR, Folsom DP, et al. Antipsychotic polypharmacy trends among Medicaid beneficiaries with schizophrenia in San Diego County, 1999-2004. Psychiatr Serv 2007;58(7):1007-10.

[177] Baandrup L, Sørensen J, Lublin H, et al. Association of antipsychotic polypharmacy with health service cost: a register-based cost analysis. Eur J Health Econ 2012;13(3):355-63.

the covariates, respectively. This corresponded to a cost difference of €5,357 in 2007 and €2,330 in 2008.

A program was developed in Florida to identify prescribers with unusual psychotherapeutic prescription patterns and track their utilization and costs in Florida Medicaid.[178] Patients prescribed two or three antipsychotics for 60 days or two antipsychotics for 90 days or more were categorized as having 'unusual' antipsychotic prescription patterns. It was seen that a disproportionately small number of prescribers were responsible for a large share of the unusual prescribing and the associated costs. The top 13 prescribers accounted for 13 percent of the total cost spent on antipsychotics by the Florida Medicaid program and 9.3 percent of the total cost for all drugs

Several studies have highlighted the high costs associated with APP. Continuing such high-cost prescribing without documented benefit might cause payors to restrict access to atypical antipsychotics due to the perception of squandering away precious resources. This would be a regrettable step in psychotherapeutics.[179] There is rising concern regarding the increasing costs of SGAs among state Medicaid program administrators and pharmaceutical insurance plan benefit managers. If polypharmacy prescribing patterns are left unchanged, it could lead to administrative efforts to cut costs and dictate prescribing practices. The rising costs of SGAs have also raised the threat that these useful resources might be restricted as Pharmacy and Therapeutics committees may make decisions to remove some of these agents from formularies based only on costs.[180] Restricting expensive practices like polypharmacy only to

[178] Becker ER, Constantine RJ, McPherson MA, Jones ME. Antipsychotic polypharmacy prescribing patterns and costs in the Florida adult and child Medicaid populations. J Health Care Finance 2013;40(1):40-67.
[179] Stahl SM. Antipsychotic polypharmacy: squandering precious resources? J Clin Psychiatry 2002;63(2):93-4.
[180] Gilmer TP, Dolder CR, Folsom DP, et al. Antipsychotic polypharmacy trends among Medicaid beneficiaries with schizophrenia in San Diego County, 1999-2004. Psychiatr Serv 2007;58(7):1007-10.

patients who fail all monotherapy treatments, including clozapine use, might be a means of eliminating formulary restrictions that could be imposed on high-cost antipsychotic medications.

2.11. Factors affecting costs of antipsychotics

A report by the Agency for Healthcare Research and Quality (AHRQ) on utilization and expenditure trends of antipsychotics calculated using the Medical Expenditure Panel Survey (MEPS), a nationally representative survey of community-dwelling US residents, showed that the expenditure on antipsychotics increased three-fold from $1.7 billion in 1997 to $7.4 billion in 2007.[181] The average annual expenditure on antipsychotics increased from $765 to $1,905 when comparing 1997 to 2007. The average expenditure per prescription for an antipsychotic increased from $96 to $228 when comparing 1997 to 2007.

The previous section described several studies that demonstrated that antipsychotic polypharmacy is an important predictor of high medical and pharmacy-related costs. In this section, other demographic and clinical factors which are associated with high costs are discussed. There is a vast literature on the predictors of high costs among users of antipsychotics; therefore, only studies that are relevant to the current study will be discussed.

Data from the Medicaid Managed Behavioral Health Care and Vulnerable Populations Project was used to estimate expenditures on antipsychotics using patients from Florida, Oregon, and Pennsylvania during 1997 and1998.[182] Patient interviews and administrative claims were used to estimate the expenditures. Medical and services costs in the six months after initial assessment for the typical, atypical, and combination antipsychotic groups were $3,463, $6,528, and $6,590, respectively. Multivariate analyses showed that even after controlling for demographic and clinical factors, the medication group was still a significant predictor of high

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181 Stagnitti, MN. Trends in Antipsychotics Purchases and Expenses for the US Civilian Noninstitutionalized Population, 1997 and 2007. Statistical Brief #275. January 2010. Agency for Healthcare Research and Quality, Rockville, MD. Available at: http://www.meps.ahrq.gov/mepsweb/data_files/publications/st275/stat275.pdf. Accessed April 3, 2014.

182 Rothbard A, Murrin MR, Jordan N, et al. Effects of antipsychotic medication on psychiatric service utilization and cost. J Ment Health Policy Econ 2005;8(2):83-93.

costs. African Americans had lower costs than Caucasians, and factors associated with higher costs included presence of a psychosis diagnosis, inpatient or outpatient use prior to interview, and medication class (particularly use of atypical antipsychotics and use of combination of typical and atypical antipsychotics).

A study conducted by Rascati et al. using Texas Medicaid data from January 1997 to August 1998 compared the costs of schizophrenia patients initiated on risperidone or olanzapine.[183] The annual mean per patient schizophrenia-related unadjusted cost was $4,892 and the total unadjusted healthcare cost was $7,101. Multivariate analyses were conducted using a two-stage instrumental variables model. Use of an atypical antipsychotic medication, number of antipsychotic medications used, prior hospitalizations, presence of co-morbidities, age, sex, region of residence, previous costs, and the number of treatment days were all significantly associated with the total schizophrenia-related expenditure. The number of antipsychotic medications used, prior hospitalizations, and number of treatment days were associated with higher costs, while the presence of nonorganic mental illnesses was associated with lower total costs. Age was found to be negatively associated with costs, and females had lower expenditures compared to males. Patients in either group who discontinued therapy had lower schizophrenia-related total costs. There was no significant difference in the total schizophrenia-related costs between patients initiated on olanzapine and risperidone. However, olanzapine users had significantly lower medical costs compared to risperidone users.

Gilmer et al. conducted a study to evaluate the effect of adherence on costs using Medicaid-eligible patients with schizophrenia from San Diego County.[184] Patients were

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183 Rascati KL, Johnsrud MT, Crismon ML, et al. Olanzapine versus risperidone in the treatment of schizophrenia. PharmacoEconomics 2003;21(10):683-97.

184 Gilmer TP, Dolder CR, Lacro JP, et al. Adherence to treatment with antipsychotic medication and health care costs among Medicaid beneficiaries with schizophrenia. Am J Psychiatry 2004;161(4):692-9.

classified into four categories depending on their cumulative MPR: non-adherent (0.00–0.49), partially adherent (0.50–0.79), adherent (0.80–1.10), and excess medication fillers (>1.10). Patients who were adherent had significantly lower pharmacy and medical costs as compared to those who were partially adherent, non-adherent, and excess fillers. Thus, adherence is an important predictor of high costs among schizophrenia patients and improving adherence has the potential to improve health of such patients without a very large increase in cost.

Marcus et al. found that gaps in the use of antipsychotic medication were associated with the cost of schizophrenia.[185] The investigators used California Medicaid data and made adjustments to provide a national estimate of $106 million higher total inpatient costs due to gaps in antipsychotic medication adherence. Svarstad et al. used claims data for severely mentally ill patients in Wisconsin and reached a similar conclusion that irregular medication use increases hospitalizations, which in turn, translates to high costs for schizophrenia.[186]

It is important to identify factors associated with high costs as this might help policy makers design interventions to target the high-risk population and curb the rising costs. Research has shown that demographic characteristics such as age, gender, race/ethnicity, and region of residence and clinical factors such as co-morbid diseases, prior inpatient and outpatient visits, and poor adherence are associated with high costs.

185 Marcus SC, Olfson M. Outpatient antipsychotic treatment and inpatient costs of schizophrenia. Schizophr Bull 2008;34(1):173-80.

186 Svarstad BL, Shireman TI, Sweeney JK. Using drug claim data to assess the relationship of medication adherence with hospitalization and costs. Psychiatr Serv 2001;52(6):805-11.

2.12. Interventions to reduce antipsychotic polypharmacy

Several interventions are being carried out to limit APP. Some of them have been successful, but studies have shown that availability and dissemination of treatment algorithms alone is not very effective in changing prescriber behavior.[187,188,189,190]

A study was carried out in the Institute of Mental Health (the only state mental health institute) in Singapore which compared the extent of APP and second-generation antipsychotic doses (among other things) in patients admitted into an early psychosis intervention program (EPIP) to their matched controls between 2001 and 2004.[191] The EPIP program emphasized use of a single antipsychotic and short-term use of benzodiazepines for disturbed behavior early during treatment rather than increasing antipsychotic dosage. There were regular audits to check compliance with guidelines. The EPIP group had lower levels of APP and more use of second-generation antipsychotics at baseline (prescribed > one antipsychotic- EPIP: 4.6%, control group: 22.7%) and at the third month (prescribed > one antipsychotic- EPIP: 5.6%, control group: 23.1%).

A performance improvement initiative carried out in a state psychiatric hospital between November 2001 and August 2002 reduced the rates of APP by 10%.[192] Baseline prescribing patterns from May 2001 were summarized for each psychiatrist. In the coming months, case

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187 Chen RS, Nadkarni PM, Levin FL, et al. Using a computer database to monitor compliance with pharmacotherapeutic guidelines for schizophrenia. Psychiatr Serv 2000;51(6):791-4.

188 Leslie DL, Rosenheck RA. Adherence of schizophrenia pharmacotherapy to published treatment recommendations: patient, facility, and provider predictors. Schizophr Bull 2004;30(3):649-58.

189 Paton C, Barnes TR, Cavanagh MR, et al. High-dose and combination antipsychotic prescribing in acute adult wards in the UK: the challenges posed by p.r.n. prescribing. Br J Psychiatry 2008;192(6):435-9.

190 Sernyak MJ, Dausey D, Desai R, et al. Prescribers' nonadherence to treatment guidelines for schizophrenia when prescribing neuroleptics. Psychiatr Serv 2003;54(2):246-8.

191 Chong SA, Ravichandran N, Poon LY, et al. Reducing polypharmacy through the introduction of a treatment algorithm: use of a treatment algorithm on the impact on polypharmacy. Ann Acad Med Singapore 2006;35(7):457-60.

192 Patrick V, Schleifer SJ, Nurenberg JR, et al. Best practices: An initiative to curtail the use of antipsychotic polypharmacy in a state psychiatric hospital. Psychiatr Serv 2006;57(1):21-3.

discussions, talks and seminars on psychopharmacology were carried out but a review of the psychiatrists' prescribing patterns in November 2001 showed no change with respect to APP. Therefore, the chief psychiatrist met individually with each psychiatrist to compare their performance with anonymous peers and also asked them to reduce APP by 10% over the following six months. The rate of APP fell from 42% in November 2001 to 31% at follow-up in August 2002.

Hazra et al. carried out a study at the Center for Addiction and Mental Health in Canada in 2006 and 2008.[193] The antipsychotic prescription claims for all patients were collected and when the pharmacist detected instances of APP, he/she contacted the physician using a scripted telephone call and advised them about an ongoing prospective study aimed at examining the safety of reduction of APP. The research team also met with clinicians and inpatient and ambulatory staff of the schizophrenia program during weekly team meetings and gave them information on the risks, benefits, and existing evidence on APP. Concomitant use of two antipsychotics decreased from 10.3% in 2006 to 6.6% in 2008 and simultaneous use of three antipsychotics decreased from 5.3% to 0%.

Goren et al. conducted a study in a regional academic health center to determine the rate of antipsychotic polytherapy at the time of patient discharge.[194] The study was conducted during three periods: a three-month baseline period (August 2006 to October 2006); in July 2007, after delivery of 4 educational seminars to psychiatrists from November 2006 to June 2007; and in June 2008, following the provision of monthly prescriber-specific audit feedback from August 2007 to June 2008. Lectures on best-practice were also given to the nurses to prepare them for

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193 Hazra M, Uchida H, Sproule B, et al. Impact of feedback from pharmacists in reducing antipsychotic polypharmacy in schizophrenia. Psychiatry Clin Neurosci 2011;65(7):676-8.

194 Gören JL, Beck SE, Mills BJ, et al. Development and delivery of a quality improvement program to reduce antipsychotic polytherapy. J Manag Care Pharm 2010;16(6):393-401.

the change. The proportion of patients prescribed two antipsychotics decreased from 33.9% at baseline to 21.8% after the educational seminars and 12.2% after the audit. The changes in the proportion prescribed three antipsychotics during the same intervals were 5.9% to 2.5% to 0%.

A three-phase intervention was carried out in the New York Office of Mental Health (NYOMH) network of psychiatric hospitals.[195] Phase one consisted of implementation of The Psychiatric Services and Clinical Knowledge Enhancement System (PSYCKES), a web-based support system to help in decision making and quality improvement, and a prior approval process to prescribe a patient more than two antipsychotics. In phase two, the hospital leaders received information from the office of the medical director identifying patients on APP. In phase 3, PSYCKES continued but prior-approval was discontinued. In phase one, APP fell from 16.9 to 9.7 inpatients per 1,000; in phase two, it decreased to 3.9 inpatients per 1,000. In phase three, the prevalence remained low at 3.1 inpatients per 1,000. On 36-month long-term follow-up, the rate of polypharmacy increased to 9.2 inpatients per 1,000, but remained below those at baseline level (16.9 per 1,000).

The Developing Evidence-Based Implementation Trial (DEBIT) was carried out in psychiatric wards in southwest England in 19 adult psychiatry units.[196] The intervention consisted of the following: an educational visit to the psychiatrists by a trained clinical pharmacist, and educational workbook and reminders on the medical charts of patients with APP. At the five-month follow-up, APP decreased modestly from 47.8% to 40.4%. After controlling for all other confounders, the odds of receiving APP were lower in the intervention group compared to the control group (Odds ratio: 0.43, 95% CI=0.21-0.90, p=0.028).

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195 Finnerty MT, Kealey E, Leckman-Westin E, et al. Long-term impact of web-based tools, leadership feedback, and policies on inpatient antipsychotic polypharmacy. Psychiatr Serv 2011;62(10):1124-6.

196 Thompson A, Sullivan SA, Barley M, et al. The DEBIT trial: an intervention to reduce antipsychotic polypharmacy prescribing in adult psychiatry wards - a cluster randomized controlled trial. Psychol Med 2008;38(5):705-15.

A controlled quasi-experimental study was performed in two municipalities in Denmark which were balanced at baseline with respect to the prevalence of APP, socioeconomic status of patients, and functional level of patients.[197] The intervention was directed towards the psychiatric healthcare providers and consisted of the following: one day of educational lectures, six three-hour long educational outreach visits, and electronic reminders while prescribing APP. The APP at baseline in the intervention and control groups was 68.5% (N=159) and 68.7% (N=241), respectively and that at one-year follow-up for the intervention and control groups was 71.8% (N=155) and 60.6% (N=234), respectively. The difference between the two groups at one-year follow-up was not statistically significant. Thus, the educational intervention failed to curb concurrent co-prescribing of antipsychotics.

Another study conducted by Paton et al. to evaluate the impact of "as needed" dosing in psychiatric wards in UK found that a quality improvement program consisting of an audit of prescribing patterns, delivery of a quality improvement intervention, and re-audit after a year found only a small change in the prescribing patterns. The prevalence of high-dose antipsychotics at baseline and re-audit was 36% and 34%, respectively and that of APP was 43% and 39%, respectively.[198]

Thus, several studies have shown that active monitoring of psychiatrists such as notifications by phone calls and letters can decrease APP.[199,200] Passive educational information

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197 Baandrup L, Allerup P, Lublin H, et al. Evaluation of a multifaceted intervention to limit excessive antipsychotic co-prescribing in schizophrenia out-patients. Acta Psychiatr Scand 2010;122(5):367-74.

198 Paton C, Barnes TR, Cavanagh MR, et al. High-dose and combination antipsychotic prescribing in acute adult wards in the UK: the challenges posed by p.r.n. prescribing. Br J Psychiatry 2008;192(6):435-9.

199 Fleischhacker WW, Uchida H. Critical review of antipsychotic polypharmacy in the treatment of schizophrenia. Int J Neuropsychopharmacol 2012;2:1-11.

200 Tani H, Uchida H, Suzuki T, et al. Interventions to reduce antipsychotic polypharmacy: a systematic review. Schizophr Res 2013;143(1):215-20.

account for small decreases in concomitant co-prescribing of antipsychotics, and existence and dissemination of guidelines have not been very successful in affecting rates of APP.

2.13. Need for studies on antipsychotic polypharmacy in Texas

Several studies have been conducted to evaluate the prevalence of APP in different settings. These have been discussed in a previous section. Antipsychotic users generally suffer from psychoses. Given the chronic and debilitating nature of such mental illnesses, these patients are often classified as low-income or disabled and hence may be eligible for Medicaid. Only a few studies have been conducted using Medicaid data at a state level; they include California, Georgia,[201] Utah, Wyoming, Nebraska, Oregon,[202] and Florida.[203,204] We did not find any study that retrospectively evaluated the extent of APP using Texas Medicaid data.

It is especially important to carry out such research for the state of Texas as it has a higher than average prevalence of patients with mental illnesses. For example, according to the state advocacy report of the National Alliance on Mental Illnesses, of the approximately 24.3 million residents of Texas, 1,121,000 (4.6%) live with serious mental illness (3.43% adults and 1.19% children).[205]

A recent study by Welsh et al. conducted in the Houston Outreach Medicine, Education, and Social Services (HOMES) Clinic, a free clinic managed by students from The University of Texas Medical School at Houston, Baylor College of Medicine, The University of Texas School of Public Health at Houston, and the University of Houston School of Pharmacy, found that of the 286 patients visiting the clinic, 8.7% had a diagnosis of schizophrenia and 15.7% had a

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201 Ganguly R, Kotzan JA, Miller LS, et al. Prevalence, trends, and factors associated with antipsychotic polypharmacy among Medicaid-eligible schizophrenia patients, 1998-2000. J Clin Psychiatry 2004;65(10):1377-88.

202 Morrato EH, Dodd S, Oderda G, et al. Prevalence, utilization patterns, and predictors of antipsychotic polypharmacy: experience in a multistate Medicaid population, 1998-2003. Clin Ther 2007;29(1):183-95.

203 Constantine RJ, Andel R, Tandon R. Trends in adult antipsychotic polypharmacy: progress and challenges in Florida's Medicaid program. Community Ment Health J 2010;46(6):523-30.

204 Constantine RJ, Boaz T, Tandon R. Antipsychotic polypharmacy in the treatment of children and adolescents in the fee-for-service component of a large state Medicaid program. Clin Ther 2010;32(5):949-59.

205 National Alliance on Mental Illness, 2010 State Advocacy Report.

diagnosis of bipolar disorder.[206] These numbers are much higher than the national averages for the prevalence of the diseases.

The use of antipsychotic medications in the Texas Medicaid program has increased tremendously in the past decade from 52,292 (2.5% of all beneficiaries) in 2001 to 128,437 (3.8% of all beneficiaries) in 2008.[207] Over the same time period, Texas Medicaid spending on antipsychotic medications increased from $55.8 million to $246.7 million. From 2001 to 2008, antipsychotics have consistently topped the list of the top 10 drug classes for pharmacy benefit use for non-dual-eligible Texas Medicaid beneficiaries in terms of total Medicaid prescription-drug spending.

Table 5 provides the total Texas Medicaid prescription expenditures on antipsychotics, number of prescriptions for antipsychotics, and proportion of all the non-dual-eligible beneficiaries who had prescriptions for antipsychotics.

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206 Welsh KJ, Patel CB, Fernando RC, et al. Prevalence of bipolar disorder and schizophrenia in Houston Outreach Medicine, Education, and Social Services (HOMES) clinic patients: implications for student-managed clinics for underserved populations. Academic Medicine: Journal of the Association of American Medical Colleges 2012;87(5):656-61.

207 Medicaid Analytic eXtract (MAX) Rx Table Listing. Available at: http://www.cms.gov/Research-Statistics-Data-and-Systems/Computer-Data-and-Systems/MedicaidDataSourcesGenInfo/Medicaid-Analytic-eXtract-MAX-Rx-Table-Listing.html. Accessed March 15, 2013.

Table 5: Medicaid spending, number of users, and percentage of users for antipsychotic medications among Texas Medicaid non-dual-eligible beneficiaries from 2001 to 2008

Year	Total Texas Medicaid Antipsychotic Prescription spending (USD) for non-dual eligible beneficiaries	Number of users	As a percentage of all beneficiaries
2001	55,788,714	52,292	2.5
2002	72,942,401	62,888	2.6
2003	116,173,901	92,128	3.1
2004	139,876,506	104,533	3.3
2005	159,260,426	109,467	3.4
2006	181,836,804	115,735	3.5
2007	213,333,877	123,402	3.7
2008	246,690,092	128,437	3.8

Source: Medicaid Analytic eXtract (MAX) Rx Table Listing. Available at: http://www.cms.gov/Research-Statistics-Data-and-Systems/Computer-Data-and-Systems/MedicaidDataSourcesGenInfo/Medicaid-Analytic-eXtract-MAX-Rx-Table-Listing.html. Accessed March 15, 2013

The high prevalence of mental health conditions in Texas coupled with the extremely high spending on antipsychotics by the state Medicaid program supports the conduct of a study evaluating the prevalence and outcomes of APP in this state. This is especially important in the light of the very limited evidence that supports co-prescription of multiple antipsychotic medications.

2.14. Rationale for the study

The practice of APP is widespread with prevalence estimates ranging between 4% and 65% depending on the definition of APP used in the study, the settings, and the year of the study. Some studies have shown that APP is associated with high costs but there is a paucity of literature on healthcare resource utilization and adherence to medication in patients prescribed APP. The widespread use of APP occurs despite the very limited evidence supporting the use of this practice. In fact, simultaneous use of multiple antipsychotics could lead to drug interactions, undesirable side effects, loss of the advantage of using an atypical antipsychotic when it is used in combination with a typical antipsychotic, and high costs.

Texas has a higher than average prevalence of mental illnesses such as schizophrenia and bipolar disorder. Yet, the literature search did not reveal any study examining the prevalence and outcomes associated with APP in Texas. It is important to carry out such studies as the state Medicaid program spends a significant amount of money each year on antipsychotics. In fact, from 2001 to 2008, antipsychotics have topped the list of drug classes in terms of Texas Medicaid prescription drug spending.

2.14.1. RATIONALE FOR OBJECTIVES 1-3

Studies have estimated the prevalence and trends of APP using Medicaid data from California, Georgia,[208] Utah, Wyoming, Nebraska, Oregon,[209] and Florida.[210,211] However, despite the high prevalence of mental illnesses in Texas and the significant amount of money spent each year by Texas Medicaid on antipsychotics, there is no study examining the prevalence of APP in the Texas Medicaid program.

Objectives 1 and 2 are to:

1. Estimate the incidence of APP and classify patients into the monotherapy (MT) and APP groups;

   Patients on monotherapy will be classified into one of the following subgroups:

   i. typical,

   ii. atypical, and

   iii. clozapine.

   Patients on APP will be classified into one of the following subgroups:

   i. typical + typical,

   ii. atypical + atypical,

   iii. typical + atypical,

   iv. clozapine + typical, and

   v. clozapine + atypical.

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[208] Ganguly R, Kotzan JA, Miller LS, et al. Prevalence, trends, and factors associated with antipsychotic polypharmacy among Medicaid-eligible schizophrenia patients, 1998-2000. J Clin Psychiatry 2004;65(10):1377-88.

[209] Morrato EH, Dodd S, Oderda G, et al. Prevalence, utilization patterns, and predictors of antipsychotic polypharmacy: experience in a multistate Medicaid population, 1998-2003. Clin Ther 2007;29(1):183-95.

[210] Constantine RJ, Andel R, Tandon R. Trends in adult antipsychotic polypharmacy: progress and challenges in Florida's Medicaid program. Community Ment Health J 2010;46(6):523-30.

[211] Constantine RJ, Boaz T, Tandon R. Antipsychotic polypharmacy in the treatment of children and adolescents in the fee-for-service component of a large state Medicaid program. Clin Ther 2010;32(5):949-59.

2. Describe and compare the demographic, clinical, physician, and prior utilization characteristics of patients between the MT and APP groups.

2.14.2. RATIONALE FOR OBJECTIVE 3

Several studies have shown that demographic characteristics, presence of schizophrenia diagnoses, number of mental health-related comorbidities, use of typical antipsychotics, use of anticholinergic drugs, and prior psychiatric-related healthcare services utilization are associated with APP.[212,213,214] Ganguly et al. also found non-mental health-related drug use, non-mental health comorbidities, and year of initiation of drug therapy to be associated with APP.[215] Patel et al. reported that physician specialty affected prescription of antipsychotics among youths in the Texas Medicaid program.[216] They found that prescriptions written by psychiatrists accounted for 80% of the antipsychotic prescriptions; the proportion of youths receiving such prescriptions from primary care physicians remained constant between 1996 and 2001.

Objective 3 is to:

3. To determine demographic, clinical, physician, and prior-utilization characteristics associated with increased likelihood of APP.

   The hypotheses related to objective 3 are:

   $H_{3.1}$: **Younger patients** are more likely to be on APP compared to **older patients** after controlling for other demographic, clinical, physician, and prior utilization characteristics.

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212 Morrato EH, Dodd S, Oderda G, et al. Prevalence, utilization patterns, and predictors of antipsychotic polypharmacy: experience in a multistate Medicaid population, 1998-2003. Clin Ther 2007;29(1):183-95.

213 Kreyenbuhl JA, Valenstein M, McCarthy JF, et al. Long-term antipsychotic polypharmacy in the VA health system: patient characteristics and treatment patterns. Psychiatr Serv 2007;58(4):489-95.

214 Ye W, Ascher-Svanum H, Flynn JA, et al. Predictors of antipsychotic monotherapy with olanzapine during a 1-year naturalistic study of schizophrenia patients in Japan. Clinicoecon Outcomes Res 2012;4:13-9.

215 Ganguly R, Kotzan JA, Miller LS, et al. Prevalence, trends, and factors associated with antipsychotic polypharmacy among Medicaid-eligible schizophrenia patients, 1998-2000. J Clin Psychiatry 2004;65(10):1377-88.

216 Patel NC, Crismon ML, Hoagwood K, et al. Physician specialty associated with antipsychotic prescribing for youths in the Texas Medicaid program. Med Care 2006;44(1):87-90.

$H_{3.2}$: **Male** patients are more likely to be on APP compared to **female** patients after controlling for other demographic, clinical, physician, and prior utilization characteristics.

$H_{3.3}$: **Caucasian** patients are more likely to be on APP compared to the **other ethnicities** after controlling for other demographic, clinical, physician, and prior utilization characteristics.

$H_{3.4}$: Patients with an index antipsychotic claim in **2010** are more likely to be on APP compared to those with an index claim in **other years** after controlling for other demographic, clinical, physician, and prior utilization characteristics.

$H_{3.5}$: Patients with a **schizophrenia/schizoaffective disorder** diagnosis are more likely to be on APP compared to those with **other mental health diagnoses** after controlling for other demographic, clinical, physician, and prior utilization characteristics.

$H_{3.6}$: Patients **without a substance abuse diagnosis** are more likely to be on APP compared to those **with such a diagnosis** after controlling for other demographic, clinical, physician, and prior utilization characteristics.

$H_{3.7}$: The **likelihood of APP increases** with **each additional comorbidity** experienced by patients after controlling for other demographic, clinical, physician, and prior utilization characteristics.

$H_{3.8}$: Patients with a **lower pre-index period CCI score** are more likely to be on APP compared to those with **a higher score** after controlling for other demographic, clinical, physician, and prior utilization characteristics.

$H_{3.9}$: Patients with a **lower pre-index period CDS score** are more likely to be on APP compared to those with a **higher score** after controlling for other demographic, clinical, physician, and prior utilization characteristics.

$H_{3.10}$: Patients initiated on **typical antipsychotics** are more likely to be on APP compared to those initiated on **atypical antipsychotics** after controlling for other demographic, clinical, physician, and prior utilization characteristics.

$H_{3.11}$: Patients initiated on **oral antipsychotics** are more likely to be on APP compared to those initiated on **intramuscular antipsychotics** after controlling for other demographic, clinical, physician, and prior utilization characteristics.

$H_{3.12}$: Patients **with non-antipsychotic psychotropic drug** use in addition to antipsychotic use are more likely to be on APP compared to those **without it** after controlling for other demographic, clinical, physician, and prior utilization characteristics.

$H_{3.13}$: Patients **with anticholinergic drug** use in addition to antipsychotic use are more likely to be on APP compared to those **without it** after controlling for other demographic, clinical, physician, and prior utilization characteristics.

$H_{3.14}$: **Physician specialty is not associated** with the likelihood of being on APP after controlling for other demographic, clinical, physician, and prior utilization characteristics.

$H_{3.15}$: Patients with **multiple physicians prescribing antipsychotics** are more likely to be on APP compared to those with a **single physician prescribing antipsychotics** after controlling for other demographic, clinical, physician, and prior utilization characteristics.

$H_{3.16}$: Patients whose prescribers are from **rural areas** are more likely to be prescribed APP compared to those whose physicians are from **urban areas** after controlling for other demographic, clinical, physician, and prior utilization characteristics.

$H_{3.17}$: Patients with **a greater number of prior mental health-related hospitalizations** are more likely to be on APP compared to those with **fewer prior mental health-related hospitalizations** after controlling for other demographic, clinical, physician, and prior utilization characteristics.

$H_{3.18}$: Patients with a **greater number of prior mental health-related outpatient/emergency department visits** are more likely to be on APP compared to those with **fewer prior mental health-related outpatient/emergency department visits** after controlling for other demographic, clinical, physician, and prior utilization characteristics.

2.14.3. RATIONALE FOR OBJECTIVE 4

In general, non-adherence rates for psychotropic medications are quite high. Non-adherence rates of 40% to 60% have been reported for antipsychotics, 18% to 56% for mood stabilizers, and 30% to 97% (median 63%) for antidepressants.[217,218,219] There is limited literature that compares adherence rates in the APP and MT populations. A few studies have shown that patients on APP had higher adherence compared to those on MT.[220,221]

Objective 4 is to:

4. Compare adherence (measured as proportion of days covered [PDC]) and persistence between the MT and APP groups after controlling for age, sex, race/ethnicity, year of initiation of index antipsychotic, mental health diagnosis, substance abuse diagnosis, number of mental health comorbidities, pre-index CCI, pre-index CDS, index antipsychotic drug, mode of administration of index antipsychotic, use of psychotropic therapy, use of anticholinergic medications, clinical specialty of prescribing physician, number of physicians prescribing antipsychotics, urban/rural status for prescribing physician, number of mental health-related inpatient hospitalizations in the pre-index period, and number of mental health-related outpatient and emergency department visits in the pre-index period.

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217 Scott J, Pope M. Nonadherence with mood stabilizers: prevalence and predictors. J Clin Psychiatry 2002; 63(5): 384–90.

218 Zygmunt A, Olfson M, Boyer CA, Mechanic D. Interventions to improve medication adherence in schizophrenia. Am J Psychiatry 2002; 159(10):1653–64.

219 Pampallona S, Bollini P, Tibaldi G, Kupelnick B, Munnizza C. Patient adherence in the treatment of depression. Br J Psychiatry 2002; 180:104–9.

220 Essock SM, Schooler NR, Stroup TS, et al. Effectiveness of switching from antipsychotic polypharmacy to monotherapy. Am J Psychiatry 2011;168(7):702-8.

221 Morrato EH, Dodd S, Oderda G, et al. Prevalence, utilization patterns, and predictors of antipsychotic polypharmacy: experience in a multistate Medicaid population, 1998-2003. Clin Ther 2007;29(1):183-95.

The hypothesis related to objective 9 is:

$H_{4.1}$: **The adjusted adherence (PDC)** is **lower** for the **APP group** compared to the **MT group** after controlling for covariates.

$H_{4.2}$: **The odds of being adherent** are **lower** for the **APP group** compared to the **MT group** after controlling for covariates.

$H_{4.3}$: The **adjusted persistence** is **lower** for the **APP group** compared to the **MT group** after controlling for covariates.

2.14.4. RATIONALE FOR OBJECTIVES 5-7

There is very limited literature[222] that compares the health resource utilization between patients on MT and APP; however, since costs vary between these two groups, we expect their healthcare utilization to vary as well.

Objectives 5 through 7 are to:

5. Compare the likelihood of a post-index all-cause inpatient hospitalization between the MT and APP groups after controlling for age, sex, race/ethnicity, year of initiation of index antipsychotic, mental health diagnosis, substance abuse diagnosis, number of mental health comorbidities, pre-index CCI, pre-index CDS, index antipsychotic drug, mode of administration of index antipsychotic, use of psychotropic therapy, use of anticholinergic medications, clinical specialty of prescribing physician, number of physicians prescribing antipsychotics, urban/rural status for prescribing physician, number of mental health-related inpatient hospitalizations in the pre-index period, and number of mental health-related outpatient and emergency department visits in the pre-index period.

   The hypothesis related to objective 5 is:

   $H_{5.1}$: The **likelihood of an all-cause inpatient hospitalization** in the post-index period is **higher** for the **APP group** compared to the **MT group** after controlling for covariates.

222 Gilmer TP, Dolder CR, Folsom DP, et al. Antipsychotic polypharmacy trends among Medicaid beneficiaries with schizophrenia in San Diego County, 1999-2004. Psychiatr Serv 2007;58(7):1007-10.

6. Compare the all-cause length of stay in an inpatient facility during the post-index period between the MT and APP groups after controlling for age, sex, race/ethnicity, year of initiation of index antipsychotic, mental health diagnosis, substance abuse diagnosis, number of mental health comorbidities, pre-index CCI, pre-index CDS index antipsychotic drug, mode of administration of index antipsychotic, use of psychotropic therapy, use of anticholinergic medications, clinical specialty of prescribing physician, number of physicians prescribing antipsychotics, urban/rural status for prescribing physician, number of mental health-related inpatient hospitalizations in the pre-index period, and number of mental health-related outpatient and emergency department visits in the pre-index period.

The hypothesis related to objective 6 is:

$H_{6.1}$: The **adjusted all-cause length of stay in an inpatient facility** during the post-index period is **higher** for the **APP group** compared to the **MT group** after controlling for covariates.

7. Compare the number of all-cause post-index outpatient visits between the MT and APP groups after controlling for age, sex, race/ethnicity, year of initiation of index antipsychotic, mental health diagnosis, substance abuse diagnosis, number of mental health comorbidities, pre-index CCI, pre-index CDS, index antipsychotic drug, mode of administration of index antipsychotic, use of psychotropic therapy, use of anticholinergic medications, clinical specialty of prescribing physician, number of physicians prescribing antipsychotics, urban/rural status for prescribing physician, number of mental health-related inpatient hospitalizations in the pre-index period, and number of mental health-related outpatient and emergency department visits in the pre-index period.

The hypothesis related to objective 7 is:

$H_{7.1}$: The **adjusted number of all-cause outpatient/emergency department visits** is **higher** for the **APP group** compared to the **MT group** after controlling for covariates.

2.14.5. RATIONALE FOR OBJECTIVE 8

Loosbrock et al.[223] noted that patients with APP spent an average of $7,109 more than those in the MT group while Stahl et al.[224] noted a 3-fold increase in costs for patients concomitantly using multiple antipsychotics. APP is associated with a 2-fold increase in the likelihood of being in the high-cost group (i.e., patients in the top 20% of total healthcare costs).[225] Gilmer et al. noted a per-patient increase of close to $1,000 in patients switching from MT to APP during the five-year study period.[226] Thus, several studies have reported high costs in patients being prescribed APP.

Objective 8 was to:

8. Compare all-cause pharmacy, medical and total healthcare costs between the MT and APP groups after controlling for age, sex, race/ethnicity, year of initiation of index antipsychotic, mental health diagnosis, substance abuse diagnosis, number of mental health comorbidities, pre-index CCI, pre-index CDS, index antipsychotic drug, mode of administration of index antipsychotic, use of psychotropic therapy, use of anticholinergic medications, clinical specialty of prescribing physician, number of physicians prescribing antipsychotics, urban/rural status for prescribing physician, number of mental health-related inpatient hospitalizations in the pre-index period, and number of mental health-related outpatient and emergency department visits in the pre-index period.

   The hypotheses related to objective 8 are:

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223 Loosbrock DL, Zhao Z, Johnstone BM, et al. Antipsychotic medication use patterns and associated costs of care for individuals with schizophrenia. J Ment Health Policy Econ 2003;6(2):67-75.

224 Stahl SM, Grady MM. High-cost use of second-generation antipsychotics under California's Medicaid program. Psychiatr Serv 2006;57(1):127-9.

225 Valuck RJ, Morrato EH, Dodd S, et al. How expensive is antipsychotic polypharmacy? Experience from five US state Medicaid programs. Curr Med Res Opin 2007;23(10):2567-76.

226 Gilmer TP, Dolder CR, Folsom DP, et al. Antipsychotic polypharmacy trends among Medicaid beneficiaries with schizophrenia in San Diego County, 1999-2004. Psychiatr Serv 2007;58(7):1007-10.

$H_{8.1}$: The **adjusted all-cause medical costs** are **higher** for the **APP group** compared to the **MT group** after controlling for the covariates.

$H_{8.2}$: The **adjusted all-cause drug costs** are **higher** for the **APP group** compared to the **MT group** after controlling for the covariates.

$H_{8.3}$: The **adjusted all-cause total costs** are **higher** for the **APP group** compared to the **MT group** after controlling for the covariates.

3. Methods

3.1. Chapter outline

Prescription and medical claims data from Texas Medicaid were utilized to meet the objectives and test the hypotheses presented in the previous chapter. This chapter describes the data source, study population, sample selection, study design, study variables, and statistical procedures used to meet the study objectives. The sensitivity analyses that were conducted to account for uncertainty in the estimates are described. A priori sample size calculations are also described.

3.2. Institutional Review Board (IRB) approval

The study was approved by the Institutional Review Board (IRB) of The University of Texas at Austin (IRB protocol number: 2012-11-0021). A waiver of informed consent was obtained because the research contains no more than minimal risk to the subjects, the waiver does not affect the rights and welfare of the subjects, and the research cannot reasonably be conducted without the waiver. In accordance with the IRB requirements, only de-identified data were provided to the researchers to ensure confidentiality of patient information.

3.3. Data source

The study was a retrospective database analysis using Texas Medicaid prescription and medical claims data. Medicaid was established in Texas in 1967 and is administered by the Texas Health and Human Services Commission (HHSC). It is jointly funded by the state and federal governments.[227] In December 2011, 3.7 million (out of 25.9 million) Texans relied on Medicaid for health insurance or long-term services. It provides medical coverage for low-income families, non-disabled children, individuals with disabilities, elderly people, pregnant women, and caretakers of dependent children. Medicaid is an entitlement program—the government cannot limit the number of people enrolled in it and Medicaid must pay for services covered under the program. In 2011, women and children accounted for a large proportion of the Medicaid population. About 55% of the beneficiaries were female and 77% were under 21 years of age. Although white non-disabled children comprise almost 66% of the Texas Medicaid population, they only account for 33% of the spending on direct healthcare services. Elderly, blind, or disabled people represent 25% of the Texas Medicaid population but are responsible for 58% of the spending. The subjects for this study consisted of patients with claims for antipsychotic medications.

227 Texas Medicaid in Perspective. In: Texas Medicaid and CHIP in Perspective, 9th ed. Texas Health and Human Services Commission, 2012. Available at: http://www.hhsc.state.tx.us/medicaid/reports/PB9/1_PB_9th_ed_Introduction.pdf. Accessed on February 14, 2013.

3.4. Study population and sample selection

3.4.1. Data collection

Texas Medicaid data from January 1, 2006 to December 31, 2011 were extracted for the study. Subjects were identified based on having a claim for an oral or injectable antipsychotic between July 1, 2006 and December 31, 2010. The index date is the date of first antipsychotic prescription claim. *Table 6* provides a list of the antipsychotic medications that were included in this study. Subjects in the APP group have an additional index date—the date of initiation of APP. This index date also fell between July 1, 2006 and December 31, 2010. For objectives 1 to 4, patient medical and prescription claims were analyzed over an 18-month study period: six months pre-index and 12 months post-index. For objectives 5 to 8, medical and prescription claims were analyzed over a minimum 18-month period: six months pre-index and at least 12 months post-index (more explanation regarding the timeline for each group is provided in section 3.4.4).

Figure 1 provides an illustration of the data extraction and subject identification periods for Objectives 1 to 4 and Objectives 5 to 8.

Table 6: Antipsychotic medications included in the study[228,229,230]

Medication class Medication	Usual dosage range (mg/day)	Maximum dose (mg/day)
Typical antipsychotics		
Chlorpromazine	100-800	2,000
Fluphenazine	2-20	40
Haloperidol	2-20	100
Loxapine	10-80	250
Molindone	10-100	225
Perphenazine	10-64	64
Pimozide[231]	Initiate at 1-2	10
Thioridazine	100-800	800
Thiothixene	4-40	60
Trifluoperazine	5-40	80
Atypical antipsychotics		
Aripiprazole	15-30	30
Asenapine	10-20	20
Clozapine	50-500	900
Iloperidone	2-24	24
Lurasidone[232]	40	80
Olanzapine	10-20	20
Paliperidone[a]	3-9	12
Quetiapine	250-500	800
Risperidone[b]	2-8	16
Ziprasidone	40-160	200

[a] For long-acting injectable, the dosage range = 39-234 mg/day and manufacturer-recommended maximum = 234 mg/day

[b] For long-acting injectable (Risperdal Consta), the dosage range = 2-50 mg every 2 weeks and manufacturer-recommended maximum = 50 mg/day

228 US Food and Drug Administration. Atypical Antipsychotic Drugs Information. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm094303.htm. Accessed on October 15, 2012.

229 US Food and Drug Administration. Information on Conventional Antipsychotics. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107211.htm. Accessed on October 15, 2012.

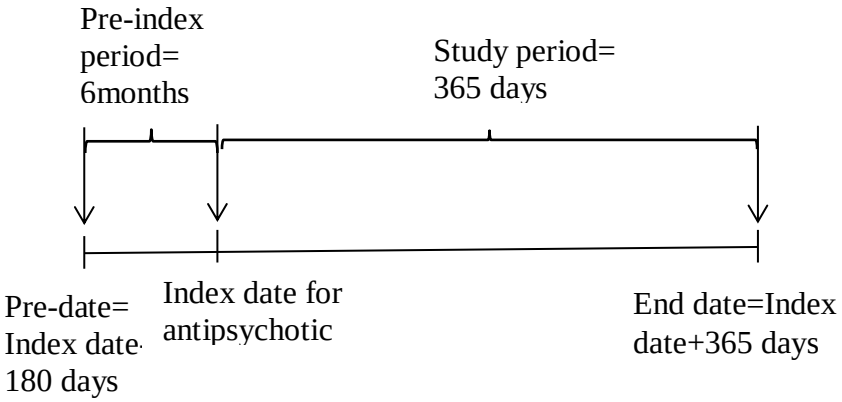
230 Crismon L., Argo T.R., Buckley P.F. (2011). Chapter 76. Schizophrenia. In R.L. Talbert, J.T. DiPiro, G.R. Matzke, L.M. Posey, B.G. Wells, G.C. Yee (Eds), Pharmacotherapy: A Pathophysiologic Approach, 8th edition. Retrieved December 3, 2012 from http://www.accesspharmacy.com/content.aspx?aID=7987911.

231 Lexi Comp. Pimozide. Available at: http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7494#f_dosages. Accessed December 3, 2012.

232 Lexi Comp. Lurasidone. Available at: http://online.lexi.com/lco/action/doc/retrieve/docid/250/3543687#dosage. Accessed December 3, 2012.

<u>Figure 1:</u> Data extraction and subject identification periods

<u>Objectives 1-4 Antipsychotic polypharmacy (APP) and Monotherapy (MT) groups</u>



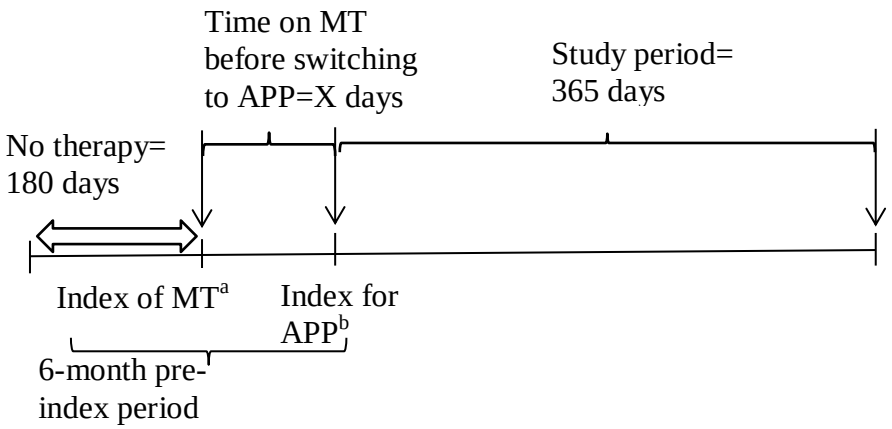
One or more episodes of APP (at least 60 days of prescription of two or more antipsychotics without a gap in polypharmacy of more than 31 days) could occur for the APP group during the 365-day study period

Figure 2: Data extraction and subject identification periods (continued)

Objectives 5-8

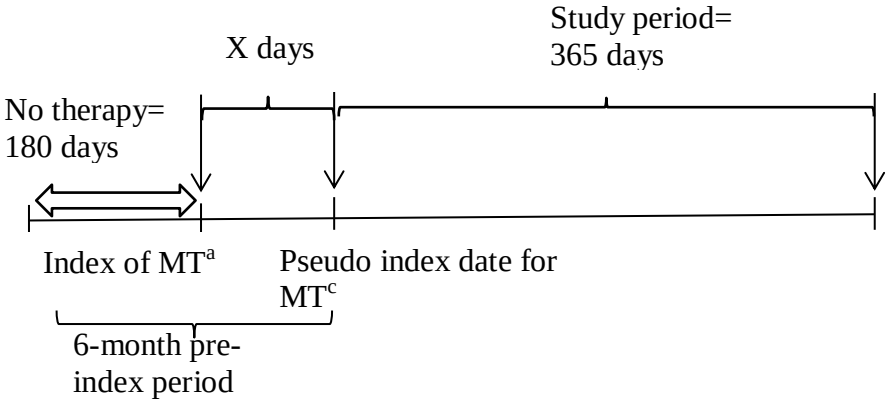
Antipsychotic Polypharmacy (APP) group

Pre-period start=Index APP-180



Monotherapy (MT) group

Pre-period start=Index MT+X-180=Pseudo index date for MT-180



APP- Antipsychotic polypharmacy

[a] Index date for antipsychotic is the day of the first prescription for an antipsychotic in patients who did not have any antipsychotic in the prior 6 months

[b] Index date for APP is defined as the start of at least 60 days of prescription of two or more antipsychotics with no gap in polypharmacy for greater than 31 days and no gap in therapy for more than 31 days

[c] Pseudo index date for MT is the date X days after start of MT

(more explanation provided in section 3.4.4)

3.4.2. Inclusion criteria

The claims data from 2006 to 2008 included only those patients enrolled in the FFS component of the Texas Medicaid program. Data from 2009 to 2011 included enrollees from both the FFS and managed care components of Texas Medicaid.

Patients meeting the following eligibility criteria were included in the study:

(1) between 18-63 years of age at the index date;

(2) newly initiated on any of the antipsychotics listed in *Table 6* (i.e., no antipsychotics in the 6 months preceding the index date for the antipsychotic); and

(3) continuously enrolled in Medicaid 180 days before the index date and throughout the post-index study period over which the patients are observed.

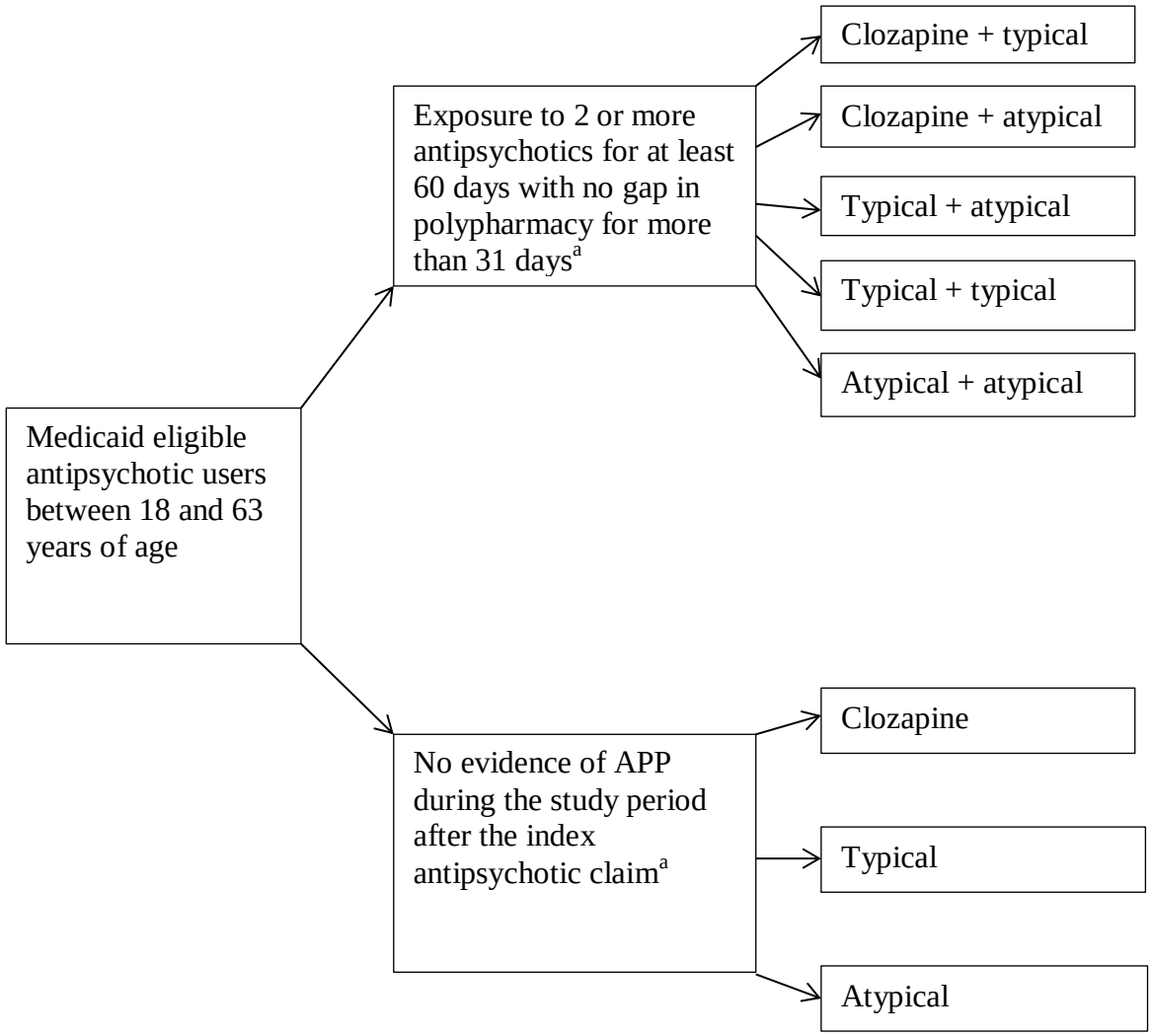
3.4.3. Definition of antipsychotic polypharmacy and monotherapy

Patients were classified as receiving APP if they received concomitant treatment with more than one antipsychotic medication for at least 60 days without a gap of more than 31 days.[233] A gap was defined as a period when the patient has only one or no antipsychotic medication.

Patients were considered to be on monotherapy (MT) if there is no evidence of APP (as defined above) during the study period after the index antipsychotic claim. This allows inclusion of patients who may have had more than one antipsychotic drug for less than 60 days in the MT group. The cut-off point of 60 days was chosen because some guidelines recognize short-term polypharmacy (less than 60 days) as acceptable treatment for patients while switching from one antipsychotic medication to another.[234] *Figure 3* provides a depiction of how the patients will be characterized into the APP and MT groups.

233 Morrato EH, Dodd S, Oderda G, et al. Prevalence, utilization patterns, and predictors of antipsychotic polypharmacy: experience in a multistate Medicaid population, 1998-2003. Clin Ther 2007;29(1):183-95.
234 The expert consensus guideline series. Treatment of schizophrenia. J Clin Psychiatry 1999; 60 suppl 11:3-80.

<u>Figure 3:</u> Classification of patients into the APP and MT groups



[a] The definitions provided in the figure were those used for objectives 1-4. For objectives 5-8 the following definitions were used:
APP: Exposure to 2 or more antipsychotics for at least 60 days with no gap in polypharmacy for more than 31 days and no gap in therapy for more than 31 days
MT: No evidence of APP after the index antipsychotic claim and no gap in therapy for more than 31 days

3.4.4. Patient selection

Objectives 1-4:

Objectives 1-4 involved evaluating the incidence of APP, comparing the characteristics of MT and APP patients, identifying predictors of APP and comparing the adherence and persistence in the MT and APP groups. Newly initiated antipsychotic users with at least two prescription claims for any of the study antipsychotic medications (listed in *Table 6*) were followed for 365-days after the index antipsychotic claim. The pre-period for these patients was defined as the 6-month period before the index date for the antipsychotic medication. The patients were checked for continuous Medicaid enrollment 180 days before and 365 days after the index antipsychotic claim. APP was defined as exposure to two or more antipsychotics for at least 60 days with no gap in polypharmacy for greater than 31 days. MT was defined as no exposure to APP in the one-year period after the index antipsychotic claim.

Objectives 5-8:

Patients having continuous therapy with antipsychotics during the study period without a gap in therapy of 31 days were included in these analyses. Hence, APP was defined as exposure to two or more antipsychotics for at least 60 days with no gap in polypharmacy for greater than 31 days and no gap in any therapy for more than 31 days and MT was defined as no evidence of APP after the index antipsychotic claim and no gap in therapy for more than 31 days. This might decrease the external validity compared to a scenario in which patients with gaps in therapy of greater than 31 days are included (Objectives 1-4). However, it will improve internal validity and will enable us to investigate the association between APP and the observed outcomes.

In order to ensure that patients in the APP and MT groups have had comparable exposure to antipsychotic medications, each patient in the APP group was matched to a patient in the MT

group with an almost equal time period (within a ±30 day range) of exposure to antipsychotics. For example, consider a patient in the APP group who was on monotherapy for three months before switching to APP. Once he switches to APP, he will be followed for one year (365 days). Thus, this patient will be matched to a patient in the MT group who was on MT between 14 to 16 months (3 months + 12 month follow-up = 15 months ± 30 days range = 14 to 16 months). This would ensure that the patients have had exposure to antipsychotics for comparable lengths of time. The outcomes for both patients will be assessed in the last 12 months (i.e., Index date for APP+ 365 days period for the APP group; Pseudo index date for MT+ 365 days for the MT group). This ensures that outcomes are compared in the two groups after comparable periods of exposure to antipsychotics. The patients were matched based only on duration of exposure to antipsychotics; all other variables were controlled for in the regression analyses. This was done to ensure that we obtain a sufficiently large sample size for each analysis.

The pre-period for each group will be defined as follows (refer to *Figure* **1**)*:*

APP group: Pre-period=Index APP-180

MT group: Pre-period=Index MT+X-180=Pseudo index date for MT-180

For the APP group, the pre-period could be a period of no antipsychotic therapy, antipsychotic monotherapy, or a combination of the two, depending on the number of days the patient was on monotherapy prior to switching to APP. For the MT group, the pre-period could also be no antipsychotic therapy, antipsychotic monotherapy, or a combination of the two, depending on the pseudo index date for MT.

Patients were checked for continuous Medicaid enrollment during the pre- and post-index periods.

3.5. Study design

This study was a retrospective database analysis using Texas Medicaid medical and prescription claims data from 2006 to 2011. Incidence of APP, characteristics of patients in the MT and APP groups, and predictors of APP were determined. Furthermore, patients were classified into the APP and MT groups, and outcomes such as medication adherence and persistence, healthcare utilization, and costs were compared between the two groups. This analysis was conducted using an intention to treat perspective.

3.6. Study variables

This section provides the operational definitions for the variables that were used in the study.

3.6.1. Demographic characteristics

Age, sex, and race/ethnicity were identified for each patient. Age was defined at the time of the index prescription.

3.6.2. Clinical characteristics

The year of initiation of the index antipsychotic was identified. The presence of a medical claim with a primary or secondary diagnosis represented by an International Classification of Disease, 9th revision (ICD-9) code for a mental illness was used as an indicator for the presence of mental illness during the study period. The presence of an ICD-9 code of 295.XX was used to identify schizophrenia or schizoaffective disorder and ICD-9 codes of 296.4X-296.7X were used to identify bipolar disorder. Depression was identified with ICD-9 codes of 296.2X, 296.3X, 300.4X and 311. The presence of other mental illnesses were identified using ICD-9 codes between 290 and 319 excluding the ones previously mentioned. Patients were assigned the diagnosis that appeared most frequently in their claims. If two diagnoses appeared with equal frequency, the patient was classified as having 'multiple diagnoses.' Current substance abuse was identified using ICD-9 codes 303, 304, and 305. The presence of at least two prescription claims for antidepressants, anti-anxiety medications, and antimanic medications was used as an indicator for non-antipsychotic psychotropic therapy use during the study period.[235] Using a method similar to Paulose-Ram et al., American Hospital Formulary Service (AHFS) codes were

235 Morrato EH, Dodd S, Oderda G, et al. Prevalence, utilization patterns, and predictors of antipsychotic polypharmacy: experience in a multistate Medicaid population, 1998-2003. Clin Ther 2007;29(1):183-95.

used to identify psychotropic medications.[236] The following categories were identified: (1) antidepressants (AHFS Drug Code: 28:16:04), (2) anxiolytics/sedatives/hypnotics (ASH) (28:24), and (3) antimanics (28:28). The presence of at least two prescription claims for trihexyphenidyl, biperiden, benztropine, promethazine, procyclidine, amantadine, piroheptine, or mazaticol was used as an indicator for the use of anticholinergic medications during the study period.[237]

The number of unique mental health-related comorbidities was calculated for each patient during the 365-day study period. In order to assess the comorbidity burden in patients, the CCI was used. It was initially developed by Charlson and her colleagues by examining medical records of patients admitted in a New York hospital to derive a weighted comorbidity index.[238] It has been widely used for risk adjustment in administrative databases and has also been used in studies of antipsychotic use.[239,240,241] The CCI for the pre-index period was calculated. In addition, the Chronic Disease Score (CDS) during the pre-index period was calculated. The CDS is a measure of disease severity that was suggested by Von Korff and others.[242] It uses pharmacy claims data to determine the number of selected prescription medications used by the patient.

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236 Paulose-Ram R, Safran MA, Jonas BS, et al. Trends in psychotropic medication use among U.S. adults. Pharmacoepidemiol Drug Saf 2007;16(5):560-70.

237 Xiang YT, Dickerson F, Kreyenbuhl J, et al. Common use of anticholinergic medications in older patients with schizophrenia: findings of the Research on Asian Psychotropic Prescription Pattern (REAP) study, 2001-2009. Int J Geriatr Psychiatry 2012. doi: 10.1002/gps.3827. [Epub ahead of print].

238 Charlson ME, Pompei P, Ales KL, et al. A New Method of Classifying Prognostic Comorbidity in Longitudinal Studies: Development and Validation. J Chronic Dis 1987;40(5):373-83.

239 D'Hoore W, Bouckaert A, Tilquin C. Practical considerations on the use of the Charlson comorbidity index with administrative data bases. J Clin Epidemiol 1996;49(12):1429-33.

240 Needham DM, Scales DC, Laupacis A, et al. A systematic review of the Charlson comorbidity index using Canadian administrative databases: a perspective on risk adjustment in critical care research. J Crit Care 2005;20(1):12-9.

241 Bera R, Offord S, Zubek D, et al. Impact on healthcare resource usage and costs among Medicaid-insured schizophrenia patients after initiation of treatment with long-acting injectable antipsychotics. J Med Econ 2013. [Epub ahead of print].

242 Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. J Clin Epidemiol 1992; 45(2):197–203.

3.6.3. Physician characteristics

Previous research has shown that physician specialty affects the prescription of antipsychotics. For this study, the clinical specialty of the physician was classified as psychiatry, family practice, other, and data unavailable. The number of physicians prescribing antipsychotics to each patient were also identified. The geographic location of the prescriber (urban/rural) was also identified. This was done using the county of residence of the patient as a proxy.

3.6.4. Prior utilization

The number of mental health-related inpatient hospitalizations and outpatient/emergency department visits in the six months prior to the index date were evaluated to determine pre-index utilization of health resources. This dataset did not allow for the classification of outpatient visits as physician visit, outpatient hospital visit, or emergency department visit. The designation of "outpatient" visit encompasses all of these places of service.

Table 7 contains a list of all variables and their operational definitions. These variables were used as covariates in all the regression models.

Table 7: Variable list

Variable	Operational definition
Demographic characteristics	
Sex	Dichotomized as: Males and Females
Age	Continuous variable denoting age at the time of index claim
Race/ethnicity	Categorized into: Caucasians, African Americans, Hispanics, and Others
Clinical characteristics	
Year of initiation of index antipsychotic	Categorized as: 2006, 2007, 2008, 2009, and 2010
Mental health diagnosis	Categorized as: Schizophrenia/schizoaffective disorders (ICD-9 code 295.XX); Bipolar disorders (ICD-9 codes 296.4X-296.7X); Depression (ICD-9 codes 296.2X, 296.3X, 300.4X, and 311); Other mental health diagnoses (ICD-9 codes between 290 and 319 excluding the ones mentioned above); No mental health diagnoses; and Multiple (more than one of the above diagnoses)
Current substance abuse	Dichotomized as Yes: in the presence of ICD-9 codes 303-305; or No
Number of unique mental health diagnoses	Count variable (presence of a medical claim for ICD-9 codes 290-319 [inclusive])
CCI-pre index	Continuous variable indicating the Charlson comorbidity score for the 180-day pre-index period before the APP index date for APP group and pseudo index date for MT group

Table 7: Variable list (continued)

Variable	Operational definition
CDS-pre index	Continuous variable indicating the Chronic Disease Score the 180-day pre-index period before the APP index date for APP group and pseudo index date for MT group
Index antipsychotic drug[a]	Categorized as Typical, Atypical, or Combination
Mode of administration of the index antipsychotic[a]	Categorized as: Oral, or Intramuscular
Use of psychotropic therapy during study period	Categorized as: Yes in the presence of at least 2 prescription claims for antidepressants, ASH, or antimanic drugs, or No
Use of anticholinergic medications during study period	Dichotomized as Yes: in the presence of at least two prescription claims for: Trihexyphenidyl, Biperiden, Benztropine, Promethazine, Procyclidine, Amantadine, Piroheptine, Mazaticol; or No
Physician characteristics	
Clinical specialty of prescribing physician	Categorized as: Psychiatry, Family practice, Neurology, Other, or Data unavailable
Number of physicians prescribing antipsychotics	Count variable denoting number of physicians prescribing antipsychotics to each patient
Geographic location of prescribing physician	Categorized as: Urban, Rural, or Unknown

Table 7: Variable list (continued)

Variable	Operational definition
Prior utilization	
Number of mental health-related inpatient hospitalizations in six-month pre-index period (six months before index date for antipsychotic)	Count variable—Includes all hospitalizations associated with an ICD-9 code of 290-319 (inclusive)
Number of mental health-related outpatient/ emergency department visits in six-month pre-index period (six months before index date for antipsychotic)	Count variable—Includes all outpatient/emergency department visits associated with an ICD-9 code of 290-319 (inclusive)

ICD-9—International Classification of Disease, 9th revision
AHFS—American Hospital Formulary Service
ASH—anxiolytics/sedative/hypnotics
CCI—Charlson Comorbidity Index
CDS—Chronic Disease Score
[a] Measured at index of antipsychotic therapy

3.6.5. Study outcomes

The primary outcome of the study is the incidence of APP. Based on the definitions provided previously, patients were classified into the MT and APP cohorts; the characteristics of the cohorts were described and the predictors of APP were evaluated. Medication adherence (calculated as the proportion of days covered [PDC]) and persistence to antipsychotic medication was calculated and compared between the MT and APP groups. Patients in the MT and APP cohorts with no gap in polypharmacy for greater than 31 days and no gap in therapy of greater than 31 days were followed over a 365-day post-index (MT group: 365 days after pseudo index date; APP group: 365 days after APP start date) study period and the following outcomes were examined: likelihood of a post-index all-cause inpatient hospitalization, all-cause length of stay in inpatient facilities, number of post-index all-cause outpatient/emergency department visits, all-cause medical costs, all-cause drug costs, all-cause total costs (drug + medical). All costs were converted to 2011 US dollars using medical consumer price indices.[243]

Table 8 provides operational definitions for the study outcomes.

[243] Consumer Price Index. Bureau of Labor Statistics. Available at: http://www.bls.gov/cpi/. Accessed on: April 3, 2014.

Table 8: Outcomes assessed in the study

Variable	Operational definition
Presence of APP[a]	Dichotomized as: Yes (exposure to 2 or more antipsychotics for at least 60 days with no gap in polypharmacy of more than 31 days); or No (no evidence of APP during the study period after the index antipsychotic claim)
Medication adherence (PDC)	Proportion of days during the 365-day post-index period that: The patient had at least two antipsychotics (for APP group)[c]; The patient had at least one antipsychotic** (for MT group)
Medication persistence	Count variable—number of days on an antipsychotic prior to discontinuation (defined as a gap in therapy of greater than 31 days)
Likelihood of an inpatient hospitalizations[b]	Dichotomous variable: Yes (presence of post-index all-cause inpatient hospitalization); No (absence of post-index all-cause inpatient hospitalization)
Length of stay[b]	Count variable—post-index all-cause length of stay (in days) in an inpatient setting
Number of outpatient visits[b]	Count variable—post-index all-cause outpatient visits
Medical costs[b]	Continuous variable—post-index all-cause medical costs (in USD)
Drug costs[b]	Continuous variable—post-index all-cause drug costs (in USD)
Total costs[b]	Continuous variable—post-index all-cause drug costs + medical costs (in USD)

PDC-proportion of days covered

[a] The definition provided is the one used for objectives 1-4

For objectives 5-8 the APP and MT definitions were as follows:

Presence of APP—Dichotomized as:

Yes (exposure to 2 or more antipsychotics for at least 60 days with no gap in polypharmacy for more than 31 days and no gap in any therapy for more than 31 days); or

No (exposure to no more than 1 antipsychotic during the study period after the index antipsychotic claim and no gap in therapy for more than 31 days)

[b] The outcome in the APP group after the index date for APP was examined

[c] The adherence for the APP group was calculated in two ways. The first one is provided in the table (Scenario 1). The definition for Scenario 2 was:

The patient had at least one antipsychotic for both MT and APP groups

**Patient in the MT group may have more than one antipsychotic for certain periods but not long enough to be categorized as APP

3.7. Statistical procedure

The statistical procedures and tests that were conducted to meet each study objective are described below.

3.7.1. Objectives 1-4

3.7.1.1. Incidence of APP, characteristics of MT and APP groups and predictors of APP

Objective 1:

Categorizing patients into the APP and MT groups

The Expert Consensus Guidelines on the care of patients with schizophrenia state that APP is acceptable for patients for up to 8 weeks while switching from one antipsychotic to another.[244] For this the first four objectives of this study, APP was defined as concomitant use of two or more antipsychotics for at least 60 days without a gap in polypharmacy for more than 31 days. MT was defined as exposure to no more than one antipsychotic in the one year period after the index antipsychotic claim. Patients were classified into the APP and MT groups.

The number and proportion of patients on APP were evaluated. The patients were then classified into one of the following categories:

- Clozapine + atypical
- Clozapine + typical
- Typical + typical
- Atypical + atypical
- Atypical + typical

244 The expert consensus guideline series. Treatment of schizophrenia. J Clin Psychiatry 1999; 60 suppl 11:3-80.

The classification into groups was based on the medications used at the index of the longest APP episode if more than one episode was present.

The mean and median number of days between start of antipsychotic therapy and start of polypharmacy and the mean and median number of days on polypharmacy during the 365-day study period have been reported in the Results. The mean and median number of APP episodes was also reported.

The patients on monotherapy were classified into one of the following categories based on the index antipsychotic medication:

- Typical
- Atypical
- Clozapine

Objective 2:

Characteristics of patients on APP and MT

Descriptive statistics have been provided for demographic, clinical, physician, and utilization characteristics of patients on APP and MT. Frequencies and percentages have been provided for categorical variables and means (or medians) and standard deviations (interquartile ranges) for the continuous variables.

Differences between the APP and MT groups with respect to gender, race/ethnicity, year of initiation of antipsychotic, type of mental health diagnosis, presence of substance abuse, type of index antipsychotic, mode of administration of index antipsychotic, use of psychotropic medications, use of anticholinergic medications, clinical specialty of the prescribing physician and geographic location of prescriber were tested using chi-square tests. Independent sample t-tests were used to test the difference in age and Mann Whitney U tests were used to test the difference in number of physicians prescribing antipsychotics, number of mental health diagnoses, pre-index CCI, pre-index CDS, and number of mental health-related inpatient and outpatient/emergency department visits during the pre-index period between the two groups.

Objective 3:

Predictors of antipsychotic polypharmacy

A logistic regression model was used to identify predictors of APP. Logistic regression is used when the dependent variable is dichotomous in nature (i.e., presence or absence of APP). The independent variables can be categorical or continuous. The odds of having APP were evaluated for each listed factor.

The dependent variable was presence of APP dichotomized as yes or no. The independent variables included sex, age, race/ethnicity, year of initiation of index antipsychotic, mental health diagnosis, current substance abuse, number of mental health diagnoses, pre-index CCI, pre-index CDS, index antipsychotic drug, mode of administration of index antipsychotic, use of psychotropic therapy during the study period, use of anticholinergic medications during the study period, clinical specialty of prescribing physician, number of physicians prescribing antipsychotics, geographic location of prescriber, and number of mental health-related inpatient hospitalizations and outpatient/emergency department visits in the six-month pre-index period.

3.7.1.2. Adherence and persistence

Adherence to therapy was evaluated using proportion of days covered (PDC). PDC is calculated by dividing the number of days that the patient had the drug(s) by the number of days in the particular time interval.[245]

$$\text{PDC} = \frac{\text{total days all drug(s) available}}{\text{days in follow-up period}}$$

The numerator is not just a sum of the days' supply; rather, it is calculated to avoid double counting of days.

Calculating PDC for multiple medications

The example provided below calculates the PDC for patients who are supposed to be concurrently taking two drugs. Consider 2 patients, A and B (*Figure 4*).[246] Patient A had four months of overlap of the two drugs while patient B had no overlap of the two drugs.

245 Peterson AM, Nau DP, Cramer JA, et al. A checklist for medication compliance and persistence studies using retrospective databases. Value Health 2007;10(1):3-12.

246 Barner JC. Medication adherence: focus on secondary database analysis. International Society for Pharmacoeconomic and Outcomes Research (ISPOR) Student Forum Presentation. February 2010.

<u>Figure 4:</u> Example for proportion of days covered (PDC)

Patient A

Drug	Day's supply	Month (30 days/month)											
		1	2	3	4	5	6	7	8	9	10	11	12
X	360												
Y	120												

$PDC_A = 120/360 = 0.33$

Patient B

Drug	Day's supply	Month (30 days/month)											
		1	2	3	4	5	6	7	8	9	10	11	12
X													
Y													

$PDC_B = 0/360 = 0.00$

PDC is always a value between 0 and 1. It provides a more conservative estimate of adherence for patients taking multiple medications compared to the medication possession ratio (MPR).

For the APP group, PDC was evaluated in two ways. In scenario 1, it was defined as the number of days the patient had at least two medications (for them to be considered adherent) and in scenario 2 it was defined as the number of days that the patient had at least one medication (for them to be considered adherent). This was done because there was no way of knowing what the patient was prescribed for the study period; we only know what claims they filled. The patients in the APP group could have multiple episodes of long-term (as per the definition used in the current study) polypharmacy during the 12-month observation period; they may not be prescribed polypharmacy for all 12 months. The two described scenarios provide the upper and

lower bounds of adherence for the patients in the APP group. For the MT group, the PDC was defined as the number of days that the patient had at least one medication.

Persistence in both the APP and MT groups was defined as the number of days on the antipsychotic prior to discontinuation of all medications. Discontinuation was defined as a gap in therapy of greater than 31 days. Patients in both groups were considered persistent on a given day if they had at least one medication on that day. This is because not all patients in the APP group started on multiple antipsychotics and it was not possible to tell from the claims data which patients were prescribed multiple antipsychotics for what time intervals—we only knew what claims were filled. Survival analysis was used to compare the time to discontinuation of the antipsychotic between the MT and APP groups. Survival time is the time that elapses from the first day of observation (index date for the antipsychotic) until the day the patient experiences the event of interest (discontinuation of the antipsychotic).[247] This is the number of days that the patients were persistent with their medication. Those patients that do not experience the event of interest have unknown survival times and are referred to as being 'censored.' In this study we used the Kaplan-Meier Estimator to plot survival curves; however, this cannot estimate the effect of individual variables on the survival time after controlling for covariates.[248] In order to control for covariates, Cox proportional hazards regression was used.

247 Allison PD, SAS Institute. Survival analysis using the SAS system: a practical guide. Cary, NC: SAS Institute; 1995.

248 Woodward M. Epidemiology: study design and data analysis. Boca Raton, FL: Chapman & Hall/CRC Press; 1999.

Objective 4:

Comparing adherence between the APP and MT groups

The unadjusted value of adherence was calculated for the MT and APP groups using the PDC. The PDC measuring the proportion of days that patients in the APP group had two or more antipsychotics (Scenario 1) or at least one antipsychotic (Scenario 2), and patients in the MT group had at least one antipsychotic was used for the analyses. An independent group t-test was used to compare the unadjusted PDC between the MT and APP groups. A chi-square test was used to compare the proportion of adherent patients (PDC $\geq$ 80%) between the MT and APP groups. Multiple linear regression was used to compare the adjusted PDC between the two groups while controlling for the covariates. Logistic regression was used to compare the likelihood of adherence between the MT and APP groups while controlling for the covariates.

Dependent variable: adherence to antipsychotics (measured as PDC)

Primary independent variable: presence of APP dichotomized as yes/no

In order to compare the unadjusted persistence between the MT and APP groups, Kaplan-Meier estimates were used. Cox proportional hazards regression was used to compare the time to discontinuation of antipsychotic medications between the MT and APP groups while controlling for covariates.

Dependent variable: persistence with antipsychotics

Primary independent variable: presence of APP dichotomized as yes/no

3.7.2. Objectives 5-8

For Objectives 5-8, the cohorts of APP and MT patients were matched on their duration of exposure to antipsychotics. This was done to improve internal validity and to enable us to assess the association between APP and the observed outcomes. The variables provided in *Table* **7** were used as covariates for Objectives 5 to 8.

3.7.2.1. Healthcare utilization and costs and for APP and MT groups

Since healthcare utilization and cost data are generally not normally distributed, analysis using ordinary least squares (OLS) regression may not be appropriate.[249] In order to compare the costs and healthcare utilization of the APP and MT groups, generalized linear model (GzLM) regression was used.[250] The modified Park test was used to select the appropriate distribution. This test is conducted by regressing the natural log of the squared residual on the natural log of the predicted value of the dependent variable. The value for γ and the corresponding distribution to be used are provided in *Table 9*.

Table 9: Modified Park test results

Value of gamma (γ)	Family of distribution to be used
0	Normal distribution
1	Poisson distribution
2	Gamma distribution
3	Wald or inverse Gaussian distribution

249 Diehr P, Yanez D, Ash A, et al. Methods for analyzing health care utilization and costs. Annu Rev Public Health 1999;20:125-44.

250 Deb P, Manning W, Norton E. Modeling health care costs and counts. Association for the Study of Higher Education, Madison Conference, 2006.

Healthcare utilization variables such as inpatient hospitalizations, length of stay, and outpatient/emergency department visits are count data and could be modeled using a Poisson regression.[251] Poisson regression assumes that the variance is proportional to the mean. This is often not the case with medical utilization data; sometimes the variance is more than the mean. In this case, negative binomial regression can be used as it includes a random component that involves unobserved variance among cases. The negative binomial regression model can be used in the presence of over dispersion (i.e., variance greater than mean). Another issue that can arise with health utilization data is a preponderance of zeros since many patients may not have utilized any healthcare service. In this case, a zero-inflated regression model or a hurdle model can be used. The appropriate regression model was selected based on the mean-variance relationship and the number of zeros in the data. The choice between a zero-inflated models and a hurdle model depends on the source of the zeros.[252] Sampling zeros are those that occur by chance and structural zeros are those that are observed due to some specific structure in the data. If the zeros are a combination of sampling and structural zeros, a zero-inflated model might be better suited. In case of hurdle models, all zeros are from one structural source and the positive data have a sampling origin. These regression models can examine predictive relationships with a count dependent variable in the absence of normality and homoscedasticity.

GzLM regression with a gamma distribution and a log-link was used to compare the drug, medical, and total costs between the APP and MT groups while controlling for covariates. The gamma distribution assumes that the variance is proportional to the square of its mean.

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251 Elhai JD, Calhoun PS, Ford JD. Statistical procedures for analyzing mental health services data. Psychiatry Res 2008;160(2):129-36.

252 Hu MC, Pavlicova M, Nunes EV. Zero-inflated and hurdle models of count data with extra zeros: examples from an HIV-risk reduction intervention trial. Am J Drug Alcohol Abuse 2011;37(5):367-75. doi: 10.3109/00952990.2011.597280.

Objective 5:

Comparing likelihood of an inpatient hospitalization between the APP and MT groups

A chi-square test was used to compare the presence of inpatient hospitalizations between the APP and MT groups. A logistic regression model was used to compare the likelihood of an inpatient hospitalization between the two groups after controlling for all covariates. The odds of having an inpatient hospitalization in the APP group compared to the MT group after controlling for covariates was obtained.

Dependent variable: presence of an all-cause inpatient hospitalization dichotomized as yes/no

Primary independent variable: presence of APP dichotomized as yes/no

Objective 6:

Comparing length of stay between the APP and MT groups

A Mann-Whitney U test was used to compare the unadjusted length of stay between the APP and MT groups. A patient could have a zero length of hospital stay only if he was not hospitalized. So all the zeros came from a structural source and the positive outcomes had a sampling origin. Thus, a hurdle model was used for the analysis where the first part was a logistic regression identifying the patients with non-zero length of stay and the second part was a zero-truncated negative binomial regression among patients who had a non-zero length of stay.[253] The adjusted length of stay for the APP and MT groups after controlling for the covariates was obtained. This was done by multiplying the predicted probability of hospitalization with the predicted length of stay. This newly created adjusted length of stay variable was compared between the MT and APP groups using a Wilcoxon signed rank test.

Dependent variable: all-cause length of stay in the inpatient settings

Primary independent variable: presence of APP dichotomized as yes/no

253 Hu MC, Pavlicova M, Nunes EV. Zero-inflated and hurdle models of count data with extra zeros: examples from an HIV-risk reduction intervention trial. Am J Drug Alcohol Abuse 2011;37(5):367-75. doi: 10.3109/00952990.2011.597280.

Objective 7:

Comparing outpatient/emergency department visits between the APP and MT groups

A paired sample t-test was used to compare the unadjusted number of outpatient/emergency department visits between the APP and MT groups. A Poisson regression model was used to compare the adjusted number of outpatient visits between the two groups. The number of outpatient visits for the APP and MT groups after controlling for the covariates were obtained.

Dependent variable: number of all-cause outpatient visits

Primary independent variable: presence of APP dichotomized as yes/no

Objective 8:

Comparing costs between the APP and MT groups

The unadjusted mean costs for the MT and APP groups were reported. Mean total healthcare costs and costs for the following categories were reported: inpatient hospitalizations, outpatient/emergency department visits, and prescription drug costs. Non-psychiatric and psychiatric-related costs were reported but separate regression models were not carried out to evaluate the adjusted non-psychiatric and psychiatric costs.

In order to calculate the adjusted costs, the demographic, clinical, physician, and prior utilization characteristics were used as covariates in the GzLM regressions with gamma distributions and log-link functions.

Dependent variables: all-cause costs (medical, drug, and total)

Primary independent variable: presence of APP dichotomized as yes/no

Separate regressions were carried out for all-cause medical costs, drug costs, and total healthcare costs. The adjusted costs of each category (medical, drug, and total) for the APP and MT groups were reported.

3.7.3. Statistical analyses

All data management and statistical analyses were conducted using SAS for Windows, Version 9.3 (SAS Institute, Cary, NC) and Stata 11 (StataCorp LP, College Station, TX, USA). Frequencies, histograms, and box plots were used to check for data abnormalities and normality assumptions. An a priori significance level of α=0.05 was used. While conducting regression analyses on the patients who were matched on their duration of exposure to antipsychotics, cluster robust standard errors were used to account for the correlation between the patients matched on the duration of antipsychotic exposure variable.

Table 10 provides a list of the objectives and the corresponding statistical tests that were carried out.

Table 10: Objectives and statistical tests

Objective	Dependent Variable	Measurement Level	Independent Variable	Measurement Level	Statistical Tests/Procedures
Objective 1: Determine the incidence of APP — overall and by subgroup and classify patients into the MT and APP groups	Number of patients	Continuous	Presence of APP/ Type of antipsychotic or type of antipsychotic combination	Dichotomous/Categorical	Descriptive statistics
Objective 2: Describe and compare the demographic, clinical, physician, and prior utilization characteristics of patients in the APP and MT groups	Demographic: Sex ($H_{3.1}$) Age($H_{3.2}$) Race/ethnicity ($H_{3.3}$) Clinical: Year of initiation of index antipsychotic ($H_{3.4}$), Mental health diagnosis ($H_{3.5}$), Current substance abuse ($H_{3.6}$), Number of-mental health diagnoses ($H_{3.7}$), Post-index CCI ($H_{3.8}$), Post-index CDS ($H_{3.9}$),	Categorical and continuous	Presence of APP	Dichotomous	T-tests (Mann-Whitney U tests in case of non-normality) for continuous variables and χ^2 tests for categorical variables

Table 10: Objectives and statistical tests (continued)

Objective	Dependent Variable	Measurement Level	Independent Variable	Measurement Level	Statistical Tests/Procedures
Objective 2: Describe and compare the demographic, clinical, physician, and prior utilization characteristics of patients in the APP and MT groups	Index antipsychotic drug class ($H_{3.10}$), Mode of administration of the antipsychotic ($H_{3.11}$), Use of psychotropic therapy during study period ($H_{3.12}$), Use of anticholinergic medications during study period ($H_{3.13}$) Physician: Clinical specialty of prescribing physician ($H_{3.14}$), Number of physicians prescribing antipsychotics ($H_{3.15}$), Geographic location of prescriber ($H_{3.16}$)	Categorical and continuous	Presence of APP	Dichotomous	T-tests (Mann-Whitney U tests in case of non-normality) for continuous variables and χ^2 tests for categorical variables

Table 10: Objectives and statistical tests (continued)

Objective	Dependent Variable	Measurement Level	Independent Variable	Measurement Level	Statistical Tests/Procedures
Objective 2: Describe and compare the demographic, clinical, physician, and prior utilization characteristics of patients in the APP and MT groups	Prior utilization: Number of mental health-related inpatient and outpatient/ED visits ($H_{3.17\text{-}3.18}$)	Categorical and continuous	Presence of APP	Dichotomous	T-tests (Mann-Whitney U tests in case of non-normality) for continuous variables and χ^2 tests for categorical variables
Objective 3: Identify the characteristics of patients most likely to be prescribed APP	Presence of APP	Dichotomous	Demographic: Sex, Age, Race/ethnicity Clinical: Year of initiation of index antipsychotic, Mental health diagnosis, Current substance abuse, Number of mental health diagnoses, Post-index CCI and CDS, Index antipsychotic drug class,	Continuous and categorical	Logistic regression

Table 10: Objectives and statistical tests (continued)

Objective	Dependent Variable	Measurement Level	Independent Variable	Measurement Level	Statistical Tests/Procedures
Objective 3: Identify the characteristics of patients most likely to be prescribed APP	Presence of APP	Dichotomous	Mode of administration of the antipsychotic, Use of psychotropic therapy during study period, Use of anticholinergic medications during study period Physician: Clinical specialty of prescribing physician, Number of physicians prescribing antipsychotics, Geographic location of prescriber	Continuous and categorical	Logistic regression

Table 10: Objectives and statistical tests (continued)

Objective	Dependent Variable	Measurement Level	Independent Variable	Measurement Level	Statistical Tests/Procedures
Objective 3: Identify the characteristics of patients most likely to be prescribed APP	Presence of APP	Dichotomous	Prior utilization: Number of mental health-related inpatient and outpatient visits	Continuous and categorical	Logistic regression
Objective 4: Compare adjusted adherence (PDC) and persistence between MT and APP groups while controlling for covariates	Adherence (PDC) ($H_{4.1}$)/ PDC $\geq$ 80%($H_{4.2}$)/ Days on antipsychotic prior to discontinuation ($H_{4.3}$)	Continuous/ Categorical/ Count	Presence of APP (covariates)	Dichotomous	Multiple regression/ Logistic regression/ Cox proportional hazards regression
Objective 5: Compare likelihood of an all-cause inpatient hospitalization between the MT and APP groups while controlling for covariates	Presence of an all-cause inpatient hospitalization ($H_{5.1}$)	Dichotomous	Presence of APP (covariates)	Dichotomous	Logistic regression

Table 10: Objectives and statistical tests (continued)

Objective	Dependent Variable	Measurement Level	Independent Variable	Measurement Level	Statistical Tests/Procedures
Objective 6: Compare all-cause length of stay between the MT and APP groups while controlling for covariates	All-cause length of stay ($H_{6.1}$)	Count	Presence of APP (covariates)	Dichotomous	Hurdle model
Objective 7: Compare number of all-cause outpatient/ emergency department visits between the MT and APP groups while controlling for covariates	Number of all-cause outpatient visits ($H_{7.1}$)	Count	Presence of APP (covariates)	Dichotomous	Poisson regression with log link function
Objective 8: To compare all-cause drug, medical and total (separate models) healthcare costs between the MT and APP groups while controlling for the covariates	All-cause drug, medical, or total costs ($H_{8.1\text{-}8.3}$)	Continuous	Presence of APP (covariates)	Dichotomous	GzLM with gamma distribution and log-link function

3.8. Sensitivity analyses

Due to the uncertainty associated with some assumptions and values selected for the study, sensitivity analyses were performed to estimate the extent to which modifications in operational definitions would influence the overall results.

3.8.1. Psychiatric-related vs. all-cause costs and utilization outcomes

In the original analyses, the operational definitions for hospitalizations, outpatient/emergency department visits, and costs did not differentiate between the psychiatric-related and non-psychiatric-related measures. In order to get a better sense of the relationship between APP and psychiatric outcomes, the operational definitions for the outcomes was modified to only include resource utilization and costs associated with mental illnesses. Only resource utilization and costs associated with mental illnesses (ICD-9 codes 290-319) were considered while evaluating post-index healthcare utilization and costs to determine how modification in the operational definition affected the results.

3.8.2. APP definition

In this study, the following definition of APP was used: exposure to two or more antipsychotics for at least 60 days with no gap in polypharmacy for greater than 31 days and no gap in therapy for greater than 31 days. The following definition of monotherapy was used: exposure to no more than 1 antipsychotic with no gap in therapy for greater than 31 days. The overlap duration was modified to 120 days and 180 days and the gap duration was modified to 15 days and 45 days to estimate how the change in definition influences the overall results.

3.9. Assumptions and sample size calculations

3.9.1. General Linear Models

3.9.1.1. ***Multiple Regression***

The assumptions for multiple regression are as follows:[254]

- linear relationship between independent and dependent variables;
- normality of residuals;
- homoscedasticity (constant variance) of errors;
- independence of prediction errors; and
- no multicollinearity among independent variables.

The sample size requirement for multiple regression was checked using G*Power software.[255] For the sample size calculation, the software requires an effect size measure, alpha level, required power, and the number of predictors. Assuming a small effect size (f^2=0.02), with 19 predictors, α=0.05, and power=0.80, a minimum sample size of 1,043 is needed.

254 Multiple Regression. In: Stevens JP. Applied Multivariate Statistics for the Social Sciences 5th ed. New York, NY:Taylor & Francis Group, 2009.

255 Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39(2):175-91.

3.9.2. Generalized Linear Models

Generalized Linear Models (GzLM) are a class of statistical models that can link the response to a linear combination of predictors.[256] In addition to continuous dependent variables, these models can handle rates and proportions, binary, ordinal and multinomial variables and counts. A GzLM has three components[257]:

Random component: specifying the conditional distribution of the response variable Y_i which may be a member of an exponential family, such as the Gaussian (normal), binomial, Poisson, gamma, or inverse-Gaussian families of distributions. The use of GzLMs also extend to multivariate exponential families (such as the multinomial distribution), to certain non-exponential families (such as the two-parameter negative-binomial distribution), and to some situations in which the distribution of Y_i is not specified completely.

Linear combination of predictors:

$$\eta i = \alpha + \beta_1 X_{i1} + \beta_2 X_{i2} + \cdots + \beta_k X_{ik}$$

Link function: $g(\cdot)$; transforms the expectation of the response variable, $\mu i \equiv E(Yi)$, to the linear predictor.

$$g(\mu_i) = \eta_i = \alpha + \beta_1 X_{i1} + \beta_2 X_{i2} + \cdots + \beta_k X_{ik}$$

Some of the commonly used distributions, link functions, and their response ranges are presented in *Table 11*.[258]

256 Jackman S. Generalized Linear Models. Available at: http://jackman.stanford.edu/papers/glm.pdf. Accessed December 7, 2012.

257 Generalized Linear Models. In: Fox J. Applied Regression Analysis and Generalized Linear Models 2nd ed Chapter 15. Thousand Oaks, CA: Sage Publications, 2008.

258 Generalized Linear Models In: Fox J. Applied Regression Analysis and Generalized Linear Models 2nd ed Chapter 15. Thousand Oaks, CA: Sage Publications, 2008.

Table 11: Canonical link and response range for commonly used distribution families

Family	Canonical Link	Range of Y_i
Gaussian	Identity	$(-\infty,\infty)$
Binomial	Logit	$(0,1,\ldots n_i)/n_i$
Poisson	Log	0,1,2,..
Gamma	Inverse	$(0,\infty)$
Inverse-Gaussian	Inverse-square	$(0,\infty)$

Source: Generalized Linear Models In: Fox J. *Applied Regression Analysis and Generalized Linear Models 2nd ed Chapter 15.* Thousand Oaks, CA: Sage Publications, 2008.

A general linear model (linear regression) is a special case of the generalized linear model with the dependent variable normally distributed and an identity link function.

The key assumptions for Generalized Linear Models include[259]:

- statistical independence of the observations;
- correct specification of the link and variance functions;
- correct scale for measurement of the explanatory variables; and
- lack of undue influence of individual observations on the fitted model.

3.9.2.1. Logistic regression

Logistic regression is an example of a GzLM with a binomial distribution and a logit link function. The assumptions for logistic regression are as follows:[260]

- the observations are independent of one another;
- no extraneous variables are included and no important variables are excluded;
- the IVs (independent variables) are measured without error; and
- the IVs are not a linear combination of each other.

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259 Breslow NE. Generalized linear models: checking assumptions and strengthening conclusions. Available at: http://biostat.georgiahealth.edu/~dryu/course/stat9110spring12/land16_ref.pdf. Accessed December 5, 2012.

260 Logistic Regression Diagnostics. In: Chen X, Ender P, Mitchell M, et al. Logistic Regression with Stata. UCLA: Academic Technology Services, Statistical Consulting Group. Available at: http://www.ats.ucla.edu/stat/stata/ado/analysis/. Accessed: December 5, 2012.

In order to calculate the required sample size for logistic regression, the G*Power software was used. The odds ratios for sample size calculations were varied over a wide range (1.5-15.0) and the probability of the event was assumed to have a low value which translates into a high sample size. A two-tailed alpha level of 0.05 was used and the power was fixed at 0.80. *Table 12* provides the different sample sizes obtained as the parameters were varied.

Table 12: Sample size calculation for logistic regression

Odds Ratio	1.5	5.0	15.0
R-squared[a]	0.1	0.1	0.1
Total Sample Size	4,638	201	60
Odds Ratio	1.5	5.0	15.0
R-squared[a]	0.2	0.2	0.2
Total Sample Size	5,218	226	67
Odds Ratio	1.5	5.0	15.0
R-squared[a]	0.3	0.3	0.3
Total Sample Size	5,963	258	77

Y = dependent variable, X = independent variable
Binomial distribution was assumed for the IV of interest
Probability of event was assumed at a low value (0.04) which translates into a high sample size.
[a] The value obtained when X1 is regressed over other independent variables or covariates in the regression

Based on the estimates obtained, a minimum sample size of 5,807 is needed for the logistic regression.

3.9.2.2. GzLM with gamma distribution and negative binomial distribution

Gamma and negative binomial distributions with log-link functions are examples of GzLMs. There is limited information in the literature regarding sample size requirements for GzLM with a gamma distribution and a negative binomial distribution. However, for GzLM with a gamma distribution, if the minimum sample size requirement for multiple regression is met, the study will be sufficiently powered.[261]

G*Power software was used to estimate the sample size for the Poisson regression procedure (as it does not have the provision to estimate sample size for a negative binomial regression model). The baseline rate of healthcare utilization was varied from 5% to 20% and the sample size required to detect a difference of 10% (Exp(β1)=1.1) was estimated. The independent variable was assumed to have a binomial distribution with 5% of patients on APP. A one-sided alpha of 0.05 and a power of 0.80 was used. *Table 13* provides the different sample sizes obtained as the parameters were varied.

Table 13: Sample size calculation for Poisson regression

Base rate	0.05	0.10	0.20
R-squared[a]	0.1	0.1	0.1
Total sample size	821	411	206
Base rate	0.05	0.10	0.20
R-squared[a]	0.2	0.2	0.2
Total sample size	924	462	231
Base rate	0.05	0.10	0.20
R-squared[a]	0.3	0.3	0.3
Total sample size	1,056	528	264

The mean time of exposure was set at 365 days. The calculated sample size is to detect a 10% or more increase in healthcare utilization (Exp(β1)=1.1).

261 Jin H, Zhao X. Transformation and sample size. 2009. Available at: http://www.statistics.du.se/essays/D09_Hui_Zhao.pdf. Accessed December 5, 2012.

[a] The value obtained when the independent variable was regressed over other independent variables or covariates in the regression

Based on the sample sizes obtained in the power analyses, a minimum sample size of 1,056 would be required for the Poisson regression analyses (used as a proxy for negative binomial regression analyses).

3.9.3. Cox Proportional Hazards Regression Analysis

The Cox proportional hazards regression is a semi-parametric model with model assumptions similar to those for parametric models but it makes no assumptions about the form or shape of the underlying hazard (h(t)). It assumes parametric form for the effect of the predictors on the hazard and interprets parameter estimates in the same way as obtained in parametric models.[262,263]

$h(t/X) = h(t) \exp(X1\beta1 + \ldots\ldots + Xn\beta n)$

- h(t) is the hazard function and represents risk changes with time and it is the non-parametric part of the model
- exp represents the effect of covariates
- X1 to Xn are the predictor variables and are assumed to act addictively on log h(t/x)
- β1 to βn are the regression coefficients
- log h(t/x) changes linearly with the βs
- The effect of the predictors is the same at all times t

[262] Allison PD, SAS Institute. Survival analysis using the SAS system: a practical guide. Cary, NC: SAS Institute; 1995.
[263] Woodward M. Epidemiology: study design and data analysis. Boca Raton, FL: Chapman & Hall/CRC Press; 1999.

Table 14 provides the sample size calculation for the Cox proportional hazards regression. It was carried out using the PASS 13 software. Based on the calculation (power=80% and alpha=0.05), a sample size of 9,192 was required for the analyses.

Table 14: Sample size calculation for Cox proportional hazard regression

B (Hazard ratio)[a]	0.2	0.2	0.2
P(Overall Event Rate)[b]	0.2	0.25	0.3
R-squared[c]	0.1	0.1	0.1
Total Sample Size	**1,327**	**1,061**	**885**
B (Hazard ratio)[a]	0.2	0.2	0.2
P(Overall Event Rate)[b]	0.2	0.25	0.3
R-squared[c]	0.2	0.2	0.2
Total Sample Size	**1,492**	**1,194**	**995**
B (Hazard ratio)[a]	0.2	0.2	0.2
P (Overall Event Rate)[b]	0.2	0.25	0.3
R-squared[c]	0.3	0.3	0.3
Total Sample Size	**1,705**	**1,364**	**1,137**
B (Hazard ratio)[a]	2.0	2.0	2.0
P(Overall Event Rate)[b]	0.2	0.25	0.3
R-squared[c]	0.1	0.1	0.1
Total Sample Size	**7,149**	**5,720**	**4,766**
B (Hazard ratio)[a]	2.0	2.0	2.0
P(Overall Event Rate)[b]	0.2	0.25	0.3
R-squared[c]	0.2	0.2	0.2
Total Sample Size	**8,043**	**6,435**	**5,362**
B (Hazard ratio)[a]	2.0	2.0	2.0
P (Overall Event Rate)[b]	0.2	0.25	0.3
R-squared[c]	0.3	0.3	0.3
Total Sample Size	**9,192**	**7,354**	**6,128**

Y=dependent variable; X= independent variables (IV); $\alpha = 0.05$ (one-tailed), $\beta = 0.20$ (power = 80%)

[a] Known as the regression coefficient defined as the predicted change in log(base e) hazards at one unit change in X_1 when the other covariates are held constant

[b] Denotes the proportion of subjects in which the event of interest occurs during the duration of the study (Based on values reported in the across studies in the literature). The modeled event was medication discontinuation over a 12 month follow-up period

[c] The value achieved when X_1 is regressed on the other IVs or covariates in the regression

4. RESULTS

This chapter provides a detailed description of the study results. The results pertaining to the patient selection process, patient characteristics, and the hypotheses tests are provided.

4.1. Objectives 1-4

Objectives 1 to 4 involved estimating the incidence of APP in the Texas Medicaid population, classifying patients into the MT and APP groups, describing the characteristics of the patients in each group, identifying characteristics associated with prescription of APP and comparing the medication adherence and persistence between the MT and APP groups.

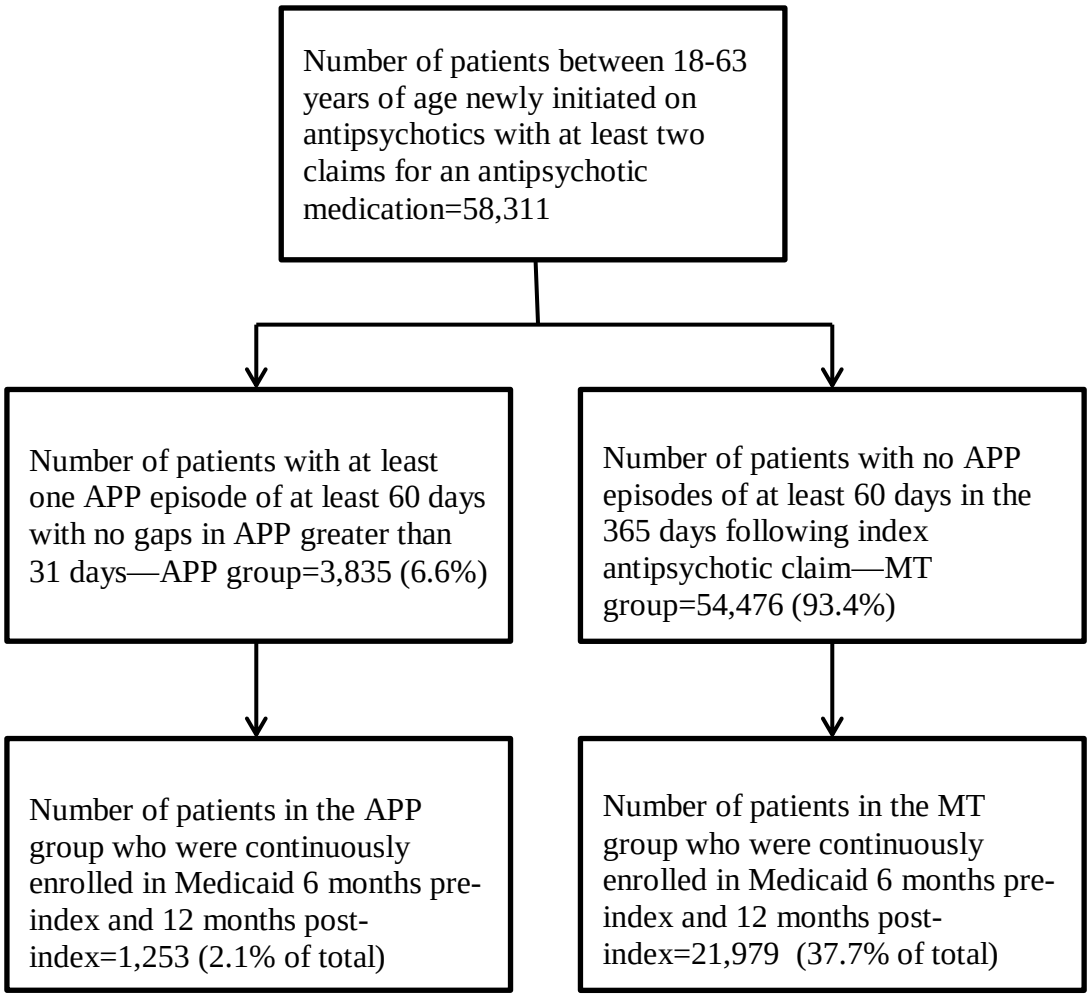
Patients newly initiated on antipsychotics were followed for one year from the index date and were classified into the MT and APP groups. Patients prescribed at least two antipsychotics for at least 60 days with no gaps in polypharmacy for more than 31 days were classified as APP and patients with no evidence of APP in the one year following the index antipsychotic claim were classified as MT.

4.1.1. PATIENT SELECTION

There were 58,311 patients between 18 to 63 years of age newly initiated on antipsychotics with claims for antipsychotics between July 1, 2006 and December 31, 2010. A total of 3,835 (6.6%) patients had at least one APP episode, defined as exposure to two or more antipsychotics for at least 60 days with no gaps in polypharmacy of greater than 31 days. Of these, 1,253 (2.1% of the total) were enrolled in Medicaid for the duration of the study period (365 days after the index date for an antipsychotic medication) and in the 180 days prior to the index date. A total of 54,476 (93.4%) patients did not have any APP episodes during the 365-day study period following the index antipsychotic claim and 21,979 (37.7% of the total) of these

were continuously enrolled in Medicaid in the 180-day pre-index and 365 day post-index periods. *Figure 5* provides a flowchart showing application of the patient inclusion criteria.

Figure 5: Inclusion criteria for patients (Objectives 1-4)



4.1.2. INCIDENCE OF APP, CATEGORIZING PATIENTS INTO MT AND APP GROUPS, CHARACTERISTICS OF PATIENTS IN MT AND APP GROUPS AND PREDICTORS OF APP

Objective 1 was to estimate the incidence of APP in the Texas Medicaid population and classify patients into the MT and APP groups. The incidence of APP in the Texas Medicaid population continuously enrolled 6 months pre-index to 12 months post-index was 5.4% (1,253/23,232). *Table 15* provides a classification of the patients into the MT and APP groups. The MT patients were classified based on their index drug and the APP patients were classified based on the index drug combination for the longest APP episode. Hence, for the APP group, patients may not remain on the reported drug combination through the entire study period. The reported combination was the one observed at the index of the longest APP episode and might change to another drug combination as time progresses.

Table 15: Classification of patients into the MT and APP groups overall and by sub group

Category	Number of patients	Percentage
Antipsychotic Monotherapy		
Typical	1,531	7.0
Atypical	20,411	92.9
Clozapine	37	0.2
Total	**21,979**	**100.1**
Antipsychotic polypharmacy		
Typical + typical	14	1.1
Atypical + atypical	878	70.1
Typical + atypical	347	27.7
Typical + clozapine	4	0.3
Atypical + clozapine	10	0.8
Total	**1,253**	**100**

*Total does not sum to 100 due to rounding error

Patients with APP had a mean ± SD of 106.6±94.2 (Median = 86, interquartile range [IQR] = 168) days from index of an antipsychotic drug to start of polypharmacy. The mean number of APP episodes per patient was 1.1±0.3 (Median = 1, IQR = 0). About 90% (1,126/1,253) of the patients in the APP group had only one episode of APP during the one year after initiation of antipsychotic therapy. In the one year following the index claim for an antipsychotic medication, patients in the APP group had a mean of 141.4±77.7 (Median = 118, IQR = 108) days on polypharmacy with antipsychotics.

Objective 2 was to compare the characteristics of patients in the MT and APP groups. *Table 16* provides a comparison of the characteristics of the patients in the MT and APP groups. A greater proportion of females had APP compared to males. African Americans, Caucasians, and those with race categorized as 'other' had a higher proportion of patients with APP compared to Hispanics and those with race categorized as 'unknown.' A greater proportion of patients with a schizophrenia diagnosis had APP compared to those with other diagnoses. Those with a substance abuse diagnosis had a greater proportion of patients using APP compared to those without such a diagnosis. The APP patients also had a greater number of unique mental illnesses but they had a lower pre-index CCI (and proportion of patients with a pre-index CCI>0) and pre-index CDS mean score compared to the MT patients. A greater proportion of patients initiated on combinations or typical antipsychotics had APP compared to those initiated on atypical antipsychotics. A greater proportion of those initiated on intramuscular antipsychotics had APP compared to those initiated on orals. Anticholinergic and psychotropic medication users had a greater proportion of APP patients compared to non-users of these medication classes. As compared to family practitioners, a greater proportion of patients with psychiatrists and 'other' prescribing physicians had APP. The APP group had a higher number of physicians prescribing

the antipsychotic medications. Finally, APP patients had a greater mean number of pre-index psychiatry-related inpatient hospitalizations (and a greater proportion of patients with a mental health-related pre-index hospitalization) and outpatient/emergency department visits compared to those with MT.

Although it is hard to comment on the difference in the overall health status between the two groups, the severity of mental illnesses was higher in the APP vs. MT group as denoted by the higher number of mental health diagnoses during the study period and greater mental health-related healthcare utilization during the pre-index period.

Table 16: Comparison of demographic, clinical, physician, and prior utilization characteristics of MT and APP groups

Characteristic	Categories	Antipsychotic Monotherapy (N=21,979)		Antipsychotic Polypharmacy (N=1,253)		Test statistic	p value
		N	Row % (Col %)	N	Row % (Col %)		
Demographic Characteristics							
Age (Mean, SD)		39.7	12.5	39.6	12.4	t=0.26	0.7910
Sex	Male	7,936	93.4 (36.1)	557	6.6 (44.5)	χ^2=35.60	<0.0001
	Female	14,043	95.3 (63.9)	696	4.7 (55.5)		
Race/Ethnicity	Caucasians	7,702	94.6 (35.0)	443	5.4 (35.4)	χ^2=22.37	0.0002
	African Americans	6,254	94.2 (28.5)	383	5.8 (30.6)		
	Hispanics	4,911	95.3 (22.3)	245	4.7 (19.6)		
	Others	2,,330	93.6 (10.6)	160	6.4 (12.8)		
	Unknown	782	97.3 (3.6)	22	2.7 (1.8)		

Table 16: Comparison of demographic, clinical, physician, and prior utilization characteristics of MT and APP groups (continued)

Characteristic	Categories	Antipsychotic Monotherapy (N=21,979)		Antipsychotic Polypharmacy (N=1,253)		Test statistic	p value
		N	Row % (Col %)	N	Row % (Col %)		
Clinical Characteristics							
Year of initiation of index antipsychotic	2006	2,765	94.7 (12.6)	155	5.3 (12.4)	χ^2=7.33	0.1196
	2007	4,550	95.2 (20.7)	232	4.8 (18.5)		
	2008	2,769	95.0 (12.6)	146	5.0 (11.7)		
	2009	5,003	94.6 (22.7)	288	5.4 (23.0)		
	2010	6,892	94.1 (31.4)	432	5.9 (34.5)		
Mental health diagnosis	Schizophrenia/schizo affective disorder	2,329	88.6 (10.6)	301	11.4 (24.0)	χ^2=248.99	<0.0001
	Bipolar disorder	2,292	94.5 (10.4)	133	5.5 (10.6)		
	Depression	3,780	96.4 (17.2)	142	3.6 (11.3)		
	Other mental health diagnoses	7,476	94.4 (34.0)	440	5.6 (35.1)		
	Multiple mental illnesses	1,151	95.5 (5.2)	54	4.5 (4.3)		
	No mental health diagnoses	4,951	96.4 (22.5)	183	3.6 (14.6)		

Table 16: Comparison of demographic, clinical, physician, and prior utilization characteristics of MT and APP groups (continued)

Characteristic	Categories	Antipsychotic Monotherapy (N=21,979)		Antipsychotic Polypharmacy (N=1,253)		Test statistic	p value
		N	Row % (Col %)	N	Row % (Col %)		
Current substance abuse	Yes	4,101	93.2 (18.4)	300	6.8 (23.9)	χ^2=21.55	<0.0001
	No	17,878	94.9 (81.3)	953	5.1 (76.1)		
Number of unique mental health diagnoses (Mean, SD)		1.7	1.5	2.2	1.9	z=9.88	<0.0001
CCI-pre index (Mean, SD)		0.54	1.2	0.45	1.1	z=-3.04	0.0024
Number of patients with CCI-pre>0		5,952	95.4 (27.1)	290	4.7 (23.1)	χ^2=9.35	0.0022
CDS-pre index (Mean, SD)		3.4	2.6	2.8	2.7	z=-8.93	<0.0001
Index antipsychotic drug[a]	Typical	1,525	91.9 (6.9)	134	8.1 (10.7)	χ^2=60.19	<0.0001
	Atypical	20,448	94.8 (93.0)	1,114	5.2 (88.9)		
	Combination	6	54.6 (0.03)	5	45.5 (0.4)		
Mode of administration of the index antipsychotic[a]	Oral	21,628	94.7 (98.4)	1,217	5.3 (97.1)	χ^2=11.79	0.0006
	Intramuscular	351	90.7 (1.6)	36	9.3 (2.9)		

Table 16: Comparison of demographic, clinical, physician, and prior utilization characteristics of MT and APP groups (continued)

Characteristic	Categories	Antipsychotic Monotherapy (N=21,979)		Antipsychotic Polypharmacy (N=1,253)		Test statistic	p value
		N	Row % (Col %)	N	Row % (Col %)		
Use of non-antipsychotic psychotropic therapy during study period	Yes	17,031	94.3 (77.5)	1,026	5.7 (81.9)	χ^2=13.23	0.0003
	No	4,948	95.6 (22.5)	227	4.4 (18.1)		
Use of anticholinergic medications during study period	Yes	1,439	84.3 (6.5)	268	15.7 (21.4)	χ^2=383.55	<0.0001
	No	20,540	95.4 (93.5)	985	4.6 (78.6)		
Physician Characteristics							
Clinical specialty of prescribing physician	Psychiatry	12,624	94.1 (57.4)	789	5.9 (63.0)	χ^2=16.85	0.0008
	General/Family practice	3,108	95.7 (14.1)	141	4.3 (11.3)		
	Other	4,319	94.9 (19.7)	230	5.1 (18.4)		
	Unknown	1,928	95.4 (8.8)	93	4.6 (7.4)		
Number of physicians prescribing antipsychotics (Mean, SD)		1.7	1.0	2.3	1.4	z=17.00	<0.0001

Table 16: Comparison of demographic, clinical, physician, and prior utilization characteristics of MT and APP groups (continued)

Characteristic	Categories	Antipsychotic Monotherapy (N=21,979)		Antipsychotic Polypharmacy (N=1,253)		Test statistic	p value
		N	Row % (Col %)	N	Row % (Col %)		
Urban/rural status	Urban	17,253	94.5 (78.5)	1,007	5.5 (80.4)	χ^2=7.06	0.0294
	Rural	3,844	94.7 (17.5)	214	5.3 (17.1)		
	Unknown	882	96.5 (4.0)	32	3.5 (2.5)		
Prior utilization characteristics							
Number of mental health-related inpatient hospitalizations in six-month pre-index period (Mean, SD)		0.2	0.7	0.4	1.2	z=8.89	<0.0001
Number of patients with mental health-related inpatient hospitalizations during the six-month pre-index period		1,933	90.0 (8.8)	216	10.1 (17.2)	χ^2=100.7	<0.0001
Number of mental health-related outpatient/emergency department visits in six-month pre-index period (Mean, SD)		3.7	6.2	5.1	9.5	z=5.12	<0.0001

Col—Column; CCI—Charlson Comorbidity Index; CDS—Chronic Disease Score

[a] Measured at index of antipsychotic therapy

Objective 3 was to identify characteristics associated with prescription of APP. In order to identify characteristics associated with APP, a logistic regression was carried out. The overall model was statistically significant (Wald's χ^2=829.29, df=31, p<0.0001). *Table 17* provides the regression coefficients, Wald's Chi-square values, odds ratios, and 95% confidence intervals of the odds ratios for all the variables included in the model.

While controlling for all covariates, with a one-year increase in age, patients were 1.01 times more likely to have APP. Females were 12% less likely to have APP compared to males while those patients whose race was categorized as unknown were 60% less likely to have APP compared to Caucasians. Patients with bipolar disorder, depression, other mental health diagnoses, multiple mental health diagnoses, and no mental health diagnoses were 44%, 59%, 43%, 53%, and 45%, respectively, less likely to have APP compared to those with schizophrenia or schizoaffective disorder. Those with current substance abuse were 22% less likely to have APP. A 1-unit increase in the number of unique mental illnesses increased the likelihood of APP 1.13 times while a 1-point increase in the pre-index CDS decreased the likelihood of APP by 6%. Use of psychotropic drugs and anticholinergic drugs increased the likelihood of APP 1.40 and 2.76 times, respectively. The likelihood of APP when the prescribing physician was a general practitioner was 17% lower than that for psychiatrists and that for those categorized as 'unknown' was 37% lower than that for psychiatrists. With a 1-unit increase in the number of prescribers prescribing antipsychotics, the likelihood of APP increased 1.38 times while a 1-unit increase in the number of pre-index psychiatric-related outpatient/emergency department visits increased the likelihood of APP only 1.01 times.

Table 17: Logistic regression results to identify relationships between APP and demographic, clinical, physician, and prior utilization characteristics

Characteristic	Categories	Estimate	Wald's Chi-square	Odds Ratio	95% CI of odds ratio		p-value
					Lower	Upper	
Demographic Characteristics							
Age*		0.0071	7.63	1.01	1.00	1.01	0.0058
Sex (Reference=Male)*	Female	-0.1268	4.03	0.88	0.78	1.00	0.0058
Race (Reference= Caucasian)	African Americans	-0.0453	0.34	0.96	0.82	1.11	0.5589
	Hispanics	-0.1530	3.14	0.86	0.73	1.02	0.0765
	Others	0.0470	0.22	1.05	0.86	1.28	0.6389
	Unknown	-0.9061	4.86	0.40	0.18	0.90	0.0272
Clinical Characteristics							
Year of initiation of index antipsychotic (Reference=2010)	2006	0.0138	0.02	1.01	0.83	1.24	0.8939
	2007	-0.0415	0.21	0.96	0.80	1.15	0.6482
	2008	0.0489	0.22	1.05	0.86	1.29	0.6371
	2009	-0.0061	0.01	0.99	0.85	1.17	0.9403
Mental health diagnosis (Reference= Schizophrenia/schizoaffective disorder)	Bipolar disorder	-0.5875	26.06	0.56	0.44	0.70	<0.0001
	Depression	-0.8977	63.55	0.41	0.33	0.51	<0.0001
	Other mental health diagnoses	-0.5676	40.20	0.57	0.48	0.68	<0.0001
	Multiple diagnoses	-0.7506	22.44	0.47	0.35	0.64	<0.0001
	No mental health diagnoses	-0.6062	28.54	0.55	0.44	0.68	<0.0001

Table 17: Logistic regression results to identify relationships between APP and demographic, clinical, physician, and prior utilization characteristics (continued)

Characteristic	Categories	Estimate	Wald's Chi-square	Odds Ratio	95% CI of odds ratio		p-value
					Lower	Upper	
Current substance abuse (Reference=No)	Yes	-0.2447	8.18	0.78	0.66	0.93	0.0042
Number of unique mental health diagnoses (Mean, SD)		0.1248	22.91	1.13	1.08	1.19	<0.0001
CCI-pre index (Mean, SD)		-0.0283	0.99	0.97	0.92	1.03	0.3199
CDS-pre index (Mean, SD)		-0.0643	23.90	0.94	0.91	0.96	<0.0001
Index antipsychotic drug[a,b] (Reference=Typical)	Atypical	-0.1549	2.07	0.86	0.69	1.06	0.1498
Mode of administration of the index antipsychotic[a] (Reference=Oral)	Intramuscular	0.2641	1.82	1.30	0.89	1.91	0.1777
Use of psychotropic therapy during study period (Reference=No)	Yes	0.3385	17.59	1.40	1.20	1.64	<0.0001
Use of anticholinergic medications during study period (Reference=No)	Yes	1.0141	155.41	2.76	2.35	3.23	<0.0001
Physician Characteristics							
Clinical specialty of prescribing physician (Reference=Psychiatry)*	Family practice	-0.1901	3.86	0.83	0.68	1.00	0.0495
	Other	-0.0179	0.05	0.98	0.84	1.15	0.8253
	Unknown	-0.4606	14.96	0.63	0.50	0.80	0.0001

Table 17: Logistic regression results to identify relationships between APP and demographic, clinical, physician, and prior utilization characteristics (continued)

Characteristic	Categories	Estimate	Wald's Chi-square	Odds Ratio	95% CI of odds ratio		p-value
					Lower	Upper	
Number of physicians prescribing antipsychotics		0.3195	168.49	1.38	1.31	1.44	<0.0001
Urban/Rural status (Reference=Rural)	Urban	-0.0443	0.28	0.96	0.81	1.13	0.5968
	Unknown	0.4646	1.78	1.59	0.80	3.15	0.1825
Prior utilization Characteristics							
Number of mental health-related inpatient hospitalizations in six-month pre-index period		0.0377	1.41	1.04	0.98	1.11	0.2348
Number of mental health-related outpatient/ emergency department visits in six-month pre-index period*		0.0095	5.86	1.01	1.00	1.02	0.0155

APP is the dependent variable in this analysis (APP=1; MT=0).
Logistic regression was used to identify characteristics associated with prescription of APP.
[a] Measured at index of antipsychotic therapy
[b] Patients on initiated on combinations combined with atypical antipsychotics due to small sample size in the combinations group
*Although the p-values were significant at an alpha level of 0.05, the 95% CI included 1.0

4.1.3. ADHERENCE AND PERSISTENCE FOR THE MT AND APP GROUPS

Objective 4 consisted of comparing the medication adherence and persistence between the MT and APP groups. Patients in the APP group may have been prescribed multiple antipsychotics for varying durations during the 12-month study period (they may not have been prescribed polypharmacy for the entire 12-month period). Based on insurance claims data, it is not possible to determine the length of time for which the patients in the APP group were prescribed multiple antipsychotics—we only know what prescription claims were filled. Thus, adherence was calculated in two different ways for the APP group. In scenario 1, APP patients were considered adherent on a given day if they had at least two antipsychotics on that day. This gives a conservative estimate of the adherence for the APP group. In scenario 2, APP patients were considered adherent on a given day if they had at least one antipsychotic on that day. This gives a very liberal estimate of the adherence for the APP group. These two scenarios give the two extremes of the adherence levels in the APP group. In both scenarios MT patients were considered adherent on a given day when they had at least one antipsychotic on that day.

Multiple regression was used to compare adjusted adherence between the two groups. When a patient had a PDC $\geq$ 80%, s/he was considered to be adherent for the duration of the study period. Logistic regression was used to compare the adjusted likelihood of adherence between the two groups. Persistence to medication (or time to medication discontinuation) was measured as the number of days the patients had at least one antipsychotic medication before discontinuation of all medications.

Unadjusted adherence was higher in the MT group compared to the APP group (0.51 vs. 0.39) in scenario 1 and the proportion of adherent patients (PDC $\geq$ 80%) was also higher in the MT group (21.6% vs. 6.3%). In scenario 2, the adherence (0.77 vs. 0.51) and proportion of

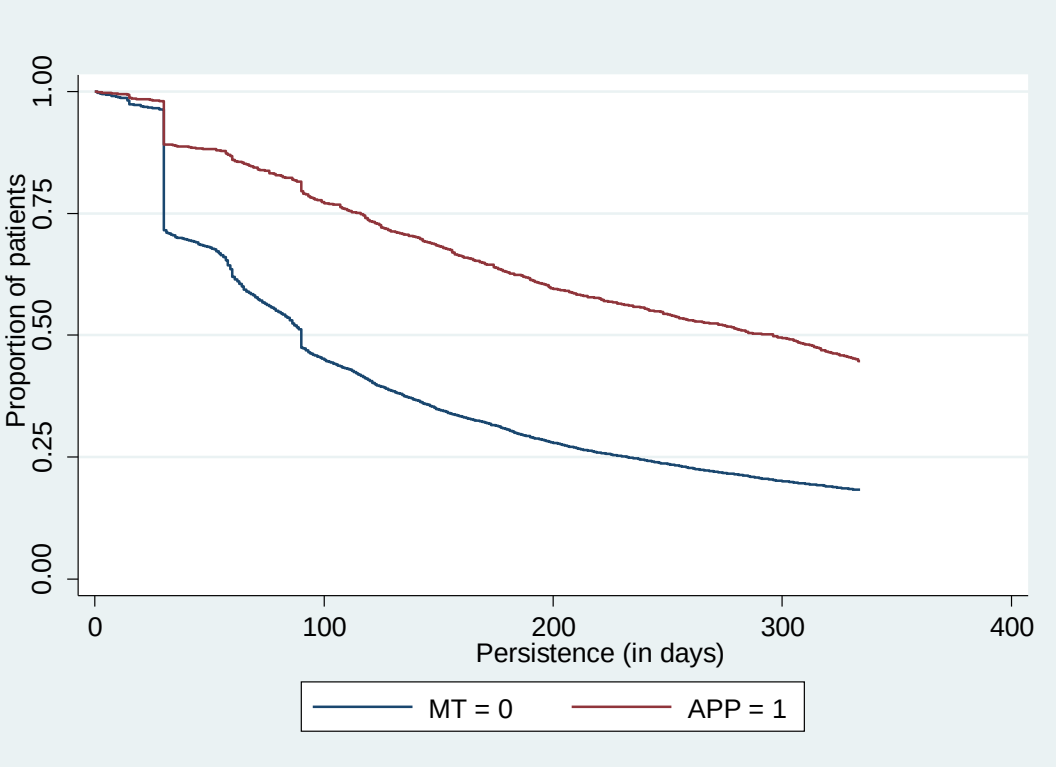
adherent patients (55.0% vs. 21.6%) was higher in the APP group compared to the MT group. The log rank test on the number of days persistent with an antipsychotic showed that the survival curves (*Figure 6*) differed significantly between the two groups and persistence (or time to medication discontinuation) was better in the APP group than in the MT group. About 25% of the patients in the APP group had a greater than 31 days gap in therapy prior to starting APP. This must be kept in mind while interpreting the results. The results are provided in *Table 18*.

Table 18: Comparison of unadjusted adherence and persistence between the MT and APP groups

Adherence/persistence	Antipsychotic Monotherapy Mean (SD) [Median (IQR)] (N=21,979)	Antipsychotic Polypharmacy Mean (SD) [Median (IQR)] (N=1,253)	Test statistic	p-value
Scenario 1				
Adherence—PDC	0.51 (0.28) [0.49 (0.52)]	0.39 (0.21) [0.32 (0.30)]	t=18.83	<0.0001
Proportion of patients adherent	4,737 (21.6)	79 (6.3)	χ^2=167.71	<0.0001
Scenario 2				
Adherence—PDC	0.51 (0.28) [0.49 (0.52)]	0.77 (0.19) [0.82 (0.27)]	t=-45.53	<0.0001
Proportion of patients adherent	4,737 (21.6)	689 (55.0)	χ^2=740.31	<0.0001
Persistence[a,b]	137.3 (116.2) [90 (218)]	227.9 (118.2) [296 (100)]	χ^2=476.86	<0.0001

[a] A log rank test was conducted to compare the two groups
[b] In the APP group, 25% of the patients had a greater than 31 day gap in therapy prior to start of APP

<u>Figure 6:</u> Graph of unadjusted persistence time (in days) of the MT and APP groups (Kaplan Meier survival estimates)



After adjusting for other covariates, the adherence results for scenarios 1 and 2 remained similar to the unadjusted case. In scenario 1, after controlling for covariates, APP patients were 83% less likely to be adherent compared to the MT patients and in scenario 2, APP patients were almost 4 times more likely to be adherent compared to the MT patients. The Cox proportional hazards regression showed that there was a significant difference in the time of medication use prior to discontinuation (persistence) (Hazard Ratio=0.49 [95% CI: 0.45-0.53] and the patients in

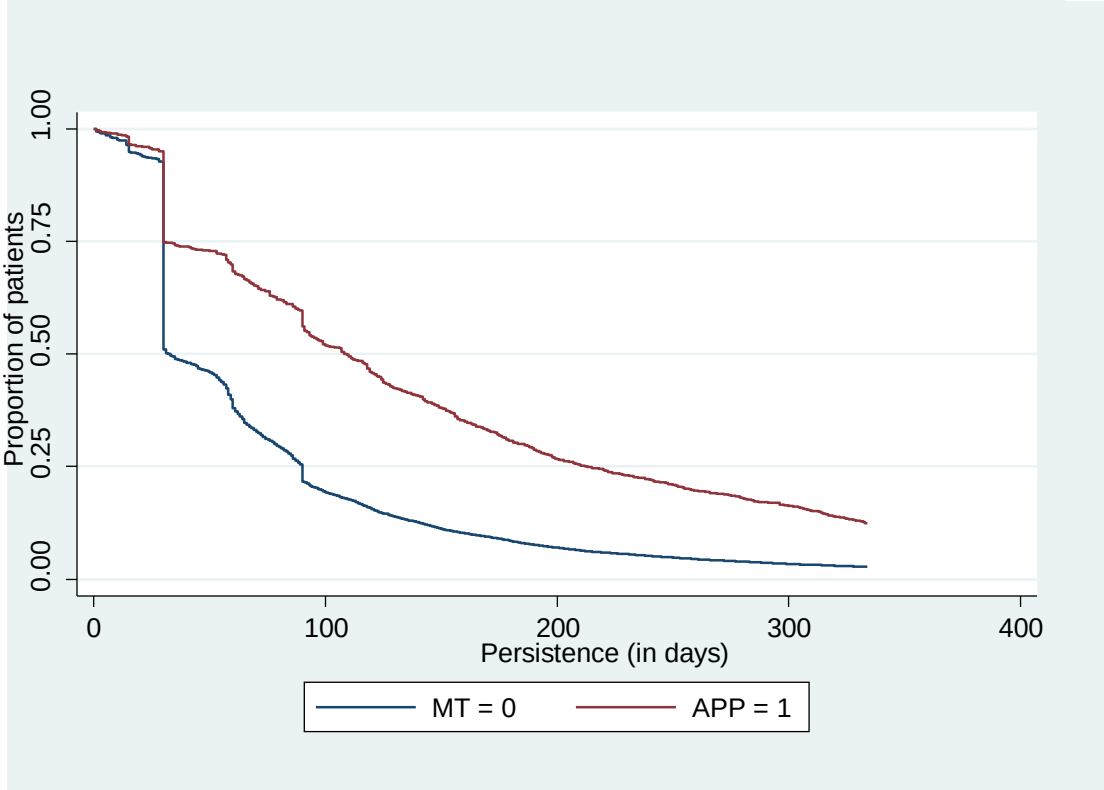
the APP group were more persistent (51% less likely to discontinue their medication) than those in the MT group (*Figure 7*). The results are provided in *Table 19*.

Table 19: Comparison of adjusted adherence and persistence between the MT and APP groups

Adherence/persistence	Antipsychotic Monotherapy Mean (SD) (N=21,979)	Antipsychotic Polypharmacy Mean (SD) (N=1,253)	Test statistic	p-value
Scenario 1				
Adherence—PDC*	0.51 (0.09)	0.39 (0.11)	z=-25.79	<0.001
Odds of being adherent [PDC≥80%] (Reference group: MT) [OR (95% CI)]**	0.17 (0.14-0.22)		z=-14.11	<0.001
Scenario 2				
Adherence—PDC*	0.51(0.10)	0.77 (0.11)	z=33.45	<0.001
Odds of being adherent [PDC≥80%] (Reference group: MT) [OR (95% CI)]**	3.90 (3.44-4.42)		z=21.20	<0.001
Persistence[a] (Reference group: MT) [Hazard Ratio (95% CI)]***	0.49 (0.45-0.53)		z=-18.36	<0.001

* Multiple regression; ** Logistic regression; *** Cox proportional hazards regression
[a]In the APP group, 25% of the patients had a greater than 31 day gap in therapy prior to start of APP

<u>Figure 7:</u> Graph of adjusted persistence time (in days) of the MT and APP groups



This graph adjusts for age, sex, race/ethnicity, year of initiation of index antipsychotic, mental health diagnosis, substance abuse diagnosis, number of mental health comorbidities, pre-index CCI, pre-index CDS, index antipsychotic drug, mode of administration of the antipsychotic, use of psychotropic therapy, use of anticholinergic medications, clinical specialty of prescribing physician, number of physicians prescribing antipsychotics, urban/rural status for prescribing physician, number of mental health-related inpatient hospitalizations in the pre-index period, and number of mental health-related outpatient and emergency department visits in the pre-index period.

4.2. Objectives 5-8

Objectives 5-8 involved comparing the MT and APP groups with respect to: the likelihood of an inpatient hospitalization; length of hospital stay; number of outpatient/emergency department visits; and medical, pharmacy and total costs. Patients newly initiated on antipsychotics were classified into the MT and APP groups. APP was defined as at least 60 days of at least two antipsychotics with no gap in polypharmacy for greater than 31 days and no gap in therapy for greater than 31 days. MT was defined as no evidence of APP after the index antipsychotic claim with no gap in therapy for greater than 31 days. The patients in the MT and APP groups were then matched based on duration of exposure to an antipsychotic. The matched cohorts were used for these analyses.

4.2.1. PATIENT SELECTION

There were 58,311 patients between 18-63 years of age newly initiated on antipsychotics with claims for antipsychotic medications between July 1, 2006 and December 31, 2010. A total of 2,136 (3.7%) patients had at least one APP episode, defined as exposure to two or more antipsychotics for at least 60 days with no gaps in polypharmacy of greater than 31 days and no gap in therapy for greater than 31 days. Of these, 453 (0.8% of the total) were enrolled in Medicaid for the duration of the study period and in the 180 days prior to the index antipsychotic claim. A total of 6,485 (11.1%) patients did not have any APP episodes and had no gaps in antipsychotic therapy of greater than 31 days after the index antipsychotic claim. Of these, 3,407 (5.8% of the total) patients were continuously enrolled in Medicaid in the 180-day pre-index period and the duration of the post-index study period. The prevalence of APP in the Texas Medicaid population among continuously eligible patients with no gap in antipsychotic therapy of greater than 31 days was 11.7% (453/3,860). The patients in the APP and MT groups were

matched to each other based on the duration of exposure to an antipsychotic medication. Post matching, each group had 453 patients. *Figure 8* provides a flowchart showing the execution of the patient inclusion criteria.

Figure 8: Inclusion criteria for patients (Objectives 5-8)

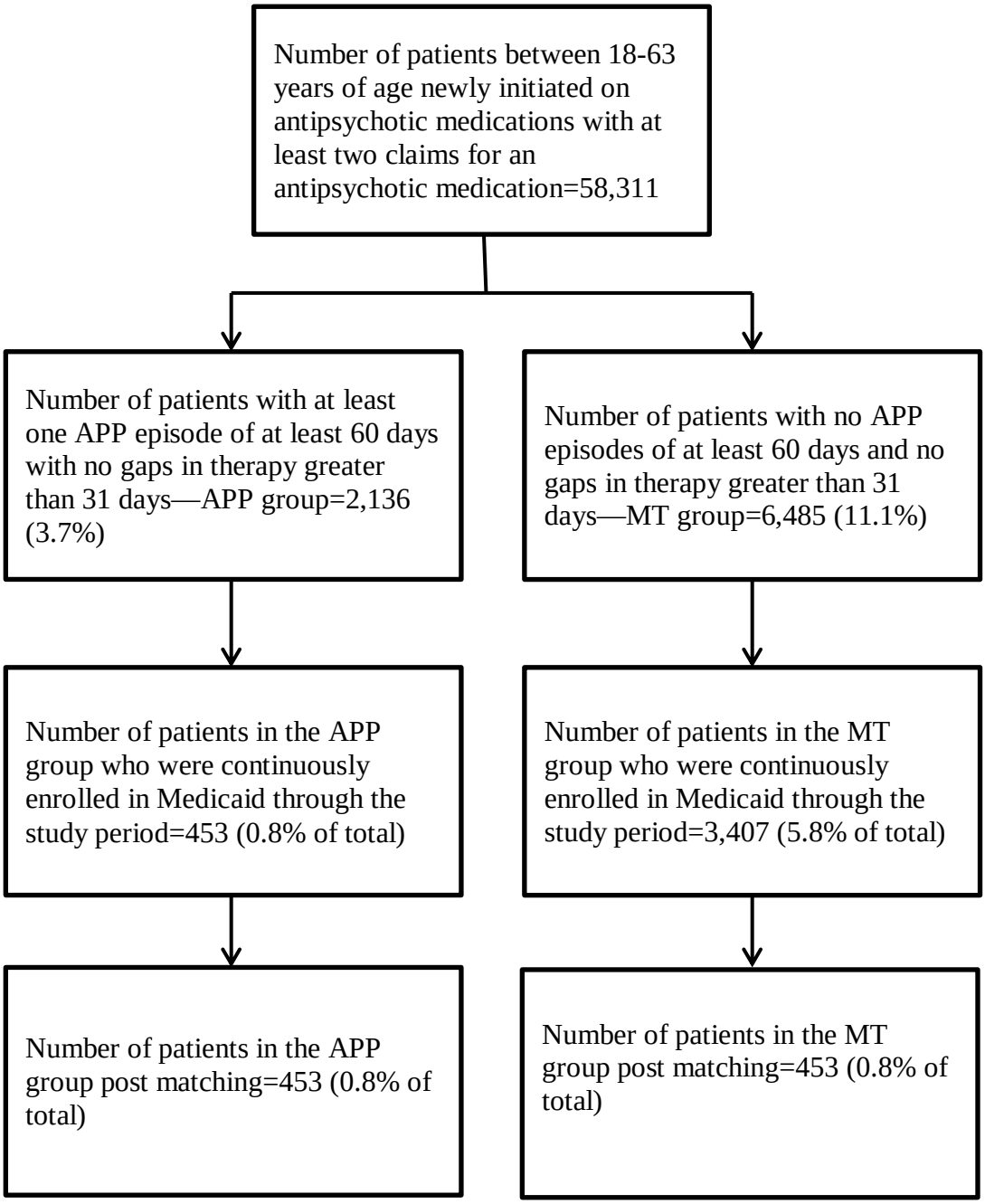


Table 20 provides the characteristics of patients (matched based on duration of exposure to an antipsychotic) in the MT and APP groups. Patients in the APP group had younger patients compared to the MT group. A greater proportion of patients in the APP group were males compared to the MT group. The two groups, APP and MT, differed with respect to the year of their index antipsychotic. Greater proportion of patients in the APP group had a diagnosis of schizophrenia or schizoaffective disorder compared to the MT group. A greater proportion of patients with APP had current substance abuse, used a typical antipsychotic at index, and used anticholinergic drugs. Patients in the APP group had a greater number of unique mental illnesses and higher mean pre-index CDS scores. The APP group also had greater number of prescribers prescribing the antipsychotics and more pre-index psychiatric-related hospitalizations and outpatient visits compared to the MT group. Overall, the APP group consisted of sicker patients with multiple mental health diseases.

Table 20: Comparison of demographic, clinical, physician, and prior utilization characteristics for the matched patients in the MT and APP groups

Characteristic	Categories	Antipsychotic Monotherapy (N=453)		Antipsychotic Polypharmacy (N=453)		Test statistic	p value
		N	%	N	%		
Demographic Characteristics							
Age (Mean, SD)*		41.8	11.8	40.0	12.3	t=2.32	0.0209
Sex**	Male	172	38.0	202	44.6	S=4.02	0.0450
	Female	281	62.0	251	55.4		
Race**	Caucasians	175	38.6	203	44.8	S=14.77	0.1408
	African Americans	115	25.4	114	25.2		
	Hispanics	125	27.6	102	22.5		
	Others	24	5.3	31	6.8		
	Unknown	14	3.1	3	0.7		
Clinical Characteristics							
Year of initiation of index antipsychotic**	2006	54	11.9	45	9.9	S=23.52	0.0090
	2007	122	26.9	102	22.5		
	2008	77	17.0	61	13.5		
	2009	121	26.7	125	27.6		
	2010	79	17.4	120	26.5		

Table 20: Comparison of demographic, clinical, physician, and prior utilization characteristics for the matched patients in the MT and APP groups (continued)

Characteristic	Categories	Antipsychotic Monotherapy (N=453)		Antipsychotic Polypharmacy (N=453)		Test statistic	p value
		N	%	N	%		
Mental health diagnosis**	Schizophrenia/schizo affective disorder	46	10.2	122	26.9	S=52.54	<0.0001
	Bipolar disorder	47	10.4	43	9.5		
	Depression	76	16.9	36	8.0		
	Other mental health diagnoses	174	38.4	168	37.1		
	Multiple mental illnesses	21	4.6	15	3.3		
	No mental health diagnoses	89	14.8	69	15.2		
Current substance abuse**	Yes	62	13.7	87	19.2	S=5.17	0.0230
	No	391	86.3	366	80.8		
Number of unique mental health diagnoses (Mean, SD)*		1.5	1.3	2.0	1.7	t=-4.83	<0.0001
CCI-pre index (Mean, SD)*		0.7	1.3	0.7	1.4	t=-0.31	0.7558
Number of patients with CCI-pre>0**		149	32.9	146	32.2	S=0.05	0.8282
CDS-pre index (Mean, SD)*		4.6	2.5	5.0	2.8	t=-2.63	0.0089
Index antipsychotic drug[a,b,]**	Typical	26	5.7	43	9.5	S=4.31	0.0378
	Atypical	427	94.3	410	90.5		
Mode of administration of the index antipsychotic[a,]**	Oral	441	97.3	433	95.6	S=2.13	0.1441
	Intramuscular	12	2.7	20	4.4		

Table 20: Comparison of demographic, clinical, physician, and prior utilization characteristics for the matched patients in the MT and APP groups (continued)

Characteristic	Categories	Antipsychotic Monotherapy (N=453)		Antipsychotic Polypharmacy (N=453)		Test statistic	p value
		N	%	N	%		
Use of psychotropic therapy during study period**	Yes	358	79.0	377	83.2	S=2.46	0.1171
	No	95	21.0	76	16.8		
Use of anticholinergic medications during study period**	Yes	52	11.5	133	29.4	S=43.45	<0.0001
	No	401	88.5	320	70.6		
Physician Characteristics							
Clinical specialty of prescribing physician**	Psychiatry	256	56.5	267	58.9	S=5.40	0.4933
	General/Family practice	67	14.8	53	11.7		
	Other	104	23.0	96	21.2		
	Unknown	26	5.7	37	8.2		
Number of physicians prescribing antipsychotics (Mean, SD)*		1.6	0.9	2.1	1.3	t=-5.66	<0.0001
Urban/rural status**	Urban	353	77.9	368	81.2	S=8.35	0.0393
	Rural	83	18.3	80	17.7		
	Unknown	17	3.7	5	1.1		

Table 20: Comparison of demographic, clinical, physician, and prior utilization characteristics for the matched patients in the MT and APP groups (continued)

Characteristic	Categories	Antipsychotic Monotherapy (N=453)		Antipsychotic Polypharmacy (N=453)		Test statistic	p value
		N	%	N	%		
Prior utilization characteristics							
Number of mental health-related inpatient hospitalizations in six-month pre-index period (Mean, SD)* **		0.05	0.2	0.2	0.6	S=791	<0.0001
Number of patients with mental health-related inpatient hospitalizations during the six-month pre-index period **		64	14.3	104	23.0	S=11.42	0.0007
Number of mental health-related outpatient visits in six-month pre-index period (Mean, SD)* **		4.8	7.9	7.5	11.4	S=11488	<0.0001

[a] Measured at index of antipsychotic therapy

[b] Patients on initiated on combinations combined with atypical antipsychotics due to small sample size in the combinations group

* Paired sample t-tests; ** McNemar's tests; *** Wilcoxon sign rank tests

4.2.2. HEALTH CARE UTILIZATION FOR MT AND APP GROUPS

Objectives 5-7 involved comparing the likelihood of an inpatient hospitalization, hospital length of stay, and the number of outpatient and emergency department visits between the MT and APP groups. *Table 21* provides a comparison of the unadjusted healthcare utilization between the MT and APP groups. A significantly greater proportion of APP patients had been hospitalized during the study period compared to MT patients (23.0% vs. 14.1%). The APP group had a significantly greater mean number of inpatient hospitalizations (0.5 [1.1] vs. 0.2 [0.8]), days of hospital stay (5.0 [12.2] vs. 2.4 [7.4]), and outpatient visits (46.1 [43.0] vs. 35.9 [37.4]) compared to the MT group.

Table 21: Comparison of unadjusted all-cause healthcare utilization between the MT and APP groups

Health care utilization category	Antipsychotic Monotherapy Mean (SD) [Median (IQR)] (N=453)	Antipsychotic Polypharmacy Mean (SD) [Median (IQR)] (N=453)	Test statistic	p-value
Number of patients with inpatient hospitalizations N (%)[a]	64 (14.1)	104 (23.0)	S=11.43	0.0007
Inpatient hospitalizations[b]	0.2 (0.8) [0 (0)]	0.5 (1.1) [0 (0)]	S=1819.5	0.0002
Length of hospital stay[b]	1.2 (4.5) [0 (0)]	2.6 (8.7) [0 (0)]	S=1982.5	0.0001
Outpatient visits[c]	35.9 (37.4) [26 (36)]	46.1 (43.0) [35 (52)]	t=3.97	<0.0001

[a] McNemars test; [b] Wilcoxon sign rank test; [c] Paired sample t-test

In the regression models used to compare the adjusted healthcare utilization between the MT and APP groups, all demographic, clinical, physician, and prior utilization characteristics were used as covariates. Comparison of the adjusted likelihood of an inpatient hospitalization between the MT and APP groups was done using logistic regression; the odds between the two groups did not vary significantly (Odds ratio=1.47, 95% CI: 0.97-2.25, z=1.80, p=0.072). The adjusted mean length of hospital stay (in days) was higher for the APP group compared to the MT group (2.6 [4.7] vs. 1.2 [1.9]; p<0.001). This comparison was done using a hurdle model. In order to compare the adjusted number of outpatient/emergency department visits between the APP and MT groups, a GzLM regression with a Poisson distribution and a log link function (Modified Park's coefficient 1.3) was used; the adjusted number of outpatient/ emergency department visits between the two groups did not vary significantly (*Table 22*).

Table 22: Results of regression models for the comparison of adjusted all-cause healthcare utilization between the MT and APP groups

Health care utilization category	**Odds Ratio [OR] (95% CI of OR) (N=453)**		**Test statistic**	**p-value**
Odds of having an inpatient hospitalization (Reference group—MT) [OR (95% CI)][a]	1.47 (0.97-2.25)		z=1.80	0.072
Health care utilization category	**Antipsychotic Monotherapy Mean (SD) (N=453)**	**Antipsychotic Polypharmacy Mean (SD) (N=453)**	**Test statistic**	**p-value**
Length of hospital stay[b]	1.2 (1.9)	2.6 (4.7)	S=19680.5	<0.001
Outpatient/emergency department visits[c]	35.9 (20.7)	46.1 (30.0)	z=1.38	0.167

SD: Standard Deviation
[a] Logistic regression; [b] Hurdle model;
[c] GzLM regression with Poisson distribution and a log-link function

4.2.3. COSTS FOR MT AND APP GROUPS

Objective 8 involved comparing the pharmacy, medical and total costs between the MT and APP groups. The regression models that compared the adjusted costs between the two groups used all demographic, clinical, physician, and prior utilization characteristics as covariates. *Table 23* provides the unadjusted costs for the MT and APP groups. Costs are categorized by type of healthcare utilization—medical costs, which includes costs associated with inpatient hospitalizations and outpatient/emergency department visits; and drug costs. In addition, costs are also categorized by whether they are psychiatric related or non-psychiatric related. The costs for the APP group were statistically significantly higher for all categories except the non-psychiatric related costs.

Table 23: Comparison of unadjusted costs (in USD) between the MT and APP groups

Cost Category*	Antipsychotic Monotherapy Mean (SD) (N=453)	Antipsychotic Monotherapy Median (IQR) (N=453)	Antipsychotic Polypharmacy Mean (SD) (N=453)	Antipsychotic Polypharmacy Median (IQR) (N=453)	Test statistic	p-value
Medical Costs						
Inpatient costs	1,237.12 (4,736.36)	0 (0)	2,293.78 (6,649.58)	0 (0)	S=1977.5	0.0003
Outpatient costs	4,872.70 (7,446.06)	2,362.21 (4,737.13)	6,742.21 (8,584.19)	4,027.73 (8,063.81)	S=10765.5	<0.0001
Total medical costs[a]	6,109.82 (9,850.89)	2,687.82 (5,913.03)]	9,035.99 (12,662.64)	4,589.13 (10,687.52)	S=12770.5	<0.0001
Drug costs	9,700.83 (7,250.23)	8,213.39 (7,018.40)	14,655.56 (9,528.85)	12,513.90 (10,103.83)	S=25823.5	<0.0001
Psychiatric Status						
Psychiatric costs	5,806.10 (4,314.73)	5,257.87 (4,700.43)	12,160.25 (8,315.85)	9,896.63 (9,330.03)	S=37233.5	<0.0001
Non-psychiatric costs	10,004.55 (12,239.75)	6,115.08 (10,291.19)	11,531.29 (14,648.67)	6,650.81 (11,998.62)	S=2164.5	0.4381
Total costs[b,c]	15,810.65 (13,240.11)	12,640.22 (11,257.31)	23,691.54 (17,229.56)	18,404.69 (18,554.56)	S=22510.5	<0.0001

* All comparisons were conducted using Wilcoxon signed rank tests [a] Total medical costs = inpatient costs + outpatient costs
[b] Total costs = medical costs + drug costs; [c] Total costs = psychiatric costs + non-psychiatric costs

In the regression analyses used to compare the adjusted costs between the MT and APP groups, demographic, clinical, physician, and prior utilization characteristics were controlled. GzLM regression was used to estimate the costs (medical, drug, and total costs as per objective 8) after adjusting for the covariates. In order to identify the appropriate family to be used for the GzLM regression, a Modified Park's test was used. The Modified Park's tests produced gamma coefficients (γ) of 1.6, 1.6, and 2.1 for medical, drug, and total costs, respectively. A γ coefficient of 2 denotes that a gamma distribution would be most appropriate for the regression analysis (*Table 9* provides the γ coefficient values for other commonly used distributions). Thus, GzLM with a gamma distribution and a log link function was used to estimate the adjusted drug, medical, and total costs for the APP and MT groups. Results are provided in *Table 24*. The adjusted medical costs (mean [SD] $10,040.47 [$11,984.24] vs. $6,242.64 [$6,055.36]), drug costs ($14,909.13 [$5,103.79] vs. $9,579.34 [$2,826.93]), and total costs ($24,426.28 [$12,289.23] vs. $15,503.87 [$6,806.68]) were significantly higher in the APP group compared to the MT group.

Table 24: Results of the regression models for comparison of adjusted all-cause costs (in USD) between the MT and APP groups

Cost Category*	Antipsychotic Monotherapy Mean (SD) (N=453)	Antipsychotic Polypharmacy Mean (SD) (N=453)	Test statistic	p-value
Medical costs	6,242.64 (6,055.36)	10,040.47 (11,984.24)	z=1.99	0.047
Drug costs	9,579.34 (2,826.93)	14,909.13 (5,103.79)	z=10.88	<0.001
Total costs	15,503.87 (6,806.68)	24,426.28 (12,289.23)	z=8.21	<0.001

***** GLzM regression with a gamma distribution and a log link function were used for the adjusted all-cause cost comparisons

4.3. Sensitivity Analysis

1. All cause costs vs. psychiatric-related costs

In the base case healthcare utilization and cost calculations, we used all-cause outcomes and costs. This is because the effect of APP is not well known; non-mental health-related healthcare utilization and cost outcomes could also be affected in addition to the mental health-related outcomes—such as, increased use of antipsychotics may lead to increase in cardiometabolic diseases such as diabetes which could lead to increased health resource utilization and outcomes. In addition, high antipsychotic medication use could also cause extrapyramidal symptoms leading to increased healthcare utilization and costs. As a sensitivity analysis, we included psychiatric-related utilization and costs instead of the all-cause ones in order to get a sense of the relationship between the psychiatric-related outcomes and APP. The results of the sensitivity analyses associated with the all-cause vs. psychiatric-related utilization and cost outcomes are provided in *Table 25*.

Table 25: Comparison of healthcare utilization and cost (in USD) outcomes between the MT and APP groups for all-cause outcomes and psychiatric-related outcomes

Category	All-cause outcomes (Baseline) (N=453)				Psychiatric-related outcomes (N=453)			
	Antipsychotic Monotherapy Mean (SD)	Antipsychotic Polypharmacy Mean (SD)	Test statistic	p-value	Antipsychotic Monotherapy Mean (SD)	Antipsychotic Polypharmacy Mean (SD)	Test statistic	p-value
Health care utilization								
Odds of having an inpatient hospitalization (Reference Group: MT) [OR (95% CI)]	1.47 (0.97-2.25)		z=1.80	0.072	2.20 (1.10-4.41)		z=2.22	0.026
Length of hospital stay[a]	1.2 (1.9)	2.6 (4.7)	S=19680.5	<0.001	0.3 (1.3)	1.9 (13.2)	S=19804.5	<0.001
Outpatient/ emergency department visits	35.9 (20.7)	46.1 (30.0)	z=1.38	0.167	10.0 (12.2)	18.3 (23.6)	z=2.18	0.029
Costs (in USA)								
Medical costs[b]	6,242.64 (6,055.36)	10,040.47 (11,984.24)	z=1.99	0.047	2,511.00 (15,313.80)	8,290.86 (35,051.37)	z=3.25	0.001
Drug costs	9,579.34 (2,826.93)	14,909.13 (5,103.79)	z=10.88	<0.001	4,577.12 (839.03)	9,353.19 (1,892.04)	z=13.86	<0.001
Total costs	15,503.87 (6,806.68)	24,426.28 (12,289.23)	z=8.21	<0.001	5,705.42 (2,192.48)	12,440.25 (5,466.31)	z=13.11	<0.001

[a] In the length of hospital stay model for psychiatric-related outcomes, mode of administration (oral vs. intramuscular) was not included as a covariate as it caused model convergence issues

[b] In the medical costs model for psychiatric-related outcomes, the variable denoting the specific diagnosis of the patient was not included as it caused model convergence issues

When only psychiatric-related outcomes were included, APP patients were twice as likely as MT patients to have an inpatient hospitalization (OR=2.20, 95% CI=1.10-4.41, z=2.22, p=0.026) and the adjusted length of stay was significantly higher for the APP vs. the MT group (1.9 [13.2] vs. 0.3 [1.3], p<0.001). The number of outpatient visits was significantly higher in the APP group compared to the MT group (18.3 [23.6] vs. 10.0 [12.2], z=2.18, p=0.029). The adjusted psychiatric-related medical cost ($8,290.86 [$35,051.37] vs. $2,511.00 [$15,313.80])), drug costs ($9,353.19 [$1,892.04] vs. $4,577.12 [$839.0]) and total costs ($12,440.25 [$5,466.31] vs. $5,705.42 [$2,192.48]) were significantly higher in the APP group compared to the MT group.

2. Varying the definition of APP

a) Varying the overlap period

In the base case, APP was defined as exposure to two or more antipsychotics for at least 60 days with no gap in polypharmacy of greater than 31 days and no gap in therapy of more than 31 days. The overlap period was increased to 120 days and 180 days to determine how that would affect the prevalence and outcomes associated with APP. When the overlap period was increased to 120 days, there were 590 patients in the APP group and these were used for the incidence and adherence analyses. A total of 271 patients did not have any gaps in polypharmacy for greater than 31 days and no gap in therapy for greater than 31 days and could be matched to MT patients (on duration of exposure to an antipsychotic); thus, this set was used for healthcare utilization and cost outcomes analysis. When the overlap period was further increased to 180 days, there were 316 patients in the APP group who were used for the incidence and adherence analyses. A total of 221 patients had no gap in polypharmacy for greater than 31 days and no gap in therapy for greater than 31 days and could be matched to the MT patients (on duration of exposure to an antipsychotic). This set was used for the healthcare utilization and cost outcomes analysis. *Table 26* provides the results for these sensitivity analyses.

Table 26: Comparison of healthcare utilization and cost (in USD) outcomes when APP was defined as at least 60 days (base case), 120 days, and 180 days of antipsychotic medication overlap

Category	60 days definition for APP (Baseline)			120 days definition for APP			180 days definition for APP		
	MT Mean (SD)	APP Mean (SD)	Test statistic; p-value	MT Mean (SD)	APP Mean (SD)	Test statistic; p-value	MT Mean (SD)	APP Mean (SD)	Test statistic; p-value
Incidence, adherence, and persistence									
	N=21,979	N=1,253		N=22,642	N=590		N=22,916	N=316	
APP incidence	5.4%			2.5%			1.4%		
Scenario 1: Adherence	0.51 (0.09)	0.39 (0.11)	z=-25.79; <0.001	0.51 (0.10)	0.55 (0.12)	z=-3.59; <0.001	0.52 (0.10)	0.67 (0.12)	z=6.69; <0.001
Scenario 2: Adherence	0.51 (0.10)	0.77 (0.11)	z=33.45; <0.001	0.51 (0.10)	0.84 (0.12)	z=34.23; <0.001	0.52 (0.10)	0.89 (0.12)	z=33.41; <0.001
Scenario 1: Odds of being adherent [PDC≥80%] (Reference Group: MT) [OR (95% CI)]	0.17 (0.14-0.22)		z=-14.11; <0.001	0.38 (0.29-0.49)		z=-7.38; <0.001	0.77 (0.58-1.03)		z=-1.78; 0.075
Scenario 2: Odds of being adherent [PDC≥80%] (Reference Group: MT) [OR (95% CI)]	3.90 (3.44-4.42)		z=21.20; <0.001	6.92 (5.72-8.39)		z=19.78; <0.001	14.97 (10.92-20.51)		z=16.83; <0.001
Persistence (Reference Group: MT) [Hazard Ratio (95% CI)]	0.49 (0.45-0.53)		z=-18.36; <0.001	0.34 (0.30-0.38)[a]		z=-16.72; <0.001	0.22 (0.18-0.27)[b]		z=-14.20; <0.001

Table 26: Comparison of healthcare utilization and cost (in USD) outcomes when APP was defined as at least 60 days (base case), 120 days, and 180 days of antipsychotic medication overlap (continued)

Category	60 days definition for APP (Baseline)			120 days definition for APP			180 days definition for APP		
	MT Mean (SD)	APP Mean (SD)	Test statistic; p-value	MT Mean (SD)	APP Mean (SD)	Test statistic; p-value	MT Mean (SD)	APP Mean (SD)	Test statistic; p-value
Health care utilization									
	N=453 per group			N=271 per group			N=221 per group		
Odds of having an inpatient hospitalization (Reference Group: MT) [OR (95% CI)]	1.47 (0.97-2.25)		z=1.80 0.072	1.36 (0.78-2.35)		z=1.09; 0.276	1.44 (0.77-2.72)		z=1.13; 0.257
Length of hospital stay	1.2 (1.9)	2.6 (4.7)	S=19680.5; <0.001	1.0 (1.1)	2.2 (4.2)	S=7431; <0.001	0.9 (1.2)	2.3 (5.1)	S=3737.5; <0.001
Outpatient/ emergency department visits	35.9 (20.7)	46.1 (30.0)	z=1.38; 0.167	37.3 (19.3)	43.0 (30.8)	z=-0.23 0.814	38.5 (19.2)	45.9 (33.7)	z=-0.10; 0.921
Costs (in USD)									
Medical costs	6,242.64 (6,055.36)	10,040.47 (11,984.24)	z=1.99; 0.047	6,723.66 (5,721.09)	9,369.86 (11,693.67)	z=1.20; 0.232	7,098.36 (5,782.68)	10,607.59 (13,116.49)	z=1.68; 0.092
Drug costs	9,579.34 (2,826.93)	14,909.13 (5,103.79)	z=10.88; <0.001	9,866.10 (3,127.41)	15,562.20 (5,829.68)	z= 9.56; p<0.001	10,361.99 (3,084.92)	17,335.30 (5,794.23)	z=9.51; <0.001
Total costs	15,503.87 (6,806.68)	24,426.28 (12,289.23)	z=8.21; <0.001	16,143.40 (6,706.17)	24,566.49 (12,639.42)	z=7.52; P<0.001	17,123.14 (7,020.62)	27,333.52 (13,650.06)	z=7.56; <0.001

MT: Antipsychotic monotherapy; APP: Antipsychotic polypharmacy

[a] In the APP group, 19% of the patients had a 31 days gap in therapy prior to start of APP

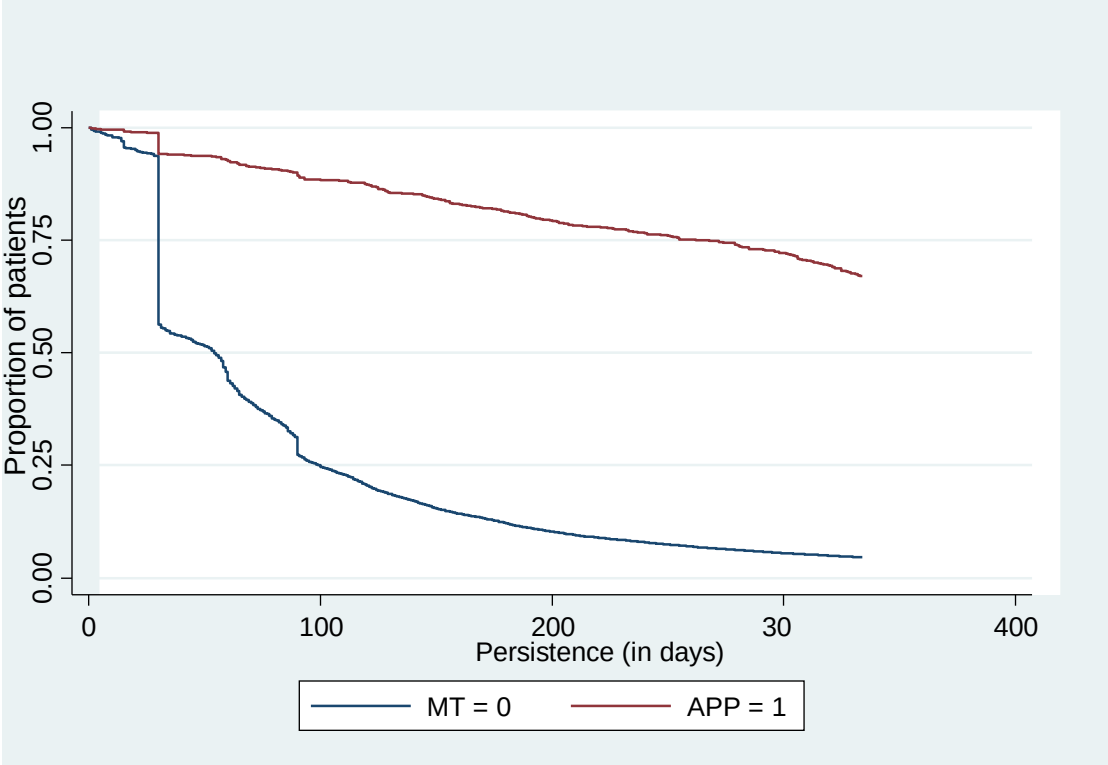
[b] In the APP group, 10% of the patients had a 31 days gap in therapy prior to start of APP

When 120-day and 180-day overlap periods were used to define APP, the incidence of APP changed to 2.5% and 1.4%, respectively. With respect to adherence, as the overlap period was increased (from 60 to 120 and 180 days), the adherence in the APP group increased and was higher than the MT group in scenarios 1 and 2. Patients with a PDC≥80% were considered to be adherent. For the 120-day overlap period, the odds of MT patients being adherent were higher than APP patients for scenario 1 and the opposite was true for scenario 2. For the 180-day overlap period (scenario 1) the odds of being adherent were not significantly different between the MT and APP groups. For scenario 2 (with a 180-day overlap period), the results were similar to the base case; adherence and odds of being adherent were higher in the APP group compared to the MT group. The duration of medication use prior to discontinuation (persistence) varied between the MT and APP groups in both sensitivity analyses cases and number of days of medication use prior to discontinuation (persistence) was higher in the APP group. *Figure 9* provides the graphs showing the adjusted persistence for the MT and APP groups.

The odds of a hospitalization did not differ significantly between the MT and APP groups for the 120 and 180 days overlap period. The adjusted length of hospital stay was higher in the APP group compared to the MT group in both sensitivity analyses cases. Like the base care scenario, drug costs and total costs were higher in the APP group compared to the MT group for both sensitivity analysis cases, when the overlap period was increased to 120 days and 180 days. The difference in medical costs between the APP and MT groups was not statistically significant for the 120- and 180-days overlap scenarios.

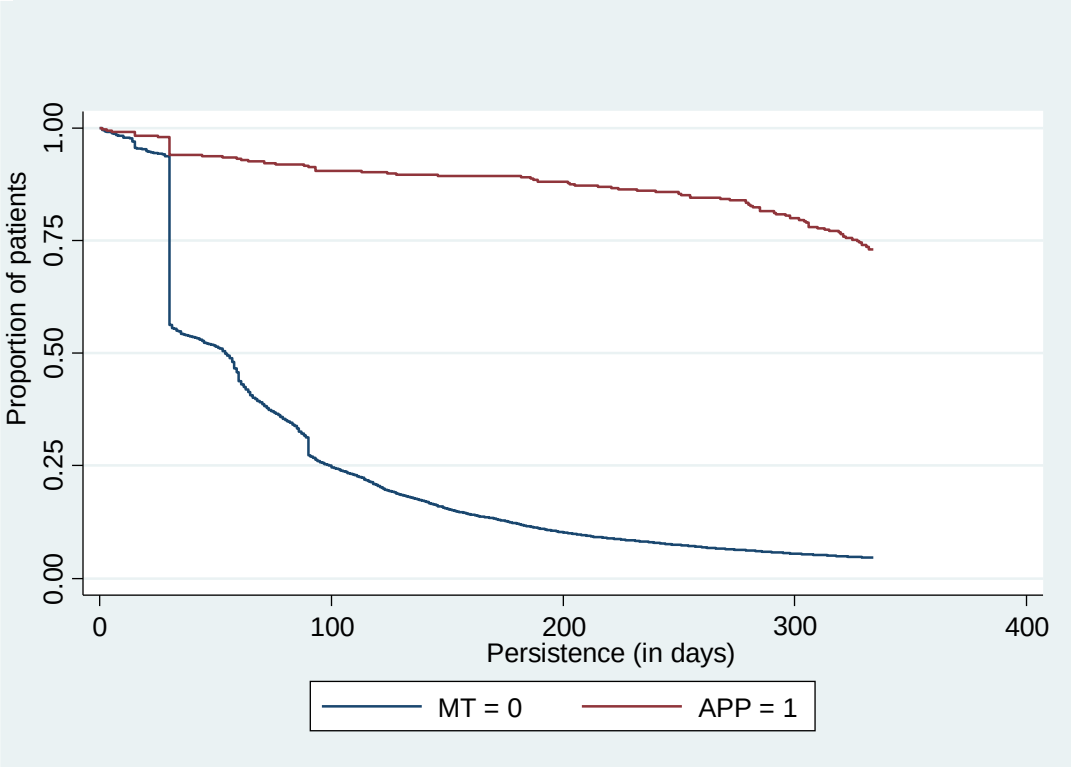
<u>Figure 9:</u> Graphs for adjusted persistence (in days) for the sensitivity analyses of days of overlap in therapy

(a) Overlap period = 120 days



This graph adjusts for age, sex, race/ethnicity, year of initiation of index antipsychotic, mental health diagnosis, substance abuse diagnosis, number of mental health comorbidities, pre-index CCI, pre-index CDS, index antipsychotic drug, mode of administration of the antipsychotic, use of psychotropic therapy, use of anticholinergic medications, clinical specialty of prescribing physician, number of physicians prescribing antipsychotics, urban/rural status for prescribing physician, number of mental health-related inpatient hospitalizations in the pre-index period, and number of mental health-related outpatient and emergency department visits in the pre-index period.

(b) Overlap period = 180 days



This graph adjusts for age, sex, race/ethnicity, year of initiation of index antipsychotic, mental health diagnosis, substance abuse diagnosis, number of mental health comorbidities, pre-index CCI, pre-index CDS, index antipsychotic drug, mode of administration of the antipsychotic, use of psychotropic therapy, use of anticholinergic medications, clinical specialty of prescribing physician, number of physicians prescribing antipsychotics, urban/rural status for prescribing physician, number of mental health-related inpatient hospitalizations in the pre-index period, and number of mental health-related outpatient and emergency department visits in the pre-index period.

b) Varying the gap in therapy

In the base case, APP was defined as two or more antipsychotics for at least 60 days with no gap in polypharmacy for greater than 31days. As a sensitivity analysis, the gap was varied to 15 days and 45 days. When a gap period of 15 days was used, 1,076 patients were classified as APP. They were used for the incidence and adherence analyses. Of these, 174 patients had no gaps in polypharmacy of greater than 15 days and no gap in therapy of greater than 15 days and could be matched to patients in the MT group (on duration of exposure to an antipsychotic). They were used for the healthcare utilization and cost analyses. When 45 days was used as the gap period, 1,369 patients were classified as APP and were used for the incidence and adherence analyses. Of these, 601 patients had no gaps in any polypharmacy for greater than 45 days and no gap in therapy of greater than 45 days and could be matched to MT patients (on duration of exposure to an antipsychotic); these patients were used for the healthcare utilization and cost outcomes. *Table 27* provides the results of the sensitivity analyses.

Table 27: Comparison of healthcare utilization and cost (in USD) outcomes with gap in therapy defined as at least 31 days, 15 days, and 45 days

Category	31 days gap in therapy (Baseline)			15 days gap in therapy			45 days gap in therapy		
	MT Mean (SD)	APP Mean (SD)	Test statistic; p-value	MT Mean (SD)	APP Mean (SD)	Test statistic; p-value	MT Mean (SD)	APP Mean (SD)	Test statistic; p-value
Incidence, adherence, and persistence									
	N=21,979	N=1,253		N=22,156	N=1,076		N=21,863	N=1,369	
APP incidence	5.4%			4.6%			5.9%		
Scenario 1: Adherence	0.51 (0.09)	0.39 (0.11)	z=-25.79; <0.001	0.51 (0.10)	0.42 (0.11)	z=-20.41; <0.001	0.51 (0.09)	0.37 (0.11)	z=-29.24; <0.001
Scenario 2: Adherence	0.51 (0.10)	0.77 (0.11)	z=33.45; <0.001	0.51 (0.10)	0.79 (0.11)	z=33.79; <0.001	0.51 (0.09)	0.76 (0.11)	z=33.33; <0.001
Scenario 1: Odds of being adherent [PDC≥80%] (Reference group: MT) [OR (95% CI)]	0.17 (0.14-0.22)		z=-14.11; <0.001	0.20 (0.16-0.26)		z=-12.84; <0.001	0.16 (0.12-0.20)		z=-14.92; <0.001
Scenario 2: Odds of being adherent [PDC≥80%] (Reference group: MT) [OR (95% CI)]	3.90 (3.44-4.42)		z=21.20; <0.001	4.37 (3.81-5.00)		z=21.33; <0.001	3.64 (3.22-4.10)		z=20.91, <0.001
Persistence (Reference group: MT) [Hazard Ratio (95% CI)]	0.49 (0.45-0.53)		z=-18.36; <0.001	0.46 (0.42-0.50)[a]		z=-17.99; <0.001	0.51 (0.47-0.55)[b]		z=-18.27; <0.001

Table 27: Comparison of healthcare utilization and cost (in USD) outcomes with gap in therapy defined as at least 31 days, 15 days, and 45 days (continued)

Category	31 days gap in therapy (Baseline)			15 days gap in therapy			45 days gap in therapy		
	MT Mean (SD)	APP Mean (SD)	Test statistic; p-value	MT Mean (SD)	APP Mean (SD)	Test statistic; p-value	MT Mean (SD)	APP Mean (SD)	Test statistic; p-value
Health care utilization									
	N=453 per group			N=174 per group			N=601 per group		
Odds of having an inpatient hospitalization (Reference Group: MT) [OR (95% CI)]	1.47 (0.97-2.25)		z=1.80 0.072	1.48 (0.71-3.08)		z=1.04; 0.299	1.91 (1.32-2.76)		z=3.44; 0.001
Length of hospital stay	1.2 (1.9)	2.6 (4.7)	S=19680.5; <0.001	1.0 (1.5)	1.8 (3.9)	S=1934.5; 0.003	0.9 (1.2)	2.7 (5.6)	S=44564.5; <0.001
Outpatient/emergency department visits	35.9 (20.7)	46.1 (30.0)	z=1.38; 0.167	37.1 (22.8)	47.0 (36.3)	z=0.76; 0.445	35.7 (21.8)	45.0 (48.7)	z=-0.55; 0.583
Costs (in USD)									
Medical costs	6,242.64 (6,055.36)	10,040.47 (11,984.24)	z=1.99; 0.047	6,501.29 (10,083.32)	10,554.23 (17,596.12)	z=1.78; 0.075	6,053.27 (7,098.10)	10,803.46 (20,206.67)	z=3.07; 0.002
Drug costs	9,579.34 (2,826.93)	14,909.13 (5,103.79)	z=10.88; <0.001	9,976.26 (3,042.03)	14,740.72 (4,728.49)	z=5.31; <0.001	8,835.61 (2,426.34)	13,657.07 (4,557.73)	z=11.31; <0.001
Total costs	15,503.87 (6,806.68)	24,426.28 (12,289.23)	z=8.21; <0.001	15,828.10 (7,791.11)	23818.02 (11,607.83)	z=4.93; <0.001	14,500.13 (6,419.17)	23,063.52 (13,314.79)	z=8.83; <0.001

MT: Antipsychotic monotherapy; APP: Antipsychotic polypharmacy

[a] In the APP group, 24% of the patients had a 31 days gap in therapy prior to start of APP

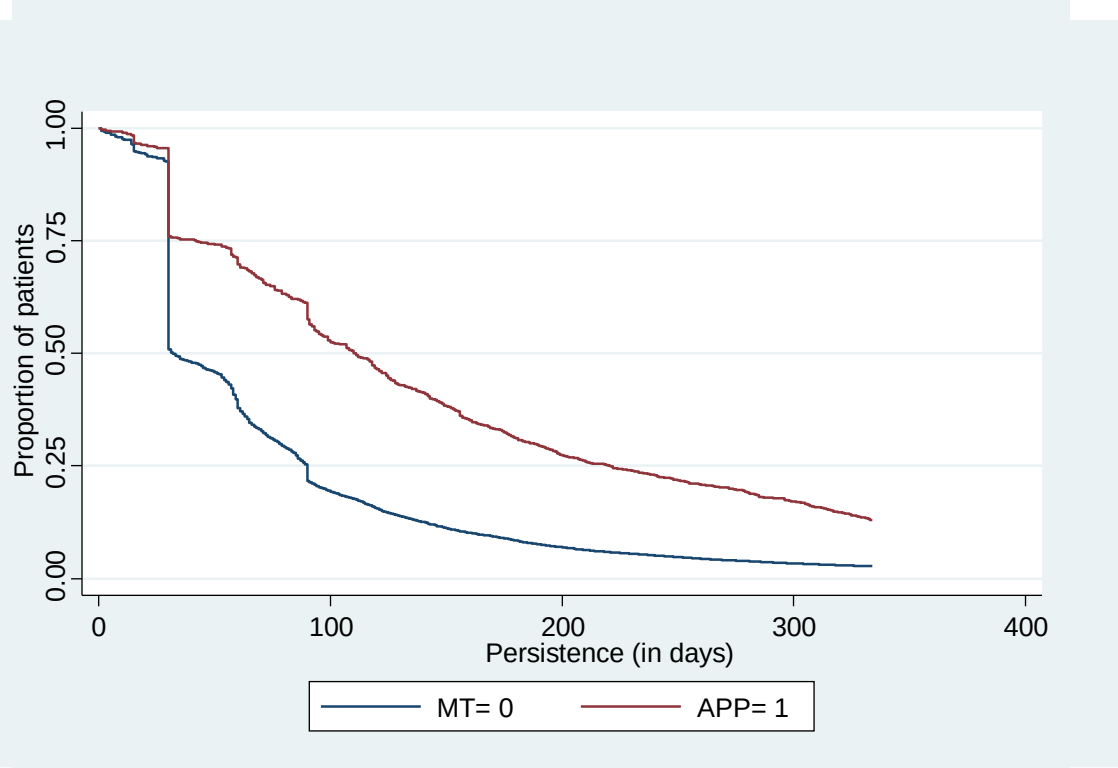
[b] In the APP group, 25% of the patients had a 31 days gap in therapy prior to start of APP

When the gap period was changed to 15 days and 45 days, the incidence of APP changed to 4.6% and 5.9%, respectively. With respect to adherence, varying the gap period produced results similar to those in the base case for both scenarios 1 and 2; adherence was higher and the odds of being adherent were higher in the MT group compared to the APP group in scenario1 and the opposite was true for scenario 2. The duration of medication use prior to discontinuation (persistence) varied between the MT and APP groups in both sensitivity analyses cases and time to medication discontinuation (persistence) was higher in the APP group. *Figure 10* provides the graphs showing the adjusted persistence for the MT and APP groups.

When the gap in therapy was increased to 45 days, patients in the APP group were almost twice as likely (OR: 1.91 [95% CI: 1.32-2.76]) to have an inpatient hospitalization compared to the MT group. This difference was not statistically significant for the 15 days gap scenario. The adjusted length of hospital stay was higher in the APP group compared to the MT group when the gap in therapy was varied to 15 days and 45 days. The number of outpatient/emergency department visits did not differ significantly between the MT and APP groups in both sensitivity analyses cases. The APP patients had higher medical, drug, and total costs compared to the MT group when the gap in therapy was 45 days. When the gap in therapy was reduced to 15 days, the pharmacy and total costs were higher in the APP group compared to the MT group. There was no difference in the medical costs between the two groups when the gap period was reduced to 15 days.

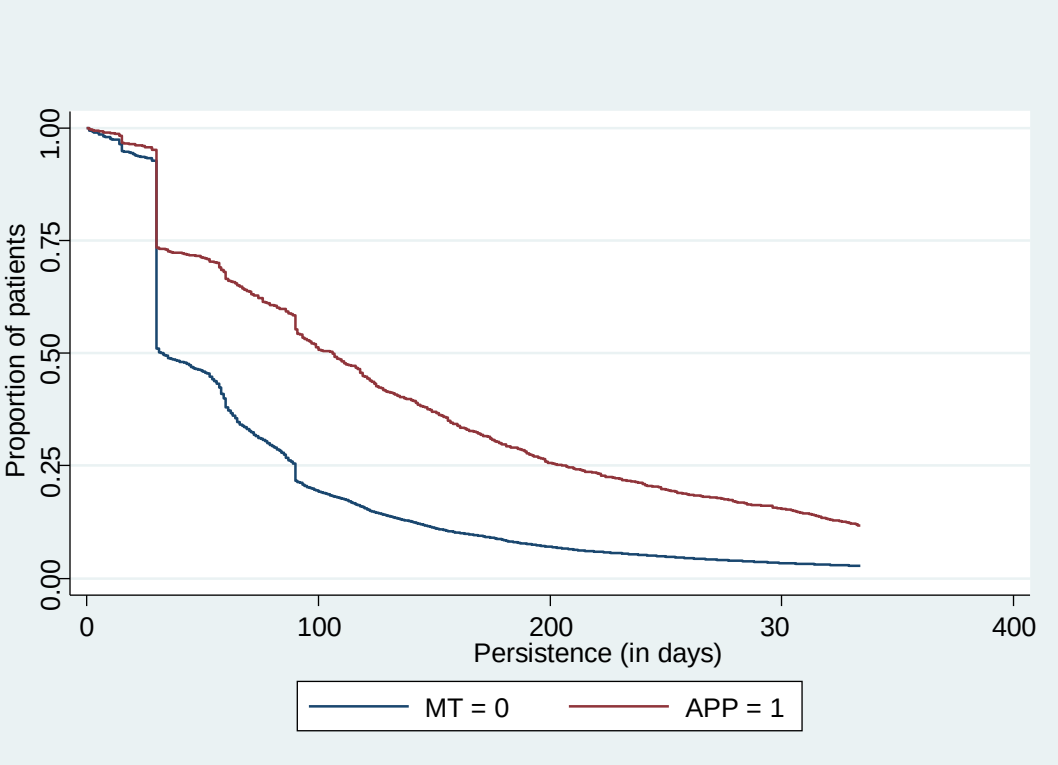
<u>Figure 10:</u> Graphs for adjusted persistence (in days) for the sensitivity analyses of gap in therapy

(a) Gap in therapy = 15 days



This graph adjusts for age, sex, race/ethnicity, year of initiation of index antipsychotic, mental health diagnosis, substance abuse diagnosis, number of mental health comorbidities, pre-index CCI, pre-index CDS, index antipsychotic drug, mode of administration of the antipsychotic, use of psychotropic therapy, use of anticholinergic medications, clinical specialty of prescribing physician, number of physicians prescribing antipsychotics, urban/rural status for prescribing physician, number of mental health-related inpatient hospitalizations in the pre-index period, and number of mental health-related outpatient and emergency department visits in the pre-index period

(b) Gap in therapy = 45 days



This graph adjusts for age, sex, race/ethnicity, year of initiation of index antipsychotic, mental health diagnosis, substance abuse diagnosis, number of mental health comorbidities, pre-index CCI, pre-index CDS, index antipsychotic drug, mode of administration of the antipsychotic, use of psychotropic therapy, use of anticholinergic medications, clinical specialty of prescribing physician, number of physicians prescribing antipsychotics, urban/rural status for prescribing physician, number of mental health-related inpatient hospitalizations in the pre-index period, and number of mental health-related outpatient and emergency department visits in the pre-index period

In all the analyses conducted for this study, mean values have been provided for the healthcare utilization and cost outcomes for the MT and APP groups. In order to better assess the difference in outcomes and costs between the MT and APP groups, *Table 28* provides the difference between the APP and MT groups for both utilization and costs. The difference (APP-MT) is provided for the base case as well as the five sensitivity analyses cases. As can be noted from the table, the magnitude of utilization and cost outcomes were higher for the APP group compared to the MT group. The likelihood of an inpatient hospitalization was represented as an odds ratio and hence no difference is provided.

Table 28: Difference in healthcare utilization and cost outcomes between MT and APP groups for base case and all sensitivity analyses cases

Adjusted outcomes (APP-MT)[a]	Base case Difference (SD) (N=453 per group)	Psychiatric-related outcomes Difference (SD) (N=453 per group)	120-day overlap Difference (SD) (N=271 per group)	180-day overlap Difference (SD) (N=221 per group)	15-day gap Difference (SD) (N=174 per group)	45-days gap Difference (SD) (N=601 per group)
Healthcare utilization						
All-cause hospital length of stay	1.42* (5.12)	1.55* (13.29)	1.22* (4.26)	1.39* (5.20)	0.84* (4.05)	1.79* (5.66)
All-cause number of outpatient/emergency department visits	10.23 (34.79)	8.31* (25.76)	5.71 (34.67)	7.43 (37.05)	9.87 (41.84)	9.29 (53.77)
Costs (in USD)						
All-cause medical costs	3,797.84* (12,967.67)	5,779.86* (37,596.87)	2,646.195 (12,281.04)	3,509.23 (13,514.51)	4,052.95 (20,421.81)	4,750.19* (21,492.38)
All-cause drug costs	5,329.79* (5,810.30)	4,776.07* (2,110.83)	5,696.10* (6,865.45)	6,973.30* (6,766.65)	4,764.47* (5,594.83)	4,821.46* (5,086.56)
All-cause total costs	8,922.41* (13,840.41)	6,734.83* (5,802.58)	8,423.09* (13,916.12)	10,210.38* (14,917.98)	7,989.92* (13,759.09)	8,563.39* (14,647.87)

[a] adjusted for age, sex, race/ethnicity, year of initiation of index antipsychotic, mental health diagnosis, substance abuse diagnosis, number of mental health comorbidities, pre-index CCI, pre-index CDS, index antipsychotic drug, mode of administration of the antipsychotic, use of psychotropic therapy, use of anticholinergic medications, clinical specialty of prescribing physician, number of physicians prescribing antipsychotics, urban/rural status for prescribing physician, number of mental health-related inpatient hospitalizations in the pre-index period, and number of mental health-related outpatient and emergency department visits in the pre-index period

* Difference between APP and MT statistically significant at $p<0.05$

Table 29 provides the results of the hypotheses tests carried out in this study.

Table 29: Results of hypotheses tests

Objectives/Hypotheses	Result
Objective 1: Determine the incidence of APP —overall and by subgroup and classify patients into the MT and APP groups	No hypothesis
Objective 2: Describe and compare the demographic, clinical, physician, and prior utilization characteristics of patients in the APP and MT groups	No hypothesis
Objective 3: Identify the characteristics of patients most likely to be prescribed APP	
$H_{3.1}$: **Younger patients** are more likely to be on APP compared to **older patients** after controlling for other demographic, clinical, physician, and prior utilization characteristics.	Rejected
$H_{3.2}$: **Male** patients are more likely to be on APP compared to **female** patients after controlling for other demographic, clinical, physician, and prior utilization characteristics.	Failed to reject
$H_{3.3}$: **Caucasian** patients are more likely to be on APP compared to the **other ethnicities** after controlling for other demographic, clinical, physician, and prior utilization characteristics.	Rejected
$H_{3.4}$: Patients with an index antipsychotic claim in **2010** are more likely to be on APP compared to those with an index claim in **other years** after controlling for other demographic, clinical, physician, and prior utilization characteristics.	Rejected
$H_{3.5}$: Patients with a **schizophrenia/schizoaffective disorder** diagnosis are more likely to be on APP compared to those with **other mental health diagnoses** after controlling for other demographic, clinical, physician, and prior utilization characteristics.	Failed to reject
$H_{3.6}$: Patients **without a substance abuse diagnosis** are more likely to be on APP compared to those **with such a diagnosis** after controlling for other demographic, clinical, physician, and prior utilization characteristics.	Failed to reject
$H_{3.7}$: The **likelihood of APP increases** with **each additional comorbidity** experienced by patients after controlling for other demographic, clinical, physician, and prior utilization characteristics.	Failed to reject
$H_{3.8}$: Patients with a **lower pre-index period CCI score** are more likely to be on APP compared to those with **a higher score** after controlling for other demographic, clinical, physician, and prior utilization characteristics.	Rejected

Table 29: Results of hypotheses tests (continued)

Objectives/Hypotheses	Result
$H_{3.9}$: Patients with a **lower pre-index period CDS score** are more likely to be on APP compared to those with a **higher score** after controlling for other demographic, clinical, physician, and prior utilization characteristics.	Failed to reject
$H_{3.10}$: Patients initiated on **typical antipsychotics** are more likely to be on APP compared to those initiated on **atypical antipsychotics** after controlling for other demographic, clinical, physician, and prior utilization characteristics.	Rejected
$H_{3.11}$: Patients initiated on **oral antipsychotics** are more likely to be on APP compared to those initiated on **intramuscular antipsychotics** after controlling for other demographic, clinical, physician, and prior utilization characteristics.	Rejected
$H_{3.12}$: Patients **with non-antipsychotic psychotropic drug** use in addition to antipsychotic use are more likely to be on APP compared to those **without it** after controlling for other demographic, clinical, physician, and prior utilization characteristics.	Failed to reject
$H_{3.13}$: Patients **with anticholinergic drug** use in addition to antipsychotic use are more likely to be on APP compared to those **without it** after controlling for other demographic, clinical, physician, and prior utilization characteristics.	Failed to reject
$H_{3.14}$: **Physician specialty is not associated** with the likelihood of being on APP after controlling for other demographic, clinical, physician, and prior utilization characteristics.	Rejected
$H_{3.15}$: Patients with **multiple physicians prescribing antipsychotics** are more likely to be on APP compared to those with a **single physician prescribing antipsychotics** after controlling for other demographic, clinical, physician, and prior utilization characteristics.	Failed to reject
$H_{3.16}$: Patients whose prescribers are from **rural areas** are more likely to be prescribed APP compared to those whose physicians are from **urban areas** after controlling for other demographic, clinical, physician, and prior utilization characteristics.	Rejected
$H_{3.17}$: Patients with **a greater number of prior mental health-related hospitalizations** are more likely to be on APP compared to those with **fewer prior mental health-related hospitalizations** after controlling for other demographic, clinical, physician, and prior utilization characteristics.	Rejected
$H_{3.18}$: Patients with a **greater number of prior mental health-related outpatient visits** are more likely to be on APP compared to those with **fewer prior mental health-related outpatient visits** after controlling for other demographic, clinical, physician, and prior utilization characteristics.	Failed to reject

Table 29: Results of hypotheses tests (continued)

Objectives/Hypotheses	Result
Objective 4: Compare adjusted adherence (PDC) and persistence between MT and APP groups while controlling for covariates	
$H_{4.1}$: The **adjusted adherence (PDC)** is **lower** for the **APP group** compared to the **MT group** after controlling for covariates.	Scenario 1: Failed to reject Scenario 2: Rejected
$H_{4.2}$: The **odds of being adherent** are **lower** for the **APP group** compared to the **MT group** after controlling for covariates.	Scenario 1: Failed to reject Scenario 2: Rejected
$H_{4.3}$: The **adjusted persistence (days of medication use prior to discontinuation)** is **lower** for the **APP group** compared to the **MT group** after controlling for covariates.	Rejected
Objective 5: Compare likelihood of an all-cause inpatient hospitalization between the MT and APP groups while controlling for covariates	
$H_{5.1}$: The **likelihood of an all-cause inpatient hospitalization** in the post-index period is **higher** for the **APP group** compared to the **MT group** after controlling for covariates.	Rejected
Objective 6: Compare all-cause length of stay between the MT and APP groups while controlling for covariates	
$H_{6.1}$: The **adjusted all-cause length of stay in an inpatient facility** during the post-index period is **higher** for the **APP group** compared to the **MT group** after controlling for covariates.	Failed to reject
Objective 7: Compare number of all-cause outpatient visits between the MT and APP groups while controlling for covariates	
$H_{7.1}$: The **adjusted number of all-cause outpatient and emergency department visits** is **higher** for the **APP group** compared to the **MT group** after controlling for covariates.	Rejected
Objective 8: To compare all-cause drug, medical and total (separate models) healthcare costs between the MT and APP groups while controlling for the covariates	
$H_{8.1}$: The **adjusted all-cause medical costs** are **higher** for the **APP group** compared to the **MT group** after controlling for the covariates.	Failed to reject
$H_{8.2}$: The **adjusted all-cause drug costs** are **higher** for the **APP group** compared to the **MT group** after controlling for the covariates.	Failed to reject
$H_{8.3}$: The **adjusted all-cause total costs** are **higher** for the **APP group** compared to the **MT group** after controlling for the covariates.	Failed to reject

5. Discussion and Conclusions

5.1. Chapter overview

This chapter provides a detailed discussion of the study. It begins with reviewing the study purpose. The study results are then discussed with possible explanations and are compared and contrasted with previous studies. The chapter ends with the study implications, limitations, and potential future research.

5.2. Review of study purpose

This study aimed at estimating the incidence of APP, identifying its predictors, and comparing healthcare utilization and costs for the MT and APP groups in the Texas Medicaid population. There is very limited evidence regarding the safety and efficacy of APP from controlled clinical trials and none of the established clinical guidelines advocate its use. Previous studies have evaluated the prevalence and outcomes associated with APP in other state Medicaid programs such as California, Georgia,[264] Utah, Wyoming, Nebraska, Oregon,[265] and Florida.[266,267] However, no such study has been conducted in Texas. It is especially important to study APP in the Texas Medicaid population due to the large number of patients with mental

264 Ganguly R, Kotzan JA, Miller LS, et al. Prevalence, trends, and factors associated with antipsychotic polypharmacy among Medicaid-eligible schizophrenia patients, 1998-2000. J Clin Psychiatry 2004;65(10):1377-88.
265 Morrato EH, Dodd S, Oderda G, et al. Prevalence, utilization patterns, and predictors of antipsychotic polypharmacy: experience in a multistate Medicaid population, 1998-2003. Clin Ther 2007;29(1):183-95.
266 Constantine RJ, Andel R, Tandon R. Trends in adult antipsychotic polypharmacy: progress and challenges in Florida's Medicaid program. Community Ment Health J 2010;46(6):523-30.
267 Constantine RJ, Boaz T, Tandon R. Antipsychotic polypharmacy in the treatment of children and adolescents in the fee-for-service component of a large state Medicaid program. Clin Ther 2010;32(5):949-59.

illnesses in Texas[268] and the increase in use of antipsychotic medications and the associated costs in the Texas Medicaid program during the past decade.[269]

268 National Alliance on Mental Illness, 2010 State Advocacy Report.

269 Medicaid Analytic eXtract (MAX) Rx Table Listing. Available at: http://www.cms.gov/Research-Statistics-Data-and-Systems/Computer-Data-and-Systems/MedicaidDataSourcesGenInfo/Medicaid-Analytic-eXtract-MAX-Rx-Table-Listing.html. Accessed March 15, 2013.

5.3. Objectives 1-4

5.3.1. Patient selection

The first four objectives involved estimating the incidence of APP, describing the characteristics of patients in the MT and APP groups, identifying predictors of APP, and comparing medication adherence and persistence between the MT and APP groups. For the first four objectives, external validity was considered to be of greater value compared to internal validity. Hence, patients newly initiated on antipsychotic medications were identified and followed for one year from their index antipsychotic claim. Patients with exposure to two or more antipsychotics for at least 60 days with no gap in polypharmacy of more than 31 days were classified as APP patients and those with no evidence of APP for one year after the index antipsychotic claim were classified as MT patients. Incidence, descriptive sample statistics (for APP and MT patients), predictor relationships, and medication adherence and persistence were calculated for this sample of patients.

5.3.2. Incidence of APP

In this study, the incidence of APP was estimated at 5.4%. The definition of APP was use of at least two or more antipsychotics for at least 60 days with no gaps in APP for more than 31 days. Several studies have estimated the prevalence of APP in different practice settings. This discussion will focus on studies that used retrospective databases, particularly state Medicaid databases, and APP definitions similar to ours. There was only one study that looked at the incidence of APP (Morratto et al.—they evaluated prevalence of APP among patients newly initiated on antipsychotics which is similar to an incidence estimate); hence, the study results have been compared to studies that estimated prevalence of APP using insurance claims data and definitions of APP similar to the one used in the current study.

Moratto et al. estimated the prevalence of APP among newly initiated antipsychotic users (which is similar to an incidence estimate) from the Medicaid program of five states (California, Nebraska, Oregon, Utah and Wyoming) between 1998 and 2003.[270] Their estimate of APP was 6.4%. Polypharmacy was defined as the initiation of multiple antipsychotics or at least 60 consecutive days of concomitant antipsychotic medication overlapping the index medication. This estimate is quite similar to our estimate of 5.4%.

Ganguly et al. reported an estimated APP prevalence of 23% among Medicaid-eligible patients with schizophrenia from California and Georgia.[271] The definition of APP use was concomitant use of two or more antipsychotics for at least 61 days without a break period of 31 days or more. Using data from the FFS population of Florida's Medicaid program from 2002 to

[270] Morrato EH, Dodd S, Oderda G, et al. Prevalence, utilization patterns, and predictors of antipsychotic polypharmacy: experience in a multistate Medicaid population, 1998-2003. Clin Ther 2007;29(1):183-95.
[271] Ganguly R, Kotzan JA, Miller LS, et al. Prevalence, trends, and factors associated with antipsychotic polypharmacy among Medicaid-eligible schizophrenia patients, 1998-2000. J Clin Psychiatry 2004;65(10):1377-88.

2006, Constantine et al. estimated the prevalence of APP at 21%.[272] APP was defined as the use of two or more antipsychotics for 60 consecutive days with no gap exceeding 15 days. Again, the current study measured incidence, not prevalence. Our APP incidence estimate (5.4%) would be expected to be lower than prevalence estimates. The current study estimated occurrence of APP in patients newly initiated on antipsychotics while the other studies estimated its occurrence in continuing antipsychotic users. In addition, the studies also differed on the specific patient inclusion criteria and the definitions of APP used.

Kreyenbuhl et al. used VA patients with schizophrenia and schizoaffective disorder during 2000 and estimated the prevalence at 9.5%.[273] APP was defined as receipt of two or more antipsychotics concomitantly for at least 90 consecutive days during the study period. This study evaluated APP (defined as 90 days of overlap) among prevalent antipsychotic users—we looked at 60-day, 120-day, and 180-day overlap periods to estimate the incidence of APP; our estimates were 5.4%, 2.5%, and 1.4%, respectively. The difference is the estimates are likely due to differences in definitions of APP, differences in patient selection (prevalent vs. incident antipsychotic users), as well as the difference in the patient population (VA patients vs. Texas Medicaid beneficiaries). The VA prevalence estimate is lower than that observed in other studies since the VA study consisted only of patients with schizophrenia/schizoaffective disorder patients. Furthermore, there may be differences in utilization criteria, such as prior authorization requirements, in the VA system as compared to the Medicaid systems.

This discussion is focused only on four studies as these used data sets and APP definitions most similar to the ones used in the current study.

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[272] Constantine RJ, Andel R, Tandon R. Trends in adult antipsychotic polypharmacy: progress and challenges in Florida's Medicaid program. Community Ment Health J 2010;46(6):523-30.

[273] Kreyenbuhl J, Valenstein M, McCarthy JF, et al. Long-term combination antipsychotic treatment in VA patients with schizophrenia. Schizophr Res 2006; 84(1):90–9.

5.3.3. Patient characteristics in the MT and APP groups

In the unadjusted unmatched analyses, we found that a greater proportion of females had APP as compared to males. This trend was also observed in other studies.[274,275,276,277] A greater proportion of Caucasian patients had APP compared to patients from other racial/ethnic backgrounds and this was also observed in the study by Kreyenbuhl et al.[278]

Patients with schizophrenia had a greater proportion of APP users as compared to patients with other mental illnesses and this was also observed by Morrato et al.[279] Patients with substance abuse and those with a greater number of mental health illnesses had a greater proportion of APP users; Morrato et al. observed a similar trend in their study. The pre-index CCI and CDS were higher in the MT group compared to the APP group. A greater proportion of patients with CCI≥1 in the MT group was also observed by Kreyenbuhl et al.[280] APP was greater among those initiating on typical antipsychotics which was also observed by Morrato et al. (they observed the highest proportion of APP users among those initiated on clozapine but we did not have a separate group of clozapine users due to the low sample size). Those initiated on intramuscular antipsychotics had greater proportion of APP users compared to those initiated on

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[274] Ganguly R, Kotzan JA, Miller LS, et al. Prevalence, trends, and factors associated with antipsychotic polypharmacy among Medicaid-eligible schizophrenia patients, 1998-2000. J Clin Psychiatry 2004;65(10):1377-88.

[275] Morrato EH, Dodd S, Oderda G, et al. Prevalence, utilization patterns, and predictors of antipsychotic polypharmacy: experience in a multistate Medicaid population, 1998-2003. Clin Ther 2007;29(1):183-95.

[276] Ye W, Ascher-Svanum H, Flynn JA, et al. Predictors of antipsychotic monotherapy with olanzapine during a 1-year naturalistic study of schizophrenia patients in Japan. Clinicoecon Outcomes Res 2012;4:13-9.

[277] Constantine RJ, Andel R, Tandon R. Trends in adult antipsychotic polypharmacy: progress and challenges in Florida's Medicaid program. Community Ment Health J 2010;46(6):523-30.

[278] Kreyenbuhl J, Valenstein M, McCarthy JF, et al. Long-term antipsychotic polypharmacy in the VA health system: patient characteristics and treatment patterns. Psychiatr Serv 2007;58(4):489-95.

[279] Morrato EH, Dodd S, Oderda G, et al. Prevalence, utilization patterns, and predictors of antipsychotic polypharmacy: experience in a multistate Medicaid population, 1998-2003. Clin Ther 2007;29(1):183-95.

[280] Kreyenbuhl JA, Valenstein M, McCarthy JF, et al. Long-term antipsychotic polypharmacy in the VA health system: patient characteristics and treatment patterns. Psychiatr Serv 2007;58(4):489-95.

orals; this was also observed by Ganguly et al.[281] A greater proportion of patients prescribed APP had concurrent use of non-antipsychotic psychotropic and anticholinergic medication compared to those in the MT group.

In this study, we attempted to identify certain physician characteristics associated with APP. It was observed that patients with psychiatrists as their prescribers were more likely to have APP compared to patients with prescribers from other physician specialties. This is surprising as there are multiple guidelines discouraging the concurrent use of multiple antipsychotics and the clinical literature showing its benefits to be limited. Another potential explanation for this observation is that psychiatrists may be more experienced and hence more likely to prescribe multiple antipsychotic medications. Patients with multiple prescribers had more APP which might be due to lack of coordination between the prescribers. Urban/rural location of prescriber was also found to be significantly associated with APP but this was likely due to the low proportion of APP among those prescribers whose urban/rural status was classified as 'unknown' rather than a difference in the proportion of APP users between the 'urban' and 'rural' groups. Identifying prescriber characteristics in the APP group is critical as in most cases the decision to use multiple antipsychotics is that of the prescriber rather than the patient. More information on the characteristics of physicians likely to prescribe APP would help in efforts to understand the reason for the prescribed APP.

This study found greater mental health-related healthcare utilization events (inpatient hospitalizations and outpatient/ emergency department visits) in patients with APP compared to the MT group; this was also observed by Ganguly et al. and Kreyenbuhl et al.[282,283]

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[281] Ganguly R, Kotzan JA, Miller LS, et al. Prevalence, trends, and factors associated with antipsychotic polypharmacy among Medicaid-eligible schizophrenia patients, 1998-2000. J Clin Psychiatry 2004;65(10):1377-88.
[282] Ganguly R, Kotzan JA, Miller LS, et al. Prevalence, trends, and factors associated with antipsychotic polypharmacy among Medicaid-eligible schizophrenia patients, 1998-2000. J Clin Psychiatry 2004;65(10):1377-88.

Although, it is difficult to comment on the overall health status between the two groups, those in the APP group had more severe mental illnesses compared to the MT group.

283 Kreyenbuhl J, Valenstein M, McCarthy JF, et al. Long-term antipsychotic polypharmacy in the VA health system: patient characteristics and treatment patterns. Psychiatr Serv 2007;58(4):489-95.

5.3.4. Predictors of APP

In order to identify the independent association of the demographic, clinical, physician, and prior utilization characteristics with APP, a logistic regression model was used. This study found that APP increased with an increase in age after controlling for other covariates. This was contrary to the findings observed by Morrato et al.[284] and Kreyenbuhl et al.[285] Females were 12% (adjusted OR=0.88; 95% CI: 0.78-1.00) less likely than males to have APP; this was observed by Ganguly et al.[286], Morrato et al., Constantine et al.[287], and Kreyenbuhl et al.

The adjusted odds of APP were higher for patients with schizophrenia compared to other mental illnesses—Morrato et al. made a similar observation in their study. Patients with ongoing substance abuse were 7% less likely to have APP. Also similar to Morrato et al., we found that the adjusted odds of APP increased with an increase in the number of mental health illnesses during the study period. Patients with a lower CDS, non-antipsychotic psychotropic medication use during the study period, and anticholinergic medication use during the study period were associated with increased adjusted odds of APP. Patients prescribed APP were more likely to use anticholinergic medications possibly due to the association of antipsychotics with extrapyramidal symptoms (EPS).[288]

As observed in the unadjusted analysis, the adjusted logistic regression model showed that psychiatrists were more likely than family practitioners and prescribers with the specialty

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[284] Morrato EH, Dodd S, Oderda G, et al. Prevalence, utilization patterns, and predictors of antipsychotic polypharmacy: experience in a multistate Medicaid population, 1998-2003. Clin Ther 2007;29(1):183-95.
[285] Kreyenbuhl J, Valenstein M, McCarthy JF, et al. Long-term antipsychotic polypharmacy in the VA health system: patient characteristics and treatment patterns. Psychiatr Serv 2007;58(4):489-95.
[286] Ganguly R, Kotzan JA, Miller LS, et al. Prevalence, trends, and factors associated with antipsychotic polypharmacy among Medicaid-eligible schizophrenia patients, 1998-2000. J Clin Psychiatry 2004;65(10):1377-88.
[287] Constantine RJ, Boaz T, Tandon R. Antipsychotic polypharmacy in the treatment of children and adolescents in the fee-for-service component of a large state Medicaid program. Clin Ther 2010;32(5):949-59.
[288] Ren XS1, Huang YH, Lee AF, Miller DR, Qian S, Kazis L. Adjunctive use of atypical antipsychotics and anticholinergic drugs among patients with schizophrenia. J Clin Pharm Ther 2005;30(1):65-71.

categorized as ‘unknown’ to prescribe APP—this is surprising, especially in light of the widespread literature discouraging the use of APP. Another potential explanation could be the patients in the APP group are more severely ill and hence go to psychiatrists; due to the severe illness they are prescribed APP. Psychiatrists also could have more experience and hence are able to determine who APP should be prescribed to. Also similar to the unadjusted analysis, with an increase of one unit in the number of prescribers prescribing antipsychotics, patients were 1.38 (95% CI: 1.31-1.44) times more likely to have APP. Understanding characteristics of physicians likely to prescribe APP is an important step and a promising area for future research.

After adjusting for other covariates, the number of mental health-related inpatient hospitalizations was not significantly associated with APP. However, the number of mental health-related outpatient/emergency department visits was significantly associated with APP—with a one unit increase in the number of mental health-related outpatient or emergency department visits, the odds of APP increased by 1.03 (95% CI: 1.00-1.02). This is similar to the observation made by Ganguly et al. in their study.

The implications of these results are discussed in a later section (5.6).

5.3.5. Adherence and persistence for the MT and APP groups

In the current study, we measured medication adherence using PDC; two different definitions of adherence were used for the APP group—scenario1 and 2. In scenario 1, a patient in the APP group was considered adherent on a given day only if he had at least two antipsychotics on that day. In scenario 2, an APP patient was considered adherent on a given day if he had at least one antipsychotic on that day. These two methods give the possible range of adherence for the APP group. It was not possible to determine what the patient was prescribed based on the claims data available to us. We only had information on the prescriptions that were filled. The patients in the APP group could have one or more episodes of long term polypharmacy during the 12-month study period. Hence, we used these two extreme methods to calculate adherence.

Several studies have evaluated adherence to antipsychotic medications. This discussion is focused on studies that have compared adherence in patients with antipsychotic monotherapy and polypharmacy. We found three studies that compared medication adherence between the MT and APP groups—one was a randomized trial[289], the other was a retrospective database analysis using data from the Hungarian National Health Insurance Fund's database[290] and the third one was a retrospective database analysis using multistate Medicaid data.[291]

In a six-month randomized trial, Essock et al. assigned people on APP to either remain on APP or switch to MT. Patients assigned to the group switching to MT had a higher all-cause discontinuation rate compared to those on APP. At month six, 86% of those in the APP group

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289 Essock SM, Schooler NR, Stroup TS, et al. Effectiveness of switching from antipsychotic polypharmacy to monotherapy. Am J Psychiatry 2011;168(7):702-8.
290 Katona L, Czobor P, Bitter I. Real-world effectiveness of antipsychotic monotherapy vs. polypharmacy in schizophrenia: To switch or to combine? A nationwide study in Hungary. Schizophr Res 2014;152(1):246-54.
291 Morrato EH, Dodd S, Oderda G, et al. Prevalence, utilization patterns, and predictors of antipsychotic polypharmacy: experience in a multistate Medicaid population, 1998-2003. Clin Ther 2007;29(1):183-95.

were still using both medications while 68% in the MT group were using the medication assigned to them. We compared discontinuation of all medication therapy between the MT and APP groups and found that patients in the APP group were 51% less likely to discontinue their antipsychotic therapy compared to the MT group (after controlling for covariates). Thus, similar to Essock et al., the current study found that patients in the APP group were more persistent. However, we considered a patient in the APP group to be persistent if s/he had at least one antipsychotic on a given day (as not all patients started on multiple antipsychotics and it was not possible to determine the length of time for which the APP group patients were prescribed multiple antipsychotics; we only had information on the claims they filled). The definition of persistence used in the current study is one of the reasons for the higher persistence in the APP group. In addition, between 10%-25% (depending on definition of APP used) of the patients had a greater than 31-day gap in therapy prior to their APP start date. This must be kept in mind while interpreting the results.

Katona et al. started with patients prescribed antipsychotic monotherapy and classified them into monotherapy if they continued using one drug and polypharmacy if they used two antipsychotics. They found that the all-cause discontinuation was higher among polypharmacy users for second generation antipsychotics (both oral and depot). For first generation antipsychotics, there was no difference between the monotherapy and polypharmacy groups for oral antipsychotic users but the results showed an advantage in the polypharmacy group for the depot users. Our results on time of medication use prior to discontinuation were similar to what was observed among depot first generation antipsychotic medication users in the study by Katona et al. The observed difference between the current study results and the results on atypical antipsychotics observed by Katona et al. is likely because they followed the patients in

the polypharmacy group for one year after they started using two antipsychotics while the current study followed patients for a year from the time they started using an antipsychotic, i.e. they may have had one or more polypharmacy episodes during the one year study period.

In the study that used multistate Medicaid data, Morrato et al. measured adherence to the index antipsychotic in the MT and APP groups and found that adherence (measured as MPR) was higher in the APP group compared to the MT group. Their method of measurement most resembles our scenario 2 (described above) and we made a similar observation that the adherence (measured as PDC) was higher in the APP vs. MT group.

Despite previous studies showing poor medication adherence when patients use multiple drugs, the current study (and other studies in the literature) found the contrary. This is likely due to the method used to define an adherent patient in the APP group in the current study. In scenario 1 (described above), the adherence was higher in the MT vs. APP group. Since it is not possible to determine exactly what the patient was prescribed using insurance claims data, we had to use conservative and liberal definitions for adherent patients in the APP group; the liberal definition showed better adherence among patients with APP. Thus, the observed results are due to the definitions used because of unavailability of information on what was prescribed to the patients rather than what was filled based on the insurance claims.

5.3.6. Summary

The first four objectives provide an estimate of the incidence of APP; comparison of characteristics of the MT and APP cohorts; identify potential predictors of polypharmacy and carry out a comparative analysis of medication adherence and persistence in the two groups using varying definitions for 'adherent' patients in the APP cohort.

The incidence of APP was estimated at 5.4% in the Texas Medicaid population. Several demographic, clinical, physician, and prior utilization characteristics differed between the MT and APP groups in both the unadjusted and adjusted (logistic regression) analyses. The comparative analysis for adherence between the MT and APP groups varied depending on the definition used for an 'adherent' patient in the APP group.

These analyses provide useful information, especially regarding the Texas Medicaid system, due to the increasing costs associated with antipsychotics in recent years. [292] The predictors of APP would help providers and payers identify patients likely to be prescribed APP early on during the course of their illness. The high-risk patients can then be carefully monitored to determine if they are appropriate candidates for polytherapy with antipsychotics. If so, they could be carefully monitored to ensure that they don't experience negative health outcomes.

[292] Medicaid Analytic eXtract (MAX) Rx Table Listing. Available at: http://www.cms.gov/Research-Statistics-Data-and-Systems/Computer-Data-and-Systems/MedicaidDataSourcesGenInfo/Medicaid-Analytic-eXtract-MAX-Rx-Table-Listing.html. Accessed March 15, 2013.

5.4. Objectives 5-8

5.4.1. Patient selection

Objectives 5-8 involved comparing the likelihood of an inpatient hospitalization, length of hospital stay, number of outpatient and emergency department visits, and the medical, drug, and total costs between the MT and APP groups. For these objectives, internal validity was deemed to be more important than external validity. Hence, only patients with no gaps in antipsychotic therapy for greater than 31 days were included. This would increase the possibility of making the association between MT/APP and the outcomes as this sample would largely consist of patients adherent to their antipsychotic therapy. Prior studies have shown that non-adherence to antipsychotic therapy is associated with poor clinical and economic outcomes; only including patients with no gaps in antipsychotic therapy for more than 31 days will help exclude those patients who might experience increased healthcare utilization and/or costs due to lack of therapy rather than type of medication therapy i.e. MT vs. APP. In order to ensure that patients in the MT and APP groups had comparable exposure to antipsychotic therapy, the two groups were matched based on their exposure to antipsychotics and the outcomes for both groups were assessed during the one-year period after the APP index date (pseudo index date for MT group) (more explanation provided in section 3.4.4). This group of patients, matched on the length of exposure to an antipsychotic, was used for the comparative analysis—assessing the likelihood of an inpatient visit, length of hospital stay, number of outpatient/emergency department visits, and costs (medical, pharmacy, and total costs) between the MT and APP groups.

Demographic, clinical, physician, and prior utilization characteristics of the MT and APP patients matched on duration of antipsychotic exposure were compared. They differed on several

characteristics since they were only matched on one variable. Hence, in all regression procedures for the comparative analyses, all measured covariates were controlled for.

Due to the structure of the data for the current study, we could not differentiate between emergency department, professional, and outpatient visits; all of these visits were combined into a single category. This might have implications for the utilization and costs as emergency department visits typically are less frequent and more expensive compared to outpatient and professional visits. This must be kept in mind while interpreting the study results.

5.4.2. Healthcare utilization for patients in the MT and APP groups

There is limited research that evaluates healthcare utilization in patients with APP. Few studies have evaluated healthcare utilization in patients with schizophrenia and other mental illnesses. This discussion focuses on studies that have addressed healthcare utilization in patients with APP.

Using San Diego County Medicaid beneficiaries with schizophrenia, Gilmer et al. estimated the prevalence of APP and the proportion of patients hospitalized between 1999 and 2004.[293] The proportion of APP increased from 3.3% in 1999 to 13.7% in 2004 and the proportion of patients hospitalized over the same period increased from 7.2% to 9.0%. In the current study, we found that the likelihood of an all-cause inpatient hospitalization did not differ significantly between the APP and MT groups. However, the length of hospital stay was longer in the APP group compared to the MT group.

Chen et al. studied the effect of adjunctive mood stabilizers on antipsychotic utilization patterns and health resource utilization for Medicaid enrollees with schizophrenia.[294] The authors found that the use of emergency room services, long-term facilities, and inpatient care did not differ significantly between propensity score-matched patients with schizophrenia who did and did not use adjunctive mood stabilizers. Although the use of adjunctive mood stabilizers was not considered in the current study, we made a similar observation that the MT and APP groups did not vary significantly in the likelihood of an all-cause inpatient hospitalization and number of all-cause outpatient/emergency department visits.

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[293] Gilmer TP, Dolder CR, Folsom DP, et al. Antipsychotic polypharmacy trends among Medicaid beneficiaries with schizophrenia in San Diego County, 1999-2004. Psychiatr Serv 2007;58(7):1007-10.

[294] Chen H, Kennedy WK, Dorfman JH, et al. The effect of adjunctive mood stabilizers on antipsychotic utilization patterns and health resource utilization for Medicaid enrollees with schizophrenia. Curr Med Res Opin 2007;23(6):1351-65.

Due to the limited research of healthcare utilization in patients with APP, we have only compared our study results to the two studies. Unfortunately, only one looked at patients with multiple antipsychotics (although its study design was different from the current study—no comparator group of MT patients). The other one (Chen et al.) compared patients with schizophrenia who did and did not have adjunctive mood stabilizer therapy. This should be noted while trying to make direct comparisons of the current study to the study by Chen et al.

5.4.3. Healthcare costs in patients with MT and APP

Several studies have looked at costs associated with antipsychotic users; this discussion focuses on studies that have evaluated costs in patients using multiple antipsychotics. Care has been taken to ensure that the current study results are compared to studies using similar datasets.

In the current study, we found that the medical costs were higher in the APP group compared to the MT group. Valuck et al. found that compared to patients on MT, patients on APP had higher costs ranging from $71-$211 depending on the state Medicaid program.[295] Loosbrock et al. also found that the institutional costs (hospital inpatient, hospital outpatient, psychiatric day/night facility, nursing facility, and emergency room costs) were higher for the APP vs. MT group.[296]

The pharmacy costs in the APP group were higher than those in the MT group in this study. Stahl et al. found that patients with short- and long-term polypharmacy had greater pharmacy costs than those with monotherapy, with those on long-term polypharmacy costing almost three times as much as monotherapy patients.[297] A similar observation was made by Gilmer et al. who noted an increase in pharmacy costs from 1999 to 2004 as the prevalence of APP increased.[298] Valuck et al. also observed greater pharmacy costs in the APP vs. MT

[295] Valuck RJ, Morrato EH, Dodd S, et al. How expensive is antipsychotic polypharmacy? Experience from five US state Medicaid programs. Curr Med Res Opin 2007;23(10):2567-76.
[296] Loosbrock DL, Zhao Z, Johnstone BM, et al. Antipsychotic medication use patterns and associated costs of care for individuals with schizophrenia. J Ment Health Policy Econ 2003;6(2):67-75.
[297] Stahl SM, Grady MM. High-cost use of second-generation antipsychotics under California's Medicaid program. Psychiatr Serv 2006;57(1):127-9.
[298] Gilmer TP, Dolder CR, Folsom DP, et al. Antipsychotic polypharmacy trends among Medicaid beneficiaries with schizophrenia in San Diego County, 1999-2004. Psychiatr Serv 2007;58(7):1007-10.

group.[299] However, Loosbrock et al. found that medication costs did not differ significantly between the MT and APP groups.[300]

The total costs (sum of medical and pharmacy costs) in the current study were higher in the APP group compared to the MT group. This was also observed by Loosbrock et al. In patients with APP, the increased pharmacy costs were not offset by decreased medical costs (in fact, medical costs were higher in the APP group) which caused the total costs to be higher in the APP vs. MT group.

[299] Valuck RJ, Morrato EH, Dodd S, et al. How expensive is antipsychotic polypharmacy? Experience from five US state Medicaid programs. Curr Med Res Opin 2007;23(10):2567-76.
[300] Loosbrock DL, Zhao Z, Johnstone BM, et al. Antipsychotic medication use patterns and associated costs of care for individuals with schizophrenia. J Ment Health Policy Econ 2003;6(2):67-75.

5.4.4. Summary

Objectives 5 to 8 carried out a comparative analysis and observed the likelihood of an inpatient hospitalization, length of hospital stay, number of outpatient/emergency department visits and the costs (medical pharmacy and total) between the MT and APP groups.

The length of hospital stay was longer for the APP vs. MT group. Likelihood of an inpatient visit and the number of outpatient visits did not differ significantly between the two groups. With respect to costs, the medical, drug, and total costs were higher for the APP vs. MT group.

Although several covariates were controlled for in the regression models for the comparative analyses and patients were matched based on their duration of exposure to antipsychotics, there is still a possibility of selection bias during the formation of the MT and APP groups—patients in the APP group may be sicker at onset compared to the MT group on factors we were not able to account for. This must be noted while interpreting the results of this study. However, the comparative analysis portion of this study does provide valuable information to the extent it highlights the magnitude of extra healthcare utilization events and costs and among potentially comparable patients in the APP vs. MT groups after controlling for several patient-level demographic, clinical, physician, and prior utilization variables.

5.5. Sensitivity analyses

Several sensitivity analyses were conducted surrounding the outcomes (all-cause vs. psychiatric-related) and the definition of APP—both the overlap period (60 days vs. 120 days and 180 days) and gap period (31 days vs. 15 days and 45 days) were varied.

The definition of APP used affected the incidence. As the overlap period was increased, the incidence decreased; as the gap in therapy period was decreased, the incidence decreased. In the case of psychiatric-related outcomes, the cost outcomes were in the same direction as the base case (greater in the APP vs. MT group). Contrary to the base case, the likelihood of an inpatient hospitalization and number of outpatient and emergency department visits were significantly higher in the APP vs. MT group in some sensitivity analyses cases. The outcome with respect to hospital length of stay was higher in the APP vs. MT group which was also observed in the base case.

A detailed description of how the results changed as the definition of APP was changed has been provided in the Results chapter (section 4.3), but overall they remained quite similar to the base case which indicates that the results are robust with respect to the outcomes assessed (all-cause vs. psychiatric-related) and different definitions of APP.

5.6. Implications

The current study estimated the incidence of APP in the Texas Medicaid population, described patient characteristics in the MT and APP groups, identified predictors of APP, and compared healthcare utilization and costs between the MT and APP groups. The incidence of long-term APP was estimated at 5.4%. The results of this study have implications for several stakeholders in the healthcare delivery system.

First, it affects patients. Using multiple antipsychotics increases the possibility of side effects and adverse drug reactions; the current study found greater healthcare utilization in terms of hospital length of stay in patients with APP compared to MT. The extent to which APP has a favorable or negative impact on outcomes, in turn, also affects the families of the patients using antipsychotic medications.

Next, these results affect providers. Awareness of characteristics of patients likely to be prescribed APP could be useful to providers as it helps them identify potential APP patients early during the course of treatment; the early identification may give the providers time to determine the appropriateness of APP for the particular patients.

These results provide important information to policy makers with respect to the prevalence of long-term APP despite limited clinical evidence supporting its use. This might highlight the need for intervention programs to provide information to clinicians about the benefits and harms of APP and also help assess the appropriateness of the APP prescribed by them. This is especially important in light of the high financial burden imposed by co-prescription of multiple antipsychotics.

Finally, the results of this study have important implications for the payers—Texas Medicaid in our case, which was also the perspective of the study. This study highlights the

incidence of APP in the Texas Medicaid population and also highlights the economic burden of this practice. This is very important information for Texas Medicaid as they spend a large amount of their limited resources on antipsychotics—an expensive drug class. In fact, from 2001 to 2008, antipsychotics have consistently topped the list of the top 10 drug classes for pharmacy benefit use for non-dual-eligible Texas Medicaid beneficiaries in terms of total Medicaid prescription drug spending.[301] The results of this study could help Texas Medicaid assess the need and target physician population for intervention programs to determine the appropriateness of the prescribed APP and help in the development of programs to potentially control this expensive practice.

[301] Medicaid Analytic eXtract (MAX) Rx Table Listing. Available at: http://www.cms.gov/Research-Statistics-Data-and-Systems/Computer-Data-and-Systems/MedicaidDataSourcesGenInfo/Medicaid-Analytic-eXtract-MAX-Rx-Table-Listing.html. Accessed March 15, 2013.

5.7. Limitations

In the formation of the APP group, there is a possibility of potential selection bias—sicker patients might potentially get selected into the APP group i.e. the APP group might have sicker patients at baseline. However, in order to avoid this potential bias, patients in the MT and APP groups were matched based on their duration of antipsychotic exposure and the regression analyses controlled for several measures indicating disease severity such as pre-index CCI, pre-index CDS, number of mental health diagnoses during study period, concurrent non-antipsychotic psychotropic drug and anticholinergic drug utilization, and prior mental health-related healthcare utilization. However, there may be other variables which we were not able to control. This must be noted while interpreting the study results.

Due to the use of insurance claims data, it was not possible to determine whether the prescribed polypharmacy was appropriate or not. However, our intention was not to classify the APP as appropriate or not but rather bring forth its incidence, predictors, and the economic burden imposed by it.

Although we tried to identify several demographic, clinical, physician, and prior utilization characteristics associated with APP, there are several clinical characteristics that are not captured in the claims data. Several direct disease measures such as Positive and Negative Syndrome Scale (PANSS) which might be important predictors of APP were not captured. Also, certain other demographic characteristics such as education level, marital status, and others were not captured in the current study. We had very limited data on physician characteristics. The decision to prescribe multiple antipsychotics to patients is generally made by the prescriber and not by the patient. Hence, physician characteristics are likely to be important predictors of APP.

Since we did not have information on what the patients were prescribed, in order to calculate adherence in the APP group, we used two different definitions—one very conservative and one very liberal representing the two extremes of adherence in the APP group. These varied definitions produced varying results on the adherence measures between the MT and APP groups. In calculating medication persistence, 10%-25% (depending on the definition of APP used) of the patients had a greater than 31 days gap in therapy prior to their APP start date.

Finally, this study has limited generalizability beyond the Texas Medicaid population. Caution must be exercised while generalizing these findings to other state Medicaid programs or to other insurance settings as patient characteristics, and clinical and financial practices vary across regions and different insurance settings.

5.8. Future Research

Although the results of this study address important gaps in the literature, future studies can be conducted to improve generalizability of the results and add to the existing knowledge base. Studies should be conducted using varied patient populations, including patients insured privately and those insured using Medicare, in order to generalize the results to a broader patient population.

An important next step is to observe clinical and patient reported outcomes in actual practice in patients on MT and APP to better understand the effect of using multiple antipsychotics on patients. These studies could be conducted using electronic medical records (EMR) data. They might be limited to a smaller population due to the difficulty in obtaining detailed clinical data for a large number of patients, but they would provide essential information.

Several patient-level characteristics such as demographic, clinical, and prior healthcare utilization variables were included in the logistic regression analysis to identify predictors of APP. However, there may still be several other factors that we were not able to include due to the structure of our data which might be important predictors. Socio-demographic characteristics such as family support, education level, employment status and others might also be important factors associated with APP. We included a few physician characteristics in our analyses such as physician specialty, number of physicians prescribing the antipsychotic medications, and urban/rural status—however, there might be several other physician-level characteristics which may determine whether a patient will be prescribed APP or not. Future research could look into identifying characteristics of physicians likely to prescribe APP; this might aid our understanding of the reasons they prescribe APP despite limited evidence demonstrating its benefit and several

clinical guidelines discouraging its use. Understanding the reasons for APP would better equip us to plan interventions against APP that is not appropriate. Intervention designed to provide peer-based reviews to clinicians about their prescribing habits could also help determine whether the patients prescribed long-term APP are benefiting from the practice and are therefore appropriate candidates.

5.9. Conclusions

The incidence of APP in the Texas Medicaid population was estimated at 5.4%. Several demographic, clinical, physician, and prior utilization characteristics were identified that predicted the incidence of APP. In general, patients prescribed APP cost more (in terms of drug costs) than those with MT but did not have significantly lower healthcare utilization and/or and medical costs. Sensitivity analyses varying the definition of APP were conducted and the results were by and large similar to the base case. There is a possibility of bias where more severely ill patients might get selected into the APP group—in order to avoid this, various measures of disease severity including number of mental illnesses during study period, concurrent non-antipsychotic psychotropic and anticholinergic drug use, pre-index CCI and CDS and prior mental health utilization were controlled during the regression procedures and patients in the MT and APP groups were matched based on their duration of exposure to antipsychotics. However, the potential for selection bias still exists and this must be noted while interpreting the results of the study.

This study provides information on the characteristics of patients most likely to be prescribed APP. It also provides information on the burden of APP in terms of health resource utilization and costs. The results of this study could encourage providers to carefully consider effectiveness and economic factors while prescribing APP to patients. Payers could use this information to design interventions to control APP which might help control the increasing healthcare costs.

Although the incidence of APP in the Texas Medicaid population was low, utilization and cost outcomes remain high. This may be a subject of interest to Medicaid. However, it must be

noted that the high utilization and cost outcomes could be associated with a number of known and unknown factors, not just APP.

Long-term APP raises concern as antipsychotics are fairly expensive drugs and state Medicaid agencies are allocating their limited resources to this expensive treatment which has very scarce effectiveness data supporting its use. More research is needed to examine the risks and benefits associated with APP due to its costly nature. More effectiveness research on APP is needed to help provide prescription guidance to clinicians for patients who do not respond well to treatment with a single antipsychotic.

6. APPENDIX

The appendix provides tables with the regression coefficients for all the models carried out for the base case scenario. For the sensitivity analyses, similar models were used but the full tables are not provided in the appendix.

Table 30: Results of regression analysis comparing adherence in the MT and APP groups (Scenario 1)

Characteristics	Coef.	Robust Std. Err.	Z	P>z	[95% Conf. Interval]	
APP	-0.1774	0.0069	-25.79	0.000	-0.1908	-0.1639
Age	0.0017	0.0002	11.55	0.000	0.0015	0.0020
Male	0.0227	0.0038	6.04	0.000	0.0154	0.0301
Race/ethnicity						
African American	0.0017	0.0002	11.55	0.000	0.0015	0.0020
Other	0.0227	0.0038	6.04	0.000	0.0154	0.0301
Unknown	0.0017	0.0002	11.55	0.000	0.0015	0.0020
Caucasian	0.0227	0.0038	6.04	0.000	0.0154	0.0301
Year of initiation of index antipsychotic medication						
2007	-0.0173	0.0062	-2.81	0.005	-0.0294	-0.0052
2008	0.0009	0.0070	0.13	0.900	-0.0128	0.0146
2009	0.0091	0.0063	1.45	0.148	0.0032	0.0213
2010	0.0165	0.0060	2.75	0.006	0.0047	0.0282

Table 30: Results of regression analysis comparing adherence in the MT and APP groups (Scenario 1) (continued)

Characteristics	Coef.	Robust Std. Err.	Z	P>z	[95% Conf. Interval]	
Diagnosis						
Depression	-0.0084	0.0067	-1.26	0.209	-0.0216	0.0047
No mental illness	-0.0544	0.0072	-7.59	0.000	-0.0684	-0.0403
Other	-0.0126	0.0061	-2.06	0.039	-0.0245	-0.0006
Schizophrenia	0.0344	0.0074	4.66	0.000	0.0199	0.0488
Multiple mental illnesses	-0.0400	0.0090	-4.44	0.000	-0.0576	-0.0223
Current substance abuse	-0.0559	0.0051	-10.94	0.000	-0.0660	-0.0459
Number of unique mental illnesses	0.0040	0.0017	2.33	0.020	0.0006	0.0075
Pre-index Charlson Comorbidity Index	-0.0047	0.0015	-3.13	0.002	-0.0077	-0.0018
Pre-index Chronic Disease Score	0.0027	0.0007	3.74	0.000	0.0013	0.0042
Index antipsychotic drug						
Combination	0.1332	0.0755	1.76	0.078	-0.0148	0.2811
Typical	-0.0752	0.0070	-10.77	0.000	-0.0889	-0.0615
Injectable antipsychotic	0.0155	0.0150	1.04	0.299	-0.0138	0.0449
Psychotropic medication	0.0689	0.0044	15.56	0.000	0.0602	0.0775
Anticholinergic medication	0.1417	0.0063	22.44	0.000	0.1293	0.1540
Physician specialty						
Psychiatrist	0.0113	0.0054	2.12	0.034	0.0008	0.0218
Other	0.0057	0.0063	0.91	0.363	-0.0066	0.0181
Unknown	-0.0309	0.0075	-4.12	0.000	-0.0455	-0.0162

Table 30: Results of regression analysis comparing adherence in the MT and APP groups (Scenario 1) (continued)

Characteristics	Coef.	Robust Std. Err.	Z	P>z	[95% Conf. Interval]	
Number of physicians prescribing the antipsychotic	0.0499	0.0016	30.41	0.000	0.0467	0.0531
Urban/rural status						
Unknown	-0.0229	0.0255	-0.90	0.368	-0.0729	0.02670
Urban	-0.0318	0.0049	-6.49	0.000	-0.0414	-0.0222
Pre-index psychiatric-related inpatient hospitalizations	-0.0286	0.0024	-12.08	0.000	-0.0332	-0.0239
Pre-index psychiatric-related outpatient visits	0.0012	0.0003	3.91	0.000	0.0006	0.0018
Constant	0.3031	0.0125	24.16	0.000	0.2785	0.3277

Table 31: Results of regression analysis comparing adherence in the MT and APP groups (Scenario 2)

Characteristics	Coef.	Robust Std. Err.	Z	P>z	[95% Conf. Interval]	
APP	0.2053	0.0061	33.45	0.000	0.1933	0.2174
Age	0.0018	0.0002	11.68	0.000	0.0015	0.0021
Male	0.0206	0.0037	5.50	0.000	0.0133	0.0279
Race/ethnicity						
African American	-0.0318	0.0049	-6.54	0.000	-0.0414	-0.0223
Other	0.0283	0.0065	4.37	0.000	0.0156	0.0409
Unknown	-0.0100	0.0273	-0.37	0.715	-0.0636	0.0436
Caucasian	0.0442	0.0049	9.06	0.000	0.0346	0.0537
Year of initiation of index antipsychotic medication						
2007	-0.0178	0.0061	-2.90	0.004	-0.0298	-0.0058
2008	-0.0008	0.0069	-0.11	0.910	-0.0144	0.0128
2009	0.0072	0.0062	1.16	0.247	-0.0050	0.0194
2010	0.0148	0.0059	2.50	0.013	0.0032	0.0265
Diagnosis						
Depression	-0.0100	0.0067	-1.49	0.135	-0.0231	0.0031
No mental illness	-0.0554	0.0071	-7.78	0.000	-0.0694	-0.0414
Other	-0.0134	0.0061	-2.21	0.027	-0.0253	-0.0015
Schizophrenia	0.0302	0.0073	4.14	0.000	0.0159	0.0445
Multiple mental illnesses	-0.0410	0.0090	-4.58	0.000	-0.0586	-0.0235

Table 31: Results of regression analysis comparing adherence in the MT and APP groups (Scenario 2) (continued)

Characteristics	Coef.	Robust Std. Err.	Z	P>z	[95% Conf. Interval]	
Current substance abuse	-0.0589	0.0051	-11.60	0.000	-0.0689	-0.0489
Number of unique mental illnesses	0.0052	0.0017	3.04	0.002	0.0019	0.0086
Pre-index Charlson Comorbidity Index	-0.0048	0.0015	-3.18	0.001	-0.0077	-0.0018
Pre-index Chronic Disease Score	0.0032	0.0007	4.43	0.000	0.0018	0.0046
Index antipsychotic drug						
Combination	0.0698	0.0718	0.97	0.331	-0.0709	0.2106
Typical	-0.0724	0.0070	-10.41	0.000	-0.0860	-0.0588
Injectable antipsychotic	0.0212	0.0150	1.41	0.158	-0.0083	0.0506
Psychotropic medication	0.0710	0.0044	16.11	0.000	0.0624	0.0796
Anticholinergic medication	0.1353	0.0062	21.87	0.000	0.1232	0.1474
Physician specialty						
Psychiatrist	0.0096	0.0053	1.79	0.073	-0.0009	0.0200
Other	0.0054	0.0063	0.85	0.394	-0.0070	0.0177
Unknown	-0.0323	0.0075	-4.33	0.000	-0.0469	-0.0177
Number of physicians prescribing the antipsychotic	0.0518	0.0016	32.27	0.000	0.0487	0.0550
Urban/rural status						
Unknown	-0.0209	0.0253	-0.83	0.409	-0.0706	0.0288
Urban	-0.0346	0.0049	-7.08	0.000	-0.0442	-0.0250

Table 31: Results of regression analysis comparing adherence in the MT and APP groups (Scenario 2) (continued)

Characteristics	Coef.	Robust Std. Err.	Z	P>z	[95% Conf. Interval]	
Pre-index psychiatric-related inpatient hospitalizations	-0.0279	0.0023	-12.07	0.000	-0.0324	-0.0233
Pre-index psychiatric-related outpatient visits	0.0012	0.0003	4.23	0.000	0.0007	0.0018
Constant	0.3007	0.0125	24.11	0.000	0.2762	0.3251

Table 32: Results of logistic regression analysis comparing dichotomized adherence in the MT and APP groups (Scenario 1)

Characteristics	Odds Ratio	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
APP	0.17	0.02	-14.11	0.000	0.14	0.22
Age	1.01	0.00	9.05	0.000	1.01	1.02
Male	1.24	0.04	6.03	0.000	1.16	1.33
Race/ethnicity						
African American	0.79	0.04	-4.50	0.000	0.71	0.88
Other	1.26	0.08	3.75	0.000	1.12	1.43
Unknown	1.09	0.27	0.34	0.731	0.67	1.78
Caucasian	1.52	0.07	8.98	0.000	1.39	1.67
Year of initiation of index antipsychotic medication						
2007	1.00	0.06	0.06	0.949	0.89	1.13
2008	1.12	0.08	1.59	0.111	0.98	1.28
2009	1.21	0.08	3.08	0.002	1.07	1.37
2010	1.28	0.08	4.12	0.000	1.14	1.44
Diagnosis						
Depression	1.03	0.07	0.44	0.656	0.91	1.17
No mental illness	0.81	0.06	-2.92	0.004	0.71	0.93
Other	1.07	0.06	1.12	0.263	0.95	1.20
Schizophrenia	1.45	0.10	5.20	0.000	1.26	1.67
Multiple mental illnesses	0.80	0.08	-2.33	0.020	0.67	0.97

Table 32: Results of logistic regression analysis comparing dichotomized adherence in the MT and APP groups (Scenario 1) (continued)

Characteristics	Odds Ratio	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
Current substance abuse	0.61	0.03	-9.48	0.000	0.55	0.67
Number of unique mental illnesses	1.04	0.02	2.55	0.011	1.01	1.08
Pre-index Charlson Comorbidity Index	0.97	0.01	-2.40	0.016	0.94	0.99
Pre-index Chronic Disease Score	1.03	0.01	4.83	0.000	1.02	1.05
Index antipsychotic drug						
Combination	4.73	2.59	2.84	0.005	1.62	13.85
Typical	0.62	0.05	-6.22	0.000	0.53	0.72
Injectable antipsychotic	1.05	0.15	0.33	0.741	0.79	1.38
Psychotropic medication	1.26	0.06	5.34	0.000	1.16	1.38
Anticholinergic medication	2.28	0.14	13.34	0.000	2.02	2.57
Physician specialty						
Psychiatrist	0.93	0.05	-1.45	0.146	0.84	1.03
Other	1.01	0.06	0.26	0.796	0.91	1.14
Unknown	0.76	0.06	-3.65	0.000	0.66	0.88
Number of physicians prescribing the antipsychotic	1.18	0.02	9.31	0.000	1.14	1.22
Urban/rural status						
Unknown	1.01	0.24	0.05	0.961	0.64	1.59
Urban	0.85	0.04	-3.48	0.000	0.78	0.93

Table 32: Results of logistic regression analysis comparing dichotomized adherence in the MT and APP groups (Scenario 1) (continued)

Characteristics	Odds Ratio	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
Pre-index psychiatric-related inpatient hospitalizations	0.78	0.03	-7.60	0.000	0.73	0.83
Pre-index psychiatric-related outpatient visits	1.01	0.00	3.15	0.002	1.00	1.01

Table 33: Results of logistic regression analysis comparing dichotomized adherence in the MT and APP groups (Scenario 2)

Characteristics	Odds Ratio	Robust Std. Err.	z	P>z	[95% Conf.	Interval]
APP	3.90	0.25	21.20	0.000	3.44	4.42
Age	1.01	0.00	9.53	0.000	1.01	1.02
Male	1.22	0.04	5.58	0.000	1.13	1.30
Race/ethnicity						
African American	0.77	0.04	-5.28	0.000	0.69	0.85
Other	1.26	0.08	3.80	0.000	1.12	1.42
Unknown	1.15	0.29	0.55	0.583	0.70	1.88
Caucasian	1.50	0.07	9.00	0.000	1.37	1.64
Year of initiation of index antipsychotic medication						
2007	1.00	0.06	0.02	0.980	0.89	1.13
2008	1.09	0.07	1.27	0.205	0.95	1.24
2009	1.20	0.07	2.97	0.003	1.06	1.34
2010	1.25	0.07	3.85	0.000	1.12	1.40

Table 33: Results of logistic regression analysis comparing dichotomized adherence in the MT and APP groups (Scenario 2) (continued)

Characteristics	Odds Ratio	Robust Std. Err.	z	P>z	[95% Conf.	Interval]
Diagnosis						
Depression	1.02	0.06	0.39	0.698	0.91	1.16
No mental illness	0.81	0.06	-3.03	0.002	0.71	0.93
Other	1.07	0.06	1.19	0.234	0.96	1.20
Schizophrenia	1.41	0.10	4.94	0.000	1.23	1.62
Multiple mental illnesses	0.83	0.07	-2.06	0.039	0.70	0.99
Current substance abuse	0.59	0.03	-10.16	0.000	0.54	0.66
Number of unique mental illnesses	1.05	0.02	2.96	0.003	1.02	1.08
Pre-index Charlson Comorbidity Index	0.97	0.01	-2.47	0.013	0.94	0.99
Pre-index Chronic Disease Score	1.03	0.01	5.07	0.000	1.02	1.05
Index antipsychotic drug						
Combination	5.68	3.29	3.00	0.003	1.83	17.70
Typical	0.66	0.05	-5.70	0.000	0.58	0.76
Injectable antipsychotic	1.10	0.15	0.69	0.487	0.84	1.43
Psychotropic medication	1.26	0.05	5.50	0.000	1.16	1.37
Anticholinergic medication	2.11	0.13	12.39	0.000	1.87	2.37

Table 33: Results of logistic regression analysis comparing dichotomized adherence in the MT and APP groups (Scenario 2) (continued)

Characteristics	Odds Ratio	Robust Std. Err.	z	P>z	[95% Conf.	Interval]
Physician specialty						
Psychiatrist	0.92	0.04	-1.78	0.076	0.83	1.01
Other	1.01	0.06	0.24	0.807	0.91	1.13
Unknown	0.75	0.05	-4.04	0.000	0.65	0.86
Number of physicians prescribing the antipsychotic	1.17	0.02	9.55	0.000	1.14	1.21
Urban/rural status						
Unknown	0.92	0.21	-0.36	0.717	0.58	1.45
Urban	0.85	0.04	-3.78	0.000	0.78	0.92
Pre-index psychiatric-related inpatient hospitalizations	0.81	0.02	-7.33	0.000	0.77	0.86
Pre-index psychiatric-related outpatient visits	1.01	0.00	3.52	0.000	1.00	1.01

Table 34: Results of Cox proportional hazards regression analysis comparing medication persistence between the MT and APP groups

Characteristics	Haz. Ratio	Std. Err.	z	P>z	[95% Conf. Interval]	
APP	0.49	0.02	-18.36	0.000	0.45	0.53
Age	0.99	0.00	-8.57	0.000	0.99	1.00
Male	0.93	0.01	-4.67	0.000	0.90	0.96
Race/ethnicity						
African American	1.14	0.02	6.36	0.000	1.10	1.19
Other	0.92	0.03	-3.02	0.003	0.87	0.97
Unknown	0.95	0.11	-0.48	0.633	0.75	1.19
Caucasian	0.83	0.02	-8.84	0.000	0.80	0.87
Year of initiation of index antipsychotic medication						
2007	1.03	0.03	1.15	0.249	0.98	1.08
2008	1.00	0.03	-0.11	0.913	0.94	1.06
2009	0.92	0.02	-3.03	0.002	0.88	0.97
2010	0.90	0.02	-4.2	0.000	0.86	0.94

Table 34: Results of Cox proportional hazards regression analysis comparing medication persistence between the MT and APP groups (continued)

Characteristics	Haz. Ratio	Std. Err.	z	P>z	[95% Conf. Interval]	
Diagnosis						
Depression	1.01	0.03	0.41	0.681	0.96	1.07
No mental illness	1.13	0.03	3.85	0.000	1.06	1.20
Other	0.99	0.03	-0.27	0.784	0.94	1.05
Schizophrenia	0.87	0.03	-4.3	0.000	0.81	0.93
Multiple mental illnesses	1.10	0.04	2.36	0.018	1.02	1.19
Current substance abuse	1.26	0.03	10.33	0.000	1.20	1.31
Number of unique mental illnesses	0.98	0.01	-2.05	0.041	0.97	1.00
Pre-index Charlson Comorbidity Index	1.02	0.01	3.1	0.002	1.01	1.03
Pre-index Chronic Disease Score	0.98	0.00	-5.39	0.000	0.98	0.99
Index antipsychotic drug						
Combination	0.60	0.27	-1.15	0.250	0.25	1.44
Typical	1.38	0.04	10.67	0.000	1.30	1.46
Injectable antipsychotic	1.01	0.06	0.13	0.900	0.89	1.14
Psychotropic medication	0.85	0.02	-8.6	0.000	0.82	0.89
Anticholinergic medication	0.62	0.02	-14.79	0.000	0.59	0.66
Physician specialty						
Psychiatrist	1.02	0.02	1.08	0.279	0.98	1.07
Other	0.99	0.03	-0.32	0.746	0.94	1.04
Unknown	1.19	0.04	5.33	0.000	1.11	1.26

Table 34: Results of Cox proportional hazards regression analysis comparing medication persistence between the MT and APP groups (continued)

Characteristics	Haz. Ratio	Std. Err.	z	P>z	[95% Conf. Interval]	
Number of physicians prescribing the antipsychotic	0.91	0.01	-11.58	0.000	0.90	0.93
Urban/rural status						
Unknown	1.00	0.11	0.04	0.965	0.81	1.25
Urban	1.06	0.02	2.89	0.004	1.02	1.10
Pre-index psychiatric-related inpatient hospitalizations	1.10	0.01	9.56	0.000	1.08	1.12
Pre-index psychiatric-related outpatient visits	1.00	0.00	-3.55	0.000	0.99	1.00

Table 35: Results of logistic regression analysis comparing the likelihood of an inpatient visit between the MT and APP groups

Characteristics	Odds Ratio	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
APP	1.47	0.32	1.80	0.072	0.97	2.25
Age	1.02	0.01	2.23	0.026	1.00	1.04
Male	0.71	0.14	-1.68	0.093	0.48	1.06
Race/ethnicity						
African American	0.76	0.22	-0.95	0.344	0.42	1.35
Other	1.10	0.53	0.19	0.847	0.42	2.85
Unknown[a]	294175.90	331859.20	11.16	0.000	32238.02	2684391.00
Caucasian	0.96	0.23	-0.15	0.878	0.60	1.54
Year of initiation of index antipsychotic medication						
2007	0.44	0.16	-2.32	0.021	0.22	0.88
2008	0.83	0.31	-0.50	0.614	0.40	1.72
2009	0.55	0.19	-1.71	0.087	0.27	1.09
2010	0.65	0.24	-1.18	0.237	0.32	1.32
Diagnosis						
Depression	3.23	1.49	2.54	0.011	1.31	7.98
No mental illness	1.71	0.92	1.00	0.316	0.60	4.92
Other	2.23	0.92	1.94	0.052	0.99	5.00
Schizophrenia	3.10	1.32	2.66	0.008	1.35	7.15
Multiple mental illnesses	1.25	0.79	0.35	0.724	0.36	4.30

Table 35: Results of logistic regression analysis comparing the likelihood of an inpatient visit between the MT and APP group (continued)

Characteristics	Odds Ratio	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
Current substance abuse	1.61	0.41	1.85	0.064	0.97	2.67
Number of unique mental illnesses	1.48	0.13	4.51	0.000	1.25	1.76
Pre-index Charlson Comorbidity Index	1.04	0.07	0.62	0.536	0.91	1.19
Pre-index Chronic Disease Score	1.12	0.04	2.94	0.003	1.04	1.21
Index antipsychotic drug						
Combination	0.00	0.00	-17.87	0.000	0.00	0.00
Typical	0.71	0.31	-0.78	0.436	0.30	1.68
Injectable antipsychotic	2.08	1.19	1.28	0.202	0.68	6.38
Psychotropic medication	1.93	0.53	2.40	0.016	1.13	3.30
Anticholinergic medication	0.84	0.22	-0.67	0.505	0.50	1.41
Physician specialty						
Psychiatrist	1.12	0.36	0.35	0.730	0.59	2.11
Other	1.80	0.64	1.65	0.098	0.90	3.60
Unknown	0.63	0.31	-0.94	0.345	0.24	1.66
Number of physicians prescribing the antipsychotic	1.17	0.10	1.81	0.071	0.99	1.39
Urban/rural status						
Unknown	0.00	0.00	-22.88	0.000	0.00	0.00
Urban	0.64	0.14	-1.99	0.047	0.41	0.99

Table 35: Results of logistic regression analysis comparing the likelihood of an inpatient visit between the MT and APP group (continued)

Characteristics	Odds Ratio	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
Pre-index psychiatric-related inpatient hospitalizations	1.21	0.20	1.14	0.255	0.87	1.69
Pre-index psychiatric-related outpatient visits	0.98	0.01	-1.72	0.086	0.95	1.00

[a] Unreliable odds ratio due to small sample size in the 'Unknown' race/ethnicity group

Table 36: Results of the regression analysis (hurdle model) comparing the hospital length of stay between the MT and APP groups

Logistic regression

Characteristics	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
APP	-0.39	0.22	-1.80	0.072	-0.81	0.03
Age	-0.02	0.01	-2.23	0.026	-0.04	0.00
Male	0.34	0.20	1.68	0.093	-0.06	0.74
Race/ethnicity						
African American	0.28	0.30	0.95	0.344	-0.30	0.86
Other	-0.09	0.49	-0.19	0.847	-1.05	0.86
Unknown	-12.59	1.13	-11.16	0.000	-14.80	-10.38
Caucasian	0.04	0.24	0.15	0.878	-0.43	0.51
Year of initiation of index antipsychotic medication						
2007	0.82	0.35	2.32	0.021	0.13	1.51
2008	0.19	0.37	0.50	0.614	-0.54	0.92
2009	0.60	0.35	1.71	0.087	-0.09	1.29
2010	0.43	0.36	1.18	0.237	-0.28	1.13

<u>Table 36:</u> Results of the regression analysis (hurdle model) comparing the hospital length of stay between the MT and APP groups

Logistic regression (continued)

Characteristics	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
Diagnosis						
Depression	-1.17	0.46	-2.54	0.011	-2.08	-0.27
No mental illness	-0.54	0.54	-1.00	0.316	-1.59	0.51
Other	-0.80	0.41	-1.94	0.052	-1.61	0.01
Schizophrenia	-1.13	0.43	-2.66	0.008	-1.97	-0.30
Multiple mental illnesses	-0.22	0.63	-0.35	0.724	-1.46	1.01
Current substance abuse	-0.48	0.26	-1.85	0.064	-0.98	0.03
Number of unique mental illnesses	-0.39	0.09	-4.51	0.000	-0.56	-0.22
Pre-index Charlson Comorbidity Index	-0.04	0.07	-0.62	0.536	-0.17	0.09
Pre-index Chronic Disease Score	-0.12	0.04	-2.94	0.003	-0.19	-0.04
Index antipsychotic drug						
Combination	13.24	0.74	17.87	0.000	11.78	14.69
Typical	0.34	0.44	0.78	0.436	-0.52	1.21
Injectable antipsychotic	-0.73	0.57	-1.28	0.202	-1.85	0.39
Psychotropic medication	-0.66	0.27	-2.40	0.016	-1.19	-0.12
Anticholinergic medication	0.18	0.26	0.67	0.505	-0.34	0.70

<u>Table 36:</u> Results of the regression analysis (hurdle model) comparing the hospital length of stay between the MT and APP groups

Logistic regression (continued)

Characteristics	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
Physician specialty						
Psychiatrist	-0.11	0.32	-0.35	0.730	-0.75	0.52
Other	-0.59	0.35	-1.65	0.098	-1.28	0.11
Unknown	0.47	0.50	0.94	0.345	-0.50	1.44
Number of physicians prescribing the antipsychotic	-0.16	0.09	-1.81	0.071	-0.33	0.01
Urban/rural status						
Unknown	13.82	0.60	22.88	0.000	12.64	15.01
Urban	0.45	0.23	1.99	0.047	0.01	0.90
Pre-index psychiatric-related inpatient hospitalizations	-0.19	0.17	-1.14	0.255	-0.52	0.14
Pre-index psychiatric-related outpatient visits	0.02	0.01	1.72	0.086	0.00	0.05
Constant	5.16	0.82	6.29	0.000	3.56	6.77

Table 36: Results of the regression analysis (hurdle model) comparing the hospital length of stay between the MT and APP groups

Zero truncated negative binomial regression

Characteristics	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
APP	-0.2277	0.1777	-1.28	0.200	-0.5759	0.1206
Age	0.0052	0.0060	0.86	0.389	-0.0066	0.0169
Male	0.2979	0.1513	1.97	0.049	0.0014	0.5945
Race/ethnicity						
African American	0.1698	0.2158	0.79	0.432	-0.2533	0.5928
Other	-0.6825	0.3479	-1.96	0.050	-1.3643	-0.0006
Unknown	-0.3297	0.4428	-0.74	0.456	-1.1975	0.5380
Caucasian	0.2024	0.1887	1.07	0.283	-0.1674	0.5722
Year of initiation of index antipsychotic medication						
2007	-0.4838	0.3256	-1.49	0.137	-1.1219	0.1543
2008	-0.3725	0.2834	-1.31	0.189	-0.9280	0.1829
2009	-0.2716	0.3040	-0.89	0.372	-0.8675	0.3242
2010	-0.2672	0.2938	-0.91	0.363	-0.8431	0.3087
Diagnosis						
Depression	-0.0231	0.3427	-0.07	0.946	-0.6949	0.6486
No mental illness	0.6756	0.3683	1.83	0.067	-0.0464	1.3975
Other	0.8303	0.3380	2.46	0.014	0.1679	1.4927

Table 36: Results of the regression analysis (hurdle model) comparing the hospital length of stay between the MT and APP groups

Zero truncated negative binomial regression (continued)

Characteristics	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
Schizophrenia	1.1723	0.3443	3.40	0.001	0.4974	1.8471
Multiple mental illnesses	0.7203	0.4153	1.73	0.083	-0.0937	1.5343
Current substance abuse	-0.6568	0.1764	-3.72	0.000	-1.0026	-0.3111
Number of unique mental illnesses	0.0663	0.0522	1.27	0.204	-0.0360	0.1687
Pre-index Charlson Comorbidity Index	0.0157	0.0531	0.30	0.767	-0.0883	0.1197
Pre-index Chronic Disease Score	0.0596	0.0274	2.18	0.029	0.0060	0.1133
Typical antipsychotics	0.5240	0.3403	1.54	0.124	-0.1429	1.1910
Injectable antipsychotic	-0.5755	0.2634	-2.18	0.029	-1.0917	-0.0592
Psychotropic medication	0.3989	0.2530	1.58	0.115	-0.0970	0.8947
Anticholinergic medication	0.0956	0.2763	0.35	0.729	-0.4459	0.6371
Physician specialty						
Psychiatrist	0.0213	0.2558	0.08	0.933	-0.4799	0.5226
Other	-0.1415	0.2679	-0.53	0.597	-0.6667	0.3836
Unknown	-0.6057	0.3805	-1.59	0.111	-1.3515	0.1401
Number of physicians prescribing the antipsychotic	0.1671	0.0510	3.27	0.001	0.0670	0.2671
Urban/rural status						
Unknown	(omitted)					
Urban	0.3437	0.1813	1.90	0.058	-0.0117	0.6991

<u>Table 36:</u> Results of the regression analysis (hurdle model) comparing the hospital length of stay between the MT and APP groups

Zero truncated negative binomial regression (continued)

Characteristics	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
Pre-index psychiatric-related inpatient hospitalizations	0.2027	0.0780	2.60	0.009	0.0498	0.3556
Pre-index psychiatric-related outpatient visits	0.0210	0.0100	2.11	0.035	0.0014	0.0405
Constant	-0.2121	0.6591	-0.32	0.748	-1.5039	1.0796
/lnalpha	-0.4360	0.2188		-0.865	-0.0072	
Alpha	0.6466	0.1415		0.421	0.9928	

Table 37: Results of Poisson regression analysis comparing the number of outpatient visits between the MT and APP groups

Characteristics	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
APP	0.0748	0.0541	1.38	0.167	-0.0312	0.1808
Age	0.0084	0.0024	3.49	0.000	0.0037	0.0132
Male	-0.0613	0.0549	-1.12	0.264	-0.1689	0.0462
Race/ethnicity						
African American	-0.0767	0.0854	-0.90	0.369	-0.2441	0.0907
Other	-0.0146	0.1193	-0.12	0.902	-0.2485	0.2192
Unknown	-0.7806	0.2558	-3.05	0.002	-1.2821	-0.2792
Caucasian	-0.0786	0.0740	-1.06	0.288	-0.2237	0.0665
Year of initiation of index antipsychotic medication						
2007	0.0358	0.1180	0.30	0.762	-0.1955	0.2670
2008	0.1363	0.1211	1.13	0.260	-0.1010	0.3737
2009	0.0410	0.1069	0.38	0.701	-0.1685	0.2504
2010	0.0535	0.1152	0.46	0.643	-0.1724	0.2793
Diagnosis						
Depression	0.2046	0.0956	2.14	0.032	0.0171	0.3920
No mental illness	-0.3972	0.1422	-2.79	0.005	-0.6759	-0.1185
Other	0.2656	0.0748	3.55	0.000	0.1190	0.4122
Schizophrenia	0.3178	0.0874	3.64	0.000	0.1466	0.4891
Multiple mental illnesses	-0.1884	0.1412	-1.33	0.182	-0.4652	0.0884

Table 37: Results of Poisson regression analysis comparing the number of outpatient visits between the MT and APP groups (continued)

Characteristics	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
Current substance abuse	0.0256	0.0672	0.38	0.703	-0.1062	0.1574
Number of unique mental illnesses	0.0798	0.0165	4.84	0.000	0.0475	0.1121
Pre-index Charlson Comorbidity Index	0.1150	0.0190	6.05	0.000	0.0778	0.1523
Pre-index Chronic Disease Score	0.0445	0.0124	3.59	0.000	0.0202	0.0689
Index antipsychotic drug						
Combination	-0.0348	0.2827	-0.12	0.902	-0.5889	0.5193
Typical	-0.1876	0.0982	-1.91	0.056	-0.3801	0.0050
Injectable antipsychotic	-0.0071	0.1208	-0.06	0.953	-0.2438	0.2296
Psychotropic medication	0.1437	0.0749	1.92	0.055	-0.0032	0.2905
Anticholinergic medication	-0.0221	0.0825	-0.27	0.789	-0.1839	0.1397
Physician specialty						
Psychiatrist	0.0200	0.1047	0.19	0.849	-0.1852	0.2252
Other	0.0614	0.1077	0.57	0.569	-0.1497	0.2725
Unknown	0.1063	0.1508	0.70	0.481	-0.1893	0.4019
Number of physicians prescribing the antipsychotic	0.0445	0.0205	2.17	0.030	0.0042	0.0847
Urban/rural status						
Unknown	0.0352	0.1626	0.22	0.829	-0.2836	0.3539
Urban	-0.0982	0.0793	-1.24	0.216	-0.2536	0.0573

Table 37: Results of Poisson regression analysis comparing the number of outpatient visits between the MT and APP groups (continued)

Characteristics	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
Pre-index psychiatric-related inpatient hospitalizations	-0.0422	0.0531	-0.79	0.427	-0.1463	0.0619
Pre-index psychiatric-related outpatient visits	0.0180	0.0021	8.44	0.000	0.0138	0.0222
Constant	2.3473	0.2070	11.34	0.000	1.9416	2.7531

Table 38: Results of regression (gamma regression with log link) analysis comparing the medical costs between the MT and APP groups

Characteristics	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
APP	0.1741	0.0876	1.99	0.047	0.0024	0.3458
Age	0.0121	0.0039	3.13	0.002	0.0045	0.0196
Male	-0.1048	0.0814	-1.29	0.198	-0.2643	0.0546
Race/ethnicity						
African American	-0.2481	0.1220	-2.03	0.042	-0.4873	-0.0089
Other	-0.2623	0.1827	-1.44	0.151	-0.6205	0.0959
Unknown	-0.8863	0.4850	-1.83	0.068	-1.8369	0.0643
Caucasian	-0.2366	0.1110	-2.13	0.033	-0.4541	-0.0190
Year of initiation of index antipsychotic medication						
2007	-0.3186	0.1785	-1.78	0.074	-0.6684	0.0313
2008	0.0550	0.1872	0.29	0.769	-0.3119	0.4218
2009	-0.0195	0.1806	-0.11	0.914	-0.3735	0.3345
2010	-0.0179	0.1876	-0.10	0.924	-0.3856	0.3498
Diagnosis						
Depression	0.2453	0.1520	1.61	0.107	-0.0526	0.5432
No mental illness	-0.0959	0.1829	-0.52	0.600	-0.4544	0.2627
Other	0.4633	0.1230	3.77	0.000	0.2223	0.7043
Schizophrenia	0.4893	0.1464	3.34	0.001	0.2025	0.7762
Multiple mental illnesses	-0.1681	0.2219	-0.76	0.449	-0.6030	0.2668

Table 38: Results of regression (gamma regression with log link) analysis comparing the medical costs between the MT and APP groups (continued)

Characteristics	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
Current substance abuse	0.0994	0.1101	0.90	0.366	-0.1163	0.3152
Number of unique mental illnesses	0.1578	0.0381	4.14	0.000	0.0832	0.2325
Pre-index Charlson Comorbidity Index	0.1739	0.0379	4.59	0.000	0.0996	0.2481
Pre-index Chronic Disease Score	0.0850	0.0191	4.45	0.000	0.0476	0.1225
Index antipsychotic drug						
Combination	-1.2261	0.3455	-3.55	0.000	-1.9032	-0.5489
Typical	-0.1175	0.2175	-0.54	0.589	-0.5437	0.3087
Injectable antipsychotic	-0.2132	0.2271	-0.94	0.348	-0.6582	0.2318
Psychotropic medication	0.2891	0.1137	2.54	0.011	0.0663	0.5118
Anticholinergic medication	0.1024	0.1293	0.79	0.428	-0.1510	0.3557
Physician specialty						
Psychiatrist	0.0308	0.1495	0.21	0.837	-0.2623	0.3239
Other	0.2018	0.1693	1.19	0.233	-0.1301	0.5337
Unknown	0.1455	0.2376	0.61	0.540	-0.3203	0.6112
Number of physicians prescribing the antipsychotic	0.0109	0.0388	0.28	0.779	-0.0652	0.0870
Urban/rural status						
Unknown	-0.3340	0.3664	-0.91	0.362	-1.0522	0.3842
Urban	0.0479	0.0991	0.48	0.628	-0.1462	0.2421

Table 38: Results of regression (gamma regression with log link) analysis comparing the medical costs between the MT and APP groups (continued)

Characteristics	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
Pre-index psychiatric-related inpatient hospitalizations	0.0176	0.0928	0.19	0.850	-0.1642	0.1994
Pre-index psychiatric-related outpatient visits	0.0151	0.0037	4.11	0.000	0.0079	0.0222
Constant	6.6928	0.3156	21.21	0.000	6.0742	7.3114

Table 39: Results of regression (gamma regression with log link) analysis comparing the drug costs between the MT and APP groups

Characteristics	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
APP	0.4599	0.0423	10.88	0.000	0.3770	0.5428
Age	0.0030	0.0018	1.65	0.100	-0.0006	0.0065
Male	0.0498	0.0386	1.29	0.197	-0.0259	0.1255
Race/ethnicity						
African American	-0.2036	0.0580	-3.51	0.000	-0.3173	-0.0900
Other	-0.1553	0.0927	-1.68	0.094	-0.3370	0.0264
Unknown	-0.0032	0.3152	-0.01	0.992	-0.6210	0.6146
Caucasian	-0.0160	0.0519	-0.31	0.757	-0.1177	0.0857
Year of initiation of index antipsychotic medication						
2007	0.0082	0.0606	0.14	0.893	-0.1106	0.1270
2008	0.1730	0.0782	2.21	0.027	0.0197	0.3263
2009	-0.0097	0.0673	-0.14	0.885	-0.1416	0.1221
2010	-0.0026	0.0699	-0.04	0.971	-0.1396	0.1345
Diagnosis						
Depression	0.0251	0.0911	0.28	0.783	-0.1535	0.2036
No mental illness	-0.0192	0.0908	-0.21	0.833	-0.1971	0.1588
Other	-0.0315	0.0809	-0.39	0.697	-0.1901	0.1271
Schizophrenia	-0.0147	0.0837	-0.18	0.861	-0.1788	0.1494
Multiple mental illnesses	-0.0911	0.1172	-0.78	0.437	-0.3207	0.1386

Table 39: Results of regression (gamma regression with log link) analysis comparing the drug costs between the MT and APP groups (continued)

Characteristics	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
Current substance abuse	-0.0134	0.0624	-0.21	0.830	-0.1357	0.1089
Number of unique mental illnesses	-0.0183	0.0155	-1.18	0.240	-0.0487	0.0122
Pre-index Charlson Comorbidity Index	0.0731	0.0180	4.05	0.000	0.0377	0.1084
Pre-index Chronic Disease Score	0.0526	0.0081	6.54	0.000	0.0369	0.0684
Index antipsychotic drug						
Combination	-0.5227	0.0917	-5.70	0.000	-0.7024	-0.3430
Typical	-0.4027	0.0757	-5.32	0.000	-0.5511	-0.2544
Injectable antipsychotic	0.0383	0.1060	0.36	0.718	-0.1695	0.2460
Psychotropic medication	0.1294	0.0521	2.48	0.013	0.0273	0.2315
Anticholinergic medication	-0.1844	0.0577	-3.20	0.001	-0.2975	-0.0713
Physician specialty						
Psychiatrist	0.0695	0.0578	1.20	0.229	-0.0437	0.1828
Other	0.1503	0.0654	2.30	0.022	0.0221	0.2785
Unknown	0.0993	0.1119	0.89	0.375	-0.1199	0.3186
Number of physicians prescribing the antipsychotic	0.0092	0.0169	0.54	0.588	-0.0240	0.0424
Urban/rural status						
Unknown	-0.0474	0.2673	-0.18	0.859	-0.5713	0.4765
Urban	0.0283	0.0496	0.57	0.568	-0.0690	0.1256

Table 39: Results of regression (gamma regression with log link) analysis comparing the drug costs between the MT and APP groups (continued)

Characteristics	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
Pre-index psychiatric-related inpatient hospitalizations	-0.0036	0.0331	-0.11	0.913	-0.0684	0.0612
Pre-index psychiatric-related outpatient visits	0.0034	0.0022	1.56	0.120	-0.0009	0.0077
Constant	8.6082	0.1436	59.94	0.000	8.3267	8.8897

Table 40: Results of regression (gamma regression with log link) analysis comparing the total costs between the MT and APP groups

Characteristics	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
APP	0.3664	0.0447	8.21	0.000	0.2789	0.4540
Age	0.0051	0.0018	2.90	0.004	0.0017	0.0086
Male	-0.0114	0.0400	-0.29	0.775	-0.0898	0.0669
Race/ethnicity						
African American	-0.2303	0.0577	-3.99	0.000	-0.3434	-0.1171
Other	-0.1891	0.0902	-2.10	0.036	-0.3659	-0.0122
Unknown	-0.1471	0.2963	-0.50	0.620	-0.7277	0.4336
Caucasian	-0.0761	0.0525	-1.45	0.147	-0.1789	0.0267
Year of initiation of index antipsychotic medication						
2007	-0.0471	0.0705	-0.67	0.504	-0.1853	0.0911
2008	0.1813	0.0803	2.26	0.024	0.0240	0.3387
2009	0.0278	0.0748	0.37	0.711	-0.1188	0.1744
2010	0.0431	0.0772	0.56	0.577	-0.1083	0.1944
Diagnosis						
Depression	0.1010	0.0794	1.27	0.203	-0.0546	0.2566
No mental illness	0.0362	0.0840	0.43	0.667	-0.1285	0.2008
Other	0.1462	0.0685	2.13	0.033	0.0119	0.2805
Schizophrenia	0.1647	0.0726	2.27	0.023	0.0224	0.3071
Multiple mental illnesses	-0.1423	0.1022	-1.39	0.164	-0.3426	0.0581

Table 40: Results of regression (gamma regression with log link) analysis comparing the total costs between the MT and APP groups (continued)

Characteristics	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
Current substance abuse	0.0439	0.0596	0.74	0.461	-0.0729	0.1607
Number of unique mental illnesses	0.0451	0.0190	2.37	0.018	0.0079	0.0824
Pre-index Charlson Comorbidity Index	0.1067	0.0172	6.22	0.000	0.0730	0.1403
Pre-index Chronic Disease Score	0.0634	0.0090	7.04	0.000	0.0458	0.0810
Index antipsychotic drug						
Combination	-0.7741	0.0878	-8.82	0.000	-0.9461	-0.6021
Typical	-0.3052	0.0886	-3.44	0.001	-0.4789	-0.1316
Injectable antipsychotic	-0.0149	0.1024	-0.15	0.885	-0.2155	0.1858
Psychotropic medication	0.1887	0.0511	3.70	0.000	0.0886	0.2888
Anticholinergic medication	-0.0799	0.0652	-1.22	0.221	-0.2077	0.0480
Physician specialty						
Psychiatrist	0.0494	0.0688	0.72	0.472	-0.0854	0.1842
Other	0.1441	0.0742	1.94	0.052	-0.0014	0.2896
Unknown	0.0906	0.1188	0.76	0.446	-0.1422	0.3234
Number of physicians prescribing the antipsychotic	0.0197	0.0183	1.07	0.283	-0.0163	0.0556
Urban/rural status						
Unknown	-0.2009	0.2509	-0.80	0.423	-0.6927	0.2908
Urban	0.0546	0.0489	1.12	0.264	-0.0413	0.1505

Table 40: Results of regression (gamma regression with log link) analysis comparing the total costs between the MT and APP groups (continued)

Characteristics	Coef.	Robust Std. Err.	z	P>z	[95% Conf. Interval]	
Pre-index psychiatric-related inpatient hospitalizations	0.0291	0.0424	0.68	0.494	-0.0541	0.1123
Pre-index psychiatric-related outpatient visits	0.0068	0.0021	3.23	0.001	0.0027	0.0110
Constant	8.5702	0.1489	57.54	0.000	8.2782	8.8621

7. BIBLIOGRAPHY

1. Aggarwal NK, Sernyak MJ, Rosenheck RA. Prevalence of concomitant oral antipsychotic drug use among patients treated with long-acting, intramuscular, antipsychotic medications. J Clin Psychopharmacol 2012;32(3):323-8.
2. Alexander GC, Gallagher SA, Mascola A, et al. Increasing off-label use of antipsychotic medications in the United States, 1995-2008. Pharmacoepidemiol Drug Saf 2011;20(2):177-84.
3. Allison PD, SAS Institute. Survival analysis using the SAS system: a practical guide. Cary, NC: SAS Institute; 1995.
4. Al-Zakwani IS, Barron JJ, Bullano MF, et al. Analysis of healthcare utilization patterns and adherence in patients receiving typical and atypical antipsychotic medications. Curr Med Res Opin 2003;19(7):619-26.
5. American Psychiatric Association: Practice guidelines for the treatment of patients with schizophrenia. In Am J Psychiatry Volume 161. 2nd ed. American Psychiatric Association; 2004:1-56.
6. Anil Yagcioglu AE, Kivircik Akdede BB, Turgut TI, et al. A double-blind controlled study of adjunctive treatment with risperidone in schizophrenic patients partially responsive to clozapine:efficacy and safety. J Clin Psychiatry 2005;66(1):63–72.
7. Aparasu RR, Bhatara V, Gupta S. U.S. national trends in the use of antipsychotics during office visits, 1998-2002. Ann Clin Psychiatry 2005;17(3):147-52.
8. Ascher-Svanum H, Zhu B, Faries DE, et al. Adherence and persistence to typical and atypical antipsychotics in the naturalistic treatment of patients with schizophrenia. Patient Prefer Adherence 2008;2:67-77.
9. Baandrup L, Allerup P, Lublin H, et al. Evaluation of a multifaceted intervention to limit excessive antipsychotic co-prescribing in schizophrenia out-patients. Acta Psychiatr Scand 2010;122(5):367-74.
10. Baandrup L, Gasse C, Jensen VD, et al. Antipsychotic polypharmacy and risk of death from natural causes in patients with schizophrenia: a population-based nested case-control study. J Clin Psychiatry 2010;71(2):103-8.

11. Baandrup L, Sørensen J, Lublin H, et al. Association of antipsychotic polypharmacy with health service cost: a register-based cost analysis. Eur J Health Econ 2012;13(3):355-63.
12. Barbui C, Nosè M, Mazzi MA, et al. Persistence with polypharmacy and excessive dosing in patients with schizophrenia treated in four European countries. Int Clin Psychopharmacol 2006;21(6):355-62.
13. Barbui C, Signoretti A, Mule S, et al. Does the addition of a second antipsychotic drug improve clozapine treatment? Schizophr Bull 2009; 35(2):458–68.
14. Barner JC. Medication adherence: focus on secondary database analysis. International Society for Pharmacoeconomic and Outcomes Research (ISPOR) Student Forum Presentation. February 2010.
15. Becker ER, Constantine RJ, McPherson MA, Jones ME. Antipsychotic polypharmacy prescribing patterns and costs in the Florida adult and child Medicaid populations. J Health Care Finance 2013;40(1):40-67.
16. Becker MA, Young MS, Ochshorn E, et al. The relationship of antipsychotic medication class and adherence with treatment outcomes and costs for Florida Medicaid beneficiaries with schizophrenia. Adm Policy Ment Health 2007;34(3):307-14.
17. Bera R, Offord S, Zubek D, et al. Impact on healthcare resource usage and costs among Medicaid-insured schizophrenia patients after initiation of treatment with long-acting injectable antipsychotics. J Med Econ 2013. [Epub ahead of print].
18. Biancosino B, Barbui C, Marmai L, et al. Determinants of antipsychotic polypharmacy in psychiatric inpatients: a prospective study. Int Clin Psychopharmacol 2005;20(6):305-9.
19. Botts S, Hines H, Littrell R. Antipsychotic polypharmacy in the ambulatory care setting, 1993-2000. Psychiatr Serv 2003;54(8):1086.
20. Breslow NE. Generalized linear models: checking assumptions and strengthening conclusions. Available at: http://biostat.georgiahealth.edu/~dryu/course/stat9110spring12/land16_ref.pdf. Accessed December 5, 2012.
21. Canales PL, Olsen J, Miller AL et al. Role of antipsychotic polypharmacotherapy in the treatment of schizophrenia. CNS Drugs 1999;12(3):179-88.

22. Castle NG, Hanlon JT, Handler SM. Results of a longitudinal analysis of national data to examine relationships between organizational market characteristics and changes in antipsychotic prescribing in US nursing homes from 1996 to 2006. Am J Geriatr Pharmacother 2009;7(3):14-50.
23. Chan J, Sweeting M. Combination therapy with non-clozapine atypical antipsychotic medication: A review of current evidence. J Psychopharmacol 2007;21(6):657–64.
24. Charlson ME, Pompei P, Ales KL, et al. A New Method of Classifying Prognostic Comorbidity in Longitudinal Studies: Development and Validation. J Chronic Dis 1987;40(5):373-83.
25. Chen A. Noncompliance in community psychiatry: A review of clinical interventions. Hospital and Community Psychiatry 1991;42(3):282-7.
26. Chen H, Kennedy WK, Dorfman JH, et al. The effect of adjunctive mood stabilizers on antipsychotic utilization patterns and health resource utilization for Medicaid enrollees with schizophrenia. Curr Med Res Opin 2007;23(6):1351-65.
27. Chen RS, Nadkarni PM, Levin FL, et al. Using a computer database to monitor compliance with pharmacotherapeutic guidelines for schizophrenia. Psychiatr Serv 2000;51(6):791-4.
28. Chong SA, Ravichandran N, Poon LY, et al. Reducing polypharmacy through the introduction of a treatment algorithm: use of a treatment algorithm on the impact on polypharmacy. Ann Acad Med Singapore 2006;35(7):457-60.
29. Christian R, Saavedra L, Gaynes BN, et al. Future Research Needs for First- and Second-Generation Antipsychotics for Children and Young Adults [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012 Feb. (Future Research Needs Papers, No. 13.) Appendix A, Tables of FDA-Approved Indications for First- and Second-Generation Antipsychotics.
30. Cipriani A, Boso M, Barbui C. Clozapine combined with different antipsychotic drugs for treatment resistant schizophrenia. Cochrane Database Syst Rev 2009;(3):CD006324.
31. Clark RE, Bartels SJ, Mellman TA, et al. Recent trends in antipsychotic combination therapy of schizophrenia and schizoaffective disorder: implications for state mental health policy. Schizophr Bull 2002;28(1):75-84.

32. Comer JS, Mojtabai R, Olfson M. National trends in the antipsychotic treatment of psychiatric outpatients with anxiety disorders. Am J Psychiatry 2011;168(10):1057-65.
33. Constantine RJ, Andel R, Tandon R. Trends in adult antipsychotic polypharmacy: progress and challenges in Florida's Medicaid program. Community Ment Health J 2010;46(6):523-30.
34. Constantine RJ, Boaz T, Tandon R. Antipsychotic polypharmacy in the treatment of children and adolescents in the fee-for-service component of a large state Medicaid program. Clin Ther 2010;32(5):949-59.
35. Consumer Price Index. Bureau of Labor Statistics. Available at: http://www.bls.gov/cpi/. Accessed on: April 3, 2014.
36. Cooper WO, Arbogast PG, Ding H, et al. Trends in prescribing of antipsychotic medications for US children. Ambul Pediatr 2006;6(2):79-83.
37. Correll CU, Fredrickson AM, Kane JM, et al. Does antipsychotic polypharmacy increase the risk of metabolic syndrome? Schizophr Res 2007;89(1-3):91-100.
38. Correll CU, Gallego JA. Antipsychotic polypharmacy: a comprehensive evaluation of relevant correlates of a long-standing clinical practice. Psychiatr Clin North Am 2012;35(3):661-81.
39. Correll CU, Rummel-Kluge C, Corves C, et al. Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials. Schizophr Bull 2009; 35(2):443–57.
40. Crismon L., Argo T.R., Buckley P.F. (2011). Chapter 76. Schizophrenia. In R.L. Talbert, J.T. DiPiro, G.R. Matzke, L.M. Posey, B.G. Wells, G.C. Yee (Eds), Pharmacotherapy: A Pathophysiologic Approach, 8th edition. Retrieved December 3, 2012 from http://www.accesspharmacy.com/content.aspx?aID=7987911.
41. Daumit GL, Crum RM, Guallar E, et al. Outpatient prescriptions for atypical antipsychotics for African Americans, Hispanics, and whites in the United States. Arch Gen Psychiatry 2003;60(2):121-8.
42. Davis JM, Chen N. Dose response and dose equivalence of antipsychotics. J Clin Psychopharmacol 2004; 24(2):192-208.
43. Deb P, Manning W, Norton E. Modeling health care costs and counts. Association for the Study of Higher Education, Madison Conference, 2006.

44. Derry S, Moore RA. Atypical antipsychotics in bipolar disorder: systematic review of randomized trials. BMC Psychiatry 2007;7:40.
45. D'Hoore W, Bouckaert A, Tilquin C. Practical considerations on the use of the Charlson comorbidity index with administrative data bases. J Clin Epidemiol 1996;49(12):1429-33.
46. Dictionary.com. Polypharmacy [online]. Available from URL: http://dictionary.reference.com/browse/polypharmacy. Accessed October 23, 2012.
47. Diehr P, Yanez D, Ash A, et al. Methods for analyzing health care utilization and costs. Annu Rev Public Health 1999;20:125-44.
48. Divac N, Jasović-Gasić M, Samardzić R, et al. Antipsychotic polypharmacy at the University Psychiatric Hospital in Serbia. Pharmacoepidemiol Drug Saf 2007;16(11):1250-1.
49. Dolder CR, McKinsey J. Antipsychotic polypharmacy among patients admitted to a geriatric psychiatry unit. J Psychiatr Pract 2011;17(5):368-74.
50. Drug Utilization Review Board of California Medicaid Program. Department of Health Services, Medi-Cal Division. Sacremento, CA. 2001.
51. Eisen C, Shaner R, Unutzer J, et al. Datapoints: second-generation antipsychotic medication combinations for schizophrenia. Psychiatr Serv 2008;59(3):235.
52. Elhai JD, Calhoun PS, Ford JD. Statistical procedures for analyzing mental health services data. Psychiatry Res 2008;160(2):129-36.
53. Essock SM, Schooler NR, Stroup TS, et al. Effectiveness of switching from antipsychotic polypharmacy to monotherapy. Am J Psychiatry 2011;168(7):702-8.
54. Faries D, Ascher-Svanum H, Zhu B, et al. Antipsychotic monotherapy and polypharmacy in the naturalistic treatment of schizophrenia with atypical antipsychotics. BMC Psychiatry 2005;5:26.
55. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39(2):175-91.
56. Fenton WS, Blyler CR, Heinssen RK. Determinant of medication compliance in schizophrenia: empirical and clinical findings. Schizophr Bull 1997: 23(4):637-51.

57. Finnerty MT, Kealey E, Leckman-Westin E, et al. Long-term impact of web-based tools, leadership feedback, and policies on inpatient antipsychotic polypharmacy. Psychiatr Serv 2011;62(10):1124-6.
58. Fleischhacker WW, Uchida H. Critical review of antipsychotic polypharmacy in the treatment of schizophrenia. Int J Neuropsychopharmacol 2012;2:1-11.
59. Freudenreich O, Goff DC. Antipsychotic combination therapy in schizophrenia: a review of efficacy and risk of current combinations. Acta Psychiatr Scand 2002;106(5):323-30.
60. Freudenreich O, Henderson DC, Walsh JP, et al. Risperidone augmentation for schizophrenia partially responsive to clozapine: A double-blind, placebo-controlled trial. Schizophr Res 2007;92(1-3):90–4.
61. Fulton MM, Allen ER. Polypharmacy in the elderly: a literature review. J Am Acad Nurse Pract 2005; 17 (4): 123-32.
62. Gallego JA, Bonetti J, Zhang J, et al. Prevalence and correlates of antipsychotic polypharmacy: a systematic review and meta-regression of global and regional trends from the 1970s to 2009. Schizophr Res 2012; 138(1):18-28.
63. Ganguly R, Kotzan JA, Miller LS, et al. Prevalence, trends, and factors associated with antipsychotic polypharmacy among Medicaid-eligible schizophrenia patients, 1998-2000. J Clin Psychiatry 2004;65(10):1377-88.
64. Generalized Linear Models In: Fox J. Applied Regression Analysis and Generalized Linear Models 2nd ed Chapter 15. Thousand Oaks, CA: Sage Publications, 2008.
65. Gilmer TP, Dolder CR, Folsom DP, et al. Antipsychotic polypharmacy trends among Medicaid beneficiaries with schizophrenia in San Diego County, 1999-2004. Psychiatr Serv 2007;58(7):1007-10.
66. Gören JL, Beck SE, Mills BJ, et al. Development and delivery of a quality improvement program to reduce antipsychotic polytherapy. J Manag Care Pharm 2010;16(6):393-401.
67. Hazra M, Uchida H, Sproule B, et al. Impact of feedback from pharmacists in reducing antipsychotic polypharmacy in schizophrenia. Psychiatry Clin Neurosci 2011;65(7):676-8.
68. Hoffer ZS, Roth RL, Matthew M. Evidence for the partial dopamine receptor agonist aripiprazole as first-line treatment of psychosis in patient with iatrogenic or tumorigenic hyperprolactinemia. Psychosomatics 2009; 50(4):317-24.

69. Honer WG, Thornton AE, Chen EY, et al. Clozapine alone versus clozapine and risperidone with refractory schizophrenia. N Engl J Med 2006;354(5):472–82.
70. Hori H, Yoshimura R, Katsuki A, et al. Switching to antipsychotic monotherapy can improve attention and processing speed, and social activity in chronic schizophrenia patients. J Psychiatr Res 2013;47(12):1843-8.
71. Hu MC, Pavlicova M, Nunes EV. Zero-inflated and hurdle models of count data with extra zeros: examples from an HIV-risk reduction intervention trial. Am J Drug Alcohol Abuse 2011;37(5):367-75. doi: 10.3109/00952990.2011.597280.
72. Iasevoli F, Buonaguro EF, Marconi M, et al. Efficacy and clinical determinants of antipsychotic polypharmacy in psychotic patients experiencing an acute relapse and admitted to hospital stay: results from a cross-sectional and a subsequent longitudinal pilot study. ISRN Pharmacol 2014;2014:762127. doi: 10.1155/2014/762127.
73. Jackman S. Generalized Linear Models. Available at: http://jackman.stanford.edu/papers/glm.pdf. Accessed December 7, 2012.
74. Jaffe AB, Levine J. Antipsychotic medication coprescribing in a large state hospital system. Pharmacoepidemiol Drug Saf 2003;12(1):41-8.
75. Jin H, Zhao X. Transformation and sample size. 2009. Available at: http://www.statistics.du.se/essays/D09_Hui_Zhao.pdf. Accessed December 5, 2012.
76. Josiassen RC, Joseph A, Kohegyi E, et al. Clozapine augmented with risperidone in the treatment of schizophrenia: A randomized, double-blind, placebo-controlled trial. Am J Psychiatry 2005;162(1):130–6.
77. Kapur S, Seeman P. Antipsychotic agents differ in how fast they come off the dopamine D2 receptors. Implications for atypical antipsychotic action. J Psychiatry Neurosci 2000;25(2):161–6.
78. Kapur S, Zipursky RB, Remington G, et al. 5HT-2 and D2 receptor occupancy of olanzapine in schizophrenia: A PET investigation. Am J Psychiatry 1998;155(7):921–8.
79. Katona L, Czobor P, Bitter I. Real-world effectiveness of antipsychotic monotherapy vs. polypharmacy in schizophrenia: To switch or to combine? A nationwide study in Hungary. Schizophr Res 2014;152(1):246-54.

80. Kogut SJ, Yam F, Dufresne R. Prescribing of antipsychotic medication in a Medicaid population: use of polytherapy and off-label dosages. J Manag Care Pharm 2005;11(1):17-24.
81. Kotler M, Strous RD, Reznik I, et al. Sulpiride augmentation of olanzapine in the management of treatment-resistant chronic schizophrenia: Evidence for improvement of mood symptomatology. Int Clin Psychopharmacol 2004;19(1):23–6.
82. Kreyenbuhl J, Buchanan RW, Dickerson FB, et al. The schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2009. Schizophr Bull 2010; 36(1):94-103.
83. Kreyenbuhl J, Buchanan RW, Dickerson FB, et al. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2009. Schizophr Bull 2010; 36(1):94-103.
84. Kreyenbuhl J, Slade EP, Medoff DR, et al. Time to discontinuation of first- and second-generation antipsychotic medications in the treatment of schizophrenia. Schizophr Res 2011;131(1-3):127-32.
85. Kreyenbuhl J, Valenstein M, McCarthy JF, et al. Long-term antipsychotic polypharmacy in the VA health system: patient characteristics and treatment patterns. Psychiatr Serv 2007;58(4):489-95.
86. Kreyenbuhl J, Valenstein M, McCarthy JF, et al. Long-term combination antipsychotic treatment in VA patients with schizophrenia. Schizophr Res 2006; 84(1):90–9.
87. Lang K, Meyers JL, Korn JR, et al. Medication adherence and hospitalization among patients with schizophrenia treated with antipsychotics. Psychiatr Serv 2010;61(12):1239-47.
88. Langan J, Shajahan P. Antipsychotic polypharmacy: review of mechanisms, mortality and management. The Psychiatrist 2010; 34:58-62.
89. Lehman AF, Lieberman JA, Dixon LB, et al. Practice guidelines for the treatment of patients with schizophrenia, second edition. Am J Psychiatry 2004;161:Suppl:1-56.
90. Leslie DL, Rosenheck RA. Adherence of schizophrenia pharmacotherapy to published treatment recommendations: patient, facility, and provider predictors. Schizophr Bull 2004;30(3):649-58.

91. Leslie DL, Rosenheck RA. Use of pharmacy data to assess quality of pharmacotherapy for schizophrenia in a national health care system: Individual and facility predictors. Med Care 2001;39(9):923-33.
92. Lexi Comp. Lurasidone. Available at: http://online.lexi.com/lco/action/doc/retrieve/docid/250/3543687#dosage. Accessed December 3, 2012.
93. Lexi Comp. Pimozide. Available at: http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7494#f_dosages. Accessed December 3, 2012.
94. Lieberman JA, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Eng J Med 2005; 353(12):1209–23.
95. Lochmann van Bennekom MW1, Gijsman HJ, Zitman FG. Antipsychotic polypharmacy in psychotic disorders: a critical review of neurobiology, efficacy, tolerability and cost effectiveness. J Psychopharmacol 2013;27(4):327-36.
96. Logistic Regression Diagnostics. In: Chen X, Ender P, Mitchell M, et al. Logistic Regression with Stata. UCLA: Academic Technology Services, Statistical Consulting Group. Available at: http://www.ats.ucla.edu/stat/stata/ado/analysis/. Accessed: December 5, 2012.
97. Loosbrock DL, Zhao Z, Johnstone BM, et al. Antipsychotic medication use patterns and associated costs of care for individuals with schizophrenia. J Ment Health Policy Econ 2003;6(2):67-75.
98. López de Torre A, Lertxundi U, Hernández R, et al. Antipsychotic polypharmacy: a needle in a haystack? Gen Hosp Psychiatry 2012;34(4):423-32.
99. Maglione M, Ruelaz Maher A, Hu J, Wang Z, Shanman R, Shekelle PG, Roth B, Hilton L, Suttorp MJ, Ewing BA, Motala A, Perry T. Off-Label use of atypical antipsychotics: An update. Comparative Effectiveness Review No. 43. (Prepared by the Southern California Evidence-based Practice Center under Contract No. HHSA290-2007-10062-1.) Rockville, MD: Agency for Healthcare Research and Quality. September 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed April 1, 2014.
100. Marcus SC, Olfson M. Outpatient antipsychotic treatment and inpatient costs of schizophrenia. Schizophr Bull 2008;34(1):173-80.

101. McCue RE, Waheed R, Urcuyo L. Polypharmacy in patients with schizophrenia. J Clin Psychiatry 2003;64(9):984-9.
102. Medicaid Analytic eXtract (MAX) Rx Table Listing. Available at: http://www.cms.gov/Research-Statistics-Data-and-Systems/Computer-Data-and-Systems/MedicaidDataSourcesGenInfo/Medicaid-Analytic-eXtract-MAX-Rx-Table-Listing.html. Accessed March 15, 2013.
103. Meltzer HY. Mechanism of action of atypical antipsychotics. In: Davis KL, Chamey D, Nemeroff CL, et al., eds. Neuropsychopharmacology: The Fifth Generation of Progress. Philadelphia, PA: Lippincott, Williams and Wilkins;2002.
104. Miller AL, Craig CS. Combination antipsychotics: pros, cons, and questions. Schizophr Bull 2002; 28(1):105-9.
105. Miller AL, Hall CS, Buchanan RW, et al. The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2003 update. J Clin Psychiatry 2004; 65(4):500-8.
106. Moisan J, Grégoire JP. Patterns of discontinuation of atypical antipsychotics in the province of Québec: A retrospective prescription claims database analysis. Clin Ther 2010;32 Suppl 1:S21-31.
107. Mood Disorders. In: First MB ed. Diagnostic and Statistical Manual of Mental Disorders 4th ed. Washington (DC): American Psychiatric Association, 2000.
108. Moore TA, Buchanan RW, Buckley PF, et al. The Texas medication algorithm project antipsychotic algorithm for schizophrenia: 2006 update. J Clin Psychiatry 2007;68(11):1751-62.
109. Morrato EH, Dodd S, Oderda G, et al. Prevalence, utilization patterns, and predictors of antipsychotic polypharmacy: experience in a multistate Medicaid population, 1998-2003. Clin Ther 2007;29(1):183-95.
110. Mullins CD, Obeidat NA, Cuffel BJ, et al. Risk of discontinuation of atypical antipsychotic agents in the treatment of schizophrenia. Schizophr Res 2008;98(1-3):8-15.
111. Multiple Regression. In: Stevens JP. Applied Multivariate Statistics for the Social Sciences 5th ed. New York, NY:Taylor & Francis Group, 2009.
112. National Alliance on Mental Illness, 2010 State Advocacy Report.

113. National Institute for Clinical Excellence: Core interventions in the treatment and management of schizophrenia in adults in primary and secondary care. NICE Clinical Guideline 82; 2009.
114. Needham DM, Scales DC, Laupacis A, et al. A systematic review of the Charlson comorbidity index using Canadian administrative databases: a perspective on risk adjustment in critical care research. J Crit Care 2005;20(1):12-9.
115. Noordsy DL, Phillips GA, Ball DE, et al. Antipsychotic adherence, switching, and health care service utilization among Medicaid recipients with schizophrenia. Patient Prefer Adherence 2010;4:263-71.
116. Nordstrom AL, Farde L,Wiesel FA, et al. Central D2-dopamine receptor occupancy in relation to antipsychotic drug effects: A double-blind PET study of schizophrenic patients. Biol Psychiatry 1993;33(4):227–35.
117. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353(5):487-97.
118. Pampallona S, Bollini P, Tibaldi G, Kupelnick B, Munnizza C. Patient adherence in the treatment of depression. Br J Psychiatry 2002; 180:104–9.
119. Pandurangi AK, Dalkilic A. Polypharmacy with second-generation antipsychotics: a review of evidence. J Psychiatr Pract 2008;14(6):345-67.
120. Patel MX, David AS. Medication adherence: predictive factors and enhancement strategies. Psychiatry 2007; 6(9):357-61.
121. Patel NC, Crismon ML, Hoagwood K, et al. Physician specialty associated with antipsychotic prescribing for youths in the Texas Medicaid program. Med Care 2006;44(1):87-90.
122. Paton C, Barnes TR, Cavanagh MR, et al. High-dose and combination antipsychotic prescribing in acute adult wards in the UK: the challenges posed by p.r.n. prescribing. Br J Psychiatry 2008;192(6):435-9.
123. Paton C, Lelliott P, Harrington M, et al. Patterns of antipsychotic and anticholinergic prescribing for hospital inpatients. J Psychopharmacol 2003;17(2):223-9.
124. Paton C, Whittington C, Barnes TR. Augmentation with a second antipsychotic in patients with schizophrenia who partially respond to clozapine: a meta-analysis. J Clin Psychopharmacol 2007(2); 27:198–204.

125. Patrick V, Levin E, Schleifer S. Antipsychotic polypharmacy: Is there evidence for its use? J Psychiatr Pract 2005;11(4):248–57.
126. Patrick V, Schleifer SJ, Nurenberg JR, et al. Best practices: An initiative to curtail the use of antipsychotic polypharmacy in a state psychiatric hospital. Psychiatr Serv 2006;57(1):21-3.
127. Paulose-Ram R, Safran MA, Jonas BS, et al. Trends in psychotropic medication use among U.S. adults. Pharmacoepidemiol Drug Saf 2007;16(5):560-70.
128. Peterson AM, Nau DP, Cramer JA, et al. A checklist for medication compliance and persistence studies using retrospective databases. Value Health 2007;10(1):3-12.
129. Pillarella J, Higashi A, Alexander GC, et al. Trends in use of second-generation antipsychotics for treatment of bipolar disorder in the United States, 1998-2009. Psychiatr Serv 2012;63(1):83-6.
130. Potkin SG, Thyrum PT, Alva G, et al. The safety and pharmacokinetics of quetiapine when co-administered with haloperidol, risperidone, or thioridazine. J Clin Psychopharmacol 2002(2);22:121–30.
131. Procyshyn RM, Honer WG, Wu TK, et al. Persistent antipsychotic polypharmacy and excessive dosing in the community psychiatric treatment setting: a review of medication profiles in 435 Canadian outpatients. J Clin Psychiatry 2010;71(5):566-73.
132. Psychiatric Medicine. In: Kasper D, Braunwald E, Fauci AS, eds. Harrison's Manual of Internal Medicine. 16th ed. New York: McGraw Hill; 2005:962-969.
133. Ranceva N, Ashraf W, Odelola D. Antipsychotic polypharmacy in outpatients at Birch Hill Hospital: incidence and adherence to guidelines. J Clin Pharmacol 2010;50(6):699-704.
134. Rascati KL, Johnsrud MT, Crismon ML, et al. Olanzapine versus risperidone in the treatment of schizophrenia. PharmacoEconomics 2003;21(10):683-97.
135. Ren XS1, Huang YH, Lee AF, Miller DR, Qian S, Kazis L. Adjunctive use of atypical antipsychotics and anticholinergic drugs among patients with schizophrenia. J Clin Pharm Ther 2005;30(1):65-71.
136. Reus VI. Mental Disorders. In: , Kasper D, Braunwald E, Hauser SL, Longo DL, Jameson JL, Fauci AS, eds. Harrison's Principles of Internal Medicine. 16th ed. New York: McGraw Hill; 2004.

137. Rothbard A, Murrin MR, Jordan N, et al. Effects of antipsychotic medication on psychiatric service utilization and cost. J Ment Health Policy Econ 2005;8(2):83-93.
138. Sajatovic M, Sultana D, Bingham CR, et al. Gender related differences in clinical characteristics and hospital based resource utilization among older adults with schizophrenia. Int J Geriatr Psychiatry 2002;17(6):542-8.
139. Sajatovic M, Valenstein M, Blow FC, et al. Treatment adherence with antipsychotic medications in bipolar disorder. Bipolar Disord 2006;8(3):232-41.
140. Sankaranarayanan J, Puumala SE. Antipsychotic use at adult ambulatory care visits by patients with mental health disorders in the United States, 1996-2003: national estimates and associated factors. Clin Ther 2007;29(4):723-41.
141. Santone G, Bellantuono C, Rucci P, et al. Patient characteristics and process factors associated with antipsychotic polypharmacy in a nationwide sample of psychiatric inpatients in Italy. Pharmacoepidemiol Drug Saf 2011;20(5):441-9.
142. Schizophrenia-Mayo Clinic Staff, Mayo Clinic. Available at: http://www.mayoclinic.com/health/schizophrenia/DS00196. Accessed on October 15, 2010
143. Schumacher JE, Makela EH, Griffin HR. Multiple antipsychotic medication prescribing patterns. Ann Pharmacother 2003;37(7-8):951-5.
144. Scott J, Pope M. Nonadherence with mood stabilizers: prevalence and predictors. J Clin Psychiatry 2002; 63(5):384–90.
145. Sernyak MJ, Dausey D, Desai R, et al. Prescribers' nonadherence to treatment guidelines for schizophrenia when prescribing neuroleptics. Psychiatr Serv 2003;54(2):246-8.
146. Shiloh R, Zemishlany Z, Aizenberg D, et al. Sulpiride augmentation in people with schizophrenia partially responsive to clozapine. A double blind, placebo-controlled study. Br J Psychiatry 1997;171:569–73.
147. Shim JC, Shim JG, Kelly DL, et al. Adjunctive therapy with a dopamine partial agonist, aripiprazole, for antipsychotic-induced hyperprolactinemia: a placebo controlled trial. Am J Psychiatry 2007; 164(9):1404-10.

148. Stagnitti, M. N. Trends in Antipsychotics Purchases and Expenses for the US Civilian Noninstitutionalized Population, 1997 and 2007. Statistical Brief #275. January 2010. Agency for Healthcare Research and Quality, Rockville, MD. Available at: http://www.meps.ahrq.gov/mepsweb/data_files/publications/st275/stat275.pdf. Accessed April 3, 2014.
149. Stahl SM, Grady MM. A critical review of atypical antipsychotic utilization: Comparing monotherapy with polypharmacy and augmentation. Curr Med Chem 2004;11(3):313–27.
150. Stahl SM, Grady MM. High-cost use of second-generation antipsychotics under California's Medicaid program. Psychiatr Serv 2006;57(1):127-9.
151. Stahl SM. Antipsychotic polypharmacy, Part 1: Therapeutic option or dirty little secret? J Clin Psychiatry 1999;60(7):425–6.
152. Stahl SM. Antipsychotic polypharmacy: squandering precious resources? J Clin Psychiatry 2002;63(2):93-4.
153. Stahl SM. Essential Pharmacology, 2nd ed. New York, NY: Cambridge University Press; 2000.
154. Svarstad BL, Shireman TI, Sweeney JK. Using drug claim data to assess the relationship of medication adherence with hospitalization and costs. Psychiatr Serv 2001;52(6):805-11
155. Tani H, Uchida H, Suzuki T, et al. Interventions to reduce antipsychotic polypharmacy: a systematic review. Schizophr Res 2013;143(1):215-20.
156. Taylor D, Atkinson J, Fischetti C, et al. A prospective 6-month analysis of the naturalistic use of aripiprazole: factors predicting favorable outcome. Acta Psychiatr Scand 2007; 116(6):461-6
157. Taylor DM, Smith L. Augmentation of clozapine with a second antipsychotic: a meta-analysis of randomized, placebo-controlled studies. Acta Psychiatr Scand 2009; 119(6):419–25.
158. Texas Medicaid in Perspective. In: Texas Medicaid and CHIP in Perspective, 9th ed. Texas Health and Human Services Commission, 2012. Available at: http://www.hhsc.state.tx.us/medicaid/reports/PB9/1_PB_9th_ed_Introduction.pdf. Accessed on February 14, 2013.
159. The expert consensus guideline series. Treatment of schizophrenia. J Clin Psychiatry 1999; 60 suppl 11:3-80.

160. The International Psychopharmacology Algorithm Project. IPAP schizophrenia algorithm. Available at: www.ipap.org/schiz. Accessed October 9, 2012.
161. Thompson A, Sullivan SA, Barley M, et al. The DEBIT trial: an intervention to reduce antipsychotic polypharmacy prescribing in adult psychiatry wards - a cluster randomized controlled trial. Psychol Med 2008;38(5):705-15.
162. Tohen M, Vieta E. Antipsychotic agents in the treatment of bipolar mania. Bipolar Disord 2009;11 Suppl 2:45-54.
163. Toteja N1, Gallego JA, Saito E, et al. Prevalence and correlates of antipsychotic polypharmacy in children and adolescents receiving antipsychotic treatment. Int J Neuropsychopharmacol 2013; 14:1-11. [Epub ahead of print].
164. Tranulis C, Skalli L, Lalonde P, et al. Benefits and risks of antipsychotic polypharmacy: an evidence-based review of the literature. Drug Saf 2008;31(1):7-20.
165. Tungaraza TE, Gupta S, Jones J, et al. Polypharmacy and high-dose antipsychotic regimes in the community. The Psychiatrist 2010; 34(2):44-6.
166. US Food and Drug Administration. Atypical Antipsychotic Drugs Information. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm094303.htm. Accessed on October 15, 2012.
167. US Food and Drug Administration. Information on Conventional Antipsychotics. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107211.htm. Accessed on October 15, 2012.
168. US National Library of Medicine. Bipolar Disorder. Available at: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001924/. Accessed on October 11, 2012.
169. Valenstein M, Blow FC, Copeland LA, et al. Poor antipsychotic adherence among patients with schizophrenia: medication and patient factors. Schizophr Bull 2004;30(2):255-64.
170. Valenstein M, Ganoczy D, McCarthy JF, et al. Antipsychotic adherence over time among patients receiving treatment for schizophrenia: a retrospective review. J Clin Psychiatry 2006;67(10):1542-50.

171. Valuck RJ, Morrato EH, Dodd S, et al. How expensive is antipsychotic polypharmacy? Experience from five US state Medicaid programs. Curr Med Res Opin 2007;23(10):2567-76.
172. Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. J Clin Epidemiol 1992; 45(2):197–203.
173. Weinmann S, Read J, Aderhold V. Influence of antipsychotics on mortality in schizophrenia: systematic review. Schizophr Res 2009;113(1):1-11.
174. Weintraub D, Chen P, Ignacio RV, et al. Patterns and trends in antipsychotic prescribing for Parkinson disease psychosis. Arch Neurol 2011;68(7):899-904.
175. Weissman EM. Antipsychotic prescribing practices in the Veterans Healthcare Administration--New York metropolitan region. Schizophr Bull 2002;28(1):31-42.
176. Welsh KJ, Patel CB, Fernando RC, et al. Prevalence of bipolar disorder and schizophrenia in Houston Outreach Medicine, Education, and Social Services (HOMES) clinic patients: implications for student-managed clinics for underserved populations. Academic Medicine: Journal of the Association of American Medical Colleges 2012;87(5):656-61.
177. Woodward M. Epidemiology: study design and data analysis. Boca Raton, FL: Chapman & Hall/CRC Press;1999.
178. Xiang YT, Dickerson F, Kreyenbuhl J, et al. Common use of anticholinergic medications in older patients with schizophrenia: findings of the Research on Asian Psychotropic Prescription Pattern (REAP) study, 2001-2009. Int J Geriatr Psychiatry 2012. doi: 10.1002/gps.3827. [Epub ahead of print].
179. Xiang YT, Weng YZ, Leung CM, et al. Clinical and social determinants of antipsychotic polypharmacy for Chinese patients with schizophrenia. Pharmacopsychiatry 2007;40(2):47-52.
180. Yang M, Barner JC, Lawson KA, et al. Antipsychotic medication utilization trends among Texas veterans: 1997-2002. Ann Pharmacother 2008;42(9):1229-38.
181. Ye W, Ascher-Svanum H, Flynn JA, et al. Predictors of antipsychotic monotherapy with olanzapine during a 1-year naturalistic study of schizophrenia patients in Japan. Clinicoecon Outcomes Res 2012;4:13-9.
182. Zhu B, Ascher-Svanum H, Faries DE, et al. Cost of antipsychotic polypharmacy in the treatment of schizophrenia. BMC Psychiatry 2008;8:19.

183. Zink M, Englisch S, Meyer-Lindenberg A. Polypharmacy in schizophrenia. Curr Opin Psychiatry 2010;23(2):103-11.
184. Zygmunt A, Olfson M, Boyer CA, Mechanic D. Interventions to improve medication adherence in schizophrenia. Am J Psychiatry 2002; 159(10):1653–64.