ANTIPSYCHOTIC POLYPHARMACY VS. MONOTHERAPY IN THE TREATMENT OF SCHIZOPHRENIA

by

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(Under the Direction of Bradley C. Martin)

ABSTRACT

Antipsychotic polypharmacy or concomitant use of multiple antipsychotics is prevalent in up to 40% of schizophrenia patients despite lack of clinical evidence or support from treatment guidelines. The objective of this study was to estimate the prevalence and trends of antipsychotic polypharmacy, identify patient factors associated with its use and determine its effect on health care cost and community tenure.

Medicaid recipients >=16 years of age with at least one primary diagnosis of schizophrenia (ICD-9-CM=295.**) between 1998-2000 were identified from the Georgia and California (20% random sample) Medicaid claims databases. Antipsychotic polypharmacy cohorts were built in a hierarchical fashion based on antipsychotic use profile i.e. any antipsychotic polypharmacy, clozapine (clozapine + atypical; clozapine + conventional), non-clozapine (atypical+atypical; conventional+conventional; and atypical+conventional) and long-term i.e. duration of use > 2 months and compared with monotherapy controls. 3-year prevalence rates, year wise trends, per capita net one-year expenditure and one-year hazard rates for hospitalization were reported after adjusting for selection bias.

Out of a total of 31,435 persons with schizophrenia, the overall prevalence of antipsychotic polypharmacy was 40% (n=12,549, mean age: 43 years, white: 47%,

female: 48%) over 1998-2000 and prevalence of atypical polypharmacy had increased between 1998 and 2000. Long-term antipsychotic polypharmacy had a prevalence rate of 23% (n=7,222) with a long-term episode lasting a median of 197 days. The one-year per capita expenditure for the long-term antipsychotic polypharmacy group was $13,891 which was significantly higher ($3,829 95% Confidence Interval [CI], 3,347 to 4,310) than the monotherapy group ($10,062) and remained higher even after adjustment for selection bias ($1,699 95% CI 760 to 2,638). Polypharmacy was associated with a higher one-year (1.25, 95% CI 1.09 TO 1.41) and two-year (1.45, 95% CI 1.27 to 1.63) hospitalization risk.

We did not find any evidence of economic and hospitalization risk related benefit with antipsychotic polypharmacy except a significant net cost in the clozapine+conventional vs clozapine sensitivity analysis ($p < 0.0001$). Our findings raise concerns regarding the value of antipsychotic polypharmacy and emphasize the need to critically evaluate such treatment decisions in schizophrenia patients.

INDEX WORDS: Antipsychotic, Schizophrenia, Polypharmacy, Medicaid, Cost, Community Tenure

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CHAPTER 1

INTRODUCTION

Antipsychotic polypharmacy or concomitant use of multiple antipsychotics in schizophrenia is regarded as one of the most practiced and least investigated phenomena in clinical psychopharmacology. This has become a larger concern with the recent introduction of five new antipsychotics. It is estimated that antipsychotic polypharmacy is prescribed for up to 40% of schizophrenia patients. However the researchers could only find one controlled trial involving sulpiride, which is not approved for use in the US, and no observational studies that estimate the effect of antipsychotic polypharmacy. The paucity of evidence on the effect of antipsychotic polypharmacy makes it a clinical concern due to the potential for serious side effects and is an economic concern because of the high costs.

The primary objective of this research is to estimate the effect of antipsychotic polypharmacy vs. monotherapy on total health care cost and community tenure among Medicaid eligible persons diagnosed with schizophrenia. Community tenure is defined as the number of days from the start of a treatment episode to the first hospitalization episode. A retrospective study was performed using a combined two-state (Georgia and California) Medicaid claims database for the years 1998 through 2000. Multiple cohorts was built in a hierarchical fashion, narrowing the definition of antipsychotic polypharmacy with each consecutive step according to type and duration of antipsychotic use, for e.g. any antipsychotic polypharmacy, long-term polypharmacy (more than 2 months usage), clozapine (clozapine+conventional, clozapine+atypical) and non clozapine

(atypical+atypical, atypical+conventional, conventional+conventional) antipsychotic polypharmacy. A comparison group formed of patients on monotherapy was built for each antipsychotic polypharmacy cohort for e.g. clozapine+atypical polypharmacy subjects were compared with subjects on clozapine monotherapy.

Two separate techniques, the Propensity score matching and Heckman two-stage estimator was used to reduce selection bias inherent in an observational database and estimate effect by comparing the antipsychotic polypharmacy cohort (experimental group) and corresponding monotherapy cohort (comparison group). A survival analysis with the Cox proportional hazards regression was used to examine the effect of antipsychotic polypharmacy vs. monotherapy on community tenure.

The specific aims of the research are to:

1. Study the prevalence and trend of antipsychotic polypharmacy over a 3 year period, 1998 through 2000 in Medicaid eligible persons diagnosed with schizophrenia.
2. Determine patient characteristics associated with antipsychotic polypharmacy for Medicaid eligible persons diagnosed with schizophrenia.
3. Estimate the effect of antipsychotic polypharmacy vs. monotherapy on two main outcome measures: total health care cost and community tenure, among Medicaid eligible persons diagnosed with schizophrenia for the following groups of antipsychotic polypharmacy users
    - exposed to antipsychotic polypharmacy for more than 2 months (long-term polypharmacy)
    - long term antipsychotic polypharmacy use with any exposure to clozapine subdivided by class of antipsychotics used :clozapine + atypical, clozapine + conventional

- long term antipsychotic polypharmacy users with no exposure to clozapine subdivided by class of antipsychotics used: atypical + atypical, atypical + conventional, conventional + conventional

This project will test the following hypothesis:

1. Ha (Alternate hypothesis): Antipsychotic polypharmacy and antipsychotic monotherapy differ significantly in total health care cost and community tenure among Medicaid eligible persons diagnosed with schizophrenia.

   The hypothesis was tested separately employing various sensitivity analyses:

   - Varying lengths of observation period e.g. one year, two years and length of the antipsychotic use episode.
   - Total health care outcomes e.g. total health care cost, time-to-any hospitalization and specifically mental health and substance abuse related outcomes e.g. Mental health related costs, time-to-mental health related hospitalization.

Model validation was performed on a random validation sample held out from the original two state sample wherever necessary.

CHAPTER 2

BACKGROUND AND SIGNIFICANCE

PHARMACOTHERAPY OF SCHIZOPHRENIA

Schizophrenia is a relatively common and severe psychological disorder that affects approximately 1 in 100 people in the course of their lives (Birchwood 2001). There are 20 new cases of schizophrenia per 100,000 population per year and the financial burden to the health care system is around $33 billion, nearly half of which is attributable to hospitalizations (Sevy 1995). Much of the morbidity associated with the disease is due to acute psychotic episodes and frequent relapses. Presently antipsychotics are used extensively for acute psychosis and maintenance therapy to prevent relapses in schizophrenia.

The newer antipsychotics called the "atypicals" were introduced through the 90's starting with clozapine (1989), risperidone (1994), olanzapine (1996), quetiapine (1997) and ziprasidone (2001). Before "atypicals," the older antipsychotics or "conventionals" (e.g. haloperidol, chlorpromazine) were the only form of clinically approved pharmacologic treatment for schizophrenia. Since the atypicals are considered more effective and safe, all published treatment guidelines recommend starting and staying with monotherapy with an atypical antipsychotic (clozapine excluded) (Lehman 98, American Psychiatric Assoc. 97, Miller et al. 1999, McEnvoy 99) and shifting to monotherapy with a conventional if all atypicals fail. Clozapine is reserved as a last option for treatment resistant cases.

TREATMENT GUIDELINES

Four published treatment guidelines were identified from the literature – the Texas Medication Algorithm Project (TMAP), Patient Outcomes Research Team (PORT), American Psychiatric Association (APA) and Journal of Clinical Psychiatry (JCP) guidelines. The TMAP (Miller 1999) recommends antipsychotic polypharmacy if clozapine therapy or clozapine plus augmentation therapy fails or is refused after trying all possible monotherapies. It has been reported that 40 – 70% of patients treated with clozapine, may show an inadequate response, more than 20% may withdraw because of adverse effects, and more than 10% may withdraw because of slow onset of clinical response (Canales 1999). In this case a trial of an atypical combined with a conventional or atypical combined with another atypical is recommended.

The JCP guideline (McEnvoy 1999) recommends antipsychotic polypharmacy for up to 8 weeks only when switching from monotherapy with one antipsychotic to another, gradually weaning the patient off the first antipsychotic in the process. Such switches are quite common and one study reports that approximately 25% of all patients switched from one antipsychotic to a different antipsychotic during a 12 month period (Williams 1999). The PORT (Lehman 1998) and APA (American Psychiatric Association 1997) guidelines do not recommend any form of antipsychotic polypharmacy.

While review articles on antipsychotic usage generally advocate monotherapy (Stahl 1999; Hellewel 1999; Canales 1999; Yuzda 2001), the majority of them also recognize antipsychotic polypharmacy as a possible option in two specific situations; short-term or PRN use for "Symptom control" (Stahl 1999; Canales 1999; Yuzda 2001) and short-term tactic while switching from one monotherapy to another (Stahl 1999; Canales 1999; Yuzda 2001). However they also acknowledge the lack of published evidence and potential for less well-tolerated regimens with antipsychotic polypharmacy.

PHARMACOLOGICAL BASIS OF ANTIPSYCHOTIC POLYPHARMACY

The therapeutic actions of conventional antipsychotic drugs is due to blockade of D2 receptors specifically in the mesolimbic dopamine pathway in the brain (Stahl 2000). This has the effect of reducing the hyperactivity in this pathway that is postulated to cause positive symptoms of psychosis. However, along with mesolimbic dopamine pathway, these agents also block 3 other dopamine pathways causing side-effects such as increased negative symptoms, extrapyramidal symptoms, tardive dyskinesia and hyperprolactinemia. Also some conventional antipsychotics have a muscarinic cholinergic blocking property which increases anticholinergic type side effects (e.g. dry mouth, blurred vision) but reduces extrapyramidal side effects. Although side-effect profiles might differ between conventional antipsychotics, they have similar therapeutic profiles, which implies that multiple conventional antipsychotic polypharmacy may not have any advantage over monotherapy.

Atypical antipsychotics block both dopamine D2 receptors and serotonin 5HT2A receptors and are also known as serotonin-dopamine (SDA) antagonists (Stahl 2000). 5HT2A blockade and the subsequent serotonergic control of dopamine release in each of the four dopamine pathways in the brain sets atypicals apart from the conventionals. Simultaneous blockade of D2 and 5HT2A receptors cause differential effects on the 4 dopamine pathways greatly reducing their side-effect profile. No two atypical agents have exactly identical properties, including multiple pharmacologic actions at serotonin and dopamine receptor subtypes in addition to SDA actions (e.g. D1, D3, and D4 as well as 5HT1A, 5HT1D, 5HT2C, 5HT3, 5HT6 and 5HT7) and multiple pharmacologic actions at other neurotransmitter receptors (such as alpha 1 and alpha 2 noradrenergic, muscarinic cholinergic, and histaminic 1 receptors) (Stahl 2000). Due to the differing receptor profiles there may be a theoretical justification of combining atypicals with conventionals or atypicals with other atypicals to achieve specific therapeutic goals. For

example, Clozapine can bind with several receptor sites (5HT2A, 5HT1A, 5HT2C, 5HT3, 5HT6, 5HT7, D4, D3, D2, D1, alpha 1 and 2, H1 and M1) and has a higher D1/D2 binding ratio than other agents. Risperidone can bind with 5HT2A, 5HT7, D2, alpha1/2 and has a favorable 5HT2A/D2 binding ratio. Thus, combining clozapine and low doses of risperidone could theoretically lead to a greater reduction in positive and negative symptoms (Canales 1999).

EFFECTS OF USING ANTIPSYCHOTIC POLYPHARMACY

Although there is a possible pharmacological rationale behind antipsychotic polypharmacy use, there is a paucity of published clinical evidence regarding the effect of antipsychotic polypharmacy. There are no randomized controlled trials of combination therapy except one with sulpiride and clozapine, which provides little guidance in the U.S. since sulpiride is not available in the US (Yuzda 2000). Apart from this study, there have been case reports (Stubbs 2000,Lerner 2000,Chue 2001,Mujica 2001,Rhoads 2000,Raskin 2000,Morera 1999,Cooke 1999,Gupta 1998) and open uncontrolled nonrandomized trials (Taylor 2001,Kapur 2001,de groot 2001,Waring 1999,Waddington 1998) that report the effects of antipsychotic polypharmacy.

Yuzda (2000) performed a Medline review from 1966 through 2000 for literature on antipsychotic polypharmacy and identified 8 studies (1 randomized controlled trial, 2 open prospective trials, 1 retrospective review and 4 case reports). Six of the studies were on clozapine augmentation with sulpiride, pimozide, risperidone, loxapine and olanzapine and 2 case reports on other conventional augmentation with atypical antipsychotics. All except 1 study reported improvement in Brief Psychiatric Rating Scale (BPRS) scores over baseline with combination therapy. Increased serum prolactin levels, akathisia, hyper salivation were reported as side effects. Based on the reviewed evidence, Yuzda discourages augmentation of an atypical with a conventional due to lack of evidence and risk for increased adverse effects, cost and compliance.

The researchers performed an updated Medline review through April 2002 and 11 articles (9 case reports and 2 open trial) not included in the Yuzda article were identified. Six of the articles were on clozapine augmentation, half of which reported improvement over baseline (Taylor 2001, Rhoads 2000, Morera 2000) and the rest reported prolactin elevation (Kapur 2001), deterioration (Cooke 1999) and no change (De groot 2001). Four other articles were on non clozapine augmentation and all except one article reported improvements (Lerner 2000, Chue 2001, Raskin 2000). The one article that did not report improvement (Mujica 2001) reported the evidence of neuroleptic malignant syndrome when olanzapine was augmented with haloperidol. One other open prospective trial (Waddington 1998) of 88 patients found that antipsychotic polypharmacy was associated with increased risk of mortality (Relative Risk: 2.46) in schizophrenia patients when followed over a 10 year period.

In summary, most of the literature on antipsychotic polypharmacy has focused on clozapine augmentation and report some improvement with antipsychotic polypharmacy and some report an increased incidence of adverse events. However it has to be noted that besides the obvious design limitations of such uncontrolled trials, these studies were limited by small sample sizes (most of them are 1 or 2 patient case reports) and incomplete reporting of adverse effects. These shortcomings along with the possible effects of a publication bias in reporting make it difficult to draw meaningful conclusions about the effect of antipsychotic polypharmacy without further research.

PREVALENCE OF ANTIPSYCHOTIC POLYPHARMACY

Surveys conducted over the last 30 years have shown that antipsychotic polypharmacy has been used in up to 40% of patients with schizophrenia, with up to 24% of them receiving 3 or more antipsychotic agents (Canales 99). A recent observational study on a Veteran Affairs mental health database (n = 34,925) found that 6.8% of patients were exposed to antipsychotic polypharmacy in a 4 month period

(Leslie 2001). Another observational study (Wang 2000) found one in six patients of schizophrenia and other psychotic disorders using two or more antipsychotics. A Canadian study (Procyshyn 2001) surveyed hospital outpatients to find the rate of antipsychotic polypharmacy to be at 27.5%. The current data on prevalence of antipsychotic polypharmacy raises serious concerns given the lack of evidence justifying antipsychotic polypharmacy use in the form a controlled trial or observational study.

RATIONALE AND SIGNIFICANCE

As far as the researchers are aware, this would be the first study aimed at estimating the effect of antipsychotic polypharmacy using a large observational database. Additionally this study will report the trend of antipsychotic polypharmacy over a three-year period to determine if this is a growing or diminishing concern. It will also identify important physician and patient characteristics that are associated with such use.

Community tenure is an important outcome of treatment given the shift in the locus of care from institutional to community based programs and the growing importance of the philosophy of community integration in the mental health field. Therefore, information on the effect of antipsychotic polypharmacy on community tenure will be useful for physicians and other health care personnel involved in managing schizophrenia.

Information on the effect of antipsychotic polypharmacy on cost will aid decision making for policy makers in Medicaid administrations and HMO's who make significant financial commitments (McCombs 99) when providing atypical antipsychotic benefits to their enrollees. The import of the issue can be appreciated from the fact that prescription drug costs for schizophrenia are estimated to increase from 2.3% of direct costs ($397 million) in 1990 (Rice 1999) to 10% of direct costs by the year 2000 (Glazer 1998). This increase is largely due to the higher acquisition cost of newer atypical antipsychotics that

are up to 400 times costlier than generic conventionals (Docherty 1999). For e.g. Clozapine + Risperidone polypharmacy could cost anywhere between $500 and $3000 per month in medication costs (Drug Topics Red Book 2002, Drug Facts and Comparisons 2002). Though there are several studies documenting the economic benefits of atypical antipsychotics (Foster 1998), no study has been published justifying the use of multiple concurrent antipsychotics on economic grounds.

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CHAPTER 3

METHODS

OVERVIEW

A retrospective observational non-equivalent control group design was employed using a combined two-state Medicaid database. Claims data from January 1998 through December 2000 for Medicaid recipients from the state of Georgia and California was combined to build this two-state database. Schizophrenia patients were selected according to specified inclusion criteria. Based on their antipsychotic episode profile over the study period, each patient was classified into any one of the antipsychotic polypharmacy or monotherapy cohorts described in Figure 3.1. One 'index episode' was selected for each patient and an intent-to-treat analysis was performed observing each patient for a period of one year following the first day of this index episode referred to as the 'index date'. Differences in annual outcome between an antipsychotic polypharmacy patient (experimental subject) and monotherapy patient (comparison subject) provided an estimate of the effect of antipsychotic polypharmacy treatment.

DATA SOURCE

This combined two-state database was built using three sources, the Georgia Medicaid files maintained by the Georgia Department of Medical Assistance (GDMA), Georgia state based institutional data files maintained by the Department of Human Resources (DHR) and California Medicaid 20% sample (Medi-Cal).

Georgia Medicaid claims data

Medicaid claims data from 1998 through 2000 were obtained from The MEDSTAT Group, Inc. (http://www.medstat.com). All data was output in character and numeric and compared to supplied documentation to verify the record layout. The data files were converted to SAS (SAS 2002) data sets and stored on 3490E 76KBPI cartridges on the University of Georgia IBM ES/9000-720 mainframe. The Georgia Medicaid data have been found to be valid in previous epidemiologic studies. (Martin 1998; Kotzan 1999; Martin 2001). The Georgia Medicaid files contain eligibility details, demographics and claims history for various health care services, including Medicaid paid amount, outpatient prescription drugs, inpatient stays, and disease diagnosis.

Georgia state based institutional data

A common resource available to Georgia Medicaid patients are the 8 psychiatric hospitals managed by the Department of Human Resources (DHR) which do not bill Medicaid for services rendered to persons age 21 to 64 years. Records from all these 8 hospitals were combined to form the DHR file that contains a system wide record of each visit a patient received at any one of the 8 system inpatient institutions in operation. This DHR data is available through the year 2000 as SAS dataset on a password protected limited entry server. This file describes admission and discharge dates, some client demographic information, client ID number, as well as some limited diagnostic information.

Georgia data – Medicaid claims and state institutional data combined

To capture psychiatric episodes of care, the DHR files (state based institutional data) were linked by patient identifiers to the GDMA files (Georgia Medicaid claims data). This patient linked or merged data provided a complete picture of the medical resources consumed for each Medicaid eligible patients with schizophrenia in Georgia.

GDMA and DHR data for 16,227 persons diagnosed with schizophrenia from 1990 through 1994 had already been linked by patient identifiers for a previous study by Martin (1998). This data was updated through 2000 as a part of a current study to develop risk adjustment indices for persons suffering from schizophrenia (Agency for Healthcare Research and Quality (AHRQ) RO3 HS10815-01). The process of linking the two databases and forming a combined database was approved by The University of Georgia, Institutional Review Board, Project Number: H1997-10644-3 and The Georgia Department of Human Resources (DHR) Institutional Review Board, IRB study number: 990901. After combining the two databases, the patient identifiers were removed. The resulting combined data files do not contain any patient level identifiers such as name, SSN, address etc. and are stored on a stand alone, password protected server. Identifiers, used to link claims, are specific to the database and are pre encrypted to keep the data anonymous.

The final cohort consisted of 27,181 persons diagnosed with schizophrenia between 1990 and 2000. This cohort had an average age of 36 years and consisted of 59% females and 35% whites. These data have been found valid for use in studying persons with schizophrenia and to our knowledge is the largest data set published for persons with schizophrenia.

California Medicaid (Medi-Cal 20% sample)

These claims files are a 20% random sample of Fee For Service (FFS) Medi-Cal medical claims, plus (medical) mental inpatient consolidation claims provided by the Department of Mental Health. These files were prepared by the California Department of Health Services and sampling was done by the last two or three bytes of the beneficiary SSN. Thus, all claims rendered to the same 20% beneficiary population were contained in these files. The beneficiary SSN is considered a reliable variable on which to sample since it is almost always checked for validity within the claims processing system. The

final files were encrypted in a consistent fashion so outside researchers could track the same person throughout the data set without having any knowledge of the actual identity of the patient. California Medicaid reimburses 4 state psychiatric hospitals for inpatient services rendered to Medicaid eligibles so there is no need to link state psychiatric hospitals with the claims data. These files contain monthly eligibility details, medical claims and prescription claims for the recipients. Outpatient prescription claims are recorded, however like the GDMA data there is no record of prescriptions received as an inpatient. Eligibility and claims files from January 1998 through December 2000 were uploaded as SAS datasets on a password protected stand alone server. California Medicaid claims data has been used in the past for epidemiological studies (McCombs 1999, Ganguly 2001, Malkin 2002) and contains similar variables as in the Georgia database.

Two-state sample (Georgia and California combined)

Schizophrenia patients who were Medicaid eligible between January 1998 and December 2000 in Georgia and California were identified. The Georgia and California cohorts were combined to form one two-state combined sample. A variable identifying the patient's state of Medicaid eligibility (Georgia or California) was maintained to estimate and report state wise differences in prevalence and effect, if any.

Validation sample

A 30% random sample from the two-state schizophrenia cohort was held out for model validation wherever appropriate.

OPERATIONAL DEFINITIONS

Research subjects

Patients were selected for inclusion in the primary cohort based on the following inclusion criteria

- ⇒ Primary diagnosis of schizophrenia (ICD-9-CM = 295.**) recorded on at least one paid claim during the period Jan 1998 through Dec 2000
- ⇒ At least 16 years of age as of Jan 1st 1998
- ⇒ A continuous Medicaid eligibility and one claim every 90 days criteria was applied to the 6 months prior period and 1 year post index date observation period while identifying the associated factors and effect of polypharmacy on outcomes.

Building antipsychotic polypharmacy and monotherapy cohorts

After identifying the research subjects, the first step was to identify all antipsychotic use episodes for each patient for the period July 1998 through December 2000. An 'index episode' (defined below) of polypharmacy was identified for each patient in the antipsychotic polypharmacy cohort. Subjects who have at least one antipsychotic polypharmacy episode were grouped in the 'any polypharmacy' cohort. (Table 3.1). Since the JCP guideline does not recommend polypharmacy for more than 8 weeks or 2 months, subjects with an 'index episode' greater than 2 months duration (more than 60 days) were categorized into the long-term antipsychotic polypharmacy cohort(s) (Table 3.1). Long-term users were further subdivided into clozapine users and non clozapine users as clozapine is usually reserved for treatment resistant patients. These two groups were further divided by class of antipsychotic used in combination (Table 3.1).

Patients without any exposure to polypharmacy, and who have at least one antipsychotic prescription were grouped in a monotherapy cohort. Each of the antipsychotic polypharmacy groups identified above will have a corresponding monotherapy comparison group described in table 3.1.

Defining an episode of antipsychotic polypharmacy and monotherapy

Antipsychotic polypharmacy is defined as the concomitant use of two or more antipsychotics. For the purpose of this study, antipsychotic polypharmacy has been

defined as two or more chemically distinct antipsychotics prescribed concurrently where there is at least an overlap of 14 or more days of therapy taken concurrently (Kotzan 2002). Concurrent therapy of 14 or more days between consecutive or concurrent prescription fill dates were identified by estimating the days supply for each antipsychotic prescription filled for each person and comparing that to dates antipsychotic prescriptions are filled. The first day of that episode (defined below) of overlap or concurrent use of the two antipsychotics was considered as the episode start date for that antipsychotic polypharmacy episode.

An episode of antipsychotic polypharmacy is defined as a period of continuous, antipsychotic polypharmacy, without a break period of 31 or more days (Svarstad 2001). Break period is defined as a period when the patient has no supply of drugs. Hospital stays that occur within 31 days of an antipsychotic use period was considered as a continuation of the preceding episode and not a part of the break period if the therapy remains the same after discharge. A shift between "antipsychotic polypharmacy" and "monotherapy" in the any antipsychotic polypharmacy and long-term antipsychotic polypharmacy groups and a shift between different classes of antipsychotic polypharmacy in the clozapine and non clozapine groups would terminate an episode.

For each episode the treatment days (no. of days on polypharmacy or monotherapy) were calculated initially using the ‘days supply’ variable as the primary source to determine treatment days supply. If substantial discrepancies are noticed between the days supply variable and quantity of medication supplies variable, the quantity supplied variable along with the dosage strength variable was used to create a measure of days supply based on typical dosing regimens for oral antipsychotics. Administration of an intramuscular depot preparation (Haloperidol decanoate) was considered as a 30-day supply as indicated in the product prescribing information (http://www.ortho-mcneil.com/).

Antipsychotic use episodes where a single antipsychotic is prescribed for 14 or more days without a break period of 31 or more days was referred to as monotherapy episodes. If there is a shift between monotherapy with one agent to monotherapy with another agent this will not be considered as a new episode, but a continuation of one overall monotherapy episode. In the clozapine group, shifts between clozapine and non-clozapine monotherapy will terminate the episode.

Selecting an index episode for each patient

For patients with multiple antipsychotic polypharmacy or monotherapy episodes over the study period, one episode was selected to study the effect of antipsychotic polypharmacy. This episode is referred to as the 'index episode' and the start date for the 'index episode' is referred to as the 'index date'.

The index episode was chosen based on the following criteria:

⇒ Highest exposure to treatment: The episode with the largest number of antipsychotic polypharmacy / monotherapy days (measure of exposure) was selected.

⇒ Most recent year: If for a certain patient, two or more episodes met all the criteria and have the same number of antipsychotic polypharmacy or monotherapy days, the most recent period was selected for analysis.

Observation period

To have a sufficiently long period to assess differences in community tenure and to account for the effect of antipsychotic drug therapy that may develop three months after discontinuation (Maj 1999), patients were observed for a period of one year following the start date of the index episode to capture the effects of therapy. To ensure persons that are eligible for Medicaid benefits have not withdrawn form the system (e.g.: prison) each patient should have at least one paid claim for each 90 day window

(McCombs 1999) for a year following the index date and six months preceding the index date.

A sensitivity analysis was performed varying the observation period to estimate the long-term effects of antipsychotic polypharmacy for a two year period. Also a patient may switch to another treatment or no treatment within the one year period potentially confounding the effect of the original therapy. To avoid this potential confounding effect, a second sensitivity analysis was performed limiting the observation period to the duration of the index episode. A detailed discussion is presented below in the section titled 'sensitivity analysis'.

Measurement of outcomes

The two outcome measures, cost using the government payer perspective and community tenure were calculated for both antipsychotic polypharmacy and monotherapy subjects.

Total health care expenditures incurred by Medicaid and any other state agencies (Department of Human Resources, Mental health) for these Medicaid eligible schizophrenia patients was used as a measure of cost. For Georgia Medicaid patients, the cost to Medicaid was calculated by summing the Medicaid paid amount over the observation period. The cost to state Department of Human Resources (DHR) for Georgia patients who have had one or more admissions to state psychiatric facilities was assessed by merging the DHR file with the most recent DHR Hospital Budget and Utilization Report. A facility and ward specific per-diem operating cost was derived from DHR budget reports and a facility specific per-diem overhead rate was added to the operating cost. The DHR cost was calculated by multiplying the inpatient days by the per diem rates and summing over the observation period. The California paid amounts include both Medicaid and state mental health costs and was summed to calculate the total cost. All costs were reported in 2000 US dollars. Since the effect of antipsychotic

polypharmacy is relatively unknown and could predispose persons to non-mental health conditions, the initial analysis includes total costs and does not distinguish between mental health and non mental health cost. However a sensitivity analysis was performed restricting the definition of cost to mental health and substance abuse costs. The effect of antipsychotic polypharmacy on different cost categories – inpatient, outpatient, physician and prescription will also be reported.

Community tenure was defined as the number of days from the start of a treatment episode (index date) to the start of the first hospitalization episode. A hospitalization episode was initially defined as an inpatient visit with at least one day between admission and discharge. 'Community tenure' has been used as an outcome measure in previous studies and is also referred to as 'community survival' (Hunt 2002) or 'time in the community before relapse' (Appleby 1993). As in the case of cost, the initial analysis does not distinguish between mental health or non mental health related hospitalizations and the first hospitalization could be any hospitalization for the initial analysis. However a sensitivity analysis was performed restricting the definition of first hospitalization to mental health (and substance abuse) related hospitalizations.

PROPENSITY SCORE MATCHING TECHNIQUE

The propensity score matching technique is commonly used to reduce selection bias and estimate effect of treatment in health services research (D'Agostino 1998;Stone 1995;Connors 1996;Reinisch 1995). It has also been used in some recent studies in schizophrenia patients (Sernyak 2001a; Sernyak 2001b; Irish 2002).

The basic idea of propensity score methods is to replace the collection of confounding covariates in an observational study with one scalar function of these covariates, called the propensity score i.e. in this case the propensity to receive antipsychotic polypharmacy rather than monotherapy.

Mathematically, the propensity or probability to receive treatment is represented as Pr (z = 1| x) where z indicates treatment assignment (z = 1 for antipsychotic polypharmacy and z = 0 for monotherapy or no antipsychotic polypharmacy) and x is a vector of covariates (e.g. age, gender, race etc.). A propensity score was estimated for each subject in the antipsychotic polypharmacy and monotherapy cohorts and then each patient in the antipsychotic polypharmacy cohort was matched with one patient in the monotherapy cohort with the closest propensity score. Effect of antipsychotic polypharmacy was estimated from the difference scores between matched pairs.

Initial list of covariates

McIntosh and Rubin (1999) recommend that all potential confounders or variables that relate to both treatment choice (antipsychotic polypharmacy) and outcome (cost and community tenure) should be included in this initial list. A very liberal inclusion criterion was used to identify and include as many relevant covariates as possible as it has been found that the loss of efficiency in the model due to many covariates will likely be offset by further reduction in bias.

The first step, forming a comprehensive list of covariates, was accomplished by a survey of published literature. A Medline search was performed using mesh terms for schizophrenia, predictors of cost, community tenure (length of stay, rehospitalization) and prescribing trends. Table 3.2 presents candidate covariates that could influence treatment assignment, cost and community tenure along with reference source.

Comorbidities or comorbidity based risk adjustment models have been shown to account for more than 10% variation in cost (Kronik 2000) and may also influence decision to use a particular therapy. However no schizophrenia specific claims based risk adjustment models were found (Lehman 1987;Sharfstein 1991). The results of the AHRQ small grant to develop and validate risk adjustment models for persons suffering from schizophrenia (RO3 HS10815-01) was used for a comprehensive list of

comorbidities. This model will also be used to adjust for any non antipsychotic mental health related drug use during the episode for e.g. SSRI's, Lithium etc.

Seasonality and cohort-year effect could be a concern if an antipsychotic polypharmacy episode and matching monotherapy episode have different episode start dates. Therefore, the month and year of the episode start date was also included in the list of covariates.

Appropriate variables were identified from the Medicaid database that directly measure or are suitable proxies for the identified factors. However it should be noted that the Medicaid database does not contain a direct or proxy measure for some of the currently identified variables for e.g. social adjustments (Marital status, employment), number of times transferred between services while inpatient and cognitive impairment (WCST scores).

Final list of covariates 'x' and estimating propensity scores

A stepwise logistic variable selection procedure was used to select the final list of covariates. The binary treatment indicator (1 = antipsychotic polypharmacy, 0 = monotherapy) was modeled and main effects and interaction effects of covariates were entered into the model if they are significant at 0.50 level (Rosenbaum 1984; D'Agostino 1998). Two-sample t-statistic and standardized percentage differences were calculated to explore the differences in distribution of the selected covariates between the antipsychotic polypharmacy and monotherapy groups (D'Agostino, 1998) prior to matching.

The final list of covariates was entered in a logistic regression model to estimate the propensity score for each patient

The model:

$$\text{Log}\left[\frac{p_i}{1 - p_i}\right] = \text{alpha} + \text{beta}*x \qquad \text{(equation 1)}$$

where Log [$\frac{p_i}{1 - p_i}$] = logit or log-odds

p_i = probability or propensity that $y_i = 1$

alpha = intercept term

beta = vector of regression coefficients for the selected covariates $beta_1$ to $beta_i$

x = vector of covariates from x_1 to x_I

p_i or the propensity score is estimated from the equation

$$p_i = \frac{\exp (alpha + beta*x)}{1 + \exp (alpha + beta*x)} \qquad \text{(equation 1.1)}$$

A new set of propensity scores have to be obtained for a each set of comparisons e.g. antipsychotic polypharmacy vs. monotherapy, long term antipsychotic polypharmacy vs. long term monotherapy, as propensity for a different type of antipsychotic polypharmacy is estimated for each comparison.

Matching by propensity scores

After estimating the propensity score for each patient in the antipsychotic polypharmacy and monotherapy groups, each antipsychotic polypharmacy patient was matched with one monotherapy patient with similar propensity score. Matching was accomplished using the 'nearest available metric matching within calipers defined by propensity score' technique (D'Agostino 1998). This technique has been found to produce the best balance between the covariates in the treated and comparison groups (D'Agostino 1998, Rosenbaum 1985). The steps in the matching procedure are described below

The antipsychotic polypharmacy subjects were randomly ordered and the first subject was selected. All monotherapy subjects within a caliper of the selected antipsychotic polypharmacy subjects' logit of the propensity score are selected. Usually

this caliper is set at a quarter of the standard deviation of the logit of the propensity score distribution in the treated group.

Mahalonobis distance was calculated between the antipsychotic polypharmacy subject and the group of monotherapy subjects that fall within the caliper using the equation.

$$d(i,j) = (u - v)TC\text{-}1(u - v)$$

d(I,j) = distance

u = covariates for antipsychotic polypharmacy subject

v = covariates for monotherapy subjects

C = variance covariance matrix for covariates

The monotherapy subject with lowest d value was selected and the remaining were added back to the pool of prospective comparisons. Two-sample t-statistic for continuous variables and standardized percentage differences were calculated to explore the differences in distribution of covariates between the antipsychotic polypharmacy and monotherapy groups after matching (D'Agostino, 1998). SAS programs used to obtain propensity score and perform matching by propensity score have been included in Appendix A.

Post-match analysis plan

All statistical analysis was carried out using SAS 8.2 (SAS 2002) hosted on the mainframe, server, or Windows PC platforms. Difference scores for cost was calculated between the antipsychotic polypharmacy subjects and matched monotherapy subjects. Statistically significant differences in outcomes was detected by calculating 95% confidence intervals for these difference scores.

Community tenure, a corresponding censoring status variable (1 = not censored, 0 = censored) and a treatment variable (1 = antipsychotic polypharmacy, 0 = monotherapy) was used to perform the survival analytic procedure (Allison 1997). Mean

community tenure was reported for the matched antipsychotic polypharmacy and monotherapy groups. Hazard ratio, 95% confidence interval and p values were reported to examine the risk of first hospital admission one year after initiation of antipsychotic polypharmacy vs. monotherapy.

HECKMAN TWO-STAGE ESTIMATOR

The propensity score matching technique controls for observable confounders only for e.g. those identified in table 3.2 and are available in the data. However selection bias may continue to exist to some extent even after propensity matching due to unobservable confounders. For example, the Brief Psychiatric Scale Scores (BPRS) are not available in the data base. The Heckman two-stage estimation method (Heckman 1976, Terza 1999), corrects for selection bias due to observable confounders (X in equation 2.2) and also accounts for the fact that bias may continue to exist after controlling for observable confounders by including the expected value of error from the first stage (equation 2.1) as an additional regressor in the second stage equation (M1 in equation 2.2). The two-stage estimator was introduced by Heckman (1976) and has been used in the past to estimate effect in health services research (Terza 1999, Treglia 1999, Neslusan 1999). The detailed method is given below (Madalla 1983, Terza 1999).

Stage 1

In the first stage the binary outcome of receiving or not receiving antipsychotic polypharmacy (P) was modeled from selected covariates that influence treatment assignment (Z) using a probit equation. Z may include all or some of the covariates in vector X previously identified in the propensity scoring process. Alpha, the vector of coefficients of Z is estimated through this model and is further used to calculate the expected value of error (M).

Probit model: $P = Z*alpha + U$ (equation 2)

where P = Treatment assignment (1 = Antipsychotic polypharmacy, 0 = if no

polypharmacy)

Z = Vector of covariates that influence treatment assignment

alpha = Vector of coefficients of Z

U = error term

After estimating alpha we use it to estimate M

$$M1 = \frac{pdf(Z*alpha1)}{cdf(Z*alpha1)} \qquad \text{(equation 2.1)}$$

where M1 = estimate of expected value of error

alpha1 = estimate of alpha

pdf = probability density function

cdf = cumulative density function

Stage 2

Cost was modeled using Ordinary Least Square (OLS) regression and community tenure was modeled using a survival analytic procedure similar to the one described for propensity method. The estimate of the expected value of error (M1) is used as an additional regressor, along with other regressors shown in equation 2.2 below. T provides an estimate of the effect of antipsychotic polypharmacy.

Cost = X*beta + M1*theta + P*T + E (equation 2.2)

Where Cost = total health care cost

X = vector of covariates that influence treatment and outcome. X had to have at least Z+1 number of variables. "Total prior 6 month cost" variable was not included in Z. Non mental cost (Total – Mental cost) was included in X as the Z+1th variable.

Beta = coefficient for covariates

M1 = estimate of expected value of error term

Theta = coefficient for error term

P = Treatment assignment (1 = Antipsychotic polypharmacy, 0 = if no antipsychotic polypharmacy)

T = coefficient for treatment assignment

E = error term

SAS program to perform heckman 2-stage estimation has been included in Appendix B. Statistically significant differences in outcomes were detected by calculating 95% confidence intervals and p values on the coefficient for treatment assignment term T. Similar tests on the theta term was performed to detect the influence of the error term.

Costs were also reported by the category of service - prescription, inpatient, outpatient and physician. Statistically significant differences in costs between antipsychotic polypharmacy and monotherapy subjects by category of service were also detected and reported.

Effect on community tenure was analyzed by the same survival analytic methods used in the propensity matched groups. In addition to community tenure, the corresponding censoring status variable and a treatment variable (P) the survival analytic procedure here also involved additional regressors X and M1. Mean community tenure, hazard ratio, 95% confidence interval and p values were reported to examine the risk of first hospital admission one year after initiation of antipsychotic polypharmacy vs. monotherapy.

SENSITIVITY ANALYSIS

Sensitivity analyses was performed to estimate the extent to which the results are influenced by changes in operational definitions.

Extending the observation period to 2 years

Initially the patients were observed for one year to estimate the concurrent and shorter term effects of antipsychotic polypharmacy. This was also considered a reasonable length of time to ensure adequate sample sizes given the limited study

period of three years. However since schizophrenia is a chronic disorder requiring long periods of treatment it was important to estimate the long-term effects of antipsychotic polypharmacy. Therefore a sensitivity analysis was performed extending the observation period to two years.

Subsets of the original cohorts who met the continuous eligibility and 90-day claim window criteria for 2 years post index date were used for this sensitivity analyses. The same analytical procedure was followed to estimate the effect of antipsychotic polypharmacy. Cost was summed over a period of two years and observations were censored at 2 years for the community tenure outcome.

Restricting the observation period to index episode

A patient may switch to another treatment or no treatment within the one year period potentially confounding the effect of the original therapy. To avoid this potential confounding effect, a sensitivity analysis was performed restricting the observation period to the duration of the index episode. This cohort was the same as the original cohort except that the observation period was variable as it was restricted to the length of the episode. Therefore the cost outcome measured over the observation period was annualized using the number of days in the observation period

$$\text{Annual outcome} = \frac{\text{Outcome over observation period}}{\text{Days in observation period}} \times 365$$

In estimating community tenure 'random censoring' occurs as there is a single termination time December 31st 2000, but entry time or index dates vary randomly across patients. The month and year of the index date (entry time) was included as a covariate to address this issue (Allison 1997). The rest of the procedure was the same as described for the one-year cohorts.

Differentiating mental health and substance abuse related outcomes

The operational definitions for cost and community tenure did not differentiate between mental health related and non mental health related events. This may confound the effect of antipsychotic polypharmacy due to inclusion of non mental health related events that may not be associated with antipsychotic polypharmacy treatment. Therefore a sensitivity analysis was performed restricting the outcomes to mental health related events.

Mental health and substance abuse cost was operationally defined based on the criteria used by Ettner (1998). Claims with a primary diagnosis that falls into the following categories: 290.**, 291.**, 292.**, 293.**, 295.**, 302.**, 303.**, 304.**, 305.**, 306.**, 314.**, 783.0, 780.1, V11.3, V61.41 or V79.1 or have a CPT-4 code that falls in the range of 90801 – 90899 were defined as mental health and substance abuse costs. Additionally, all resource utilization occurring within state psychiatric institutions was defined as mental health and substance abuse resource utilization.

In the case of community tenure, a sensitivity analysis was performed restricting the definition of 'first hospitalization' to mental health (and substance abuse) related hospitalizations. Mental health and substance abuse related inpatient stays, as defined by the above mentioned primary diagnosis codes were considered as events of first hospitalization. All stays occurring within state psychiatric institutions regardless of diagnosis was considered mental health related hospitalization.

MODEL VALIDATION

The models used to identify factors associated with polypharmacy were specified in the original sample using statistical variable selection techniques and were validated using the random hold out validation sample. Propensity score estimation utilizes a variable selection procedure but this procedure is used to compute the propensity score and not to develop a predictive model and does not require validation. None of the other

models were specified using the variable selection procedure and therefore did not require validation.

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Table 3.1: Brief description of antipsychotic polypharmacy and corresponding monotherapy comparison cohorts

Antipsychotic polypharmacy Cohort	**Antipsychotic monotherapy comparison cohort**
Any polypharmacy	Any monotherapy
Any Long term* polypharmacy	Any Long term* monotherapy
Long term* clozapine + atypical	Long term* clozapine monotherapy
Long term* clozapine + conventional	Long term* clozapine monotherapy
Long term* atypical + atypical and no exposure to clozapine at any time	Long term* atypical monotherapy and no exposure to clozapine
Long term* atypical + conventional and no exposure to clozapine at any time	Long term* monotherapy and no exposure to clozapine
Long term* conventional + conventional and no exposure to clozapine at any time	Long term* conventional monotherapy and no exposure to clozapine

* Long Term is defined as use for at least 61 days

Table 3.2: Initial list of covariates that may influence treatment assignment and outcomes along with published source.

Item	Cost	Community tenure	Decision to use antipsychotic
PATIENT RELATED			
Comorbidity based risk adjustment model[1] (31 variables)	*1*		*3*
Alcohol or drug abuse	*1*	*4,5*	
Mood disorders	*1*	*4*	
Dementia	*1*	*6*	
Mental retardation	*1*	*6*	
Demographics (Age, Gender, Race)	*2,13*	*12*	*3*
Number of previous psychiatric, medical or surgical hospitalizations	*13*	*4,12*	*3*
Duration of latest hospital admission		*12*	
History for clozapine use			*3*
Suicide attempts in previous year		*7*	
First manifestation of psychosis		*7*	
Social adjustments (Marital status, employment)	*13*	*7*	
Receipt of electroconvulsive therapy		*9*	
Number of psychiatric, medical and surgical visits in past year	*13*		
Number of times transferred between services while inpatient	*13*		
Irregular use of medication		*10*	
Recent visits to psychiatrist			*11*
Medicaid eligibility category (Blind/Disabled, Poverty related, Pregnant women, Other medical)	*2*		
Cognitive impairment (WCST scores)		*14*	
Concurrent use of non antipsychotic mental health related drugs	*	*	*
Mental health expenditure in prior period			
FACILITY RELATED		*8*	*6*
High occupancy			
Profit or non profit			
Chain			
Size			
PRESCRIBER RELATED			
GP vs. Psychiatrist			*
Proportion of time prescriber prescribes antipsychotic polypharmacy			*

References:

*1) Ricci 2002 2) Ash 2000 3) Irish 2001 4) Huntley 1998 5) Gerding 1999 6) Hughes, 2000 7) Doering 1998 8) Melle 1996 9) Stoskopf 1992 10) Svarstad 2001 11) Wang 2000 12) Mortensen 1994 13) Sernyak 2001a 14) Jackson 2001 * Expert opinion*

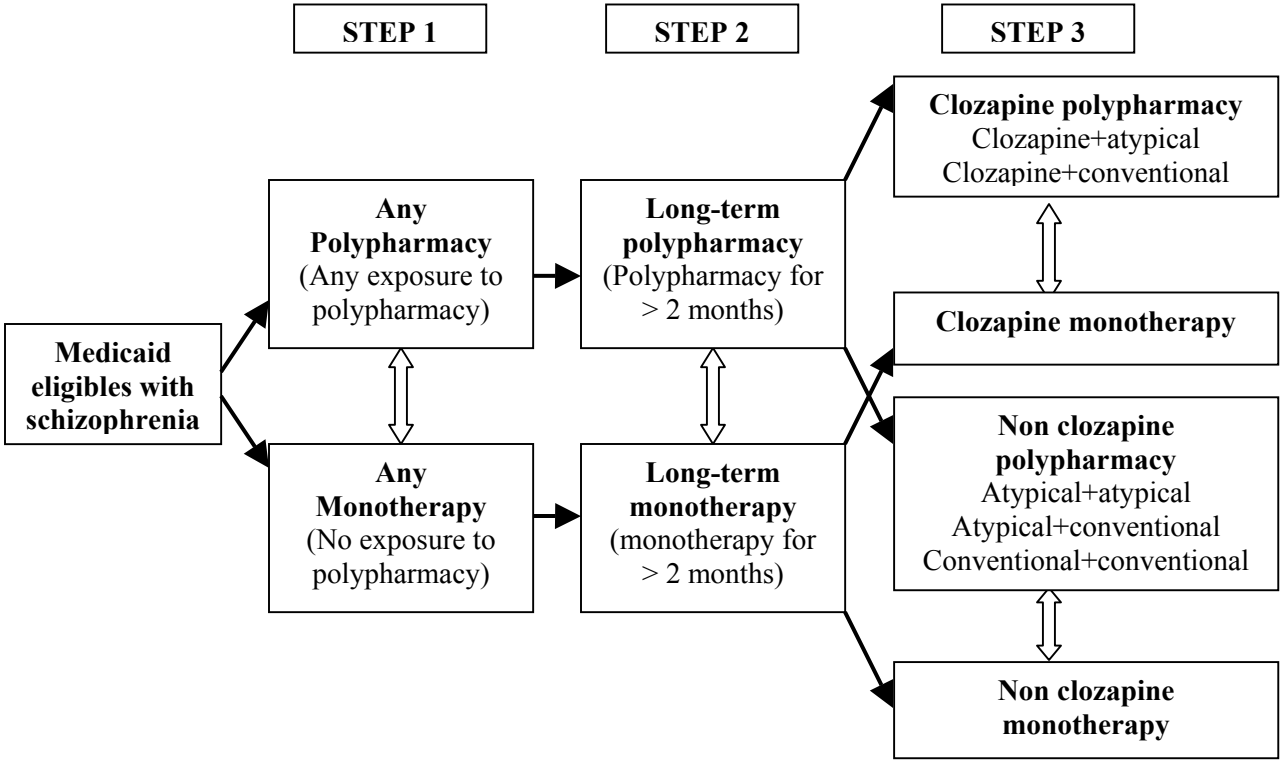

Figure 3.1: Different forms of antipsychotic polypharmacy and monotherapy

CHAPTER 4

PREVALENCE, TRENDS AND FACTORS ASSOCIATED WITH ANTIPSYCHOTIC POLYPHARMACY AMONG MEDICAID ELIGIBLE SCHIZOPHRENIA PATIENTS, 1998-2000[1]

[1] R. Ganguly, J.A. Kotzan, K. Kennedy, L.S. Miller, B.C. Martin. To be submitted to *Journal of clinical psychiatry*

ABSTRACT

Background: Antipsychotic polypharmacy or concomitant use of multiple antipsychotics is prevalent in up to 40% of schizophrenia patients despite lack of clinical evidence or support from treatment guidelines. The objective of this study was to determine the prevalence, trends and factors associated with antipsychotic polypharmacy, categorize antipsychotic polypharmacy according to type of antipsychotic and duration of use and contrast usage patterns with published treatment guidelines.

Methods: A retrospective cohort study was designed and Medicaid recipients >= 16 years of age with a primary diagnosis of schizophrenia (ICD-9-CM=295.**) between 1998-2000 were identified from the Georgia and California (20% random sample) Medicaid claims databases. 7 antipsychotic polypharmacy cohorts e.g. any antipsychotic polypharmacy, clozapine (2 subtypes), non-clozapine (3 subtypes) and long-term i.e. duration of use > 2 months and corresponding monotherapy cohorts were built. 3-year prevalence of antipsychotic polypharmacy, mean/median duration of episodes and year wise trends in usage were estimated. A stepwise logistic variable selection procedure was used to identify factors associated with antipsychotic polypharmacy.

Results: Out of a total of 31,435 persons with schizophrenia, the overall prevalence of antipsychotic polypharmacy was 40% (n=12,549, mean age: 43 years, white: 47%, female: 48%) over 1998-2000 and prevalence of atypical polypharmacy had increased between 1998 and 2000 (Cochran-Armitage test; $p<0.0001$). Long-term antipsychotic polypharmacy had a prevalence rate of 23% (n=7,222) with a long-term episode lasting a median of 197 days. Use of newer atypicals, for e.g. quetiapine (OR: 18.27, 95% CI 13.05 to 25.58), and older conventionals, for e.g. chlorpromazine (OR: 28.87 95% CI 21.14 to 39.42), were strongly associated with long-term antipsychotic polypharmacy.

Conclusion: Antipsychotic polypharmacy is highly prevalent, is prescribed for long durations and is an increasing phenomenon among Medicaid eligible schizophrenia

patients. Further research to study the effects of antipsychotic polypharmacy in schizophrenia patients may be an important step toward defining the scope and potential for such use.

Keyword: Polypharmacy, Antipsychotic, Schizophrenia, Medicaid, Prevalence

INTRODUCTION

Antipsychotic polypharmacy or concomitant use of multiple antipsychotics in schizophrenia is regarded as one of the "most practiced and least investigated phenomena in clinical psychopharmacology" (Stahl 2000). It is estimated that antipsychotic polypharmacy is prescribed for up to 40% of schizophrenia patients (Canales 1999). However there are no randomized controlled trials of combination therapy except one with sulpiride and clozapine, which provides little guidance in the U.S. since sulpiride is not available in the US (Yuzda 2000). Apart from this study, there are case reports (Stubbs 2000,Lerner 2000,Chue 2001,Mujica 2001,Rhoads 2000,Raskin 2000,Morera 1999,Cooke 1999,Gupta 1998) and open uncontrolled nonrandomized trials (Taylor 2001,Kapur 2001,de groot 2001,Waring 1999,Waddington 1998) that report the effects of antipsychotic polypharmacy. Almost half of these studies report an increased incidence of adverse events such as prolactin elevation, akathisia, hyper salivation (Yuzda 2000, Kapur 2001, Cooke 1999, Degroot 2001) and even an increased risk of mortality (Waddington 1998, n=88, RR: 2.46) and the rest report improvement in symptoms over baseline. However, it should be noted that besides the obvious design limitations of such uncontrolled trials, these studies were limited by small sample sizes (most of them are 1 or 2 patient case reports) and incomplete reporting of adverse effects. The recent introduction of four new antipsychotics (e.g. Olanzapine-1996, Quetiapine-1997, Ziprasidone–2001, Aripiprazole-2003) with differing receptor profiles have further increased the possibilities of combining these agents. The objective of our study was to estimate the prevalence and trends of antipsychotic polypharmacy,

categorize antipsychotic polypharmacy according to type of antipsychotic and duration of use, and contrast antipsychotic polypharmacy usage patterns with published treatment guidelines. We also estimate the factors associated with antipsychotic polypharmacy usage.

METHODS

Data sources

We built a 3-year (1998 to 2000) two-state Medicaid database using three sources, the Georgia Medicaid files maintained by the Georgia Department of Medical Assistance (GDMA), Georgia state based institutional data files maintained by the Department of Human Resources (DHR) and California Medicaid 20% sample (Medi-Cal). The Medicaid files contain eligibility details, demographics and claims history for various health care services, including Medicaid paid amount, outpatient prescription drugs, inpatient stays, and disease diagnosis. A common resource available to Georgia Medicaid patients are the 8 psychiatric hospitals managed by the Department of Human Resources (DHR) which do not bill Medicaid for services rendered to persons age 21 to 64 years. Records from all these 8 hospitals were combined to form the DHR file that contains a system wide record of each visit a patient received at any one of the 8 system inpatient institutions in operation. To capture psychiatric episodes of care, the DHR files (state based institutional data) were linked by patient identifiers to the GDMA files (Georgia Medicaid claims data). This patient linked or merged data provides a complete picture of the medical resources consumed for each Medicaid eligible patients with schizophrenia in Georgia. California Medicaid reimburses 4 state psychiatric hospitals for inpatient services rendered to Medicaid eligibles so there is no need to link state psychiatric hospitals with the claims data.

The Georgia (Martin 1998; Kotzan 1999; Martin 2001) and California (McCombs 1999, Ganguly 2001, Malkin 2002) Medicaid data have been used in the past for epidemiological studies and have been found to be valid.

Prevalence and trend analysis:

To obtain the prevalence and trend data for antipsychotic polypharmacy over the 3-year period, persons with schizophrenia were identified using the following inclusion criteria:

- Primary diagnosis of schizophrenia (ICD-9-CM = 295.**) recorded on at least one paid claim during the period Jan 1998 through Dec 2000
- At least 16 years of age as of Jan 1st 1998

After identifying the schizophrenia patients, antipsychotic polypharmacy and monotherapy episodes for each person was identified. For the purpose of this study, antipsychotic polypharmacy was defined as two or more chemically distinct antipsychotics prescribed concurrently where there is at least an overlap of 14 or more days of therapy taken concurrently (Kotzan 2002). The list of antipsychotics has been provided in table 4.1. Concurrent therapy of 14 or more days between consecutive or concurrent prescription fill dates were identified by estimating the days supply for each antipsychotic prescription filled for each person and comparing that to dates antipsychotic prescriptions are filled. The first day of that episode (defined below) of overlap or concurrent use of the two antipsychotics was considered as the episode start date for that antipsychotic polypharmacy episode.

An episode of antipsychotic polypharmacy was defined as a period of continuous, antipsychotic polypharmacy, without a break period of 31 or more days (Svarstad 2001). A break period was defined as a period when the patient had no supply of drugs. Hospital stays that occurred within 31 days of an antipsychotic use period were

considered as a continuation of the preceding episode and not a part of the break period if the therapy remained the same after discharge.

Antipsychotic use episodes where a single antipsychotic was prescribed for 14 or more days without a break period of 31 or more days was referred to as monotherapy episodes.

Antipsychotic polypharmacy was classified in a hierarchical fashion, narrowing the definition of antipsychotic polypharmacy with each consecutive step in accordance with published treatment guidelines into 7 groups (Figure 4.1). The Journal of Clinical Psychiatry treatment guideline (McEnvoy, 1999) is the only guideline that offers guidance on the duration of antipsychotic polypharmacy, and that guideline does not recommend antipsychotic polypharmacy for more than 8 weeks or 2 months. Based on that guideline, a subject with an episode greater than 2 months (at least 61 days) duration of antipsychotic polypharmacy was categorized into the long-term antipsychotic polypharmacy cohort(s) (Figure 4.1). The prevalence of each type of antipsychotic polypharmacy was calculated over the 3-years and separately for each year. The Cochran-Armitage trend test was performed to estimate temporal changes in prevalence of antipsychotic polypharmacy and t-tests were performed to estimate differences in prevalence between various categories of antipsychotic polypharmacy.

Factors associated with antipsychotic polypharmacy

The single longest episode of antipsychotic polypharmacy or monotherapy i.e. period of maximum exposure to treatment, between 1998 and 2000 was identified for each patient in the antipsychotic polypharmacy and monotherapy cohort and was referred to as the index episode. Patient who had continuous Medicaid eligibility and at least one paid claim in every 90 day window during the 6 months period preceding this episode were retained. This 6 month 'prior' period was used to collect health care utilization information prior to the start of that polypharmacy exposure. The 90-day

window criterion (McCombs 1999) was used to ensure persons that are eligible for Medicaid benefits have not withdrawn from the system (e.g. prison).

Those who were never exposed to antipsychotic polypharmacy were grouped into a monotherapy cohort and were further classified into unique monotherapy cohorts depending on the duration and type of monotherapy of their index episode (Table 4.2). Antipsychotic polypharmacy cohorts were similarly created using the index episode where subjects who had at least one antipsychotic polypharmacy episode were grouped into the 'any antipsychotic polypharmacy' cohort and subjects with an 'index episode' equal to or greater than 2 months duration were categorized into the long-term antipsychotic polypharmacy cohort(s). Long-term users were further subdivided into clozapine users and non clozapine users as clozapine is usually reserved for treatment resistant patients. These two groups were further divided by class of antipsychotic used in combination. Each of the antipsychotic polypharmacy groups identified above had a corresponding monotherapy comparison group described in table 4.2.

A comprehensive list of possible factors associated with antipsychotic polypharmacy was identified by a survey of published literature and expert opinion (Table 4.3). This list included demographics, diagnosis related comorbidities, drug classes, antipsychotic agents and prior health care utilization variables. The list of diagnosis related comorbidities and drug classes were obtained from a cost prediction model for schizophrenia patients. This model has been developed and validated on the Georgia Medicaid database as a part of an AHRQ (Agency for Health Care Research and Quality) project. The month and year of the episode start date was also included to identify any year wise or seasonal trend in use. The list of antipsychotic agents consisted of the ten most prevalent drugs identified from a frequency analysis of the prior period prescription records. Haloperidol and fluphenazine were categorized by mode of administration to differentiate between the injectable and oral dosage form. This was

done as the injectable form is generally prescribed to a less compliant group of patient (McEnvoy, 1999) and compliance in turn may be an important factor associated with choice of therapy like in the present case antipsychotic polypharmacy vs. monotherapy.

A stepwise logistic variable selection procedure was used to identify factors independently associated with antipsychotic polypharmacy. The binary treatment indicator (1 = antipsychotic polypharmacy, 0 = monotherapy) was modeled and main effects of the initial list of factors were entered into the model if they met the significance level of 0.2 and removed if they did not meet the significance level of 0.1. To guard against model specification errors using stepwise procedures, the initial model was developed on a 70% random sample from the cohort and the remaining 30% was utilized to validate the final model. The primary analysis was performed to identify factors associated with 'long term antipsychotic polypharmacy' since long-term usage is not a recommended practice and is of greater policy relevance than 'any' usage, that combines both short and long term groups. Sub analyses were performed to identify factors associated with usage by type of antipsychotic e.g. clozapine, atypical+atypical, atypical+conventional, conventional+conventional polypharmacy and any differences from the primary analysis were reported. The data was managed using SAS software Version 8.02 (SAS 2002) and statistical analysis was performed using SAS and STATA Version 6.0 (STATA Corp, 1999).

The study was approved by the University of Georgia Institutional Review Board (IRB).

RESULTS

Prevalence

32,280 persons (Georgia: 18,373, California: 13,907) had received at least one primary diagnosis of schizophrenia between 1998 and 2000 out of which 31,435 were at least 16 years of age as of Jan 1, 1998 and were retained in the cohort. The mean age

of the 31,435 persons with schizophrenia was 43 years (SD: 14 years) (both Georgia and California had mean ages of 43 years), 49% were female (Georgia: 56%, California: 43%) and 47% were white (Georgia: 38%, California: 57%). The overall prevalence of any antipsychotic polypharmacy was 40% (n=12,549, median duration = 84 days) over 1998-2000 and was 46% in California compared to 35% in Georgia (Table 4.4). California had a significantly higher prevalence of antipsychotic polypharmacy across all the antipsychotic polypharmacy categories ($p<0.0001$). Long-term antipsychotic polypharmacy had a prevalence rate of 23% (n=7,222) with a long-term episode lasting for a median of 197 days (Table 4.5). Among the long-term antipsychotic polypharmacy groups, clozapine polypharmacy accounted for 11% of all long-term polypharmacy non-clozapine polypharmacy and long-term atypical + conventional polypharmacy accounted for 68% of long-term polypharmacy. Long-term clozapine polypharmacy had a longer median duration of 230 days than an average long-term non clozapine polypharmacy episode which lasted for a median duration of 186 days (Table 4.5).

Trend

The 3-year trend of long-term antipsychotic polypharmacy has been presented in figure 4.2. Overall prevalence of antipsychotic polypharmacy increased significantly from 32% in 1998 to 41% in 2000 (Cochran-Armitage test: $p<0.0001$) and the increase in Georgia was from 24% to 30% and California 43% to 62%. Except for clozapine+conventional(no change) and conventional+conventional (decreased) polypharmacy, all antipsychotic polypharmacy prevalences increased from 1998 through 2000 (Cochran-Armitage test: $p<0.0001$).

Factors associated with antipsychotic polypharmacy

Out of the 7,222 schizophrenia patients who had received long-term antipsychotic polypharmacy between 1998 and 2000, 6,438 were continuously eligible and had at least one claim every 90 days in the six month period preceding the episode

and were retained to study the factors associated with antipsychotic polypharmacy. Additionally 8,757 patients were identified who had received long-term monotherapy and met the inclusion criteria. A 70% random sample, 4,422 antipsychotic polypharmacy subjects and 6,162 monotherapy subjects, were retained for the primary analysis and the rest were held out to estimate the validity of the final model specification. Table 4.6 gives the adjusted odds ratio, 95% confidence intervals and distribution of the factors identified from the stepwise logistic regression analysis for the long-term antipsychotic polypharmacy outcome in the primary sample. 40 variables were retained in the final model and all variables were associated with long-term antipsychotic polypharmacy at a significance level of < 0.05 except for use of antihypertensive drugs (p: 0.0579) insulin dependent diabetes (p: 0.0649) and gout (p: 0.0906). The c-statistic for the model was 0.914 (0.5 for model with no predictive power; 1 for perfect model) which shows that the model could discriminate well between long-term antipsychotic polypharmacy and monotherapy users. C-statistic for the final model in the 30% validation sample was 0.917, which showed that the model could discriminate equally well between antipsychotic polypharmacy and monotherapy in an external sample and suggesting that the initial model was correctly specified.

Being eligible for Georgia Medicaid was significantly associated with a reduced likelihood of receiving long-term antipsychotic polypharmacy as compared to being eligible for California Medicaid (OR 0.62, 95% Confidence Interval 0.54 to 0.70). Being of male gender and belonging to the disabled aid category was associated with an increased likelihood of receiving long-term antipsychotic polypharmacy. Among the diagnosis related comorbidities, being diagnosed for weight loss treatment or malnutrition was strongly associated with long-term antipsychotic polypharmacy (OR: 4.50, 95% confidence interval: 1.54 to 13.17) although the absolute numbers were small in both antipsychotic polypharmacy and monotherapy groups. Diagnosis of epilepsy,

other psychoses and other mental disorders also had a positive association with long-term antipsychotic polypharmacy.

Among the drug classes, exposure to drugs used to treat Parkinson's disease, respiratory disorders, cancer, and tuberculosis were associated with long-term antipsychotic polypharmacy.

All antipsychotic drugs selected in the model were strongly associated (p-values <0.0001, OR: 5 to 28) with a higher likelihood of long-term antipsychotic polypharmacy. Among the atypical antipsychotics, quetiapine had the highest positive association with long-term antipsychotic polypharmacy (Odds Ratio: 18.32, 95% Confidence Interval: 13.07 to 25.68), followed by olanzapine (OR: 14.45) and risperidone (OR: 9.18). Among the conventionals, chlorpromazine (OR: 28.87, 95% Confidence Interval: 21.14 to 39.42) followed by thioridazine (OR: 18.61) and thiothexene (OR: 8.44). Clozapine (OR: 11.77) were also significant factors associated with long term antipsychotic polypharmacy.

Among the prior utilization variables, regular use of Antipsychotic (one Antipsychotic prescription every 2 months) was associated (OR: 4.8) with long-term antipsychotic polypharmacy. Among the temporal variables, index dates starting in the fourth quarter (October, November, December) had a higher association with antipsychotic polypharmacy (OR: 2) compared with the first quarter. Also, the year 1999 (5.53 times) and 2000 (9.67 times) had a higher association with long-term antipsychotic polypharmacy compared with 1998.

Diagnosis of AIDS (OR: 0.52), alcohol abuse (OR: 0.58), personality disorders (OR: 0.71), drug use for cardiac conditions (OR: 0.81) were negatively associated long-term antipsychotic polypharmacy although the strength of association was low (p~0.05) for AIDS and cardiac conditions.

No additional factors were identified in the clozapine polypharmacy VS. clozapine monotherapy analyses. However in the non clozapine groups – arrhythmia (OR: 2.0

95%, CI 0.97 to 4.33), COPD (OR: 1.7, 95% CI 1.14 to 2.57), asthma (OR: 2.3, 95% CI 1.18 to 4.60), diabetes complicated (OR: 2.7, 95% CI 1.10 to 6.90) were positively associated with atypical+atypical polypharmacy; myocardial infarction (OR: 3.14, 95% CI 0.90 to 10.93) was associated with atypical+conventional polypharmacy; and coagulopathy (OR: 6.8, 95% CI 1.14 to 40.94) was associated with conventional+conventional polypharmacy.

DISCUSSION

Antipsychotic polypharmacy was prescribed in up to 40% of Medicaid eligible schizophrenia patients over a 3-year period 1998-2000. We did not find any studies that report prevalence data for Medicaid eligible schizophrenia patients. However the prevalence rate in our study was similar to that reported in a 1985 survey of 8 countries and 768 patients (overall prevalence: 40%, US prevalence: 36%) (Canales, 1999) and was higher than a 4 month prevalence reported in a recent Veteran Affairs (VA) study 6.8% (Leslie 2001), a 1997 1-year prevalence study using a physician office based data 16.7% (Wang 2000) and a Canadian study on hospital outpatients 27.5% (Procyshyn 2001). Inherent differences in patient severity or prescribing habits may account for the 11% higher prevalence of antipsychotic polypharmacy in California compared with Georgia. A competing explanation could be that since California Medicaid had removed a prior authorization rule restricting newer antipsychotic use in 1997, many more patients were being switched to newer antipsychotics starting 1998 resulting in a higher prevalence of antipsychotic polypharmacy.

None of the previous studies on antipsychotic polypharmacy have reported prevalence by length of episode and therefore its difficult to place the long-term prevalence rate of 23% in perspective. However the lack of evidence on the effectiveness of antipsychotic polypharmacy and its long-term use and absence of

support from treatment guidelines makes this a cause for concern. An 11% higher prevalence rate in the California cohort is maintained in the long-term group.

The Journal of Clinical Psychiatry (JCP) treatment guideline (McEnvoy 1999) and some review articles on antipsychotic usage (Stahl 1999; Canales 1999; Yuzda 2001) recognize antipsychotic polypharmacy as a possible option in two specific situations; short-term or PRN use for "Symptom control" and short-term tactic while switching from one monotherapy to another. However, they also acknowledge the lack of published evidence and potential for less well-tolerated regimens with antipsychotic polypharmacy although of all articles, the JCP guideline is the only one that defines 'short-term' and puts it at 2 months. Therefore it is concerning to see that the median duration of long-term antipsychotic polypharmacy was 197 days or more than 6 months. Clozapine polypharmacy episodes had an average duration of 210 days and lasted longer than non-clozapine episodes. This may be explained by the fact that clozapine is reserved for treatment refractory patients who require longer durations of combination treatment than the relatively better controlled non clozapine patients.

By the same logic we expected more long-term antipsychotic polypharmacy usage in the treatment refractory clozapine group. Although long-term non clozapine polypharmacy was around 8 times more prevalent than clozapine polypharmacy the prevalence of long-term antipsychotic polypharmacy was 36% in the clozapine exposed group, which was higher than in the atypical (29%) and conventional groups (30%).

The long-term non clozapine atypical+conventional group had the highest prevalence of 16%. The therapeutic actions of conventional antipsychotic drugs is due to blockade of dopamine (D2) receptors whereas the atypical antipsychotics block both D2 and serotonin 5HT2A receptors (Stahl 2000). Due to the differing receptor profile there may be a pharmacological justification of combining atypicals with conventionals and using them for a long duration but there are no clinical studies that provide evidence

for such use. These could be switchover or PRN patients who were started on a short-term combination therapy and then were 'stuck' on it for some reason. For example, they were stable and the physician did not want to risk a relapse. This has been quoted as a reason in other studies on antipsychotic polypharmacy (Tapp, 2003). The Tapp study (Tapp 2003) also found a lower prevalence of clozapine polypharmacy (4% of all polypharmacy) and proposes that physicians may be trying non clozapine polypharmacy more than clozapine polypharmacy to avoid the continuous monitoring requirements with clozapine use. Physicians may also be observing that their patients are stabilized on atypical+conventional combinations and there is real merit to such therapy.

The increasing trend of antipsychotic polypharmacy was as we expected. There might be two factors driving this increase. First as newer antipsychotics become available there is a higher probability of receiving antipsychotic polypharmacy as patients on older antipsychotics are switched more often in more recent years. It could also be due to changing prescribing habits among physicians as they find success in treating patients with antipsychotic polypharmacy. The rate of increase from 1998 to 2000 was notably higher (20% vs. 5%) in California than Georgia. As mentioned earlier, the reasons for this could be differential patient severity, practice differences or previous formulary restrictions.

The results of the exploratory analysis to identify factors indicates that California practitioners are much more likely to prescribe long-term antipsychotic polypharmacy compared with Georgia. The fact that long term usage was more likely in males and subjects in the disabled aid category perhaps lends credibility to that fact that long-term antipsychotic polypharmacy is being prescribed to treat sicker patients. Males generally have poorer schizophrenia outcomes than females (Birchwood 2001) and the disabled category have been found to be more expensive and therefore sicker than patients in other categories (Ash, 2000). It is still difficult to establish whether these patients have a

higher likelihood of planned long-term antipsychotic polypharmacy or being stuck on a switch over that was never completed.

Eating disorders (which meet some, but usually not all, of the criteria for anorexia nervosa, bulimia nervosa, or pica) are not rare in schizophrenia and this is probably reflected in a diagnosis of weight loss or malnutrition, which is associated with long-term antipsychotic polypharmacy. This may be a marker of disease severity requiring more intensive therapy in the form of antipsychotic polypharmacy or switch over to another therapy. Although the association is considerably high, it should be noted that there were only 16 subjects (0.4%) with this diagnosis in the antipsychotic polypharmacy group and 12 subjects (0.4%) in the monotherapy group.

The association of other psychoses or mixed psychoses (affective psychosis, paranoid states, other nonorganic psychoses, psychoses with origin specific to childhood) and other mental disorders (neurotic disorders, sexual deviation and disorders, physiological malfunction arising from mental factors, disturbance of emotions, hyperkinetic syndrome, specific delays in development special symptoms/disturbance of conduct/ psychic factors not elsewhere classified) with long-term antipsychotic polypharmacy may provide some clue on patient subgroups who were considered ideal candidates for antipsychotic polypharmacy or switch over to another therapy. We acknowledge that both groups have relatively broad definitions and it is difficult to isolate a very specific mental condition for which antipsychotic polypharmacy is prescribed.

It is possible that diagnosis of epilepsy and drug use for Parkinson's disease may be predictors of long-term antipsychotic polypharmacy as presence of these common side-effects may be inducing the physician to switch to a better tolerated treatment. However, since we did not have a medication free wash out period (49% of the antipsychotic polypharmacy patients had received polypharmacy in the prior period)

these could be side effects of prior treatment with antipsychotic polypharmacy or monotherapy. The association between diagnosis of cardiac arrythmia and non clozapine atypical + atypical polypharmacy (OR: 2.0) was as expected, given that cardiovascular side effects like tachycardia is common with atypical monotherapy. Physicians should be aware of this increased risk and exercise caution e.g. regular ECG monitoring especially while adding an atypical to another. Similarly Parkinson's disease was strongly associated ($p<0.0001$) with non clozapine polypharmacy involving conventional antipsychotic (OR: >3.5).

The association between the presence of debilitating chronic diseases (Asthma, Cancer, TB) and long-term antipsychotic polypharmacy and suggests that the antipsychotic polypharmacy groups may be sicker even in terms of their comorbidity burden and raises concerns since these patients are already on a number of drugs for other diseases.

One of the interesting findings among the antipsychotic factors was that atypical antipsychotics had an increasing trend of association where more recently launched drugs were more likely to be associated with long-term antipsychotic polypharmacy than less recent ones For example, quetiapine (launched 1997, OR: 18.32), olanzapine (launched 1996 OR: 14.45) risperidone (launched 1994 OR: 9.18). One explanation for this could be that more people on the most recent atypical are in the switch over stages. This trend is similar across all the groups.

More compliant or regular use patients had a 4.8 times more likely to be associated with antipsychotic polypharmacy. Regular use, as defined by us (at least one prescription of antipsychotic every 2 months) may reflect inherent patient compliance to medication or it may be an artifact of patient severity which results in sicker patients receiving more intensive and regular therapy than others and therefore getting more frequent prescriptions. The result that psychiatric hospitalization was associated with

antipsychotic polypharmacy was expected as it has been found to be a good marker of severity status (Sernyak 2001) and also been associated with antipsychotic prescribing decisions (Irish 2001) in schizophrenia.

The temporal factors showed that the likelihood of being treated with long-term antipsychotic polypharmacy has increased over 5 times in 1999 and 9 times in 2000 over the base period of 1998. This suggests an increasing trend in antipsychotic polypharmacy which is also evident from the trend data reported earlier.

Long-term antipsychotic polypharmacy also raises some financial concerns as the Medicaid systems have limited resources that are being allocated to expensive antipsychotic therapy. The atypical+atypical combinations are especially expensive and have been mentioned as cost drivers and a concern in the California Medicaid system (Stahl, 2002). It is worthwhile to mention that California had a higher prevalence of atypical+atypical polypharmacy. Also the year 1999 was associated with a 9 times increase in the likelihood of atypical+atypical long-term polypharmacy over 1998 and year 2000 was associated with a 21 times increase. This change was the highest among all other antipsychotic polypharmacy groups.

Some of the limitations of the study are that inpatient medication use is not recorded in this database and has not been accounted for except where the patient was prescribed the same medication before and after hospitalization. In that case the patient was assumed to be on that medication during the inpatient stay. As mentioned earlier the identified index episodes may not be the first episodes of antipsychotic polypharmacy (49% of the polypharmacy patients had received polypharmacy in the prior period) for the patient in the study period. Therefore treatment factors, for example comorbid conditions or medication use, cannot be interpreted as predictors of antipsychotic polypharmacy as they may be the result of prior therapy. Like other administrative claims databases, the Medicaid databases have coding biases as coding

is dependent on reimbursement incentives and may not be totally complete. These administrative databases do not include many direct disease measures such as PANSS scores that may be important predictors of antipsychotic polypharmacy. These results are specific to Medicaid eligible schizophrenia patients and may not be generalizable to other patient populations.

CONCLUSION

Antipsychotic polypharmacy is widely prevalent (40%), is prescribed for long durations (>6 months) and is an increasing phenomena among Medicaid eligible schizophrenia patients. The high prevalence of long-term (23%) antipsychotic polypharmacy indicates a significant discrepancy between real world practice and practice guidelines. In general, patients in the aged/disabled Medicaid aid category, males, patients on newer atypicals and older conventionals are more likely to be associated with antipsychotic polypharmacy. The fact that antipsychotic polypharmacy is widely prevalent and is becoming increasingly common with each year emphasizes the need for further research to study the effects of antipsychotic polypharmacy in schizophrenia patients that would help define the scope and potential for such use.

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Table 4.1: List of antipsychotics

Atypicals	Conventionals
Clozapine	Chlorpromazine
Olanzapine	Fluphenazine
Quetiapine	Haloperidol
Risperidone	Loxapine
Ziprasidone,	Mesoridazine
	Molindone
	Perphenazine
	Pimozide
	Prochlorperazine
	Promazine
	Thioridazine
	Thiothixene
	Trifluoperazine
	Chlorprothixene

Table 4.2: Brief description of antipsychotic polypharmacy and corresponding monotherapy comparison cohorts

Antipsychotic polypharmacy Cohort	**Antipsychotic monotherapy comparison cohort**
Any polypharmacy	Any monotherapy
Any Long term* polypharmacy	Any Long term* monotherapy
Long term* clozapine + atypical	Long term* clozapine monotherapy
Long term* clozapine + conventional	Long term* clozapine monotherapy
Long term* atypical + atypical and no exposure to clozapine at any time	Long term* atypical monotherapy and no exposure to clozapine
Long term* atypical + conventional and no exposure to clozapine at any time	Long term* monotherapy and no exposure to clozapine
Long term* conventional + conventional and no exposure to clozapine at any time	Long term* conventional monotherapy and no exposure to clozapine

* Long Term is defined as use for at least 2 months

Table 4.3: Initial list of candidate factors associated with antipsychotic polypharmacy

Demographics	Drug overdose
Age, Gender, Race	Opthalmologic disease
Eligibility categories	Anxiety states
Medicare eligible, Aid category (Aged, blind, disabled), Georgia vs California	Number of comorbidities per patient
Diagnosis related comorbidities	**Drug classes**
Congestive heart failure	4 Cardiac drug classes
Myocardial infarction	Parkinson's disease
Cardiac arrhythmias	Peripheral vascular disorder
Valvular disease	Hypertension
Peripheral vascular disorders	3 Respiratory classes
Hypertension	Insulin dependent diabetes*
Hemiplegia/paraplegia	> Oral hypoglycemic
Epilepsy*	Cancer
> Other neurological disorders	3 Epilepsy drug classes
Chronic pulmonary disease	Glaucoma
Asthma	Gout
Tuberculosis	Hyperlipidemia, hypercholesterolemia
Diabetes, uncomplicated*	Thyroid disorders
> Diabetes complicated	Menopause (HRT)
Thyroid disorder	Allergy
Renal failure and chronic disorders	Anxiety
Liver disease	Pain (terminal) Narcotic analgesic
Peptic ulcer disease	Depression
AIDS	Dementia/ Alzheimer's
Metastatic solid tumor*	Tuberculosis
> Any malignancy	Rheumatologic drugs/ Crohn's disease/ Ulcerative colitis
Rheumatoid arthritis / collagen vascular disease	Migraine
Coagulopathy	ESRD/ Transplant
Obesity	Number of Rx classes per patient (Mean)
Weight loss/malnutrition	**Antipsychotic agents, mood stabilizer**
Fluid and electrolyte disorders	Atypicals, Conventionals
Anemias	Olanzapine, Risperidone, Quetiapine, Clozapine
Sickle cell anemia	Haloperidol oral & injectable, Fluphenazine oral and injectable
Drug abuse*	Thioridazine, Chlorpromazine, Thiothixene
> Alcohol abuse	Lithium
Bipolar and manic depressive*	**Prior health care utilization, date variables**
> Other psychoses/ Mixed psychoses	Mental health cost in prior period
> Other mental disorders	Number of psychiatric outpatient physician visits, physician specialty
> Personality disorders	Psychiatric inpatient episode, latest inpatient days, cumulative inpatient days
> Depression or schizoaffective	Antipsychotic regular use (antipsychotic

	Rx every 2 months)
Cerebrovascular disease	Quarter in which episode started
Alzheimer's disease*	Year in which episode started
> Non Alzheimer's dementia	
Non-head trauma	
Head trauma	

> Indicates a hierarchy in relation to the higher cost category denoted by an asterisk (*). If both comorbidities are present, count only the higher cost category

Table 4.4: Prevalence of antipsychotic polypharmacy 1998-2000

	GEORGIA		CALIFORNIA		COMBINED	
Schizophrenia patients, <= 16 years of age (n)	17,728	17,728	13,707	13,707	31,435	31,435
	TOTAL	LONG TERM	TOTAL	LONG TERM	TOTAL	LONG TERM
Polypharmacy	34.9%	18.1%	46.4%	29.3%	39.9%	23.0%
Clozapine polypharmacy	2.3%	1.3%	6.1%	4.2%	4.0%	2.5%
Clozapine – atypical	1.7%	0.9%	4.3%	2.6%	2.8%	1.6%
Clozapine – conventional	1.0%	0.5%	3.8%	2.4%	2.2%	1.3%
Non clozapine polypharmacy	32.0%	16.1%	39.4%	23.7%	35.2%	19.4%
Atypical – atypical	7.6%	2.2%	14.6%	6.1%	10.7%	3.9%
Conventional – conventional	4.8%	2.0%	8.7%	3.7%	6.5%	2.8%
Atypical – conventional	26.7%	13.4%	31.6%	18.7%	28.9%	15.7%

Table 4.5: Median length of episode by type of antipsychotic polypharmacy

	GEORGIA		CALIFORNIA		COMBINED	
Median length of episode, days	TOTAL	LONG TERM	TOTAL	LONG TERM	TOTAL	LONG TERM
Polypharmacy	62	167	108	235	84	197
Clozapine polypharmacy	68	175	133	254	113	230
Clozapine – atypical	67	190	93	224	84	210
Clozapine – conventional	55	151	102	207	86	182
Non clozapine polypharmacy	62	167	92	220	74	186
Atypical – atypical	31	146	47	155	34	152
Conventional – conventional	40	164	50	188	47	176
Atypical – conventional	62	155	87	198	70	176

Table 4.6: Independent factors associated with long-term antipsychotic polypharmacy identified from the stepwise logistic variable selection procedure

Factors	**Polypharmacy (N = 4,422) n (% prev) or mean (std)**	**Monotherapy (N = 6,162) n (% prev) or mean (std)**	**Odds ratio**	**95% CI**	**p-value**
Eligible for Medicaid in Georgia	1,900 (43.0)	3,821 (62.0)	0.62	0.54 to 0.70	<0.0001
Demographics					
Gender: Male	2,359 (53.3)	2,792 (45.3)	1.15	1.02 to 1.29	0.0197
Eligibility categories					
Aid category (Aged, Blind or Disabled)	4,377 (99.0)	5,917 (96.0)	2.66	1.72 to 4.11	<0.0001
Diagnosis related comorbidities					
Epilepsy	505 (11.4)	211 (3.4)	1.44	1.11 to 1.87	0.0053
AIDS	32 (0.7)	71 (1.1)	0.52	0.27 to 0.98	0.0433
Weight loss/malnutrition	16 (0.4)	12 (0.2)	4.50	1.54 to 13.17	0.0060
Alcohol abuse	64 (1.4)	111 (1.8)	0.58	0.36 to 0.93	0.0237
Other psychoses/ Mixed psychoses	622 (14.1)	666 (10.8)	1.27	1.06 to 1.53	0.0096
Other mental disorders	921 (20.1)	1,109 (18.0)	1.18	1.01 to 1.37	0.0310
Personality disorders	263 (6.0)	386 (6.2)	0.71	0.55 to 0.92	0.0082
Drug classes					
First and second line antihypertensive drugs	1,076 (24.3)	1,411 (22.9)	1.15	0.99 to 1.32	0.0579
Cardiac conditions: Antiarrythmic, inotropic, cardiac vasopressor agents	413 (9.3)	607 (9.8)	0.81	0.66 to 0.99	0.0427
Parkinson's disease	3,138 (71.0)	2,850 (46.2)	2.84	2.50 to 3.23	<0.0001
Exposure to 3 respiratory drug classes	33 (0.7)	34 (0.5)	2.41	1.11 to 5.21	0.0255
Insulin dependent diabetes	149 (3.4)	274 (4.4)	0.75	0.55 to 1.02	0.0649
Cancer	58 (1.3)	53 (0.9)	1.84	1.06 to 3.19	0.0298
Epileptic drugs with psychiatric uses[A]	2,070 (46.8)	1,686 (27.4)	1.32	1.16 to 1.51	<0.0001
Gout	26 (0.6)	36 (0.6)	1.77	0.91 to	0.0906

				3.43	
Hyperlipidemia, hypercholesteremia	320 (7.2)	372 (6.0)	1.33	1.05 to 1.67	0.0175
Tuberculosis	27 (0.6)	16 (0.3)	2.48	0.99 to 6.20	0.0158
Antipsychotic agents, mood stabilizer					
Clozapine	490 (11.1)	393 (6.4)	11.77	9.23 to 15.01	<0.0001
Olanzapine	1,856 (42.0)	1,048 (17.0)	14.45	12.27 to 17.01	<0.0001
Risperidone	1,248 (28.2)	1,037 (16.8)	9.18	7.75 to 10.87	<0.0001
Quetiapine	519 (11.7)	80 (1.3)	18.32	13.07 to 25.68	<0.0001
Haloperidol oral	1,000 (22.6)	764 (12.4)	6.53	5.45 to 7.83	<0.0001
Haloperidol injectable	575 (13.0)	285 (4.6)	5.43	4.32 to 6.84	<0.0001
Fluphenazine oral	490 (11.1)	352 (5.7)	5.50	4.36 to 6.95	<0.0001
Fluphenazine injectable	422 (9.5)	291 (4.7)	5.13	4.00 to 6.60	<0.0001
Thioridazine	543 (12.3)	373 (6.0)	18.61	14.80 to 23.40	<0.0001
Chlorpromazine	418 (9.4)	114 (1.8)	28.87	21.14 to 39.42	<0.0001
Thiothixene	282 (6.4)	244 (4.0)	8.44	6.39 to 11.16	<0.0001
Lithium use	566 (12.8)	499 (8.1)	1.31	1.08 to 1.58	0.0057
Prior health care utilization, date variables					
Mental health cost Mean (std)	4,237(5,762)	2,584 (4,552)	1.00	1.00 to 1.00	<0.0001
Number of psychiatric outpatient physician visits Mean (std)	1.7 (4.5)	1.0 (2.5)	1.028	1.008 to 1.049	0.0061
Antipsychotic regular use (antipsychotic Rx every 2 months)	3,655 (82.6)	3,344 (54.3)	4.84	4.21 to 5.57	<0.0001
Psychiatric inpatient episode	695 (15.7)	589 (9.6)	1.42	1.17 to 1.73	0.0004
3rd quarter start date	1,889 (42.7)	3,688 (59.8)	0.70	0.59 to	<0.0001

(July, August, September)[B]				0.83	
4th quarter start date (October, November, December)[B]	858 (19.4)	915 (14.8)	2.46	2.03 to 2.99	<0.0001
Year 1999 start date[C]	1,644 (37.2)	1,574 (25.5)	5.53	4.67 to 6.54	<0.0001
Year 2000 start date[C]	1,275 (28.8)	1,079 (17.5)	9.67	7.93 to 11.77	<0.0001

A: This group was exposed to at least one of the following two drug classes 1) Anticonvulsants (barbiturate, certain benzodiazepines) 2) Miscellaneous anticonvulsants that could partically affect schizophrenia e.g. valproic acid.
B: 1st quarter odds ratio = 1
C: Year 1998 odds ratio = 1

Association of predicted probabilities and observed responses:
c-statistic for the final model = 0.9143
c-statistic for validation sample = 0.9174

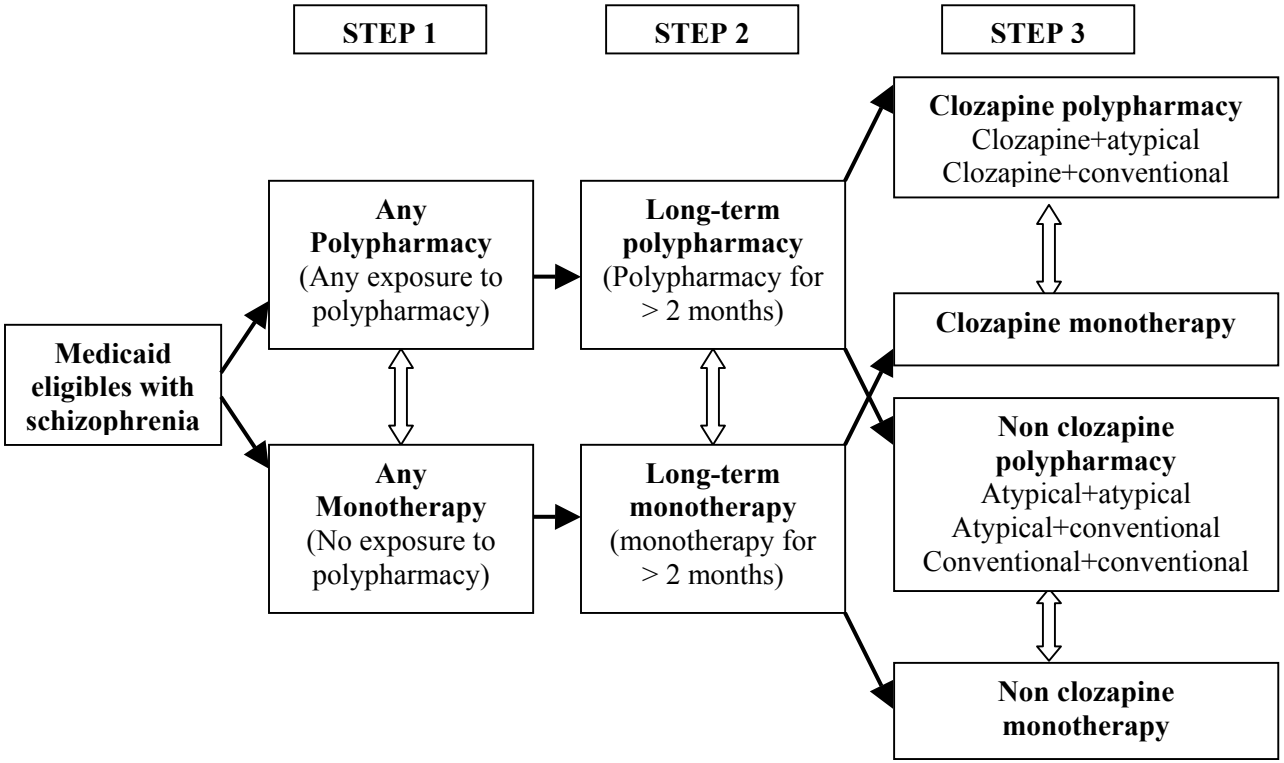

Figure 4.1: Different forms of antipsychotic polypharmacy and monotherapy

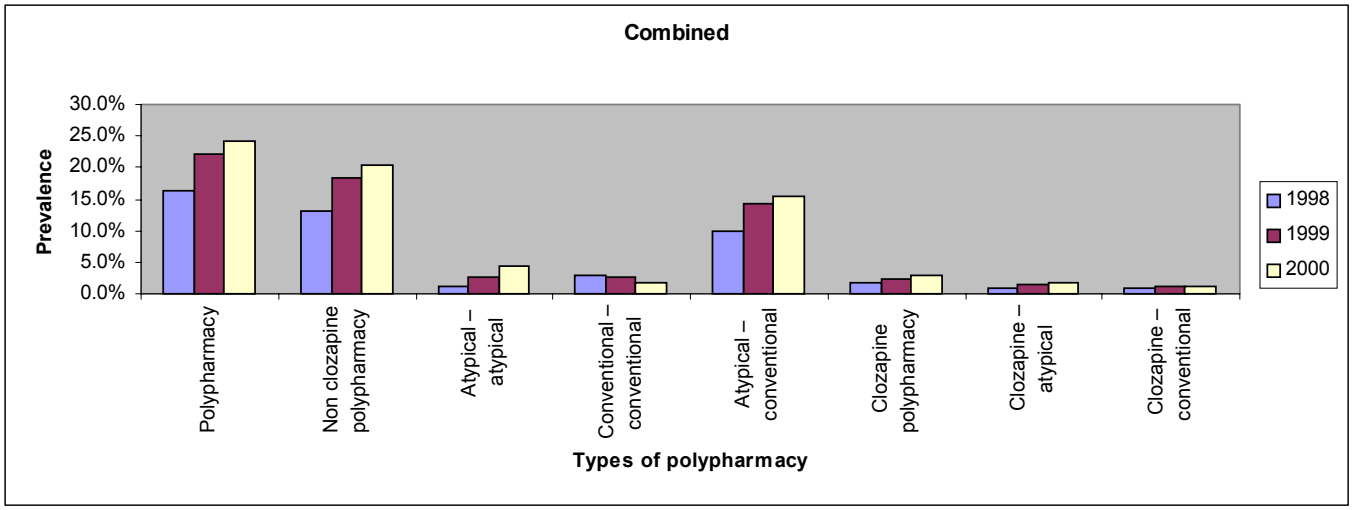

Figure 4.2: Trend of long-term antipsychotic polypharmacy 1998-2000

CHAPTER 5

ASSOCIATION BETWEEN LONG-TERM ANTIPSYCHOTIC POLYPHARMACY AND HEALTH CARE EXPENDITURE AMONG MEDICAID ELIGIBLE SCHIZOPHRENIA PATIENTS[1]

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ABSTRACT

Background: Antipsychotic polypharmacy or concomitant use of multiple antipsychotics is prevalent in up to 40% of schizophrenia patients despite lack of clinical evidence or support from treatment guidelines. The objective of our study was to estimate the association between long-term antipsychotic polypharmacy and one-year health care expenditure.

Methods: A retrospective cohort study was designed and Medicaid recipients >= 16 years of age with a primary diagnosis of schizophrenia (ICD-9-CM=295.**) between 1998-2000 were identified from the Georgia and California (20% random sample) Medicaid claims databases. 6 antipsychotic polypharmacy cohorts; long-term polypharmacy i.e. duration of use > 2 months (> 60 days), clozapine (2 subtypes), non-clozapine (3 subtypes) and corresponding monotherapy cohorts were built. Annual outcomes were compared between propensity score matched long-term antipsychotic polypharmacy (experimental group) and monotherapy (control group) subjects to obtain per capita net expenditures.

Results: Out of a total of 31,435 persons with schizophrenia (Mean age 43 years, female: 49%, white: 47%), 4,665 met inclusion criteria for long-term antipsychotic polypharmacy and 6,955 for monotherapy. 3,186 patients in 1,593 pairs treated with long-term antipsychotic polypharmacy or monotherapy were matched for all covariates using propensity scoring. The one-year per capita expenditure for the long-term antipsychotic polypharmacy group was $13,891 which was significantly higher ($3,829 95% Confidence Interval [CI], 3,347 to 4,310) than the monotherapy group ($10,062) and remained higher even after propensity matching ($1,699 95% CI 760 to 2,638). The net one year long-term antipsychotic polypharmacy expenditure was higher for almost all subgroups and were statistically significant for atypical+atypical ($4,210, 95% CI $1,742 to $6,678), conventional+conventional ($3,281, 95% CI $834 to $5,728) and

atypical+conventional vs. conventional ($2,940, 95% CI $1,141 to $4,739) groups. After Heckman 2-stage adjustment the total cost was higher for all polypharmacy groups except the clozapine+conventional group where there was a reduction in 1-year total cost (-$3,534, 95% CI -$6,210 to -$858).

Conclusion: In this observational study, long-term antipsychotic polypharmacy was associated with an increase in one-year and two-year health care expenditure compared with monotherapy which consisted largely in an increase in prescription costs, after adjusting for treatment selection bias and a variety of risk factors related to resource use. There was a trend towards higher cost for all polypharmacy subgroups and were statistically significant for atypical+atypical, conventional+conventional, and atypical+conventional vs. conventional groups. No evidence of economic benefit with antipsychotic polypharmacy was observed except for a significant positive net cost in the clozapine+conventional vs clozapine group sensitivity analysis ($p < 0.001$). These findings raise concerns regarding the value of long-term antipsychotic polypharmacy and emphasize the need to critically evaluate such treatment decisions in schizophrenia patients.

Keyword: Polypharmacy, Antipsychotic, Cost, Medicaid, Schizophrenia,Expenditure

INTRODUCTION

Antipsychotic polypharmacy or concomitant use of multiple antipsychotics in schizophrenia is regarded as one of the "most practiced and least investigated phenomena in clinical psychopharmacology" (Stahl 2000). It is estimated that antipsychotic polypharmacy is prescribed for up to 40% of schizophrenia patients (Canales 1999). However there are no randomized controlled trials of combination therapy except one with sulpiride and clozapine, which provides little guidance in the U.S. since sulpiride is not available in the US (Yuzda 2000). Apart from this study, there are case reports (Stubbs 2000,Lerner 2000,Chue 2001,Mujica 2001,Rhoads

2000,Raskin 2000,Morera 1999,Cooke 1999,Gupta 1998) and open uncontrolled nonrandomized trials (Taylor 2001,Kapur 2001,de groot 2001,Waring 1999,Waddington 1998) that report the effects of antipsychotic polypharmacy. Almost half of these studies report an increased incidence of adverse events such as prolactin elevation, akathisia, hyper salivation (Yuzda 2000, Kapur 2001, Cooke 1999, Degroot 2001) and even an increased risk of mortality (Waddington 1998, n=88, RR: 2.46) and the rest report improvement in symptoms over baseline. However, it should be noted that besides the obvious design limitations of such uncontrolled trials, these studies were limited by small sample sizes (most of them are 1 or 2 patient case reports) and incomplete reporting of adverse effects. The recent introduction of four new antipsychotics (e.g. Olanzapine-1996, Quetiapine-1997, Ziprasidone–2001, Aripiprazole-2003) with differing receptor profiles have further increased the possibilities of combining these agents.

The objective of our study was to estimate the net cost associated with long-term antipsychotic polypharmacy over a one-year period. Differences in annual cost between a long-term antipsychotic polypharmacy patient (experimental subject) and monotherapy patient (comparison subject) provided an estimate of net cost associated with long-term antipsychotic polypharmacy.

Use of atypical antipsychotics in combinations has been stated as a growing concern for Medicaid budgets (Stahl 2002) especially since atypicals have high acquisition costs. For e.g. clozapine + risperidone polypharmacy could cost anywhere between $500 and $3,000 per month per patient in medication costs (Drug Topics Red Book 2002, Drug Facts and Comparisons 2002) alone besides the indirect expenditures or savings that may result from such therapy.

METHODS

Data sources

A retrospective observational non-equivalent control group design was employed using a combined two-state Medicaid database. We built a 3-year (1998 to 2000) two-state Medicaid database using three sources, the Georgia Medicaid files maintained by the Georgia Department of Medical Assistance (GDMA), Georgia state based institutional data files maintained by the Department of Human Resources (DHR) and California Medicaid 20% sample (Medi-Cal). The California Medicaid 20% files were prepared by the California Department of Health Services and sampling was done by the last two or three bytes of the beneficiary SSN. Thus, all claims rendered to the same 20% beneficiary population were contained in these files. The beneficiary SSN is considered a reliable variable on which to sample since it is almost always checked for validity within the claims processing system. The final files were encrypted in a consistent fashion so outside researchers could track the same person throughout the data set without having any knowledge of the actual identity of the patient. The Medicaid files contain eligibility details, demographics and claims history for various health care services, including Medicaid paid amount, outpatient prescription drugs, inpatient stays, and disease diagnosis. A common resource available to Georgia Medicaid patients are the 8 psychiatric hospitals managed by the Department of Human Resources (DHR) which do not bill Medicaid for services rendered to persons age 21 to 64 years. Records from all these 8 hospitals were combined to form the DHR file that contains a system wide record of each visit a patient received at any one of the 8 system inpatient institutions in operation. To capture psychiatric episodes of care, the DHR files (state based institutional data) were linked by patient identifiers to the GDMA files (Georgia Medicaid claims data). This patient linked or merged data provides a complete picture of the medical resources consumed for each Medicaid eligible patients with schizophrenia

in Georgia. California Medicaid reimburses 4 state psychiatric hospitals for inpatient services rendered to Medicaid eligibles so there is no need to link state psychiatric hospitals with the claims data.

The Georgia (Martin 1998; Kotzan 1999; Martin 2001) and California (McCombs 1999, Ganguly 2001, Malkin 2002) Medicaid data have been used in the past for epidemiological studies and have been found to be valid.

Study population

Persons with primary diagnosis of schizophrenia (ICD-9-CM = 295.**) recorded on at least one paid claim during the period Jan 1998 through Dec 2000 and at least 16 years of age as of Jan 1st 1998 were identified. After identifying the schizophrenia patients, long-term antipsychotic polypharmacy and monotherapy episodes for each person was identified.

The Journal of Clinical Psychiatry treatment guideline (McEnvoy, 1999) is the only guideline that offers guidance on the duration of antipsychotic polypharmacy, and that guideline does not recommend antipsychotic polypharmacy for more than 8 weeks or 2 months. Based on that guideline, long-term antipsychotic polypharmacy was defined as two or more chemically distinct antipsychotics prescribed concurrently where there is an overlap of more than 2 months (more than 60 days) therapy taken concurrently. The list of antipsychotics has been provided in table 5.1. Concurrent therapy of more than 2 months between consecutive or concurrent prescription fill dates were identified by estimating the days supply for each antipsychotic prescription filled for each person and comparing that to dates antipsychotic prescriptions are filled. The first day of that episode (defined below) of overlap or concurrent use of the two antipsychotics was considered as the episode start date for that long-term antipsychotic polypharmacy episode.

An episode of long-term antipsychotic polypharmacy was defined as a period of continuous, long-term antipsychotic polypharmacy, without a break period of 31 or more days (Svarstad 2001). A break period was defined as a period when the patient had no supply of drugs. Hospital stays that occurred within 31 days of an antipsychotic use period were considered as a continuation of the preceding episode and not a part of the break period if the therapy remained the same after discharge.

Antipsychotic use episodes where a single antipsychotic was prescribed for more than 2 months (60 days) without a break period of 31 or more days was referred to as monotherapy episodes.

Long-term antipsychotic polypharmacy was for further classified in a hierarchical fashion, narrowing the definition of long-term antipsychotic polypharmacy with each consecutive step in accordance with published treatment guidelines into 6 groups (Figure 5.1).

A single longest episode of long-term antipsychotic polypharmacy or monotherapy i.e. period of maximum exposure to treatment, between 1998 and 2000 was identified for each patient in the antipsychotic polypharmacy and monotherapy cohort such that the patients had continuous Medicaid eligibility and at least one paid claim in every 90 day window during the 6 months period preceding and one year period following the start of the this episode. This 6-month 'prior' period was used to collect health care utilization information to adjust for selection bias and the one-year observation period was used to compare cost outcome. The 90-day window criterion (McCombs 1999) was used to ensure persons that are eligible for Medicaid benefits have not withdrawn from the system (e.g. prison).

Those who were never exposed to antipsychotic polypharmacy were grouped into a monotherapy cohort and were further classified into unique monotherapy cohorts depending on the duration and type of monotherapy of their index episode (Table 5.2).

Long-term antipsychotic polypharmacy cohorts were similarly created using the selected longest episode where subjects who had at least one long-term antipsychotic polypharmacy episode were grouped into the 'long-term antipsychotic polypharmacy' cohort. Long-term users were further subdivided into clozapine users and non clozapine users as clozapine is usually reserved for treatment resistant patients. These two groups were further divided by class of antipsychotic used in combination. Each of the long-term antipsychotic polypharmacy groups identified above had a corresponding monotherapy comparison group described in table 5.2.

Measurement of outcome

The outcome measure, cost using the government payer perspective was calculated for both long-term antipsychotic polypharmacy and monotherapy subjects. For Georgia Medicaid patients, the cost to Medicaid was calculated by summing the Medicaid paid amount over the observation period. The cost to state Department of Human Resources (DHR) for Georgia patients who have had one or more admissions to state psychiatric facilities was assessed by merging the DHR file with the most recent DHR Hospital Budget and Utilization Report. A facility and ward specific per-diem operating cost was derived from DHR budget reports and a facility specific per-diem overhead rate was added to the operating cost. The DHR cost was calculated by multiplying the inpatient days by the per diem rates and summing over the observation period. The California paid amounts include both Medicaid and state mental health costs and was summed to calculate the total cost. All costs were reported in 2000 US dollars. The effect of long-term antipsychotic polypharmacy on different cost categories – inpatient, outpatient, physician and prescription was also reported.

Estimating propensity score

Selection bias is commonly encountered in observational studies as the treatment selection is nonrandom and is confounded with patient factors that are also

related to outcome. For e.g. patients with more severe exacerbations maybe more likely to be selected for long-term antipsychotic polypharmacy and are also more likely to have higher costs in the future. The propensity score matching technique is commonly used to reduce selection bias and estimate effect of treatment in health services research (D'Agostino 1998;Stone 1995;Connors 1996;Reinisch 1995). It has also been used in some recent studies in schizophrenia patients (Sernyak 2001a; Sernyak 2001b; Irish 2002). The basic idea of propensity score methods is to replace the collection of observed confounding covariates or patient factors with one scalar function of these covariates, called the propensity score i.e. in this case the propensity to receive long-term antipsychotic polypharmacy rather than monotherapy. Each long-term antipsychotic polypharmacy patient is then paired with a monotherapy patient with similar propensity to receive polypharmacy and a matched pair analysis is performed to estimate the relative effect of long-term antipsychotic polypharmacy on the outcome.

A comprehensive list of all potential confounders or variables that relate to both treatment choice (long-term antipsychotic polypharmacy) and outcome (cost) was identified by a survey of published literature and expert opinion (Table 5.3). This list included demographics, diagnosis related comorbidities, drug classes, antipsychotic agents and prior health care utilization variables. The list of diagnosis related comorbidities and drug classes were obtained from a cost prediction model for schizophrenia patients. This model has been developed and validated on the Georgia Medicaid database as a part of an AHRQ (Agency for Health Care Research and Quality) project. The month and year of the episode start date was also included to identify any year wise or seasonal trend in use. The list of antipsychotic agents consisted of the ten most prevalent drugs identified from a frequency analysis of the prior period prescription records. Haloperidol and fluphenazine were categorized by mode of administration as the injectable form is generally prescribed to a less compliant group of

patient (McEnvoy, 1999) and compliance in turn may be an important factor associated with choice of therapy.

A stepwise logistic variable selection procedure was used to model the binary treatment indicator (1 = long-term antipsychotic polypharmacy, 0 = monotherapy) and main effects of covariates were entered into the model if they are significant at 0.50 level (Rosenbaum 1984; D'Agostino 1998). The probability of long-term antipsychotic polypharmacy (from 0 to 1), the propensity score, was determined for each patient.

A new set of propensity scores were obtained for each set of comparisons e.g. long term antipsychotic polypharmacy vs. long term monotherapy, as propensity for a different type of long-term antipsychotic polypharmacy is different for each comparison.

Matching long-term antipsychotic polypharmacy and monotherapy subjects based on propensity score

After estimating the propensity score for each patient in the long-term antipsychotic polypharmacy and monotherapy groups, each long-term antipsychotic polypharmacy patient was matched with one monotherapy patient with similar propensity score. Matching was accomplished using the 'nearest available metric matching within calipers defined by propensity score' technique (D'Agostino 1998). This technique has been found to produce the best balance between the covariates in the treated and comparison groups (D'Agostino 1998, Rosenbaum 1985). Long-term antipsychotic polypharmacy subjects were randomly ordered and the first subject was selected, all monotherapy subjects within a caliper of the selected long-term antipsychotic polypharmacy subjects' logit of the propensity score were selected, Mahalonobis distance was calculated between the long-term antipsychotic polypharmacy subject and the selected monotherapy subjects and the monotherapy subject with smallest distance was retained as a match. This process was continued until all possible pairs were identified.

Two-sample t-statistic and standardized percentage differences were calculated to explore the differences in distribution of the selected covariates between the long-term antipsychotic polypharmacy and monotherapy groups (D'Agostino, 1998) prior to matching and after matching.

Heckman two-stage estimation

Propensity score matching technique controls for observable confounders only, for e.g. those identified in table 5.3 and are recorded on the database. However bias due to unobservable confounders e.g. cognitive status of the patient, may continue to be a concern, especially in the context of administrative databases that have limited direct disease measures. The Heckman two-stage estimation technique may potentially address this concern as it controls for selection bias due to observable confounders in the first stage in a manner similar to propensity scoring and may also account for potential bias due to unobservable confounders that may continue to exist in the second stage. The net costs were re-estimated using the heckman two-stage estimation technique and compared with the propensity matched results as a check for validity of the results.

The two-stage estimator was introduced by Heckman (1976) and has been used in the past to estimate effect in health services research (Terza 1999, Treglia 1999, Neslusan 1999). In the first stage, the binary outcome of receiving or not receiving long-term antipsychotic polypharmacy was modeled from selected covariates that influence treatment assignment using a probit equation. The vector of coefficients of the covariates estimated through this model was used to calculate the expected value of error (M1). In the second stage, cost was modeled using the covariates in table 5.3, a dummy variable for treatment assignment (1 if long-term antipsychotic polypharmacy 0 if monotherapy) and M1 the estimate of the expected value of error obtained from the previous stage.

Analysis

The data was managed using SAS software Version 8.02 (SAS 2002) and statistical analysis was performed using SAS and STATA Version 6.0 (STATA Corp, 1999). Unadjusted net costs before matching and difference scores for cost between the long-term antipsychotic polypharmacy subjects and matched monotherapy subjects were calculated. Statistically significant differences in outcomes were detected by calculating 95% confidence intervals around the net costs.

Sensitivity analysis

A sensitivity analysis was performed restricting the definition of cost to mental health and substance abuse costs. Two-year net cost associated with the use of long-term antipsychotic polypharmacy was estimated for a subset of subjects who met the eligibility and claim window criteria for a two-year observation period. The observation period was also restricted to the duration of the selected episode to estimate the concurrent costs associated with long-term antipsychotic polypharmacy. The concurrent cost incurred over the length of the episode was annualized to adjust for unequal episode lengths.

The study was approved by the University of Georgia Institutional Review Board (IRB).

RESULTS

Description of the study population

32,280 subjects (Georgia: 18,373, California: 13,907) had received at least one primary diagnosis of schizophrenia between 1998 and 2000 out of which 31,435, were at least 16 years of age as of Jan 1, 1998. The mean age of the 31,435 subjects with schizophrenia was 43 years (SD: 14 years) (both Georgia and California had mean ages of 43 years), 49% were female (Georgia: 56%, California: 43%) and 47% were white (Georgia: 38%, California: 57%). 7,222 subjects (23%) had been exposed to at least one

long-term antipsychotic polypharmacy episode, of which 4,665 subjects met the continuous Medicaid eligibility and 90-day claim window criteria for 6 months preceding and 1 year following episode start date. 6,955 subjects, who had not been exposed to long-term polypharmacy, had at least one long-term monotherapy episode and met the Medicaid eligibility and claim window criteria were retained as potential control subjects.

Patient characteristics

The characteristics of 11,620 patients identified for the study are shown in table 5.4. The long-term antipsychotic polypharmacy cohort had more males (53.5% vs. 45%) and whites (48.6% vs. 42%) whereas the monotherapy cohort was slightly older (mean age: 46 years vs. 43.5 years). 22 covariates had standardized % difference of more than 20%. Long-term antipsychotic polypharmacy patients were less likely to be Georgia Medicaid eligible. They were also more likely to have epilepsy and Parkinson's disease and less likely to have personality disorders. These patients were also more likely to receive antipsychotics, especially the newer atypicals risperidone and quetiapine. The prior utilization in terms of total and mental health expenditure, physician visits, inpatient episodes were higher for the long-term antipsychotic polypharmacy group.

Unadjusted outcome

The one-year per capita expenditure for the long-term antipsychotic polypharmacy group was $13,891 which was significantly higher ($3,829 95% Confidence Interval [CI], 3,347 to 4,310, p-value <0.0001) than the monotherapy group ($10,062) (table 5.5). Prescription cost formed the largest component of long-term antipsychotic polypharmacy cost ($6,555 or 47%) followed by outpatient cost (20%) and long-term care cost (18%). Per capita prescription cost for the long-term antipsychotic polypharmacy group was significantly higher ($3,363 95% CI 3,220 to $3,506, p<0.0001) than monotherapy group, followed by inpatient cost ($279 95% CI 51 to 507, pvalue 0.02) and physician cost ($53, 95% CI 11 to 95, pvalue 0.01).

Propensity score and adjustment for selection bias

Before matching, long-term antipsychotic polypharmacy patients had a mean propensity score logit 2.01 (mean propensity score of 0.73 i.e. probability of receiving long-term antipsychotic polypharmacy was 0.73), while those on monotherapy had a mean score of -2.22 (mean propensity score of 0.17). 3,186 patients for 1,593 pairs treated with or without long-term antipsychotic polypharmacy were successfully matched for all the covariates using the propensity matching technique. The 22 covariates that had standardized differences of more than 20% before matching had less than 5% difference after matching (table 5.4). Post match standardized difference was highest for Thioridazine (7.3%) and below 5% for almost all the other covariates. The mean propensity score logit was –0.54 after matching for both groups.

Per capita total cost for the long-term antipsychotic polypharmacy group remained significantly higher (p-value 0.0004) than the monotherapy group ($1,699, 95% CI $760 to $2,638) after propensity matching although the difference was lesser than the unadjusted results (table 5.5). Prescription cost formed the largest component of this difference and was $1,876 higher (95% CI $1,550 to $2,201, p-value <0.0001) and none of the other differences by category of service were statistically significant.

Analysis by long-term antipsychotic polypharmacy subgroups

After matching, the per capita one-year total expenditure was higher for the long-term antipsychotic polypharmacy subjects compared with the monotherapy subjects across all polyphamacy subgroups though the increases were not always statistically significant (table 5.6). This difference was statistically significant for the comparison between atypical+atypical vs. atypical ($4,210, 95% CI 1,742 to 6,678), conventional+conventional vs. conventional ($3,281, 95% CI $834 to $5,728) and atypical+conventional vs. conventional ($2,940, 95% CI $1,141 to $4,739) groups. For those groups with statistically significant net costs, prescription cost formed the largest

component of the net difference (Atypical+atypical vs. atypical: $4,013, Conventional+conventional vs. conventional: $1,266, Atypical+conventional vs. conventional: $2,940).

Sensitivity analysis

Mental health expenditure

Per capita one-year mental health and substance abuse related expenditure was significantly higher for the long-term antipsychotic polypharmacy group ($1,717, 95% CI $1,064 to $2,369) compared with the long-term monotherapy group (table 5.7). The subgroup analyses followed a trend similar to the total expenditure and was higher for the long-term antipsychotic polypharmacy subjects compared with the monotherapy subjects across all polyphamacy subgroups although the difference was not always statistically significant. Statistically significant differences were observed in the clozapine+atypical ($3,463, 95% CI $269 to $6,657), atypical+atypical ($3,014, 95% CI $1,475 to $4,552) and atypical+conventional vs. conventional ($3,379, 95% CI $1,975 to $4,783) groups.

Two-year expenditure

Difference in expenditure between the long-term antipsychotic polypharmacy and monotherapy group was much more pronounced ($4,153, 95% CI $1,675 to $6,631) in the two-year period than in the one-year period ($1,876) (table 5.8). Long-term antipsychotic polypharmacy expenditures were higher in all the subgroups and per capita two-year net long-term antipsychotic polypharmacy expenditure was statistically significant for clozapine+atypical ($11,114, 95% CI $3,351 to $18,878), atypical+atypical ($9,611, 95% CI $1,822 to $17,399) and atypical+conventional vs. conventional ($9,322, 95% CI $3,990 to $14,655) groups.

Episode expenditure

The annualized episode expenditures have been shown in table 5.9. The net episode expenditures for the long-term antipsychotic polypharmacy groups were very similar to the one-year net expenditures and the differences were statistically significant for all the non-clozapine groups.

Heckman two-stage estimates

The heckman two-stage estimate of net one-year per capita expenditure for the long-term antipsychotic polypharmacy group ($1,765, 95% CI $1,353 to $2,177) was very close to the propensity matched estimate ($1,699) and model R-squares for the cost model ranged from 0.51 to 0.76 (table 5.10). Theta (error estimate added as an additional regressor in the second stage) was significant for the clozapine+atypical (p 0.01) and atypical+conventional vs. conventional (p 0.04) groups and close to significant (p 0.07) in the atypical+atypical group. A significant theta indicates that the selection model does not fully adjust for bias for e.g. due to unobserved variables in the first stage, which is later corrected by including the theta term in the second stage. The heckman estimates for the non clozapine groups were comparable with the propensity results and differences in the atypical+atypical ($2,337, 955 CI $1,129 to $3,545), conventional+conventional ($1,401, 95% CI $503 to $2,299), and atypical+conventional vs. conventional ($3,393, 95% CI $2,738 to $4,048) groups were statistically significant. The per capita net expenditure estimate differed in magnitude but followed the same trend (positive) for the clozapine+atypical group, but were markedly different for the clozapine+conventional group where there was a statistically significant cost saving with polypharmacy (-$3,534, 95% CI –6,210 to -$858).

DISCUSSION

Long-term antipsychotic polypharmacy was found to be widely prevalent (23%) in this two-state Medicaid eligible schizophrenia population. Long-term usage is not

supported by clinical evidence or practice guidelines and may be justified if the patients are significantly different in terms of their disease status and are not controlled with monotherapy. Propensity score matching resulted in 3,186 patients for 1,593 pairs treated with long-term polypharmacy or long-term monotherapy who were comparable in terms of observed covariates (and unobserved covariates only to the extent that they are correlated with the observed covariates).

Two reasons are commonly suggested for this differential treatment among comparable groups. First, that these could be switchover or PRN patients who were started on a short-term combination therapy and then were 'stuck' on it for some reason. For example, they were stable and the physician did not want to risk a relapse (Tapp 2003). Second these patients could also be seeing multiple physicians resulting in long-term antipsychotic polypharmacy. and there could be unobserved patient factors defining disease severity for e.g. symptom status of the patient as measured by PANSS scores, which were only observed by the physician.

Long-term antipsychotic polypharmacy was found to be associated with higher health care costs over one-year and this difference became more pronounced over a two-year period. After matching, the per capita total Medicaid costs were higher for the long-term polypharmacy group and non clozapine groups (conventional+conventional, atypical+atypical, atypical+conventional vs. conventional). No evidence of any benefit in terms of health care cost was found with antipsychotic polypharmacy except the heckman-2 stage adjusted clozapine+conventional group.

There could be several possible explanations for the association with higher cost. First obvious explanation is higher use of antipsychotics in the long-term antipsychotic polypharmacy group. This explanation is especially relevant for the atypical groups as they are expensive and an additional atypical can significantly drive costs, but not to that extent for the conventional+conventional group. If we assume that the matching resulted

in comparable patients it could be argued that the matched long-term antipsychotic polypharmacy patients could have been treated with monotherapy, resulting in significant cost savings due to reduced use of antipsychotics. The net per capita long-term polypharmacy cost of $1,699 may translate into cost savings of and 7,222 (23%) of schizophrenia patients receive long-term polypharmacy

Second, long-term antipsychotic polypharmacy may lead directly to worse patient outcomes that in turn results in higher costs. As discussed before there is very little evidence for the use of long-term antipsychotic polypharmacy, especially for long periods of time and a deleterious effect is a plausible explanation. This deleterious effect may be reflected in higher overall prescription cost as non-antipsychotic medications may be used more frequently to treat the side effects of long-term antipsychotic polypharmacy.

A third explanation could be that long-term antipsychotic polypharmacy is a marker for aggressive treatment that is reserved for severe patients. Thus the long-term antipsychotic polypharmacy patients are sicker patients and therefore have worse outcomes leading to higher costs. We performed propensity score matching to address this issue of selection bias and matched comparable long-term antipsychotic polypharmacy and monotherapy groups. Prior health care cost or cost incurred in the prior 6 months was also included as a covariate and after matching both groups had comparable prior costs (Polypharmacy: $5,438 vs. Monotherapy: $5,368). Even after matching there was evidence of higher costs with long-term antipsychotic polypharmacy.

A fourth explanation, leading from the third, could be that long-term antipsychotic polypharmacy is a marker of severity that is not reflected in any of the observed covariates. In other words our adjustment for selection bias is not sufficient, as there could be unobservable confounders. The Heckman two-stage estimation method potentially addresses this issue of continued existence of bias. The Heckman two-stage

estimates were similar to the propensity estimates in most cases, and long-term polypharmacy, atypical+atypical, conventional+conventional and atypical+conventional differences remained significant. However the clozapine group results were very different for the two analyses. This difference could be attributed to the effect of unobserved covariates, which was possibly true in the clozapine+atypical group where the error estimate obtained from the selection equation was significant when added to the survival equation (p-value: 0.01). Since Heckman estimation adjusts for the whole group and not a subgroup of matched subjects (like in propensity matching), large differences in distribution of covariates between the groups can result in differences from the propensity results. These methodological aspects of the estimation techniques should be kept in mind while interpreting the results, especially for the clozapine groups.

A fifth explanation could be that since this is an observational study and not a RCT some bias may continue to exist even after adjustments. Even if long-term antipsychotic polypharmacy patients are assumed to be sicker to start with, use of more expensive prescription therapy in the long-term antipsychotic polypharmacy group does not lead to adequate cost savings in any other categories of service for e.g. hospitalizations that could make it cost neutral in comparison with monotherapy.

However it can be also argued that there is merit to long-term antipsychotic polypharmacy and if these subjects were not treated with long-term antipsychotic polypharmacy they could have had even worse outcomes. For e.g. under treating the long-term antipsychotic polypharmacy group may have resulted in higher hospitalization costs. At least for now, excluding prescription costs the matched groups are cost neutral in terms of the other categories of service. Also we have to bear in mind that there could be significant improvements in humanistic outcomes for e.g. cognitive status of the patient that are not observed in this study. Unfortunately these arguments cannot be proved or disproved without initiating a well-controlled RCT.

To date there have been no published study that estimate the association between the use of long-term antipsychotic polypharmacy and health care cost. Our findings show that long-term antipsychotic polypharmacy is associated with higher total costs and there is no evidence of benefits in terms of cost except the heckman adjusted clozapine+conventional group. Considering the impact of such therapy on formulary budgets and lack of evidence of any benefit there seems to be a need to critically evaluate such treatment decisions. Prior authorization rule for long-term antipsychotic polypharmacy (more than 60 days) or specifically same type polypharmacy (atypical+atypical and conventional+conventional) may be explored as a policy option to evaluate such treatment on a case to case basis.

In that sense our findings tend to support practice guidelines (Texas Medication Algorithm Project Miller 1999, American Psychiatric Association APA 1997, Journal of clinical psychiatry McEnvoy 1999, Patient outcomes research team, Lehman 1998) that do not recommend long-term antipsychotic polypharmacy.

Several important limitations of this study must be noted. First, it is an observational study, not an RCT. While we have adjusted for treatment selection bias and also used multiple adjustment techniques to ensure the validity of our results, the possibility of an important missing covariate can never be excluded. Also it is worth noting that 3,072 (66%) of the 4,665 long-term antipsychotic polypharmacy patients could not be matched with a comparable monotherapy patient indicating that there were significant differences between these long-term antipsychotic polypharmacy and monotherapy groups. The unmatched groups were markedly different in the prevalence of epilepsy, personality disorder, Parkinson's disease; use of atypical antipsychotics and prior 6 month cost.

Inpatient medication use is not recorded in this database and has not been accounted for except where the patient was prescribed the same medication before and

after hospitalization. In that case the patient was assumed to be on that medication during the inpatient stay. Like other administrative claims databases, the Medicaid databases have coding biases as coding is dependent on reimbursement incentives and may not be totally complete. These results are specific to Medicaid eligible schizophrenia patients and may not be generalizable to other patient populations.

CONCLUSION

In this observational study, long-term antipsychotic polypharmacy was associated with an increase in one-year and two-year health care expenditure compared with monotherapy which consisted largely in an increase in prescription costs, after adjusting for treatment selection bias and a variety of risk factors related to resource use. There was a trend towards higher cost for all polypharmacy subgroups and were statistically significant for atypical+atypical, conventional+conventional, and atypical+conventional vs. conventional groups. No evidence of economic benefit with antipsychotic polypharmacy was observed except for a significant net cost in the clozapine+conventional vs clozapine group sensitivity analysis ($p < 0.001$). These findings raise concerns regarding the value of long-term antipsychotic polypharmacy and emphasize the need to critically evaluate such treatment decisions in schizophrenia patients.

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Table 5.1: List of antipsychotics

Atypicals	**Conventionals**
Clozapine Olanzapine Quetiapine Risperidone Ziprasidone,	Chlorpromazine Fluphenazine Haloperidol Loxapine Mesoridazine Molindone Perphenazine Pimozide Prochlorperazine Promazine Thioridazine Thiothixene Trifluoperazine Chlorprothixene

Table 5.2: Brief description of antipsychotic polypharmacy and corresponding monotherapy comparison cohorts

Antipsychotic polypharmacy Cohort	**Antipsychotic monotherapy comparison cohort**
Long term* polypharmacy	Long term* monotherapy
Long term* clozapine + atypical	Long term* clozapine monotherapy
Long term* clozapine + conventional	Long term* clozapine monotherapy
Long term* atypical + atypical and no exposure to clozapine at any time	Long term* atypical monotherapy and no exposure to clozapine
Long term* atypical + conventional and no exposure to clozapine at any time	Long term* monotherapy and no exposure to clozapine**
Long term* conventional + conventional and no exposure to clozapine at any time	Long term* conventional monotherapy and no exposure to clozapine

* Long Term is defined as use for at least 2 months

** Separate analysis was performed comparing long term atypical+conventional therapy with atypical monotherapy and conventional monotherapy

Table 5.3: Initial list of candidate factors associated with antipsychotic polypharmacy

Demographics	Drug overdose
Age, Gender, Race	Opthalmologic disease
Eligibility categories	Anxiety states
Medicare eligible, Aid category (Aged, blind, disabled)	Number of comorbidities per patient
Diagnosis related comorbidities	**Drug classes**
Congestive heart failure	4 Cardiac drug classes
Myocardial infarction	Parkinson's disease
Cardiac arrhythmias	Peripheral vascular disorder
Valvular disease	Hypertension
Peripheral vascular disorders	3 Respiratory classes
Hypertension	Insulin dependent diabetes*
Hemiplegia/paraplegia	> Oral hypoglycemic
Epilepsy*	Cancer
> Other neurological disorders	3 Epilepsy drug classes
Chronic pulmonary disease	Glaucoma
Asthma	Gout
Tuberculosis	Hyperlipidemia, hypercholesterolemia
Diabetes, uncomplicated*	Thyroid disorders
> Diabetes complicated	Menopause (HRT)
Thyroid disorder	Allergy
Renal failure and chronic disorders	Anxiety
Liver disease	Pain (terminal) Narcotic analgesic
Peptic ulcer disease	Depression
AIDS	Dementia/ Alzheimer's
Metastatic solid tumor*	Tuberculosis
> Any malignancy	Rheumatologic drugs/ Crohn's disease/ Ulcerative colitis
Rheumatoid arthritis / collagen vascular disease	Migraine
Coagulopathy	ESRD/ Transplant
Obesity	Number of Rx classes per patient (Mean)
Weight loss/malnutrition	**Antipsychotic agents, mood stabilizer**
Fluid and electrolyte disorders	Atypicals, Conventionals
Anemias	Olanzapine, Risperidone, Quetiapine, Clozapine
Sickle cell anemia	Haloperidol oral & injectable, Fluphenazine oral and injectable
Drug abuse*	Thioridazine, Chlorpromazine, Thiothixene
> Alcohol abuse	Lithium
Bipolar and manic depressive*	**Prior health care utilization, date variables**
> Other psychoses/ Mixed psychoses	Mental health cost in prior period
> Other mental disorders	Number of psychiatric outpatient physician visits, physician specialty
> Personality disorders	Psychiatric inpatient episode, latest inpatient days, cumulative inpatient days
> Depression or schizoaffective	Antipsychotic regular use (antipsychotic Rx every 2 months)
Cerebrovascular disease	Quarter in which episode started

Alzheimer's disease*	Year in which episode started
> Non Alzheimer's dementia	**Social**
Non-head trauma	Marital status, employment status
Head trauma	

> Indicates a hierarchy in relation to the higher cost category denoted by an asterisk (*). If both comorbidities are present, count only the higher cost category

Table 5.4: Group comparisons before and after propensity score matching

	BEFORE PROPENSITY MATCHING				AFTER PROPENSITY MATCHING			
	Poly	Mono			Poly	Mono		
	N = 4,665	N = 6,955		Standardized	N = 1,593	N = 1,593		Standardized
Demographics and eligibility	% prevalence or mean	% prevalence or mean	2-sample t-statistic	difference in %**	% prevalence or mean	% prevalence or mean	2-sample t-statistic	difference in %**
Georgia Medicaid Eligible	42.0	64.3	24.2	-46.0	56.3	55.1	-0.7	2.4
Age as of January 1, 1998 (Years)	43.5	46.2	10.7	-19.9	44.9	44.9	-0.2	0.6
Male	53.5	45.0	-9.1	17.2	48.8	48.9	0.1	-0.2
White	48.6	42.1	-6.8	12.9	42.9	42.9	0.0	0.0
Medicare eligible	58.9	62.0	3.4	-6.4	61.3	60.3	-0.6	2.2
Medicaid aid category - disabled	99.0	97.4	-6.7	12.1	98.1	97.9	-0.4	1.4
Diagnosis variables								
Myocardial Infarction	0.3	0.2	-0.1	0.4	0.2	0.3	0.4	-1.3
Arrhythmia	3.0	1.8	-4.2	8.1	2.1	2.0	-0.4	1.3
Valvular disease	0.8	0.7	-0.3	0.6	0.8	0.7	-0.2	0.7
Hypertension	24.4	24.2	-0.3	0.6	23.7	21.1	-1.7	6.2
Hemiplegia	1.5	1.1	-1.9	3.6	1.3	1.3	0.0	0.0
Epilepsy	11.5	3.9	-14.6	28.8	5.9	6.4	0.6	-2.1
Other neurological disorders	5.5	4.1	-3.6	6.8	4.5	4.0	-0.7	2.5
Chronic obstructive pulmonary disease	11.1	6.9	-7.7	14.8	9.0	8.7	-0.4	1.3
Asthma	2.4	1.8	-2.2	4.2	2.4	2.0	-0.7	2.6
Thyroid disorder	3.8	2.6	-3.5	6.8	2.7	3.0	0.4	-1.5
Renal failure and chronic disorders	0.5	0.5	-0.4	0.7	0.4	0.4	-0.3	0.9
Liver disease	0.7	0.7	-0.2	0.4	0.5	0.7	0.7	-2.5
Obesity	2.6	1.9	-2.6	4.9	2.2	2.3	0.1	-0.4
Weight loss	0.3	0.2	-1.4	2.7	0.3	0.2	-0.4	1.3
Anemia	6.7	4.6	-4.6	8.9	4.5	5.2	0.9	-3.2
Drug abuse	2.8	2.6	-0.5	1.1	2.6	3.0	0.5	-1.9
Alcohol abuse	1.1	1.6	2.1	-4.0	1.5	1.5	0.0	0.0
Other psychoses/ Mixed psychoses	14.3	9.8	-7.1	13.7	12.0	11.7	-0.2	0.8
Other mental disorder	20.7	18.6	-2.8	5.3	20.4	19.8	-0.4	1.4

Personality disorder	0.2	6.0	0.3	-24.5	5.2	4.6	-0.8	2.9
Schizoaffective disorder	20.8	18.2	-3.4	6.5	18.5	20.3	1.3	-4.6
Alzheimer's disease	0.2	0.2	0.7	-1.2	0.1	0.1	-0.6	2.3
Non Alzheimer dementia	1.3	1.6	1.3	-2.3	1.3	1.6	0.6	-2.1
Head trauma	2.1	1.6	-1.9	3.7	1.6	2.0	0.8	-2.9
Opthalmologic diseases	14.0	9.5	-7.3	14.0	10.6	11.5	0.9	-3.0
Anxiety states	2.1	1.8	-1.2	2.3	2.1	2.0	-0.3	0.9
Drug use variables								
Cardiac 1 (Antiarrhythmic, inotropic, vasopressors)	9.3	10.4	2.0	-3.7	9.9	9.5	-0.4	1.3
Parkinsons disease	73.4	48.4	-28.4	53.1	61.8	62.5	0.4	-1.5
Peripheral vascular disease	2.3	3.1	2.7	-4.9	2.6	2.5	-0.1	0.4
Cancer	1.3	0.9	-2.0	3.9	0.7	1.1	1.1	-4.0
Epilepsy A (Anticonvulsants - hydantoin, succinimide, oxazolidinidione)	3.8	4.7	2.5	-4.7	4.0	3.6	-0.7	2.3
Epilepsy 1 (Barbiturates, certain benzodiazepines)	47.1	27.8	-21.7	40.6	35.2	37.4	1.3	-4.7
Glaucoma	1.1	1.6	2.2	-4.0	1.3	1.4	0.2	-0.5
Gout	0.7	0.8	0.7	-1.4	0.8	0.9	0.4	-1.3
Hyperlipidemia, hypercholesterolemia	6.9	6.5	-0.9	1.8	6.6	6.7	0.1	-0.2
Thyroid disorder	8.1	5.8	-4.8	9.3	5.9	6.2	0.3	-1.1
Allergy	10.3	9.9	-0.6	1.1	10.0	10.7	0.6	-2.3
Anxiety	9.3	5.9	-8.2	12.7	7.3	7.8	0.5	-1.9
Pain (Terminal)	0.3	0.4	0.5	-1.3	0.4	0.6	0.5	-1.7
Depression	43.4	39.0	-5.0	8.9	41.8	42.1	0.2	-0.6
Alzheimer's / dementia	0.2	0.4	2.1	-3.6	0.4	0.4	0.0	0.0
Tuberculosis	0.4	0.2	-2.8	3.9	0.4	0.4	-0.3	0.9
Migraine	0.2	0.2	-0.7	0.3	0.3	0.4	0.3	-1.2
Number of drug classes	3.8	3.1	-14.7	27.4	3.4	3.4	0.1	-0.2
Antipsychotic use								
Olanzapine	43.1	16.1	-32.2	61.3	26.0	27.8	1.1	-4.0
Risperidone	26.3	16.3	-13.0	24.1	20.5	19.8	-0.5	1.9
Haloperidol oral	24.0	13.6	-13.9	26.8	17.0	17.4	0.3	-1.2
Haloperidol injectable	13.7	5.1	-15.1	29.7	8.0	9.0	1.1	-3.8

Thioridazine	12.8	6.5	-11.1	21.5	9.4	7.3	-2.1	7.3
Quetiapine	10.3	1.0	-20.1	40.9	2.3	2.6	0.6	-2.0
Fluphenazine oral	12.5	6.1	-11.3	21.9	8.8	7.7	-1.1	3.9
Clozapine	11.4	6.9	-8.0	15.5	7.6	6.0	-1.8	6.5
Fluphenazine injectable	10.4	4.9	-10.8	21.0	7.3	7.1	-0.2	0.7
Chlorpromazine	10.8	2.2	-17.7	35.6	3.6	4.3	1.1	-3.8
Thiothixene	7.3	4.2	-6.8	13.2	5.2	4.0	-1.6	5.7
Lithium	12.4	7.4	-9.1	16.5	10.7	10.5	-0.2	0.6
Prior utilization and temporal variables								
Total cost $ 2000 (Mean)	6,283.0	4,773.0	-11.6	22.2	5,438.0	5,368.0	-0.1	1.0
Mental health cost $ 2000 (Mean)	4,271.0	2,748.0	-15.2	29.3	3,493.0	3,478.0	-0.1	0.3
Psychiatric outpatient physician visits (Mean)	1.9	1.1	-11.3	22.5	1.2	1.1	-0.3	1.1
Duration of latest hospitalization (Mean days)	2.0	1.1	-6.3	12.0	1.8	2.0	0.5	-1.8
Cumulative inpatient days in prior period (Mean days)	2.5	1.4	-6.7	12.9	2.1	2.3	0.6	-2.0
Antipsychotic regular users in prior period (Antipsychotic Rx every 2 months)	86.3	61.8	-31.8	58.1	75.7	72.8	-1.9	6.6
Psychiatric inpatient episode	14.2	8.2	-9.9	19.2	11.3	12.5	1.0	-3.7
Index date in july, august or september	47.3	64.1	18.0	-34.2	50.7	48.1	-1.5	5.1
Index date in october, november or december	21.7	15.9	-7.8	14.9	20.5	22.2	1.2	-4.3
Episode in year 1999	47.9	29.1	-20.6	39.4	44.0	47.2	1.8	-6.4
Episode in year 2000	7.3	5.7	-3.3	6.3	5.7	5.7	0.1	-0.3
Logit of propensity score	2.0	-2.2	-93.2	183.8	-0.5	-0.5	-0.1	0.2

*For categorical variables: Value "1" if subject belongs to the variable category, else "0"

** The standardized difference in % is the mean difference as a percentage of the average standard deviation: 100*(TM - CM)/Sqrt{(TV - CV)/2}

TM & CM = Sample means for the covariate in the treated (TM) and control (CM) groups

TV & CV = Sample variance for the covariate in the treated (TV) and control (CV) groups

Table 5.5: One-year total cost comparisons for long-term antipsychotic polypharmacy before and after propensity score matching

	PRIOR TO MATCHING			AFTER MATCHING
	Mean Expenditure ($)	Mean Expenditure ($)	Net expenditure	Net expenditure
Duration	Polypharmacy	Monotherapy	(95% CI)	(95% CI)
	n = 4,665	n = 6,955		n = 3,186
Prescription	6,555	3,192	3,363 (3,220 to 3,506)	1,876 (1,550 to 2,201)
Physician	449	396	53 (11 to 95)	5 (-73 to 83)
Inpatient	1,179	900	279 (51 to 507)	-242 (-726 to 242)
Long-term care	2,503	2,707	-204 (-523 to 115)	-354 (-920 to 213)
Outpatient	2,761	2,571	190 (-45 to 424)	430 (-20 to 880)
Other	444	296	148 (91 to 205)	-16 (-121 to 88)
TOTAL	13,891	10,062	3,829 (3,347 to 4,310)	1,699 (760 to 2,638)

Table 5.6: One-year total cost comparisons by antipsychotic polypharmacy subgroups before and after propensity score matching

	PRIOR TO MATCHING			AFTER MATCHING
	Mean Expenditure ($) Polypharmacy	Mean Expenditure ($) Monotherapy	Net expenditure (95% CI)	Net expenditure (95% CI)
Clozapine+atypical	n = 183	n = 506		n = 108
Prescription	10,487	6,813	3,674 (3,152 to 4,196)	4,103 (2,862 to 5,344)
Physician	401	285	116 (-11 to 243)	76 (-336 to 488)
Inpatient	862	712	150 (-569 to 870)	-798 (-1,911 to 315)
Long-term care	1,619	1,228	391 (-937 to 1,718)	339 (-1,877 to 2,555)
Outpatient	3,514	3,870	-356 (-1,535 to 823)	-1,582 (-3,489 to 326)
Other	584	417	167 (-117 to 450)	628 (-149 to 1,404)
TOTAL	17,467	13,325	4,142 (2,143 to 6,140)	2,765 (-835 to 6,366)
Clozapine+ conventional	n = 137	n = 506		n = 212
Prescription	8,159	6,813	1,347 (775 to 1,919)	829 (-56 to 1,715)
Physician	255	285	-30 (-157 to 98)	-42 (-275 to 192)
Inpatient	532	712	-180 (-951 to 591)	110 (-198 to 418)
Long-term care	1,855	1,228	626 (-911 to 2,164)	-471 (-2,244 to 1,302)
Outpatient	2,391	3,870	-1479 (-2,704 to -253)	1,398 (580 to 2,215)
Other	497	417	79 (-221 to 379)	-128 (-591 to 336)
TOTAL	13,689	13,325	364 (-1,840 to 2,567)	1,697 (-628 to 4,023)
Atypical+ atypical	n = 341	n = 2,956		n = 378
Prescription	8,666	4,291	4,375 (3,994 to 4,755)	4,013 (3,373 to 4,653)
Physician	528	454	74 (-63 to 211)	182 (-205 to 569)
Inpatient	921	1,151	-229	321

			(-880 to 421)	(-874 to 1,516)
Long-term care	1,706	2,772	-1,067 (-2,031 to -103)	-692 (-2,214 to 830)
Outpatient	2,094	2,876	-782 (-1,513 to -51)	548 (-423 to 1,520)
Other	408	296	112 (-62 to 285)	-163 (-538 to 213)
TOTAL	14,322	11,840	2,482 (1,053 to 3,912)	4,210 (1,742 to 6,678)
Conventional+ conventional	n = 280	n = 3,034		N = 296
Prescription	2,691	1,430	1,261 (973 to 1,549)	1,266 (769 to 1,763)
Physician	443	350	92 (-20 to 205)	35 (-169 to 239)
Inpatient	838	748	91 (-649 to 830)	413 (-164 to 990)
Long-term care	2,182	2,723	-541 (-1,583 to 502)	1,071 (-714 to 2,856)
Outpatient	3,235	2,291	945 (276 to 1,613)	898 (-545 to 2,340)
Other	308	270	38 (-121 to 197)	-401 (-977 to 174)
TOTAL	9,697	7,812	1,886 (420 to 3,351)	3,281 (834 to 5,728)
Atypical+ conventional vs atypical	n = 2,474	n = 2,956		N = 1,248
Prescription	5,535	4,291	1,244 (1,074 to 1,414)	820 (462 to 1,178)
Physician	471	454	16 (-48 to 81)	69 (-82 to 220)
Inpatient	1,244	1,151	93 (-246 to 433)	23 (-549 to 596)
Long-term care	2,711	2,772	-62 (-533 to 409)	-333 (-1,253 to 587)
Outpatient	3,019	2,876	143 (-226 to 512)	-40 (-752 to 672)
Other	469	296	173 (82 to 263)	166 (6 to 326)
TOTAL	13,448	11,840	1,608 (896 to 2,320)	706 (-611 to 2,022)
Atypical+ conventional vs conventional	n = 2,474	n = 3,034		N = 1,090
Prescription	5,535	1,430	4,105 (3,963 to 4,246)	2,940 (2,482 to 3,398)

Physician	471	350	120 (62 to 179)	59 (-55 to 172)
Inpatient	1,244	748	497 (150 to 843)	-944 (-2,113 to 224)
Long-term care	2,711	2,723	-12 (-477 to 453)	388 (-634 to 1,410)
Outpatient	3,019	2,291	728 (407 to 1,049)	383 (-274 to 1,040)
Other	469	270	199 (114 to 283)	115 (-56 to 285)
TOTAL	13,448	7,812	5,636 (4,956 to 6,316)	2,940 (1,141 to 4,739)

Table 5.7: One-year mental health cost comparisons before and after propensity score matching

	PRIOR TO MATCHING			AFTER MATCHING
	Mean Expenditure ($) Polypharmacy	Mean Expenditure ($) Monotherapy	Net expenditure (95% CI)	Net expenditure (95% CI)
Long-term polypharmacy	n = 4,665	n = 6,955		n = 3,186
	9,450	5,594	3,856 (3,534 to 4,178)	1,717 (1,064 to 2,369)
Clozapine+atypical	n = 183	n = 506		N = 108
	14,092	10,476	3,616 (2,278 to 4,954)	3,463 (269 to 6,657)
Clozapine+ conventional	n = 137	n = 506		n = 212
	10,355	10,476	-121 (-1,567 to 1,324)	1,487 (-172 to 3,146)
Atypical+atypical	n = 341	n = 2,956		n = 378
	10,450	6,854	3,597 (2,747 to 4,446)	3,014 (1,475 to 4,552)
Conventional+ conventional	n = 280	n = 3,034		n = 296
	4,527	3,837	691 (-321 to 1,703)	1,411 (-109 to 2,930)
Atypical+ conventional vs atypical	n = 2,474	n = 2,956		n = 1,248
	8,748	6,854	1,894 (1,433 to 2,355)	389 (-462 to 1,240)
Atypical+ conventional vs conventional	n = 2,474	n = 3,034		N = 1,090
	8,748	3,837	4,911 (4,434 to 5,388)	3,379 (1,975 to 4,783)

Table 5.8: Two-year total cost comparisons before and after propensity score matching

	PRIOR TO MATCHING			AFTER MATCHING
	Mean	Mean		
	Expenditure	Expenditure		
	($)	($)	Net expenditure	Net expenditure
	Poly	Mono	(95% CI)	(95% CI)
Long-term polypharmacy	n = 4,665	n = 6,955		n = 1,736
	25,232	18,409	6,823 (5,765 to 7,882)	4,153 (1,675 to 6,631)
Clozapine+atypical	n = 183	n = 506		n = 78
	34,554	25,044	9510 (4,397 to 14,622)	11,114 (3,351 to 18,878)
Clozapine+ conventional	n = 137	n = 506		n = 126
	26,980	25,044	1,936 (-3,330 to 7,202)	2,275 (-4,150 to 8,699)
Atypical+atypical	n = 341	n = 2,956		n = 118
	29,739	23,628	6,112 (1,882 to 10,342)	9,611 (1,822 to 17,399)
Conventional+ conventional	n = 280	n = 3,034		n = 186
	19,970	15,429	4,541 (1,107 to 7,975)	5,921 (-463 to 12,305)
Atypical+ conventional vs atypical	n = 2,474	n = 2,956		n = 582
	26,558	23,628	2,931 (1,168 to 4,694)	3,621 (-454 to 7,696)
Atypical+ conventional vs conventional	n = 2,474	n = 3,034		n = 416
	26,558	15,429	11,129 (9,454 to 12,805)	9,322 (3,990 to 14,655)

Table 5.9: Annualized expenditures incurred during the episode or episode costs

	PRIOR TO MATCHING			AFTER MATCHING
	Mean	Mean		
	Expenditure	Expenditure		
	($)	($)	Net expenditure	Net expenditure
	Poly	Mono	(95% CI)	(95% CI)
Long-term	14,731	10,287	4,444 (3,950 to 4,939)	2,191 (1,210 to 3,173)
Clozapine+atypical	18,248	12,387	5,861 (4,121 to 7,600)	2,408 (-1,906 to 6,722)
Clozapine+ conventional	13,795	12,387	1,408 (-468 to 3,284)	1,842 (-452 to 4,136)
Atypical + atypical	15,735	12,241	3,494 (2,084 to 4,904)	5,154 (2,627 to 7,682)
Conventional+ conventional	9,430	7,975	1,455 (-26 to 2,935)	2,974 (460 to 5,487)
Atypical+ conventional vs atypical	14,309	12,241	2,068 (1,348 to 2,789)	1,477 (68 to 2,886)
Atypical+ conventional vs conventional	14,309	7,975	6,334 (5,634 to 7,034)	3,608 (1,799 to 5,417)

Table 5.10: Unadjusted, propensity score matched and Heckman 2-stage estimated net one-year polypharmacy expenditure

	UNADJUSTED	PROPENSITY MATCHED	HECKMAN 2-STAGE ESTIMATED
	Net expenditure (95% CI)	Net expenditure (95% CI)	Net expenditure (95% CI)
Long-term polypharmacy	3,829 (3,347 to 4,310)	1,699 (760 to 2,638)	1,765 (1,353 to 2,177)
Clozapine+atypical	4,142 (2,143 to 6,140)	2,765 (-835 to 6,366)	5,179 (3,012 to 7,346)
Clozapine+ conventional	364 (-1,840 to 2,567)	1,697 (-628 to 4,023)	-3,534 (-6,210 to –858)
Atypical+atypical	2,482 (1,053 to 3,912)	4,210 (1,742 to 6,678)	2,337 (1,129 to 3,545)
Conventional+ conventional	1,886 (420 to 3,351)	3,281 (834 to 5,728)	1,401 (503 to 2,299)
Atypical+ conventional vs atypical	1,608 (896 to 2,320)	706 (-611 to 2,022)	567 (-149 to 1,283)
Atypical+ conventional vs conventional	5,636 (4,956 to 6,316)	2,940 (1,141 to 4,739)	3,393 (2,738 to 4,048)

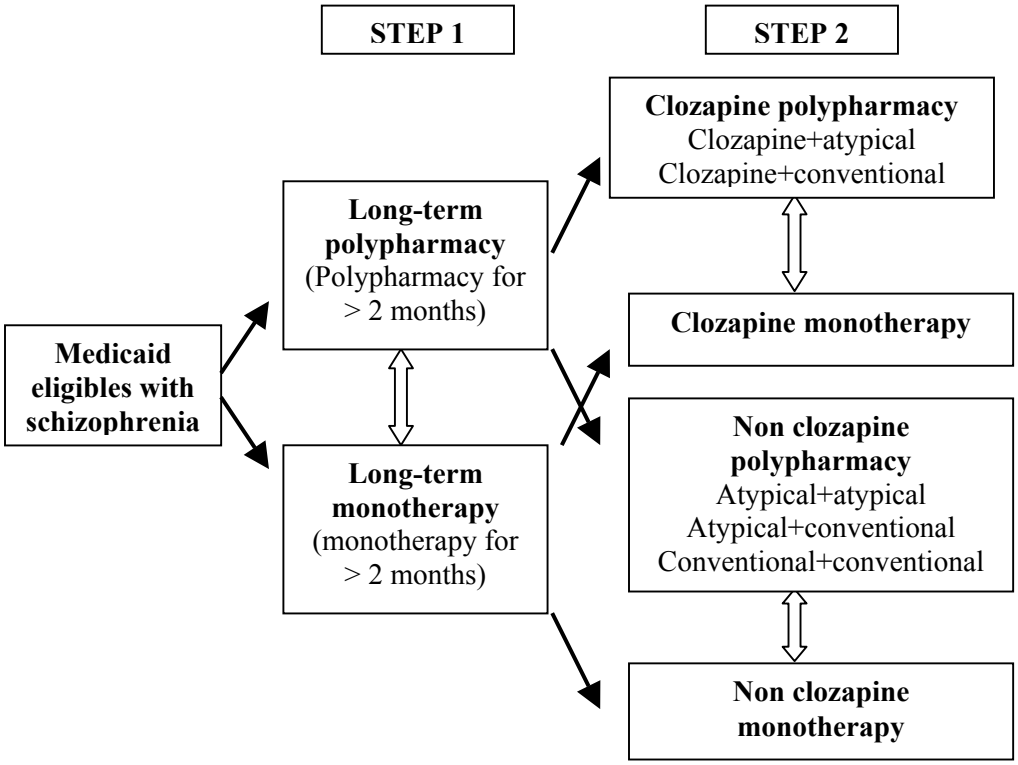

Figure 5.1: Different forms of antipsychotic polypharmacy and monotherapy

CHAPTER 6

ASSOCIATION BETWEEN LONG-TERM ANTIPSYCHOTIC POLYPHARMACY AND COMMUNITY TENURE AMONG MEDICAID ELIGIBLE SCHIZOPHRENIA PATIENTS[1]

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ABSTRACT

Background Antipsychotic polypharmacy or concomitant use of multiple antipsychotics is prevalent in up to 40% of schizophrenia patients despite lack of clinical evidence or support from treatment guidelines. The objective of our study was to estimate the association between long-term antipsychotic polypharmacy and one-year community tenure, defined as time to first hospitalization episode within a one-year period.

Methods A retrospective cohort study was designed and Medicaid recipients >= 16 years of age with a primary diagnosis of schizophrenia (ICD-9-CM=295.**) between 1998-2000 were identified from the Georgia and California (20% random sample) Medicaid claims databases. 6 antipsychotic polypharmacy cohorts e.g. long-term polypharmacy i.e. duration of use > 2 months, clozapine (2 subtypes), non-clozapine (3 subtypes) and corresponding monotherapy cohorts were built. Annual outcomes were compared between propensity score matched long-term antipsychotic polypharmacy (experimental group) and monotherapy (control group) subjects using survival analysis to estimate differences in community tenure and hospitalization risk.

Results Out of a total of 31,435 persons with schizophrenia (Mean age 43 years, female: 49%, white: 47%), 4,665 met inclusion criteria for long-term antipsychotic polypharmacy and 6,955 for monotherapy. 3,186 patients in 1,593 pairs treated with long-term antipsychotic polypharmacy or monotherapy were matched for all covariates using propensity scoring. Mean community tenure for polypharmacy was 319 days compared with 336 for monotherapy. Long-term antipsychotic polypharmacy was associated with a higher likelihood of one-year (1.25, 95% CI 1.09 TO 1.41) and two-year (1.45, 95% CI 1.27 to 1.63) hospitalization. Among subgroups, atypical+atypical (mental health related hospitalizations) and atypical+conventional (two-year period) were associated with a higher likelihood of hospitalization.

Conclusion In this observational study long-term antipsychotic polypharmacy was associated with an increased risk of one-year and two-year hospitalization after adjustment for selection bias. These findings raise concerns about the benefit of long-term antipsychotic polypharmacy in the treatment of schizophrenia patients.

Keyword: Polypharmacy, Antipsychotic, Hospitalization, Community tenure, Medicaid, Schizophrenia

INTRODUCTION

Antipsychotic polypharmacy or concomitant use of multiple antipsychotics in schizophrenia is regarded as one of the "most practiced and least investigated phenomena in clinical psychopharmacology" (Stahl 2000). It is estimated that antipsychotic polypharmacy is prescribed for up to 40% of schizophrenia patients (Canales 1999). However there are no randomized controlled trials of combination therapy except one with sulpiride and clozapine, which provides little guidance in the U.S. since sulpiride is not available in the US (Yuzda 2000). Apart from this study, there are case reports (Stubbs 2000,Lerner 2000,Chue 2001,Mujica 2001,Rhoads 2000,Raskin 2000,Morera 1999,Cooke 1999,Gupta 1998) and open uncontrolled nonrandomized trials (Taylor 2001,Kapur 2001,de groot 2001,Waring 1999,Waddington 1998) that report the effects of antipsychotic polypharmacy. Almost half of these studies report an increased incidence of adverse events such as prolactin elevation, akathisia, hyper salivation (Yuzda 2000, Kapur 2001, Cooke 1999, Degroot 2001) and even an increased risk of mortality (Waddington 1998, n=88, RR: 2.46) and the rest report improvement in symptoms over baseline. However, it should be noted that besides the obvious design limitations of such uncontrolled trials, these studies were limited by small sample sizes (most of them are 1 or 2 patient case reports) and incomplete reporting of adverse effects. The recent introduction of four new antipsychotics (e.g. olanzapine-

1996, quetiapine-1997, ziprasidone–2001, aripiprazole-2003) with differing receptor profiles have further increased the possibilities of combining these agents.

Community tenure or 'time to first hospitalization' is an important outcome of treatment given the shift in the locus of care from institutional to community based programs and the growing importance of the philosophy of community integration in the mental health field. In essence community tenure reflects the effectiveness of the treatment in preventing or delaying symptom exacerbation and relapses that result in hospitalizations. Information on the effect of antipsychotic polypharmacy on community tenure would help physicians choose appropriate therapy that would that would reduce risk of hospitalization and increase the chances of keeping the patients out in the community. ‘Community tenure’ has been used as an outcome measure in previous studies and is also referred to as ‘community survival’ (Hunt 2002) or ‘time in the community before relapse’ (Appleby 1993).

The objective of our study was to estimate the association between long-term antipsychotic polypharmacy and one-year community tenure. Differences in annual outcome between a long-term antipsychotic polypharmacy patient (experimental subject) and monotherapy patient (comparison subject) provided an estimate of association between long-term antipsychotic polypharmacy and community tenure.

METHODS

Data sources

A retrospective observational non-equivalent control group design was employed using a combined two-state Medicaid database. We built a 3-year (1998 to 2000) two-state Medicaid database using three sources, the Georgia Medicaid files maintained by the Georgia Department of Medical Assistance (GDMA), Georgia state based institutional data files maintained by the Department of Human Resources (DHR) and California Medicaid 20% sample (Medi-Cal). The Medicaid files contain eligibility details,

demographics and claims history for various health care services, including Medicaid paid amount, outpatient prescription drugs, inpatient stays, and disease diagnosis. A common resource available to Georgia Medicaid patients are the 8 psychiatric hospitals managed by the Department of Human Resources (DHR) which do not bill Medicaid for services rendered to persons age 21 to 64 years. Records from all these 8 hospitals were combined to form the DHR file that contains a system wide record of each visit a patient received at any one of the 8 system inpatient institutions in operation. To capture psychiatric episodes of care, the DHR files (state based institutional data) were linked by patient identifiers to the GDMA files (Georgia Medicaid claims data). This patient linked or merged data provides a complete picture of the medical resources consumed for each Medicaid eligible patients with schizophrenia in Georgia. California Medicaid reimburses 4 state psychiatric hospitals for inpatient services rendered to Medicaid eligibles so there was no need to link state psychiatric hospitals with the claims data.

The Georgia (Martin 1998; Kotzan 1999; Martin 2001) and California (McCombs 1999, Ganguly 2001, Malkin 2002) Medicaid data have been used in the past for epidemiological studies and have been found to be valid.

Study population

Persons with primary diagnosis of schizophrenia (ICD-9-CM = 295.**) recorded on at least one paid claim during the period Jan 1998 through Dec 2000 and at least 16 years of age as of Jan 1st 1998 were identified. After identifying the schizophrenia patients, long-term antipsychotic polypharmacy and monotherapy episodes for each person was identified.

The Journal of Clinical Psychiatry treatment guideline (McEnvoy, 1999) is the only guideline that offers guidance on the duration of antipsychotic polypharmacy, and that guideline does not recommend long-term antipsychotic polypharmacy for more than 8 weeks or 2 months. Based on that guideline, long-term antipsychotic polypharmacy

was defined as two or more chemically distinct antipsychotics prescribed concurrently where there is an overlap of 2 months or more of therapy taken concurrently. The list of antipsychotics has been provided in table 6.1. Concurrent therapy of 2 months between consecutive or concurrent prescription fill dates were identified by estimating the days supply for each antipsychotic prescription filled for each person and comparing that to dates antipsychotic prescriptions are filled. The first day of that episode (defined below) of overlap or concurrent use of the two antipsychotics was considered as the episode start date for that long-term antipsychotic polypharmacy episode.

An episode of long-term antipsychotic polypharmacy was defined as a period of continuous, antipsychotic polypharmacy, without a break period of 31 or more days (Svarstad 2001). A break period was defined as a period when the patient had no supply of drugs. Hospital stays that occurred within 31 days of an antipsychotic use period were considered as a continuation of the preceding episode and not a part of the break period if the therapy remained the same after discharge.

Antipsychotic use episodes where a single antipsychotic was prescribed for 2 months or more without a break period of 31 or more days was referred to as monotherapy episodes.

Long-term antipsychotic polypharmacy was further classified in a hierarchical fashion, narrowing the definition of antipsychotic polypharmacy with each consecutive step in accordance with published treatment guidelines into 6 groups – long-term, clozapine+atypical, clozapine+conventional, atypical+atypical, atypical+conventional, conventional+conventional (Figure 1).

A single longest episode of antipsychotic polypharmacy or monotherapy i.e. period of maximum exposure to treatment, between 1998 and 2000 was identified for each patient in the antipsychotic polypharmacy and monotherapy cohort such that the patients had continuous Medicaid eligibility and at least one paid claim in every 90 day

window during the 6 months period preceding and one year period following the start of the this episode. This 6-month 'prior' period was used to collect health care utilization information to adjust for selection bias and the one-year observation period was used to compare outcome. The 90-day window criterion (McCombs 1999) was used to ensure persons that are eligible for Medicaid benefits have not withdrawn from the system (e.g. prison).

Those who were never exposed to long-term antipsychotic polypharmacy were grouped into a monotherapy cohort and were further classified into unique monotherapy cohorts depending on the duration and type of monotherapy of the selected episode (Table 6.2). Antipsychotic polypharmacy cohorts were similarly created using the selected longest episode where subjects who had at least one long-term antipsychotic polypharmacy episode were grouped into the ‘long-term polypharmacy’ cohort. Long-term users were further subdivided into clozapine users and non clozapine users as clozapine is usually reserved for treatment resistant patients. These two groups were further divided by class of antipsychotic used in combination. Each of the antipsychotic polypharmacy groups identified above had a corresponding monotherapy comparison group described in table 6.2.

Measurement of outcome

Community tenure was defined as the number of days from the start of a treatment episode to the start of the first hospitalization episode. A hospitalization episode was defined as an inpatient visit with at least one day between admission and discharge. ‘Community tenure’ has been used as an outcome measure in previous studies and is also referred to as ‘community survival’ (Hunt 2002) or ‘time in the community before relapse’ (Appleby 1993). The initial analysis did not distinguish between mental health or non mental health related hospitalizations and the first hospitalization could be any hospitalization for the initial analysis. However a sensitivity

analysis was performed restricting the definition of first hospitalization to mental health (and substance abuse) related hospitalizations.

Estimating propensity score

Selection bias is commonly encountered in observational studies as the treatment selection is nonrandom and is confounded with patient factors that are also related to outcome. For e.g. patients with more severe exacerbations maybe more likely to be selected for antipsychotic polypharmacy and are also more likely to have relapses in the future. The propensity score matching technique is commonly used to reduce selection bias and estimate effect of treatment in health services research (D'Agostino 1998;Stone 1995;Connors 1996;Reinisch 1995). It has also been used in some recent studies in schizophrenia patients (Sernyak 2001a; Sernyak 2001b; Irish 2002). The basic idea of propensity score methods is to replace the collection of observed confounding covariates or patient factors with one scalar function of these covariates, called the propensity score i.e. in this case the propensity to receive long-term antipsychotic polypharmacy rather than monotherapy. An long-term antipsychotic polypharmacy patient is then paired with a monotherapy patient with similar propensity score and a matched pair analysis is performed to estimate the relative effect of long-term antipsychotic polypharmacy on the outcome.

A comprehensive list of all potential confounders or variables that relate to both treatment choice (long-term antipsychotic polypharmacy) and outcome (community tenure) was identified by a survey of published literature and expert opinion (Table 6.3). This list included demographics, diagnosis related comorbidities, drug classes, antipsychotic agents and prior health care utilization variables. The list of diagnosis related comorbidities and drug classes were obtained from a cost prediction model for schizophrenia patients. This model has been developed and validated on the Georgia Medicaid database as a part of an AHRQ (Agency for Health Care Research and

Quality) project. The month and year of the episode start date was also included to identify any year wise or seasonal trend in use. The list of antipsychotic agents consisted of the ten most prevalent drugs identified from a frequency analysis of the prior period prescription records. Haloperidol and fluphenazine were categorized by mode of administration as the injectable form is generally prescribed to a less compliant group of patient (McEnvoy, 1999) and compliance in turn may be an important factor associated with choice of therapy.

A stepwise logistic variable selection procedure was used to model the binary treatment indicator (1 = long-term antipsychotic polypharmacy, 0 = monotherapy) and main effects of covariates were entered into the model if they are significant at 0.50 level (Rosenbaum 1984; D'Agostino 1998). The probability of long-term antipsychotic polypharmacy (from 0 to 1), the propensity score, was determined for each patient.

A new set of propensity scores were obtained for each set of comparisons e.g. long term long-term antipsychotic polypharmacy vs. long term monotherapy, as propensity for a different type of antipsychotic polypharmacy is different for each comparison.

Matching long-term antipsychotic polypharmacy and monotherapy subjects based on propensity score

After estimating the propensity score for each patient in the long-term antipsychotic polypharmacy and monotherapy groups, each long-term antipsychotic polypharmacy patient was matched with one monotherapy patient with similar propensity score. Matching was accomplished using the 'nearest available metric matching within calipers defined by propensity score' technique (D'Agostino 1998). This technique has been found to produce the best balance between the covariates in the treated and comparison groups (D'Agostino 1998, Rosenbaum 1985). Long-term antipsychotic polypharmacy subjects were randomly ordered and the first subject was selected, all

monotherapy subjects within a caliper of the selected long-term antipsychotic polypharmacy subjects' logit of the propensity score were selected, Mahalonobis distance was calculated between the long-term antipsychotic polypharmacy subject and the selected monotherapy subjects and the monotherapy subject with smallest distance was retained as a match. This process was continued until all possible pairs were identified.

Two-sample t-statistic and standardized percentage differences were calculated to explore the differences in distribution of the selected covariates between the antipsychotic polypharmacy and monotherapy groups (D'Agostino, 1998) prior to matching and after matching.

Analysis

SAS software Version 8.02 (SAS 2002) was used to manage the data and perform statistical analysis. Community tenure (number of days to first admission), a corresponding censoring status variable (1 = not censored, 0 = censored or no admission within 1 year period) and a treatment variable (1 = long-term antipsychotic polypharmacy, 0 = monotherapy) were used to perform the survival analytic procedure (Allison 1997). Mean and standard deviation for community tenure was reported for the unmatched and matched long-term antipsychotic polypharmacy and monotherapy groups using Kaplan-Meier estimator (PROC LIFETEST). Long-term antipsychotic polypharmacy and monotherapy groups were compared using the cox proportional hazards model (PROC PHREG) and hazard ratio and 95% confidence intervals for hospitalization were reported.

Sensitivity analysis

A sensitivity analysis was performed restricting the definition of hospital admissions to mental health and substance abuse related hospital admissions. Two-year community tenure and hazard rates associated with the use of long-term antipsychotic

polypharmacy were estimated for a subset of subjects who met the eligibility and claim window criteria for a two-year observation period. Also the observation period was restricted to the duration of the selected episode to estimate the concurrent effects associated with long-term antipsychotic polypharmacy.

Heckman two-stage estimation

Propensity score matching technique controls for observable confounders only, for e.g. those identified in table 6.3 and are recorded on the database. However bias due to unobservable confounders e.g. cognitive status of the patient, may continue to be a concern, especially in the context of administrative databases that have limited direct disease measures. The Heckman two-stage estimation technique may potentially address this concern as it controls for selection bias due to observable confounders in the first stage in a manner similar to propensity scoring and may also account for potential bias due to unobservable confounders that may continue to exist in the second stage. The hazard rates were re-estimated using the heckman two-stage estimation technique and compared with the propensity matched results as a check for validity of the results.

The two-stage estimator was introduced by Heckman (1976) and has been used in the past to estimate effect in health services research (Terza 1999, Treglia 1999, Neslusan 1999). In the first stage the binary outcome of receiving or not receiving long-term antipsychotic polypharmacy was modeled from selected covariates that influence treatment assignment using a probit equation. The vector of coefficients of the covariates estimated through this model was used to calculate the expected value of error (M1). In the second stage community tenure was modeled using the covariates in table 6.3, a dummy variable for treatment assignment (1 if long-term antipsychotic polypharmacy 0 if monotherapy) and M1 the estimate of the expected value of error

obtained from the previous stage. The study was approved by the University of Georgia Institutional Review Board (IRB).

RESULTS

Description of the study population

32,280 subjects (Georgia: 18,373, California: 13,907) had received at least one primary diagnosis of schizophrenia between 1998 and 2000 out of which 31,435, were at least 16 years of age as of Jan 1, 1998. The mean age of the 31,435 subjects with schizophrenia was 43 years (SD: 14 years) (both Georgia and California had mean ages of 43 years), 49% were female (Georgia: 56%, California: 43%) and 47% were white (Georgia: 38%, California: 57%). 7,222 subjects (23%) had been exposed to at least one long-term antipsychotic polypharmacy episode out of which 4,665 subjects met the continuous Medicaid eligibility and 90-day claim window criteria for 6 months preceding and 1 year following episode start date. 6,955 subjects, who had not been exposed to long-term antipsychotic polypharmacy, had at least one long-term monotherapy episode and met the Medicaid eligibility and claim window criteria were retained as potential control subjects.

Patient characteristics

The characteristics of 11,620 patients identified for the study are shown in table 6.4. The long-term antipsychotic polypharmacy cohort had more males (53.5% vs. 45%) and whites (48.6% vs. 42%) whereas the monotherapy cohort was slightly older (mean age: 46 years vs. 43.5 years). 22 covariates had standardized % difference of more than 20%. Long-term antipsychotic polypharmacy patients were less likely to be Georgia Medicaid eligible. They were also more likely to have epilepsy and Parkinson's disease and less likely to have personality disorders. These patients were also more likely to receive most antipsychotics, especially the newer atypicals risperidone and quetiapine.

The prior utilization in terms of total and mental health expenditure, physician visits, inpatient episodes were higher for the long-term antipsychotic polypharmacy group.

Unadjusted outcome

The unadjusted one-year mean community tenure for the long-term antipsychotic polypharmacy group was 23 days less than the monotherapy group (table 6.5). This difference was more pronounced in the two-year (65 days) and episode (78 days) groups. The same trend toward shortened community tenure was observed for the mental health related hospitalizations. The likelihood of being hospitalized was consistently higher for the long-term antipsychotic polypharmacy group in the one-year (24.5% vs. 14.7%), two-year (35.8% vs. 20.2%) and episode duration (17.5% vs. 13.7%) as shown in table 6.6.

Long-term antipsychotic polypharmacy was associated with a significantly higher likelihood of hospitalization compared to monotherapy (pvalue <0.01) in the one-year, two-year and episode periods and the two-year likelihood was the highest, 1.97 (any hospitalization) and 2.23 (mental hospitalization).

Propensity score and adjustment for selection bias

Before matching, long-term antipsychotic polypharmacy patients had a mean propensity score logit 2.01 (mean propensity score of 0.73 i.e. probability of receiving long-term antipsychotic polypharmacy was 0.73), while those on monotherapy had a mean score of -2.22 (mean propensity score of 0.17). 3,186 patients in 1,593 pairs treated with or without long-term antipsychotic polypharmacy were successfully matched for all the covariates using the propensity matching technique. The 22 covariates that had standardized differences of more than 20% before matching had less than 5% difference after matching (table 6.4). Post match standardized difference was highest for Thioridazine (7.3%) and below 5% for almost all the other covariates. The mean propensity score logit was –0.54 after matching for both groups.

Mean community tenure remained shorter for the long-term antipsychotic polypharmacy groups compared with the monotherapy group even after adjustment although the difference was much lesser than the unadjusted results (table 6.5). For e.g. the one-year tenure difference of 23 days (unadjusted) was reduced to 4 days (adjusted).

Long-term antipsychotic polypharmacy was associated with a higher likelihood of hospitalization compared with monotherapy across all observations periods and even for mental health related hospitalizations (table 6.6). The likelihood increased with time and was higher in the two-year period (1.45) compared with the one-year period (1.25).

Analysis by subgroup

Most of the long-term antipsychotic polypharmacy subgroups were associated with an increased risk of hospitalization compared with the monotherapy control groups although not many of these associations were significant. Among the clozapine groups only the clozapine + conventional polypharmacy was associated with a significantly higher one-year risk of (OR 1.78, 95% CI 1.04 to 2.52) (table 6.7). Among the non clozapine groups atypical+atypical polypharmacy was associated with a significant increase in one and two-year risk of mental health related hospitalization and atypical+conventional polypharmacy was associated with an increased risk compared to atypical and conventional monotherapy at two years. The hazard rates were highest for the atypical+atypical polypharmacy vs. atypical monotherapy.

Heckman two-stage estimation

The heckman two-stage hazard rate estimates for any long-term polypharmacy were slightly higher (higher likelihood of hospitalization with polypharmacy) but followed the same trend as the propensity matched results (table 6.8). Besides clozapine+conventional and clozapine+atypical 2 year rates, most other results were comparable with the propensity matched results although the degree of association

varied in some cases. In addition to the 2-year risk with atypical+conventional polypharmacy that was identified in the propensity analysis, the 1-year risk was also found to be statistically significant in the heckman analysis.

DISCUSSION

Long-term antipsychotic polypharmacy was found to be widely prevalent (23%) in this two-state Medicaid eligible schizophrenia population. Long-term usage is not supported by clinical evidence or practice guidelines and may be justified if the patients are significantly different in terms of their disease status and are not controlled with monotherapy. The fact that 3,072 (66%) of the 4,665 long-term antipsychotic polypharmacy patients could not be matched with a comparable monotherapy patient indicates that there are significant differences between the long-term antipsychotic polypharmacy and monotherapy groups. However 1,593 (34%) were matched which raises the issue that a subgroup of patients exist, who may have been equally well maintained with monotherapy.

Propensity matching adjusts for observed covariates (and unobserved covariates only to the extent that they are correlated with the observed covariates) and there could be unobserved patient factors defining disease severity for e.g. symptom status of the patient as measured by PANSS scores, which were only observed by the physician. However after matching, the long-term antipsychotic polypharmacy and monotherapy groups were comparable in terms of their observed covariates. Two reasons are commonly suggested for this differential treatment among comparable groups. First, that these could be switchover or PRN patients who were started on a short-term combination therapy and then were 'stuck' on it for some reason. For example, they were stable and the physician did not want to risk a relapse (Tapp 2003). Second these patients could also be seeing multiple physicians resulting in long-term antipsychotic polypharmacy.

Long-term antipsychotic polypharmacy was found to be associated with an increased risk of hospitalization and reduced community tenure even after propensity adjustment. There could be several possible explanations for the association. First, long-term antipsychotic polypharmacy may lead directly to worse patient outcomes that in turn results in a relapse. As discussed before there is very little evidence for the use of long-term antipsychotic polypharmacy, especially for long periods of time and a deleterious effect is a potentially plausible explanation. This explanation is further supported by the fact that in most comparisons (atypical+atypical and atypical+conventional) the 2-year risks are higher than 1-year risks, potentially as a result of higher exposure over the 2-year period.

A second explanation could be that long-term antipsychotic polypharmacy is a marker for aggressive treatment that is reserved for severe patients. Thus the long-term antipsychotic polypharmacy patients are sicker patients and therefore have worse outcomes. We performed propensity score matching to address this issue of selection bias and matched comparable long-term antipsychotic polypharmacy and monotherapy groups. Even after matching there was evidence of higher risk of hospitalization with long-term antipsychotic polypharmacy.

A third explanation, leading from the second, could be that long-term antipsychotic polypharmacy is a marker of severity that is not reflected in any of the observed covariates. In other words our adjustment for selection bias is not sufficient as there could be unobservable confounders. The Heckman two-stage estimation method potentially addresses this issue of continued existence of bias. The Heckman two-stage estimates were similar to the propensity estimates in most cases, and long-term antipsychotic polypharmacy, atypical+atypical and atypical+conventional differences remained significant. However the clozapine 2-year group results were very different for the two analyses. This difference could be attributed to the effect of unobserved

covariates, which was possibly true in the clozapine+atypical 2-year group where the error estimate obtained from the selection equation was significant when added to the survival equation (p-value: 0.004). Since Heckman estimation adjusts for the whole group and not a subgroup of matched subjects (like in propensity matching), large differences in distribution of covariates between the groups can result in differences from the propensity results. These methodological aspects of the estimation techniques should be kept in mind while interpreting the results, especially for the clozapine groups.

A fourth explanation could be that since this is an observational study and not a RCT some bias may still continue to exist even after adjustments. Even if long-term antipsychotic polypharmacy patients are assumed to be sicker to start with, the results show that differential treatment does not result in at least comparable outcomes across the two groups and long-term antipsychotic polypharmacy subjects have worse outcomes. However it can be argued that there is merit to long-term antipsychotic polypharmacy and if these subjects were not treated with long-term antipsychotic polypharmacy they could have had even worse outcomes. This argument cannot be proved or disproved without initiating a well-controlled RCT.

To date there have been no published study that estimate the association between the use of long-term antipsychotic polypharmacy and hospitalization. Our findings show that long-term antipsychotic polypharmacy may reduce community tenure and increase hospitalization risk and fail to show any significant benefit with long-term use of long-term antipsychotic polypharmacy in schizophrenia patients. In that sense our findings tend to support practice guidelines (Texas Medication Algorithm Project Miller 1999, American Psychiatric Association APA 1997, Journal of clinical psychiatry McEnvoy 1999, Patient outcomes research team, Lehman 1998) that do not recommend long-term antipsychotic polypharmacy.

Several important limitations of this study must be noted. First, it is an observational study, not an RCT. While we have adjusted for treatment selection bias and also used multiple adjustment techniques to ensure the validity of our results, the possibility of an important missing covariate can never be excluded. Inpatient medication use is not recorded in this database and has not been accounted for except where the patient was prescribed the same medication before and after hospitalization. In that case the patient was assumed to be on that medication during the inpatient stay. Like other administrative claims databases, the Medicaid databases have coding biases as coding is dependent on reimbursement incentives and may not be totally complete. These results are specific to Medicaid eligible schizophrenia patients and may not be generalizable to other patient populations.

CONCLUSION

In this observational study, long-term antipsychotic polypharmacy was associated with an increased risk of one-year and two-year hospitalization. The risk of hospitalization trended higher for all polypharmacy subgroups and were statistically significant for atypical+atypical (mental health related hospitalizations) and atypical+conventional (two year risk) groups. These findings raise concerns regarding the value of long-term antipsychotic polypharmacy and emphasize the need to critically evaluate such treatment decisions in schizophrenia patients.

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Table 6.1: List of antipsychotics

Atypicals	Conventionals
Clozapine Olanzapine Quetiapine Risperidone Ziprasidone,	Chlorpromazine Fluphenazine Haloperidol Loxapine Mesoridazine Molindone Perphenazine Pimozide Prochlorperazine Promazine Thioridazine Thiothixene Trifluoperazine Chlorprothixene

Table 6.2: Brief description of antipsychotic polypharmacy and corresponding monotherapy comparison cohorts

Antipsychotic polypharmacy Cohort	**Antipsychotic monotherapy comparison cohort**
Long term* polypharmacy	Long term* monotherapy
Long term* clozapine + atypical	Long term* clozapine monotherapy
Long term* clozapine + conventional	Long term* clozapine monotherapy
Long term* atypical + atypical and no exposure to clozapine at any time	Long term* atypical monotherapy and no exposure to clozapine
Long term* atypical + conventional and no exposure to clozapine at any time	Long term* monotherapy and no exposure to clozapine**
Long term* conventional + conventional and no exposure to clozapine at any time	Long term* conventional monotherapy and no exposure to clozapine

* Long Term is defined as use for at least 2 months

** Separate analysis was performed comparing long term atypical+conventional therapy with atypical monotherapy and conventional monotherapy

Table 6.3: Initial list of candidate factors associated with antipsychotic polypharmacy

Demographics	Drug overdose
Age, Gender, Race	Opthalmologic disease
Eligibility categories	Anxiety states
Medicare eligible, Aid category (Aged, blind, disabled)	Number of comorbidities per patient
Diagnosis related comorbidities	**Drug classes**
Congestive heart failure	4 Cardiac drug classes
Myocardial infarction	Parkinson's disease
Cardiac arrhythmias	Peripheral vascular disorder
Valvular disease	Hypertension
Peripheral vascular disorders	3 Respiratory classes
Hypertension	Insulin dependent diabetes*
Hemiplegia/paraplegia	> Oral hypoglycemic
Epilepsy*	Cancer
> Other neurological disorders	3 Epilepsy drug classes
Chronic pulmonary disease	Glaucoma
Asthma	Gout
Tuberculosis	Hyperlipidemia, hypercholesterolemia
Diabetes, uncomplicated*	Thyroid disorders
> Diabetes complicated	Menopause (HRT)
Thyroid disorder	Allergy
Renal failure and chronic disorders	Anxiety
Liver disease	Pain (terminal) Narcotic analgesic
Peptic ulcer disease	Depression
AIDS	Dementia/ Alzheimer's
Metastatic solid tumor*	Tuberculosis
> Any malignancy	Rheumatologic drugs/ Crohn's disease/ Ulcerative colitis
Rheumatoid arthritis / collagen vascular disease	Migraine
Coagulopathy	ESRD/ Transplant
Obesity	Number of Rx classes per patient (Mean)
Weight loss/malnutrition	**Antipsychotic agents, mood stabilizer**
Fluid and electrolyte disorders	Atypicals, Conventionals
Anemias	Olanzapine, Risperidone, Quetiapine, Clozapine
Sickle cell anemia	Haloperidol oral & injectable, Fluphenazine oral and injectable
Drug abuse*	Thioridazine, Chlorpromazine, Thiothixene
> Alcohol abuse	Lithium
Bipolar and manic depressive*	**Prior health care utilization, date variables**
> Other psychoses/ Mixed psychoses	Mental health cost in prior period
> Other mental disorders	Number of psychiatric outpatient physician visits, physician specialty
> Personality disorders	Psychiatric inpatient episode, latest inpatient days, cumulative inpatient days
> Depression or schizoaffective	Antipsychotic regular use (antipsychotic Rx every 2 months)
Cerebrovascular disease	Quarter in which episode started

Alzheimer's disease*	Year in which episode started
> Non Alzheimer's dementia	**Social**
Non-head trauma	Marital status, employment status
Head trauma	

> Indicates a hierarchy in relation to the higher cost category denoted by an asterisk (*). If both comorbidities are present, count only the higher cost category

Table 6.4: Group comparisons before and after propensity score matching

	BEFORE PROPENSITY MATCHING				AFTER PROPENSITY MATCHING			
	Poly	Mono			Poly	Mono		
	N = 4,665	N = 6,955		Standardized	N = 1,593	N = 1,593		Standardized
Demographics and eligibility	% prevalence or mean	% prevalence or mean	2-sample t-statistic	difference in %**	% prevalence or mean	% prevalence or mean	2-sample t-statistic	difference in %**
Georgia Medicaid Eligible	42.0	64.3	24.2	-46.0	56.3	55.1	-0.7	2.4
Age as of January 1, 1998 (Years)	43.5	46.2	10.7	-19.9	44.9	44.9	-0.2	0.6
Male	53.5	45.0	-9.1	17.2	48.8	48.9	0.1	-0.2
White	48.6	42.1	-6.8	12.9	42.9	42.9	0.0	0.0
Medicare eligible	58.9	62.0	3.4	-6.4	61.3	60.3	-0.6	2.2
Medicaid aid category - disabled	99.0	97.4	-6.7	12.1	98.1	97.9	-0.4	1.4
Diagnosis variables								
Myocardial Infarction	0.3	0.2	-0.1	0.4	0.2	0.3	0.4	-1.3
Arrhythmia	3.0	1.8	-4.2	8.1	2.1	2.0	-0.4	1.3
Valvular disease	0.8	0.7	-0.3	0.6	0.8	0.7	-0.2	0.7
Hypertension	24.4	24.2	-0.3	0.6	23.7	21.1	-1.7	6.2
Hemiplegia	1.5	1.1	-1.9	3.6	1.3	1.3	0.0	0.0
Epilepsy	11.5	3.9	-14.6	28.8	5.9	6.4	0.6	-2.1
Other neurological disorders	5.5	4.1	-3.6	6.8	4.5	4.0	-0.7	2.5
Chronic obstructive pulmonary disease	11.1	6.9	-7.7	14.8	9.0	8.7	-0.4	1.3
Asthma	2.4	1.8	-2.2	4.2	2.4	2.0	-0.7	2.6
Thyroid disorder	3.8	2.6	-3.5	6.8	2.7	3.0	0.4	-1.5
Renal failure and chronic disorders	0.5	0.5	-0.4	0.7	0.4	0.4	-0.3	0.9
Liver disease	0.7	0.7	-0.2	0.4	0.5	0.7	0.7	-2.5
Obesity	2.6	1.9	-2.6	4.9	2.2	2.3	0.1	-0.4
Weight loss	0.3	0.2	-1.4	2.7	0.3	0.2	-0.4	1.3
Anemia	6.7	4.6	-4.6	8.9	4.5	5.2	0.9	-3.2
Drug abuse	2.8	2.6	-0.5	1.1	2.6	3.0	0.5	-1.9
Alcohol abuse	1.1	1.6	2.1	-4.0	1.5	1.5	0.0	0.0
Other psychoses/ Mixed psychoses	14.3	9.8	-7.1	13.7	12.0	11.7	-0.2	0.8
Other mental disorder	20.7	18.6	-2.8	5.3	20.4	19.8	-0.4	1.4

Personality disorder	0.2	6.0	0.3	-24.5	5.2	4.6	-0.8	2.9
Schizoaffective disorder	20.8	18.2	-3.4	6.5	18.5	20.3	1.3	-4.6
Alzheimer's disease	0.2	0.2	0.7	-1.2	0.1	0.1	-0.6	2.3
Non Alzheimer dementia	1.3	1.6	1.3	-2.3	1.3	1.6	0.6	-2.1
Head trauma	2.1	1.6	-1.9	3.7	1.6	2.0	0.8	-2.9
Opthalmologic diseases	14.0	9.5	-7.3	14.0	10.6	11.5	0.9	-3.0
Anxiety states	2.1	1.8	-1.2	2.3	2.1	2.0	-0.3	0.9
Drug use variables								
Cardiac 1 (Antiarrhythmic, inotropic, vasopressors)	9.3	10.4	2.0	-3.7	9.9	9.5	-0.4	1.3
Parkinsons disease	73.4	48.4	-28.4	53.1	61.8	62.5	0.4	-1.5
Peripheral vascular disease	2.3	3.1	2.7	-4.9	2.6	2.5	-0.1	0.4
Cancer	1.3	0.9	-2.0	3.9	0.7	1.1	1.1	-4.0
Epilepsy A (Anticonvulsants - hydantoin, succinimide, oxazolidinidione)	3.8	4.7	2.5	-4.7	4.0	3.6	-0.7	2.3
Epilepsy 1 (Barbiturates, certain benzodiazepines)	47.1	27.8	-21.7	40.6	35.2	37.4	1.3	-4.7
Glaucoma	1.1	1.6	2.2	-4.0	1.3	1.4	0.2	-0.5
Gout	0.7	0.8	0.7	-1.4	0.8	0.9	0.4	-1.3
Hyperlipidemia, hypercholesterolemia	6.9	6.5	-0.9	1.8	6.6	6.7	0.1	-0.2
Thyroid disorder	8.1	5.8	-4.8	9.3	5.9	6.2	0.3	-1.1
Allergy	10.3	9.9	-0.6	1.1	10.0	10.7	0.6	-2.3
Anxiety	9.3	5.9	-8.2	12.7	7.3	7.8	0.5	-1.9
Pain (Terminal)	0.3	0.4	0.5	-1.3	0.4	0.6	0.5	-1.7
Depression	43.4	39.0	-5.0	8.9	41.8	42.1	0.2	-0.6
Alzheimer's / dementia	0.2	0.4	2.1	-3.6	0.4	0.4	0.0	0.0
Tuberculosis	0.4	0.2	-2.8	3.9	0.4	0.4	-0.3	0.9
Migraine	0.2	0.2	-0.7	0.3	0.3	0.4	0.3	-1.2
Number of drug classes	3.8	3.1	-14.7	27.4	3.4	3.4	0.1	-0.2
Antipsychotic use								
Olanzapine	43.1	16.1	-32.2	61.3	26.0	27.8	1.1	-4.0
Risperidone	26.3	16.3	-13.0	24.1	20.5	19.8	-0.5	1.9
Haloperidol oral	24.0	13.6	-13.9	26.8	17.0	17.4	0.3	-1.2
Haloperidol injectable	13.7	5.1	-15.1	29.7	8.0	9.0	1.1	-3.8

Thioridazine	12.8	6.5	-11.1	21.5	9.4	7.3	-2.1	7.3
Quetiapine	10.3	1.0	-20.1	40.9	2.3	2.6	0.6	-2.0
Fluphenazine oral	12.5	6.1	-11.3	21.9	8.8	7.7	-1.1	3.9
Clozapine	11.4	6.9	-8.0	15.5	7.6	6.0	-1.8	6.5
Fluphenazine injectable	10.4	4.9	-10.8	21.0	7.3	7.1	-0.2	0.7
Chlorpromazine	10.8	2.2	-17.7	35.6	3.6	4.3	1.1	-3.8
Thiothixene	7.3	4.2	-6.8	13.2	5.2	4.0	-1.6	5.7
Lithium	12.4	7.4	-9.1	16.5	10.7	10.5	-0.2	0.6
Prior utilization and temporal variables								
Total cost $ 2000 (Mean)	6,283.0	4,773.0	-11.6	22.2	5,438.0	5,368.0	-0.1	1.0
Mental health cost $ 2000 (Mean)	4,271.0	2,748.0	-15.2	29.3	3,493.0	3,478.0	-0.1	0.3
Psychiatric outpatient physician visits (Mean)	1.9	1.1	-11.3	22.5	1.2	1.1	-0.3	1.1
Duration of latest hospitalization (Mean days)	2.0	1.1	-6.3	12.0	1.8	2.0	0.5	-1.8
Cumulative inpatient days in prior period (Mean days)	2.5	1.4	-6.7	12.9	2.1	2.3	0.6	-2.0
Antipsychotic regular users in prior period (Antipsychotic Rx every 2 months)	86.3	61.8	-31.8	58.1	75.7	72.8	-1.9	6.6
Psychiatric inpatient episode	14.2	8.2	-9.9	19.2	11.3	12.5	1.0	-3.7
Index date in july, august or september	47.3	64.1	18.0	-34.2	50.7	48.1	-1.5	5.1
Index date in october, november or december	21.7	15.9	-7.8	14.9	20.5	22.2	1.2	-4.3
Episode in year 1999	47.9	29.1	-20.6	39.4	44.0	47.2	1.8	-6.4
Episode in year 2000	7.3	5.7	-3.3	6.3	5.7	5.7	0.1	-0.3
Logit of propensity score	2.0	-2.2	-93.2	183.8	-0.5	-0.5	-0.1	0.2

*For categorical variables: Value "1" if subject belongs to the variable category, else "0"
** The standardized difference in % is the mean difference as a percentage of the average standard deviation: 100*(TM - CM)/Sqrt{(TV - CV)/2}
TM & CM = Sample means for the covariate in the treated (TM) and control (CM) groups
TV & CV = Sample variance for the covariate in the treated (TV) and control (CV) groups

Table 6.5: Community tenure before and after propensity score matching

	BEFORE MATCHING		**AFTER MATCHING**	
	Mean community	Mean community	Mean community	Mean community
	tenure	tenure	tenure	tenure
	Days (sd)	Days (sd)	Days (sd)	Days (sd)
Observation period	Polypharmacy	Monotherapy	Polypharmacy	Monotherapy
One year	n = 4,665	n = 6,955	n = 1,593	n = 1,593
Any	311 (1.52)	334 (1.02)	319 (2.44)	323 (2.19)
Mental health related	329 (1.29)	346 (0.78)	330 (2.01)	336 (1.75)
Two year	n = 2,886	n = 5,547	n = 868	n = 868
Any	566 (3.69)	631 (2.52)	584 (5.97)	615 (5.59)
Mental health related	619 (3.21)	673 (1.99)	633 (5.13)	659 (4.61)
Episode	n = 4,665	n = 6,955	n = 4,665	n = 6,955
	707 (5.35)	785 (3.40)	720 (8.69)	746 (7.40)
Mental health related	768 (4.60)	838 (2.57)	765 (7.18)	800 (5.77)

Table 6.6: Risk of hospitalization before and after propensity score matching

	BEFORE MATCHING			AFTER MATCHING
	N	N		
	(% hospitalized)	(% hospitalized)	OR	OR
Observation period	Polypharmacy	Monotherapy	(95% CI)	(95% CI)
One year	n = 4,665	n = 6,955		
Any	1,145 (24.5)	1,022 (14.7)	1.77 (1.69 to 1.85)	1.25 (1.09 to 1.41)
Mental health related	768 (16.5)	591 (8.5)	2.03 (1.92 to 2.14)	1.27 (1.07 to 1.47)
Two year	n = 2,886	n = 5,547		
Any	1,035 (35.8)	1,121 (20.2)	1.97 (1.89 to 2.05)	1.45 (1.27 to 1.63)
Mental health related	716 (24.8)	666 (12.0)	2.23 (2.12 to 2.34)	1.4 (1.24 to 1.56)
Episode	n = 4,665	n = 6,955		
Any	814 (17.5)	954 (13.7)	1.67 (1.58 to 1.76)	1.28 (1.10 to 1.46)
Mental health related	511 (11.0)	477 (6.9)	2.07 (1.94 to 2.20)	1.47 (1.23 to 1.71)

Table 6.7: Risk of hospitalization by type of antipsychotic polypharmacy

	AFTER PROPENSITY MATCHING		
	N	N	
	(% hospitalized)	(% hospitalized)	OR
Observation period	Polypharmacy	Monotherapy	(95% CI)
CLOZAPINE+ATYPICAL			
One year	n = 54	n = 54	
Any	13 (24.1)	11 (20.4)	1.16 (0.36 to 1.96)
Mental health related	8 (14.8)	9 (16.7)	0.86 (0.09 to 1.81)
Two year	n = 39	n = 39	
Any	9 (23.1)	11 (28.2)	0.76 (0.12 to 1.64)
Mental health related	6 (15.4)	9 (23.1)	0.61 (0.43 to 1.64)
Episode	n = 54	n = 54	
Any	11 (20.4)	14 (25.9)	1.05 (0.25 to 1.85)
Mental health related	6 (11.1)	9 (16.7)	0.79 (0.25 to 1.83)
CLOZAPINE+CONVENTIONAL			
One year	n = 106	n = 106	
Any	19 (17.9)	11 (10.4)	1.78 (1.04 to 2.52)
Mental health related	15 (14.2)	8 (7.6)	1.91 (1.05 to 2.77)
Two year	n = 63	n = 63	
Any	16 (25.4)	12 (19.1)	1.37 (0.62 to 2.12)
Mental health related	11 (17.5)	7 (11.1)	1.57 (0.62 to 2.52)
Episode	n = 106	n = 106	
Any	16 (15.1)	20 (18.9)	1.55 (0.86 to 2.24)
Mental health related	9 (8.5)	10 (9.4)	1.36 (0.44 to 2.28)
ATYPICAL+ATYPICAL			
One year	n = 189	n = 189	
Any	41 (21.7)	36 (19.1)	1.15 (0.70 to 1.60)
Mental health related	29 (15.3)	15 (7.9)	2.01 (1.39 to 2.63)
Two year	n = 59	n = 59	
Any	18 (30.5)	17 (28.8)	1.06 (0.40 to 1.72)
Mental health related	12 (20.3)	5 (8.5)	2.56 (1.52 to 3.60)
Episode	n = 189	n = 189	
Any	33 (17.5)	32 (16.9)	1.13 (0.64 to 1.62)
Mental health related	18 (9.5)	13 (6.9)	1.64 (0.91 to 2.37)
CONVENTIONAL+CONVENTIONAL			
One year	n = 148	n = 148	

Any	20 (13.5)	15 (10.1)	1.38 (0.71 to 2.05)
Mental health related	12 (8.1)	11 (7.4)	1.12 (0.30 to 1.94)
Two year	n = 93	n = 93	
Any	19 (20.4)	25 (26.9)	0.74 (0.14 to 1.33)
Mental health related	11 (11.8)	11 (11.8)	0.99 (0.15 to 1.82)
Episode	n = 148	n = 148	
Any	14 (9.5)	17 (11.5)	0.98 (0.27 to 1.69)
Mental health related	7 (4.7)	7 (4.7)	1.13 (0.08 to 2.18)
ATYPICAL+CONVENTIONAL VS ATYPICAL			
One year	n =624	n = 624	
Any	149 (23.9)	128 (20.5)	1.20 (0.96 to 1.44)
Mental health related	92 (14.7)	75 (12.0)	1.25 (0.94 to 1.55)
Two year	n = 291	n - 291	
Any	86 (29.6)	67 (23.0)	1.34 (1.02 to 1.66)
Mental health related	61 (21.0)	34 (11.7)	1.87 (1.45 to 2.29)
Episode	n = 624	n = 624	
Any	104 (16.7)	110 (17.6)	1.10 (0.83 to 1.37)
Mental health related	61 (9.8)	62 (9.9)	1.16 (0.80 to 1.52)
ATYPICAL+CONVENTIONAL VS CONVENTIONAL			
One year	n = 545	n = 545	
Any	98 (18.0)	91 (16.7)	1.08 (0.79 to 1.37)
Mental health related	62 (11.4)	52 (9.5)	1.21 (0.84 to 1.58)
Two year	n = 208	n = 208	
Any	73 (35.1)	49 (23.6)	1.59 (1.23 to 1.95)
Mental health related	46 (22.1)	32 (15.4)	1.48 (1.03 to 1.93)
Episode	n = 545	n = 545	
Any	65 (11.9)	78 (14.3)	0.99 (0.66 to 1.32)
Mental health related	43 (7.9)	41 (7.5)	1.29 (0.86 to 1.72)

Table 6.8: Unadjusted, propensity score matched and Heckman 2-stage estimated risk of hospitalization

	UNADJUSTED	PROPENSITY ADJUSTED	HECKMAN ADJUSTED
LONG-TERM Observation period	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
One year			
Any	1.77 (1.69 to 1.85)	1.25 (1.09 to 1.41)	1.32 (1.20 to 1.44)
Mental health related	2.03 (1.92 to 2.14)	1.27 (1.07 to 1.47)	1.42 (1.28 to 1.56)
Two year			
Any	1.97 (1.89 to 2.05)	1.45 (1.27 to 1.63)	1.54 (1.42 to 1.66)
Mental health related	2.23 (2.12 to 2.34)	1.4 (1.24 to 1.56)	1.74 (1.60 to 1.88)
Episode			
Any	1.67 (1.58 to 1.76)	1.28 (1.10 to 1.46)	1.31 (1.17 to 1.45)
Mental health related	2.07 (1.94 to 2.20)	1.47 (1.23 to 1.71)	1.50 (1.32 to 1.68)
CLOZAPINE + ATYPICAL			
One year			
Any	2.05 (1.63 to 2.47)	1.16 (0.36 to 1.96)	1.62 (0.76 to 2.48)
Mental health related	1.38 (0.84 to 1.92)	0.86 (0.09 to 1.81)	0.66 (-0.50 to 1.82)
Two year			
Any	2.18 (1.73 to 2.63)	0.76 (0.12 to 1.64)	4.5 (3.52 to 5.48)
Mental health related	2.08 (1.51 to 2.65)	0.61 (0.43 to 1.64)	2.56 (1.34 to 3.78)
Episode			
Any	1.75 (1.30 to 2.20)	1.05 (0.25 to 1.85)	1.06 (0.22 to 1.90)
Mental health related	0.98 (0.31 to 1.65)	0.79 (0.25 to 1.83)	0.38 (-0.97 to 1.73)
CLOZAPINE + CONVENTIONAL			
One year			
Any	1.74 (1.26 to 2.22)	1.78 (1.04 to 2.52)	1.20 (0.10 to 2.30)
Mental health related	1.67 (1.11 to 2.23)	1.91 (1.05 to 2.77)	0.92 (-0.45 to 2.29)
Two year			
Any	1.92 (1.43 to 2.41)	1.37 (0.62 to 2.12)	0.47 (-1.00 to 1.94)
Mental health related	2.16 (1.58 to 2.74)	1.57 (0.62 to 2.52)	0.39 (-1.45 to 2.23)

Episode			
Any	1.72 (1.23 to 2.21)	1.55 (0.86 to 2.24)	0.91 (-0.19 to 2.01)
Mental health related	1.44 (0.79 to 2.09)	1.36 (0.44 to 2.28)	0.45 (-1.29 to 2.19)
ATYPICAL + ATYPICAL			
One year			
Any	1.17 (0.92 to 1.42)	1.15 (0.70 to 1.60)	1.03 (0.70 to 1.36)
Mental health related	1.35 (1.04 to 1.66)	2.01 (1.39 to 2.63)	1.44 (1.03 to 1.85)
Two year			
Any	1.25 (0.90 to 1.60)	1.06 (0.40 to 1.72)	1.32 (0.83 to 1.81)
Mental health related	1.40 90.97 to 1.83)	2.56 (1.52 to 3.60)	1.48 (0.87 to 2.09)
Episode			
Any	1.12 (0.83 to 1.41)	1.13 (0.64 to 1.62)	0.96 (0.57 to 1.35)
Mental health related	1.28 (0.90 to 1.66)	1.64 (0.91 to 2.37)	0.13 (-0.38 to 0.64)
CONVENTIONAL + CONVENTIONAL			
One year			
Any	1.44 (1.12 to 1.76)	1.38 (0.71 to 2.05)	1.32 (0.91 to 1.73)
Mental health related	1.58 (1.15 to 2.01)	1.12 (0.30 to 1.94)	2.11 (1.52 to 2.70)
Two year			
Any	1.40 (1.08 to 1.72)	0.74 (0.14 to 1.33)	1.15 (0.70 to 1.60)
Mental health related	1.47 (1.05 to 1.89)	0.99 (0.15 to 1.82)	1.49 (0.88 to 2.100
Episode			
Any	1.24 (0.82 to 1.66)	0.98 (0.27 to 1.69)	1.11 (0.66 to 1.56)
Mental health related	1.17 (0.62 to 1.72)	1.13 (0.08 to 2.18)	1.08 (0.35 to 1.81)
ATYPICAL+ CONVENTIONAL VS. ATYPICAL			
One year			
Any	1.30 (1.18 to 1.42)	1.20 (0.96 to 1.44)	1.32 (1.14 to 1.50)
Mental health related	1.48 (1.33 to 1.63)	1.25 (0.94 to 1.55)	1.41 (1.17 to 1.65)
Two year			
Any	1.61 (1.47 to 1.75)	1.34 (1.02 to 1.66)	1.56 (1.34 to 1.78)
Mental health related	1.81 (1.64 to 1.98)	1.87 (1.45 to 2.29)	1.89 (1.60 to 2.18)
Episode			
Any	1.18 (1.04 to 1.32)	1.10 (0.83 to 1.37)	1.18 (0.98 to 1.38)
Mental health related	1.42 (1.24 to 1.60)	1.16 (0.80 to 1.52)	1.33 (1.06 to 1.60)

ATYPICAL+ CONVENTIONAL VS CONVENTIONAL			
One year			
Any	2.20 (2.06 to 2.34)	1.08 (0.79 to 1.37)	1.31 (1.07 to 1.55)
Mental health related	2.77 (2.59 to 2.95)	1.21 (0.84 to 1.58)	1.61 (1.32 to 1.90)
Two year			
Any	2.31 (2.17 to 2.45)	1.59 (1.23 to 1.95)	1.86 (1.59 to 2.13)
Mental health related	2.91 (2.73 to 3.09)	1.48 (1.03 to 1.93)	2.08 (1.75 to 2.41)
Episode			
Any	1.82 (1.67 to 1.97)	0.99 (0.66 to 1.32)	0.99 (0.72 to 1.26)
Mental health related	2.52 (2.32 to 2.72)	1.29 (0.86 to 1.72)	1.33 (0.98 to 1.68)

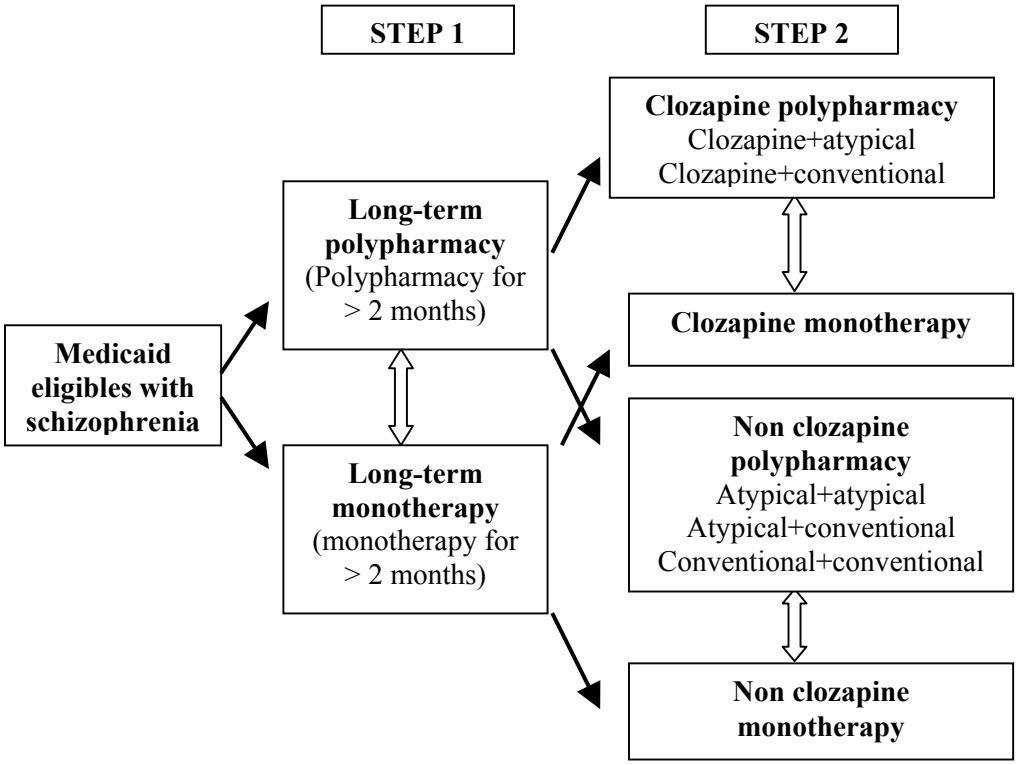

Figure 6.1: Different forms of antipsychotic polypharmacy and monotherapy

CHAPTER 7

CONCLUSION

Antipsychotic polypharmacy was found to be widely prevalent (40%), prescribed for long durations (>6 months) and is an increasing phenomenon among Medicaid eligible schizophrenia patients. The high prevalence of long-term (23%) antipsychotic polypharmacy indicates a marked discrepancy between real world practice and practice guidelines. In general, patients in the aged/disabled Medicaid aid category, males, patients on newer atypicals and older conventionals are more likely to be associated with antipsychotic polypharmacy.

Long-term antipsychotic polypharmacy was associated with increased one-year and two-year health care costs after adjustment for treatment selection bias. There was a trend towards higher cost for all polypharmacy subgroups and were statistically significant for atypical+atypical, conventional+conventional, and atypical+conventional vs. conventional groups. No evidence of economic benefit with antipsychotic polypharmacy was observed except for a significant net cost in the clozapine+conventional vs clozapine group sensitivity analysis ($p < 0.001$). Similarly long-term antipsychotic polypharmacy was also associated with an increased risk of one-year and two-year hospitalization after adjustment for treatment selection bias. The results were statistically significant for atypical+atypical (mental health hospitalization) and atypical+conventional (two year risk) groups.

Antipsychotic polypharmacy is widely prevalent and is becoming an increasingly common practice in the treatment of schizophrenia. We did not find any evidence of

economic and hospitalization risk related benefit with antipsychotic polypharmacy except a significant positive net cost in the clozapine+conventional vs clozapine sensitivity analysis ($p < 0.0001$). Our findings raise concerns regarding the value of antipsychotic polypharmacy and emphasize the need to critically evaluate such treatment decisions in schizophrenia patients. Prior authorization rule for long-term antipsychotic polypharmacy (more than 60 days) or specifically same type polypharmacy (atypical+atypical and conventional+conventional) may be explored as a policy option to evaluate such treatment on a case to case basis.

Further research in the form of well controlled randomized clinical trials or observational studies to estimate the effect of antipsychotic polypharmacy on other outcomes for e.g. clinical and humanistic outcomes are necessary to define the scope of such treatment.

APPENDIX A

SAS PROGRAM FOR PROPENSITY SCORE MATCHING

```
/*----PROPENSITY PROGRAM PART 1: COMPUTING PROPENSITY SCORE

                    AND LOGITS FOR EACH PATIENT----*/


libname IN1 'e:\Records\Pharmacy\Ganguly\Polydata1\Full\group2a';
   /*----READING IN FILE &
        RETAINING ONLY THE LONG-TERM EPISODES----*/

   DATA FIN3;
          SET IN1.FIN3;
     IF LONGTERM = 1;

        /*----MODELING COHORT2 = 1 IF POLY & 0 IF MONO
             WITH POTENTIALLY CONFOUNDING COVARIATES----*/
     PROC LOGISTIC DATA=FIN3 DESCENDING;
         MODEL  COHORT2=
         /*----CONFOUNDING COVARIATES----*/

         /*---STATE VARIABLE-------*/
         GEORGIA

         /*---DEMOGRAPHICS---------*/
                      AGE      MALE          WHITE

         /*---ELIGIBILITY CATEGORY VARIABLES-----*/
                      MEDICARE  AIDCAT

         /*---DIAGNOSTIC COMORBIDITY VARIABLES------*/
         CHF2     MI2          ARRHYTH2
         VALVE2   RXHTN        VASCULO2
               HEMIP2   EPILEP2       NEURO2     COPD2
         ASTHMA2  TB2          DIABU2     DIABC2
         HYPO2    RENAL2       LIVER2     ULCER2
         AIDS2    META2        MALIG2     RHEUM2
         COAG2    OBESE2       WTLOSS2    FLUID2
         ANEMIA2  SICKLE2      DRUG2      ALCOHOL2
         BIPOL2   PSYCH2       MENTAL2    PERSON2
         SCHIZAF2 CEREB2       ALZ2       DEMENT2
                      NTRAUMA2  HTRAUMA2       DOSE2      OPTHAL2
                      ANXIETY2  TOTALDGN

               /*----RX CLASSES--------------------------*/
         CARDIAC1  CARDIAC2       CARDIAC3   CARDIAC4
         RXPARKIS  RXPVD          RXHTN      RESP1
         RESP2     RESP3          RXINSUL    RXDIAB2
         RXCANCER  RXEPIA         EPILEP1    EPILEP2
```

```
        RXGLAUCO  RXGOUT         RXLIPID     RXLOTHY
        RXHRT     RXHIST         RXANXIO     RXOPIATE
        RXDEPRES  ALZDEM         RXTUBERC    CRONREUM
                  RXMIGRA   ESRDTRAN        RXCLASS

            /*---ANTIPSYCHOTIC USE----------------------*/
                  OLANZA2   RISPER2
                  HALORAL1  HALINJ1         THIORI2     QUETIA2
                  FLUORAL1  CLOZUSE         FLUINJ1     CHLORP2
                  THIOTH2   RXLITHUM

            /*----OTHER PRIOR USE VARIABLES-------------*/
                  PREMH2    PRETOT2   VISITS1     DURHOSP
        CUMHOSP   COMPLY    PSYHOSP   SPECIAL6
        QUARTER2  QUARTER3  QUARTER4  YR1999   YR2000

            /*PREDS=PROPENSITY SCORE OR PREDICTED PROBABILITY
                  OF RECIEVING POLYPHARMACY*/

                  /SELECTION=STEPWISE
                   SLENTRY=0.5 SLSTAY=0.5;
         OUTPUT OUT=PREDS PRED=PROPEN;

            /*COMPUTING THE LOGIT OF THE PROPENSITY SCORE*/

      DATA PREDS;
         SET PREDS;
            LOGIT = LOG(PROPEN/(1-PROPEN));

             /*WRITING THE LOGIT OUT FOR THE NEXT PART OF THE
PROGRAM*/

      DATA IN1.APROPEN1;
         SET PREDS;
            RUN;


/*----PROPENSITY PROGRAM PART2: CHOOSING CALIPER----*/

libname IN1 'e:\Records\Pharmacy\Ganguly\Polydata1\Full\group2a';

   /*-------READING IN THE FILE THAT CONTAINS THE
         LOGITS ESTIMATED IN PART 1 OF THE PROGRAM----*/
   DATA APROPEN1;
         SET IN1.APROPEN1;

         PROC SORT;
         BY COHORT2;

      /*----CALCULATING VARIANCE FOR LOGIT BY TREATED AND CONTROL
GROUP
```

```
        AND USING THE VAR TO ESTIMATE CALIPER AS PER EQUATION BELOW----
*/
       PROC MEANS MEAN VAR;
            VAR LOGIT PROPEN;
            BY COHORT;
            RUN;


         /*-------CALIPER 0.20*STD, STD=sqrt[(VARt+VARunt)/2)]
          VAR t & unt=variance of logit of treated group/untreated grp-*/

         DATA CASE;
            SET APROPEN1;
                  IF COHORT2 = 1;
                  PROC SORT;
            BY RANORDER;

  /*----WRITING OUT CASE AND CONTROL FILES----*/
    DATA IN1.CASE;
            SET CASE;

         DATA CONTROL;
            SET APROPEN1;
                  IF COHORT2 = 0;
         DATA IN1.CONTROL;
            SET CONTROL;

                  RUN;
```

/*---PROPENSITY PROGRAM PART 3: PROPENSITY MAHALONOBIS METRIC MATCHING WITHIN CALIPERS SET BY LOGIT OF PROPENSITY SCORE----*/
/*---THIS TECHNIQUE IS VERY MEMORY INTENSIVE AND TAKES A VERY LONG TIME. IF THAT IS A CONCERN THEN USE THE ALTERNATIVE METHOD "3A" THAT FOLLOWS THIS PROGRAM---*/

```
libname IN1 'e:\Records\Pharmacy\Ganguly\Polydata1\Full\group2a';

*-----READING IN THE CASE AND CONTROL FILE--------------------*;
*------CREATING A RANDOM NUMBER FOR EACH CASE WHICH WUD BE USED
LATER TO---*;
*------RANDOMLY ORDER CASES RIGHT BEFORE THE MATCHING ----------------------*;
DATA CASE;
    SET IN1.CASE(KEEP=< VARIABLE LIST>);
    RANORDER = RANUNI(10000);

DATA CONTROL;
    SET IN1.CONTROL(KEEP=<VARIABLE LIST>);

*-----CREATING AN SQL TABLE OF CASES AND POSSIBLE CONTROLS---*;
*-----THAT ARE WITHIN THE CALIPER 0.46~0.5--------------------*;
```

```
PROC SQL;
     CREATE TABLE POSMCH AS
     SELECT CASE.BASE_ID AS CASEID,
          CONTROL.BASE_ID AS CONTRLID,
          CASE.RANORDER AS RANORDER,
          CASE.LOGIT AS CASESCOR,
          CONTROL.LOGIT AS CONTSCOR,
          ABS(CASE.LOGIT - CONTROL.LOGIT) AS SCOR_DIF
          FROM CASE,CONTROL
          WHERE ABS(CASE.LOGIT - CONTROL.LOGIT)<=0.5
          ORDER BY CASEID,CONTRLID,SCOR_DIF;

*-----COMPUTING THE MAHALONOBIS DISTANCE BETWEEN THE CASE-----*;
*-----AND POSSIBLE CONTROLS IN 3 STEPS------------------------*;

*---STEP1: CREATING DATA FOR THE VARIANCE COVANRIANCE MATRIX---*;
*-----VAR-COVARIANCE MATRIX COMPUTED USING CONTROL SUBJECT-----*;
*-----DATA ONLY-----------------------------------------------*;
PROC CORR DATA=CONTROL COV NOPROB OUTP=CORROUT VAR <VARIABLE
LIST>;

*---STEP2: CREATING THE MATRIX FOR CASE COVARIATES------------*;
DATA CASECOV1;
    SET POSMCH;
          PROC SORT;
          BY CASEID;
DATA CASECOV2;
    SET CASE;
          CASEID = BASE_ID;
          PROC SORT;
          BY CASEID;
DATA CASECOV3;
    MERGE CASECOV1(IN=A) CASECOV2(IN=B);
          BY CASEID;
          IF A; IF B;
PROC DATASETS;
DELETE CASECOV1 CASECOV2;

*---STEP2: CREATING THE MATRIX FOR CONTROL COVARIATES------------*;
DATA CONTCOV1;
    SET POSMCH;
          PROC SORT;
          BY CONTRLID;
DATA CONTCOV2;
    SET CONTROL;
          CONTRLID = BASE_ID;
          PROC SORT;
          BY CONTRLID;
DATA CONTCOV3;
    MERGE CONTCOV1(IN=A) CONTCOV2(IN=B);
          BY CONTRLID;
```

```
          IF A; IF B;
PROC DATASETS;
DELETE CONTCOV1 CONTCOV2;
PROC IML;
USE CORROUT;
READ ALL VAR{   <VARIABLE LIST> } WHERE(_TYPE_='COV') INTO VARCOVAR;

USE CASECOV3;
READ ALL VAR{<VARIABLE LIST> } INTO TREAT;

USE CONTCOV3;
READ ALL VAR{<VARIABLE LIST> } INTO UNTREAT;
USE CONTCOV3;
READ ALL VAR{CASEID CONTRLID} INTO IDS;

*-----COMPUTING THE MAHALONOBIS DISTANCE FOR ALL PAIRS--------------*;
MDIST  = ((TREAT-UNTREAT))*(inv(VARCOVAR))*t(TREAT-UNTREAT);
MDIST2  = DIAG(MDIST);
MDIST3 = MDIST2[,+];
INVVAR = INV(VARCOVAR);

*-----OUTPUTTING THE DISTANCE DATA INTO A SAS FILE------------------*;
VARNAME = {DISTANCE};
CREATE DISTANCE FROM MDIST3(|COLNAME = VARNAME|);
APPEND FROM MDIST3;

QUIT;
PROC DATASETS;
DELETE CASECOV3 CONTCOV3;


*---UPDATING THE POSSIBLE MATCHES FILE WITH THE DISTANCE VARIABLE---*;
*---RANDOMLY ORDERING THE 'CASES - CONTROL' GROUPS USING THE-------*;
*---RANORDER VARIABLE. THIS ENSURES THAT MATCHES ARE IDENTIFIED----*;
*---IN A RANDOM ORDER-----------------------------------------------*;

DATA POSMCH2;
    MERGE POSMCH DISTANCE;
          PROC SORT;
    BY RANORDER CONTRLID DISTANCE;

DATA POSPRNT;
  SET POSMCH2;
  PROC PRINT DATA=POSPRNT(OBS=500);
  TITLE "SAMPLE OF FIRST DATA MATCHING";

*----SELECTING A MATCH BY SHORTEST DISTANCE-------------------------*;
*----REMOVING THAT MATCHED CASE AND CONTROL FROM THE POOL-----------*;
*----MATCHING THE REST, REPEATING THIS STEP TILL ALL CASES ARE
MATCHED---*;
```

```
DATA POSMCH2;
  SET POSMCH2;
  BY RANORDER CONTRLID;
    IF FIRST.CONTRLID THEN OUTPUT;
%MACRO MATCHUP(RESULT,POTENMCH,CASID,CONTRLID,DISTANCE);
  %LOCAL I J;
  %LET I = 0;
   %DO %UNTIL (&SQLOBS=0);
  %LET I = %EVAL(&I+1);
  PROC SORT DATA=&POTENMCH; BY &CASID &DISTANCE;
  DATA BESTMCH;
   SET &POTENMCH;
      BY &CASID;
      IF FIRST.&CASID THEN OUTPUT;
      PROC SORT DATA=BESTMCH;
        BY &CONTRLID &DISTANCE;
  DATA MATCH&I;
      SET BESTMCH;
        BY &CONTRLID;
      IF FIRST.&CONTRLID THEN OUTPUT;
  PROC SQL;
     CREATE TABLE &POTENMCH AS
     SELECT &POTENMCH..*
     FROM &POTENMCH
        WHERE &CASID NOT IN (SELECT &CASID FROM MATCH&I)
        AND &CONTRLID NOT IN (SELECT &CONTRLID FROM MATCH&I);
  %END;
     PROC DATASETS; DELETE &POTENMCH;
  DATA &RESULT;
     SET
     %DO J=1 %TO &I;
     MATCH&J
     %END;
     ;
  %MEND MATCHUP;
  %MATCHUP(MATCHES,POSMCH2,RANORDER,CONTRLID,DISTANCE);
PROC PRINT DATA=MATCHES(OBS=10);
TITLE "RESUTLS OF FINAL MATCHING";

RUN;
```

/*---PROPENSITY PROGRAM PART 3A: SIMPLE MATCHING WITHIN CALIPER SET BY LOGIT OF PROPENSITY SCORE----*/

```
libname IN1 'e:\Records\Pharmacy\Ganguly\Polydata1\Full\group2b';

/*-----READING IN THE CASE AND CONTROL FILE
      CREATING A RANDOM NUMBER FOR EACH CASE WHICH WUD BE USED
LATER TO
      RANDOMLY ORDER CASES RIGHT BEFORE THE MATCHING ----*/
DATA CASE;
```

```
    SET IN1.PCLA2CASE;
    RANORDER = RANUNI(10000);
DATA CONTROL;
    SET IN1.PCLA2CONTROL;
/*-----CREATING AN SQL TABLE OF CASES AND POSSIBLE CONTROLS
      THAT ARE WITHIN THE CALIPER 0.43 IN THIS CASE----*/
PROC SQL;
     CREATE TABLE POSMCH AS
     SELECT CASE.BASE_ID AS CASEID,
          CONTROL.BASE_ID AS CONTRLID,
          CASE.RANORDER AS RANORDER,
          CASE.LOGIT AS CASESCOR,
          CONTROL.LOGIT AS CONTSCOR,
          ABS(CASE.LOGIT - CONTROL.LOGIT) AS SCOR_DIF
          FROM CASE,CONTROL
          WHERE ABS(CASE.LOGIT - CONTROL.LOGIT)<=0.43
          ORDER BY CASEID,CONTRLID,SCOR_DIF;

*---RANDOMLY ORDERING THE 'CASES - CONTROL' GROUPS USING THE-------*;
*---RANORDER VARIABLE. THIS ENSURES THAT MATCHES ARE IDENTIFIED----*;
*---IN A RANDOM ORDER----------------------------------------------*;

DATA POSMCH2;
    SET POSMCH;
          PROC SORT;
    BY RANORDER CONTRLID SCOR_DIF;

DATA POSPRNT;
  SET POSMCH2;
  PROC PRINT DATA=POSPRNT(OBS=100);
  TITLE "SAMPLE OF FIRST DATA MATCHING";

/*----FINDING CASE - CONTROL MATCHES-------*/

DATA POSMCH2;
  SET POSMCH2;
  BY RANORDER CONTRLID;
    IF FIRST.CONTRLID THEN OUTPUT;
%MACRO MATCHUP(RESULT,POTENMCH,CASID,CONTRLID,DISTANCE);
  %LOCAL I J;
  %LET I = 0;
   %DO %UNTIL (&SQLOBS=0);
  %LET I = %EVAL(&I+1);
  PROC SORT DATA=&POTENMCH; BY &CASID &DISTANCE;
  DATA BESTMCH;
   SET &POTENMCH;
     BY &CASID;
     IF FIRST.&CASID THEN OUTPUT;
     PROC SORT DATA=BESTMCH;
       BY &CONTRLID &DISTANCE;
  DATA MATCH&I;
```

```
      SET BESTMCH;
        BY &CONTRLID;
      IF FIRST.&CONTRLID THEN OUTPUT;
  PROC SQL;
     CREATE TABLE &POTENMCH AS
     SELECT &POTENMCH..*
     FROM &POTENMCH
       WHERE &CASID NOT IN (SELECT &CASID FROM MATCH&I)
       AND &CONTRLID NOT IN (SELECT &CONTRLID FROM MATCH&I);
  %END;
     PROC DATASETS; DELETE &POTENMCH;
  DATA &RESULT;
     SET
     %DO J=1 %TO &I;
     MATCH&J
     %END;
     ;
  %MEND MATCHUP;
  %MATCHUP(MATCHES,POSMCH2,CASEID,CONTRLID,SCOR_DIF);
PROC PRINT DATA=MATCHES(OBS=500);

DATA IN1.PCLA2_PROPEN3;
   SET MATCHES;
RUN;
```

APPENDIX B

SAS PROGRAM FOR HECKMAN TWO-STAGE ESTIMATION

```
/*----HECKMAN 2-STAGE ESTIMATION----*/
   /*----STAGE 1: PROGRAM TO ESTIMATE M1 = EXPECTED VALUE OF
                ERROR----*/


libname IN1 'e:\Records\Pharmacy\Ganguly\Polydata1\Full\group2a';

   /*----ESTIMATING Z*ALFA AS Z*ALFA1, ALFA1 IS ESTIMATE OF ALFA----*/
   /*----Z  = COVARIATES THAT INFLUENCE TREATMENT SELECTION
      ALFA1 = COEFFICIENTS OF Z ESTIMATED FROM THE PROBIT MODEL
      DEPENDENT VARIABLE COHORT2 = 1 IF POLY, 0 IF MONOTHERAPY
      REMEMBER! Z HAS TO BE <= X-1 WHERE X ALL COVARIATES
      USED IN THE 2ND STAGE THAT INFLUENCE BOTH TREATMENT SELECTION
      AND OUTCOME----*/

   /*----READING IN THE FILE WITH LONG TERM POLY AND MONO----*/
   DATA PLT;
           SET IN1.FIN3;
     IF LONGTERM = 1;

   /*----RUNNING MODEL, ESTIMATING PRED = Z*ALFA & WRITING IT OUT----*/
     PROC LOGISTIC DATA=PLT DESCENDING;
           MODEL  COHORT2= <LIST OF COVARIATES >
                          /LINK=PROBIT;
            OUTPUT OUT=PREDS XBETA=ZALFA1;

   /*----ZALFA IS USED TO ESTIMATE M1 FROM EQUATION 1----*/
   DATA PREDS;
            SET PREDS;
                 PDFZALFA1 = PDF('NORMAL',ZALFA1);
                 CDFZALFA1 = CDF('NORMAL',ZALFA1);
                 P       = COHORT2;

         /*---EQUATION 1: P = 1 IF POLY, 0 IF MONO
                          PDFZALFA = NORMAL PROB DENSITY FUNCTION OF ZALFA
                          CDFZALFA = CUMULATIVE DENSITY FUNCTION OF ZALFA---
-MMILLS = MILLS RATIO*/

MMILLS  = (PDFZALFA1/CDFZALFA1);
         DATA IN1.AHEKCHEK;
       SET PREDS;
                 RUN;




/*----HECKMAN 2-STAGE ESTIMATION----*/
```

```
/*----STAGE 2: ESTIMATING TREATMENT EFFECT USING
              M1 (ESTIMATED EXPECTED VALUE OF ERROR FROM
              PREVIOUS STAGE) AS AN ADDITIONAL REGRESSOR----*/


libname IN1 'e:\Records\Pharmacy\Ganguly\Polydata1\Full\group2a';

/*-------READING IN FILE WITH M1 IN IT----*/
   DATA AHECKMAN1;
           SET IN1.AHEKCHEK;
     IF LONGTERM = 1;


   DATA AHECKMAN1;
           SET AHECKMAN1;
           ONEOT = ONETOT-(ONERX+ONEPH+ONEIN+ONELT+ONEOU);

     PROC REG DATA=AHECKMAN1;
           MODEL  ONETOT=

        /*----DUMMY VARIABLE FOR TREATMENT, 1 IF POLY 0 IF MONO----*/
         COHORT2

   /*----M1 ERROR ESTIMATE----*/
                          M1

   /*---X = ALL COVARIATES THAT INFLUENCE TREATMENT SELECTION &
                          OUTCOME I.E. COST----*/

<LIST OF VARIABLES>;


   RUN;
```