Prevalence, Trends, and Factors Associated With Antipsychotic Polypharmacy Among Medicaid-Eligible Schizophrenia Patients, 1998–2000

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Objective: To determine the prevalence, trends, and factors associated with antipsychotic polypharmacy categorized according to type of antipsychotic and duration of use and to contrast usage patterns with published treatment guidelines.

Method: A retrospective cohort study was designed, and Medicaid recipients ≥ 16 years of age with a schizophrenia diagnosis (ICD-9-CM = 295.xx) between 1998 and 2000 were identified from the California (20% random sample) and Georgia Medicaid claims databases. Use of antipsychotic polypharmacy was categorized based on duration (long-term polypharmacy was defined as lasting > 2 months), and long-term use was further categorized based on type of antipsychotic combinations (clozapine, conventional, and atypical). The prevalence, mean duration, and frequency of and yearwise trends in antipsychotic polypharmacy were estimated. A stepwise logistic variable selection procedure was used to identify factors associated with long-term antipsychotic polypharmacy.

Results: Of a total of 31,435 persons with schizophrenia, the 1998–2000 prevalence of antipsychotic polypharmacy was 40% (N = 12,549; mean age = 43 years; white, 47%; female, 48%; mean duration of polypharmacy = 149 days), and long-term antipsychotic polypharmacy prevalence was 23% (N = 7222, mean duration = 236 days). The prevalence of atypical antipsychotic polypharmacy increased between 1998 and 2000 ($p < .0001$). Use of newer atypicals such as quetiapine (OR = 18.32) and older conventionals such as chlorpromazine (OR = 28.87) was strongly associated with long-term antipsychotic polypharmacy.

Conclusion: Antipsychotic polypharmacy is widely prevalent, is prescribed for long durations, and is an increasing phenomenon among Medicaid-eligible schizophrenia patients, indicating a significant discrepancy with treatment guidelines (which do not advocate the use of any polypharmacy except for short-term periods when transitioning patients to new antipsychotics). Further research evaluating the effects of antipsychotic polypharmacy in schizophrenia patients may assist in defining the scope and potential of such use.

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It is estimated that antipsychotic polypharmacy, defined as concomitant use of multiple antipsychotics, is prescribed for up to 40% of schizophrenia patients.[1] However, there are no randomized controlled trials of combination therapy except for 1 with sulpiride and clozapine, which provides little guidance in the United States since sulpiride is not available in the United States.[2] Apart from that study, there are case reports[3–11] and open, uncontrolled, nonrandomized trials[12–17] that report the effects of antipsychotic polypharmacy. Many of these studies report improvements in symptom control[3–5,7–9,11,12,15] and instances of nonserious side effects such as drooling[11] and compulsive behavior.[12] Other studies report an increased incidence of serious adverse events such as prolactin elevation, akathisia, and hypersalivation[6,10,13,17] and even an increased risk of mortality (study N = 88, relative risk = 2.46).[16] 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), short follow-up periods, and incomplete reporting of adverse effects. The recent introduction of 4 antipsychotics (olanzapine in 1996, quetiapine in 1997, ziprasidone in 2001, and aripiprazole in 2003) with differing receptor profiles has further increased the possibilities of combining these agents. The objective of our study was to estimate the prevalence and

Table 1. Antipsychotics Included in an Analysis of Antipsychotic Polypharmacy

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

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 estimated the factors associated with antipsychotic polypharmacy usage.

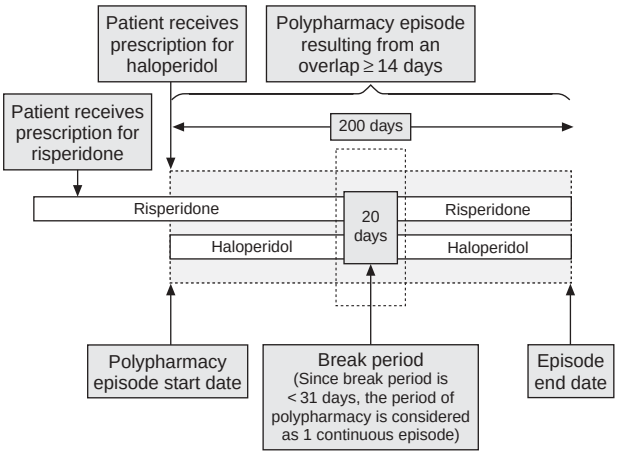
METHOD

Data Sources

A retrospective observational study design was employed using a combined 2-state Medicaid claims database. The study was approved by the University of Georgia Institutional Review Board. Claims data from January 1998 through December 2000 for Medicaid recipients from the states of Georgia and California were combined to build this 2-state database. Three sources of data were used: 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 a California Medicaid 20% random sample (Medi-Cal files).

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 is the 8 psychiatric hospitals managed by the DHR that do not bill Medicaid for services rendered to persons aged 21 to 64 years. Records from these 8 hospitals were combined to form the DHR file that contains a system-wide record of each visit a patient received at any of the 8 system inpatient institutions in operation. To capture psychiatric episodes of care, we linked the DHR files (state-based institutional data) by patient identifiers to the GDMA files (Georgia Medicaid claims data). These patient-linked or merged data provide a complete picture of the medical resources consumed for each Medicaid-eligible patient with schizophrenia in Georgia. California

Figure 1. Hypothetical Antipsychotic Polypharmacy Episode Involving Risperidone and Haloperidol



Medicaid reimburses 4 state psychiatric hospitals for inpatient services rendered to Medicaid-eligible patients, so there was no need to link state psychiatric hospitals with the claims data.

The Georgia[18–21] and California[22–24] Medicaid data have been used in the past for epidemiologic studies and have been found to be valid. The accuracy of schizophrenia diagnoses in Medicaid claims data has also been validated in a previous study.[25]

Subjects

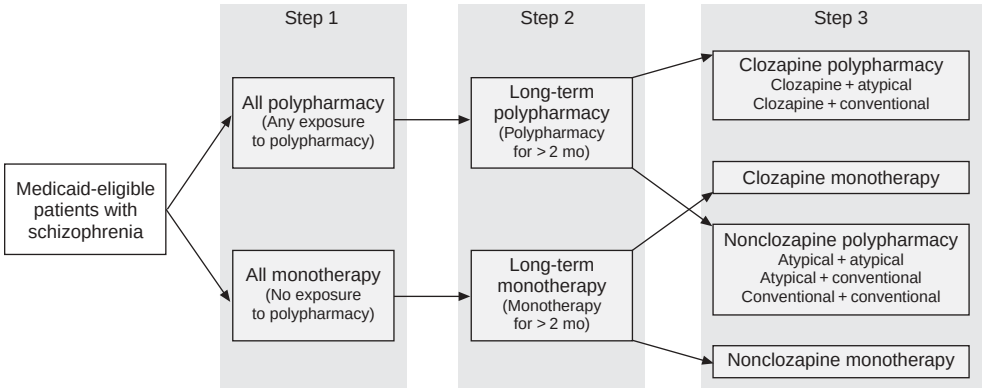
Persons with schizophrenia were identified using the following inclusion criteria: primary diagnosis of schizophrenia (ICD-9-CM = 295.xx) recorded on at least 1 paid claim during the period January 1998 through December 2000 and age of at least 16 years as of Jan. 1, 1998.

Definition of Antipsychotic Polypharmacy

After the schizophrenia patients were identified, antipsychotic polypharmacy episodes for each person were identified. For the purpose of this study, antipsychotic polypharmacy was defined as 2 or more chemically distinct antipsychotics prescribed concurrently with an overlap of at least 14 or more days of therapy.[26] The list of antipsychotics is provided in Table 1. Antipsychotic polypharmacy episodes were constructed using a "date of service" variable that recorded the prescription fill date and a "days supply" variable that recorded the intended duration of each antipsychotic prescription filled for each person. Figure 1 shows a hypothetical antipsychotic polypharmacy episode involving risperidone and haloperidol. The first day of the polypharmacy episode was considered as the episode start date.

An episode of antipsychotic polypharmacy was defined as a period of continuous antipsychotic polyphar-

Figure 2. Categories of Antipsychotic Polypharmacy and Monotherapy



macy without a break period of 31 or more days.[27] 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 polypharmacy was classified in a hierarchical fashion, narrowing the definition of antipsychotic polypharmacy with each consecutive step in accordance with published treatment guidelines as displayed in Figure 2. The *Journal of Clinical Psychiatry* treatment guideline[28] is the only guideline that offers guidance on the duration of antipsychotic polypharmacy; it recommends polypharmacy only when switching from one antipsychotic to another (cross-titration or overlap and taper) and for not more than 8 weeks or 2 months. Other guidelines do not advocate any antipsychotic polypharmacy. Based on the *Journal of Clinical Psychiatry* treatment guideline, a subject with an episode of antipsychotic polypharmacy longer than 2 months (at least 61 days) was categorized into the long-term antipsychotic polypharmacy cohort(s) (Figure 2). Since clozapine is generally reserved for treatment-resistant and comparatively more ill patients, the long-term antipsychotic polypharmacy cohort was separated into clozapine and nonclozapine cohorts for analyses. The clozapine and nonclozapine groups were further categorized into clozapine subgroups (clozapine + atypical, clozapine + conventional) and nonclozapine subgroups (atypical + atypical, atypical + conventional, conventional + conventional). 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.

Identification of Factors Associated With Long-Term Antipsychotic Polypharmacy

To identify factors associated with long-term antipsychotic polypharmacy, we included recipients who had been treated with antipsychotic polypharmacy or monotherapy for at least 61 days between 1998 and 2000. Antipsychotic use episodes in which a single antipsychotic was prescribed for at least 61 days without a break period of 31 or more days were referred to as monotherapy episodes.

Among these recipients, those who did not have at least 6 months of continuous Medicaid eligibility prior to their single longest polypharmacy or monotherapy episode were excluded. In addition, recipients who did not have at least 1 paid claim every 90 days prior to their single longest polypharmacy or monotherapy episode were excluded. The latter criterion was applied to ensure that persons who were eligible for Medicaid benefits had not withdrawn from the system (e.g., were in prison).[22] 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 recipient. Depending on the type of antipsychotic polypharmacy or monotherapy prescribed during the longest episode, e.g., long-term, clozapine, nonclozapine, clozapine + atypical, the recipient was grouped into one of the several long-term polypharmacy or monotherapy groups (Figure 2).

A comprehensive list of possible factors associated with antipsychotic polypharmacy was identified by a survey of published literature and expert opinion (Table 2). This list included demographics, diagnosis-related comorbidities, drug classes, antipsychotic agents, and prior health care utilization variables. The 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 Agency for Healthcare Re-

Table 2. Initial List of Candidate Factors Associated With Antipsychotic Polypharmacy

- Demographics
  - Age
  - Gender
  - Race
- Eligibility categories
  - Medicare-eligible
  - Aid category (aged, blind, disabled)
  - Georgia vs California
- Diagnosis-related comorbidities
  - Congestive heart failure
  - Myocardial infarction
  - Cardiac arrhythmias
  - Valvular disease
  - Peripheral vascular disorders
  - Hypertension
  - Hemiplegia/paraplegia
  - Epilepsy*
    - Other neurologic disorders†
  - Chronic pulmonary disease
  - Asthma
  - Tuberculosis
  - Diabetes, uncomplicated*
    - Diabetes, complicated†
  - Thyroid disorder
  - Renal failure and chronic disorders
  - Liver disease
  - Peptic ulcer disease
  - AIDS
  - Metastatic solid tumor*
    - Any malignancy†
  - Rheumatoid arthritis/collagen vascular disease
  - Coagulopathy
  - Obesity
  - Weight loss/malnutrition
  - Fluid and electrolyte disorders
  - Anemias
  - Sickle cell anemia
  - Drug abuse*
    - Alcohol abuse†
  - Bipolar and manic depressive illness*
    - Other psychoses/mixed psychoses†
    - Other mental disorders†
    - Personality disorders†
    - Depression or schizoaffective disorder†
  - Cerebrovascular disease
  - Alzheimer's disease*
    - Non-Alzheimer's dementia†
  - Non-head trauma
  - Head trauma
  - Drug overdose
  - Ophthalmologic disease
  - Anxiety states
  - No. of comorbidities per patient
- Drug classes
  - 4 Cardiac drug classes (antiarrhythmic + inotropic + vasopressor, ACE inhibitors, antianginal agents, loop diuretics)
  - Parkinson's disease drugs
  - Peripheral vascular disorder drugs
  - Hypertension drugs
  - 3 Respiratory drug classes (adrenergic bronchodilators + asthma vasopressors + combinations, methylxanthines, inhalants + leukotrienes + combinations)
  - Insulins*
    - Oral hypoglycemic†
  - Cancer drugs
  - 3 Epilepsy drug classes (hydantoin + succinimide + oxazolidinedione, barbiturates + certain benzodiazepines, miscellaneous anticonvulsants [valproic acid and derivatives, carbamazepine and derivatives, gabapentin, lamotrigine, tiagabine, topiramate, levetiracetam]
  - Glaucoma drugs
  - Gout drugs
  - Hyperlipidemia, hypercholesterolemia drugs
  - Thyroid disorder drugs
  - Menopause drugs (hormone replacement therapy)
  - Allergy drugs
  - Anxiety drugs
  - Pain (terminal) drugs, narcotic, analgesic
  - Depression drugs
  - Dementia/Alzheimer's drugs
  - Tuberculosis drugs
  - Rheumatologic drugs/Crohn's disease drugs/ulcerative colitis drugs
  - Migraine drugs
  - ESRD/transplant drugs
  - No. of drug classes per patient (mean)
- Antipsychotic agents
  - Atypicals: olanzapine, risperidone, quetiapine, clozapine
  - Conventionals: haloperidol oral and injectable, fluphenazine oral and injectable, thioridazine, chlorpromazine, thiothixene
- Mood stabilizer
  - Lithium
- Prior health care utilization
  - Mental health cost in prior period[a]
  - No. of psychiatric outpatient physician visits, physician specialty
  - Psychiatric inpatient episode, latest inpatient days, cumulative inpatient days
  - Regular antipsychotic use (antipsychotic prescription filled every 2 mo)
- Date variables
  - Quarter in which episode started
  - Year in which episode started

[a]The prior period was the 6 months preceding the polypharmacy or monotherapy episode.
*Indicates that a hierarchy exists in relation to the cost categories below, which are denoted by a dagger (†). If both comorbidities were present, only the higher cost category was counted.
Abbreviations: ACE = angiotensin-converting enzyme, AIDS = acquired immunodeficiency syndrome, ESRD = end-stage renal disease.

search and Quality project to develop risk adjustment indices for persons suffering from schizophrenia. The month and year of the episode start date were also included to identify any yearwise or seasonal trend in use. The list of antipsychotic agents consisted of the 10 most prevalent drugs identified from a frequency analysis of the prescription records from the prior period (the 6 months preceding polypharmacy or monotherapy). Haloperidol and fluphenazine were categorized by mode of administration to differentiate between the injectable and oral dosage forms; this was done because the injectable forms are generally prescribed to a less compliant group of patients[28] and compliance in turn may be an important factor associated with choice of therapy.

A stepwise logistic variable selection procedure was used to test the hypothesis that demographics, diagnosis-related comorbidities, drug classes, antipsychotic agents, and prior health care utilization variables (identified in

Table 3. Demographic Characteristics of a Sample of Medicaid-Eligible Schizophrenia Patients at Least 16 Years of Age

Characteristic	Georgia (N = 17,728)	California (N = 13,707)	Combined (N = 31,435)
Age, mean (SD), y	43 (17)	43 (13)	43 (14)
Women, N (%)	9928 (56)	5894 (43)	15,822 (50)
Whites, N (%)	6737 (38)	7813 (57)	14,550 (46)

Table 2) are independently associated with long-term antipsychotic polypharmacy. The binary treatment indicator (1 = long-term 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 (p value) of .2 and removed if they did not meet the significance level of .1. To guard against model specification errors using stepwise procedures, we developed the initial model with a 70% random sample and utilized the remaining 30% of the subjects 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 all usage that combines both short- and long-term use. Subanalyses were performed to identify factors associated with usage by type of antipsychotic, e.g., clozapine, atypical + atypical, atypical + conventional, and conventional + conventional polypharmacy, and any differences from the primary analysis were reported. The database was managed using SAS software Version 8.02,[29] and statistical analysis was performed using SAS and STATA Version 6.0.[30]

RESULTS

Prevalence of Antipsychotic Polypharmacy

We found that 32,280 persons (Georgia, 18,373; California, 13,907) had received at least 1 primary diagnosis of schizophrenia between 1998 and 2000, of whom 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 was 43 years (SD = 14 years) (both Georgia and California patients had mean ages of 43 years), 50% were female (Georgia, 56%; California, 43%), and 46% were white (Georgia, 38%; California, 57%) (Table 3). Of 31,435 persons, 88% (N = 27,757) had received at least 1 prescription for an antipsychotic drug. Of those who received any polypharmacy, 48% were female and 47% were white. The overall prevalence of any antipsychotic polypharmacy was 40% (N = 12,549) over the period 1998–2000 and was 46% in California compared with 35% in Georgia (p < .0001). The mean duration of polypharmacy was 149 days.

A total of 23% (N = 7222) of recipients had 1 or more long-term antipsychotic polypharmacy episodes (Table 4). California had a significantly higher prevalence of antipsychotic polypharmacy across all the antipsychotic polypharmacy categories (p < .0001). The prevalence of long-term polypharmacy was highest among subjects exposed to clozapine (36.2%).

Table 4. Prevalence of Long-Term Antipsychotic Polypharmacy in a Sample of Medicaid-Eligible Schizophrenia Patients at Least 16 Years of Age, 1998–2000

Treatment Variable	Georgia (N = 17,728)	California (N = 13,707)	Combined (N = 31,435)
Received long-term polypharmacy, %	18.1	29.3	23.0
Received long-term clozapine polypharmacy, %	1.3	4.2	2.5
Clozapine + atypical	0.9	2.6	1.6
Clozapine + conventional	0.5	2.4	1.3
Received long-term nonclozapine polypharmacy, %	16.1	23.7	19.4
Atypical + atypical	2.2	6.1	3.9
Conventional + conventional	2.0	3.7	2.8
Atypical + conventional	13.4	18.7	15.7
Exposed to clozapine therapy			
N	865	1346	2211
Received long-term polypharmacy, %	25.7	42.9	36.2
Exposed to atypical therapy			
N	11,325	8641	19,966
Received long-term polypharmacy, %	24.2	36.2	29.4
Exposed to conventional therapy			
N	10,781	7981	18,762
Received long-term polypharmacy, %	25.1	37.9	30.6

Among the 7222 persons with 1 or more long-term episodes, there were over 2.0 episodes (95% CI = 2.0 to 2.1) per recipient between 1998 and 2000, with a mean duration of 236 days per episode (95% CI = 230.3 to 241.6) (Table 5). On average, a long-term polypharmacy patient was exposed to polypharmacy for a total of 1 year (367 days) over the 3-year period, which after adjustment for differences in total months of Medicaid eligibility translated to 388 days of polypharmacy for each recipient who was continuously eligible for 3 years. A trend was observed toward higher polypharmacy episode duration for California Medicaid recipients compared with Georgia recipients across all categories. Long-term clozapine polypharmacy episodes had a longer mean duration of 301 days than long-term nonclozapine polypharmacy episodes, which lasted for a mean of 225 days (Table 5).

Among the long-term antipsychotic polypharmacy groups, clozapine polypharmacy accounted for 11% of all long-term polypharmacy, and atypical + conventional polypharmacy accounted for 68% of all long-term polypharmacy.

Trends in Antipsychotic Polypharmacy

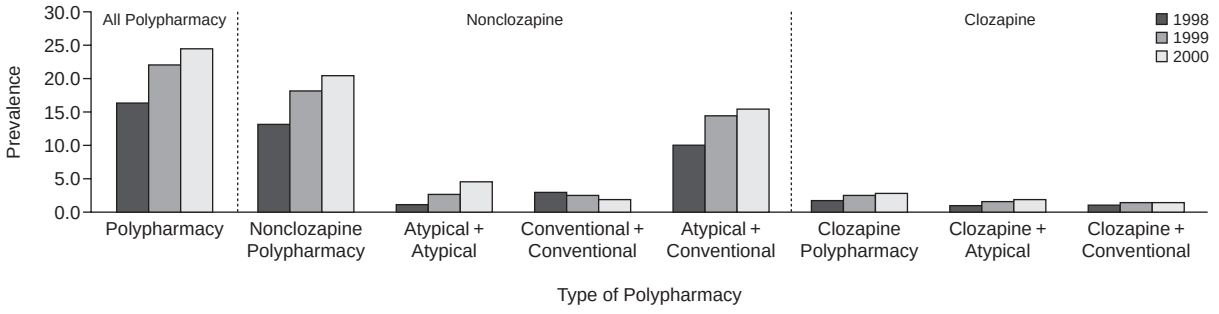
The 3-year trend of long-term antipsychotic polypharmacy is presented in Figure 3. The overall prevalence

Table 5. Number and Length of Long-Term Antipsychotic Polypharmacy Episodes by Type of Polypharmacy, 1998–2000

Polypharmacy Type	Georgia, Mean (95% CI)	California, Mean (95% CI)	Combined, Mean (95% CI)
All long-term polypharmacy			
No. of episodes	2.1 (2.1 to 2.2)	2.0 (2.0 to 2.1)	2.1 (2.0 to 2.1)
Length of episode, d	191.1 (184.4 to 197.7)	271.7 (263.2 to 280.2)	235.9 (230.3 to 241.6)
Long-term clozapine polypharmacy[a]			
No. of episodes	1.6 (1.4 to 1.7)	1.6 (1.5 to 1.7)	1.6 (1.5 to 1.6)
Length of episode, d	244.2 (212.8 to 275.5)	322.4 (298.3 to 346.5)	300.6 (281.0 to 320.2)
Clozapine + atypical			
No. of episodes	1.4 (1.2 to 1.5)	1.3 (1.2 to 1.4)	1.3 (1.2 to 1.4)
Length of episode, d	256.0 (214.0 to 298.0)	319.9 (279.3 to 360.5)	295.4 (265.6 to 325.2)
Clozapine + conventional			
No. of episodes	1.4 (1.2 to 1.7)	1.7 (1.5 to 1.9)	1.6 (1.5 to 1.8)
Length of episode, d	253.8 (177.7 to 330.0)	346.4 (294.0 to 398.8)	323.2 (279.4 to 366.9)
Long-term nonclozapine polypharmacy			
No. of episodes	2.1 (2.1 to 2.2)	2.0 (2.0 to 2.1)	2.1 (2.0 to 2.1)
Length of episode, d	188.3 (181.3 to 195.2)	257.7 (248.6 to 266.9)	225.3 (219.4 to 231.0)
Atypical + atypical			
No. of episodes	1.4 (1.4 to 1.5)	1.5 (1.4 to 1.5)	1.5 (1.4 to 1.5)
Length of episode, d	180.2 (164.8 to 195.6)	208.0 (194.7 to 221.2)	199.2 (188.9 to 209.5)
Conventional + conventional			
No. of episodes	2.1 (1.9 to 2.2)	1.8 (1.7 to 1.9)	1.9 (1.8 to 2.0)
Length of episode, d	205.0 (181.7 to 228.3)	274.6 (249.6 to 299.6)	245.8 (228.2 to 263.5)
Atypical + conventional			
No. of episodes	2.0 (1.9 to 2.0)	1.9 (1.8 to 1.9)	1.9 (1.9 to 2.0)
Length of episode, d	182.8 (175.7 to 189.9)	242.5 (233.0 to 252.1)	213.8 (207.8 to 219.9)

[a]Defined as concurrent use of clozapine and a nonclozapine antipsychotic. At this level, "nonclozapine" is not differentiated into atypical or conventional. Therefore, a clozapine + atypical episode and clozapine + conventional episode occurring within 31 days of each other would be considered 1 episode and not 2 separate episodes.

Figure 3. Prevalence of Long-Term Antipsychotic Polypharmacy by Type, 1998–2000



of all antipsychotic polypharmacy increased significantly from 32% in 1998 to 41% in 2000 (Cochran-Armitage test: $p < .0001$); the increase in Georgia was from 24% to 30% and in California from 43% to 62%. Except for clozapine + conventional polypharmacy (no change) and conventional + conventional polypharmacy (decreased), all antipsychotic polypharmacy prevalences increased from 1998 through 2000 (Cochran-Armitage test: $p < .0001$).

Factors Associated With Antipsychotic Polypharmacy

Of the 7222 schizophrenia patients who received long-term antipsychotic polypharmacy between 1998 and 2000, 6438 were continuously eligible for Medicaid and had at least 1 claim every 90 days in the 6-month period preceding the episode and were retained to study the factors associated with antipsychotic polypharmacy. A total of 8757 patients received long-term monotherapy and met the inclusion criteria. A 70% random sample, 4422 antipsychotic polypharmacy subjects and 6162 monotherapy subjects, was retained for the primary analysis, and the remaining subjects were analyzed separately to estimate the validity of the final model specification. Table 6 provides the adjusted odds ratios, 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. Forty variables were retained in the final model, and all variables were associated with long-term antipsychotic polypharmacy at a significance level of $< .05$ except for use of antihypertensive drugs ($p = .0579$), insulins ($p = .0649$), and

Table 6. Independent Factors Associated With Long-Term Antipsychotic Polypharmacy Identified From the Stepwise Logistic Variable Selection Procedure[a]

Factor	Polypharmacy (N = 4422)	Monotherapy (N = 6162)	Odds Ratio	95% CI	p Value
Eligible for Medicaid in Georgia (vs California)	1900 (43.0)	3821 (62.0)	0.62	0.54 to 0.70	< .0001
Gender, male	2359 (53.3)	2792 (45.3)	1.15	1.02 to 1.29	.0197
Eligibility category					
Aid category (aged, blind, or disabled)	4377 (99.0)	5917 (96.0)	2.66	1.72 to 4.11	< .0001
Diagnosis-related comorbidities					
Epilepsy	505 (11.4)	211 (3.4)	1.44	1.11 to 1.87	.0053
AIDS	32 (0.7)	71 (1.1)	0.52	0.27 to 0.98	.0433
Weight loss/malnutrition	16 (0.4)	12 (0.2)	4.50	1.54 to 13.17	.0060
Alcohol abuse	64 (1.4)	111 (1.8)	0.58	0.36 to 0.93	.0237
Other psychoses/mixed psychoses	622 (14.1)	666 (10.8)	1.27	1.06 to 1.53	.0096
Other mental disorders	921 (20.1)	1109 (18.0)	1.18	1.01 to 1.37	.0310
Personality disorders	263 (6.0)	386 (6.2)	0.71	0.55 to 0.92	.0082
Drug classes					
First- and second-line antihypertensive drugs	1076 (24.3)	1411 (22.9)	1.15	0.99 to 1.32	.0579
Exposure to 1 of 4 cardiac drug classes[b]	413 (9.3)	607 (9.8)	0.81	0.66 to 0.99	.0427
Parkinson's disease drugs	3138 (71.0)	2850 (46.2)	2.84	2.50 to 3.23	< .0001
Exposure to 3 of 3 respiratory drug classes[c]	33 (0.7)	34 (0.5)	2.41	1.11 to 5.21	.0255
Insulins	149 (3.4)	274 (4.4)	0.75	0.55 to 1.02	.0649
Cancer drugs	58 (1.3)	53 (0.9)	1.84	1.06 to 3.19	.0298
Exposure to 1 of 2 antiepileptic drug classes[d]	2070 (46.8)	1686 (27.4)	1.32	1.16 to 1.51	< .0001
Gout drugs	26 (0.6)	36 (0.6)	1.77	0.91 to 3.43	.0906
Hyperlipidemia, hypercholesterolemia drugs	320 (7.2)	372 (6.0)	1.33	1.05 to 1.67	.0175
Tuberculosis drugs	27 (0.6)	16 (0.3)	2.48	0.99 to 6.20	.0158
Antipsychotic agents					
Clozapine	490 (11.1)	393 (6.4)	11.77	9.23 to 15.01	< .0001
Olanzapine	1856 (42.0)	1048 (17.0)	14.45	12.27 to 17.01	< .0001
Risperidone	1248 (28.2)	1037 (16.8)	9.18	7.75 to 10.87	< .0001
Quetiapine	519 (11.7)	80 (1.3)	18.32	13.07 to 25.68	< .0001
Haloperidol					
Oral	1000 (22.6)	764 (12.4)	6.53	5.45 to 7.83	< .0001
Injectable	575 (13.0)	285 (4.6)	5.43	4.32 to 6.84	< .0001
Fluphenazine					
Oral	490 (11.1)	352 (5.7)	5.50	4.36 to 6.95	< .0001
Injectable	422 (9.5)	291 (4.7)	5.13	4.00 to 6.60	< .0001
Thioridazine	543 (12.3)	373 (6.0)	18.61	14.80 to 23.40	< .0001
Chlorpromazine	418 (9.4)	114 (1.8)	28.87	21.14 to 39.42	< .0001
Thiothixene	282 (6.4)	244 (4.0)	8.44	6.39 to 11.16	< .0001
Mood stabilizer					
Lithium	566 (12.8)	499 (8.1)	1.31	1.08 to 1.58	.0057
Health care utilization in 6 months preceding therapy episode					
Mental health cost in 6-month period, mean (SD), $	4237 (5762)	2584 (4552)	1.00	1.00 to 1.00	< .0001
No. of psychiatric outpatient physician visits, mean (SD)	1.7 (4.5)	1.0 (2.5)	1.03	1.01 to 1.05	.0061
Regular antipsychotic use (antipsychotic prescription filled every 2 mo)	3655 (82.6)	3344 (54.3)	4.84	4.21 to 5.57	< .0001
Psychiatric inpatient episode	695 (15.7)	589 (9.6)	1.42	1.17 to 1.73	.0004
Date variables					
3rd quarter start date (July, August, September)[e]	1889 (42.7)	3688 (59.8)	0.70	0.59 to 0.83	< .0001
4th quarter start date (October, November, December)[e]	858 (19.4)	915 (14.8)	2.46	2.03 to 2.99	< .0001
Year 1999 start date[f]	1644 (37.2)	1574 (25.5)	5.53	4.67 to 6.54	< .0001
Year 2000 start date[f]	1275 (28.8)	1079 (17.5)	9.67	7.93 to 11.77	< .0001

[a]Values shown as N (%) unless otherwise noted. Association of predicted probabilities and observed responses: c-statistic for the final model = 0.9143, c-statistic for validation sample = 0.9174.
[b]Cardiac drug classes are (1) antiarrhythmic + inotropic + vasopressor, (2) angiotensin-converting enzyme (ACE) inhibitors, (3) antianginal agents, and (4) loop diuretics.
[c]Respiratory drug classes are (1) adrenergic bronchodilators + asthma vasopressors + combinations, (2) methylxanthines, and (3) inhalants + leukotrienes + combinations.
[d]Antiepileptic drug classes are barbiturates + certain benzodiazepines and miscellaneous anticonvulsants (valproic acid and derivatives, carbamazepine and derivatives, gabapentin, lamotrigine, tiagabine, topiramate, levetiracetam).
[e]1st quarter odds ratio = 1.
[f]Year 1998 odds ratio = 1.
Abbreviation: AIDS = acquired immunodeficiency syndrome.

gout drugs (p = .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 those who used long-term antipsychotic polypharmacy and those who used monotherapy. The c-statistic for the final model in the 30% validation sample was 0.917, which shows that the model could discriminate equally well between antipsychotic polypharmacy and monotherapy in an external sample and suggests 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 with being eligible for California Medicaid (OR = 0.62, 95% CI = 0.54 to 0.70). Being of male gender and belonging to the aid category (aged, blind, disabled) were associated with an increased likelihood of receiving long-term antipsychotic polypharmacy. Among the diagnosis-related comorbidities, weight loss or malnutrition was strongly associated with long-term antipsychotic polypharmacy (OR = 4.50, 95% CI = 1.54 to 13.17), although the absolute numbers were small in both the antipsychotic polypharmacy and monotherapy groups. Diagnosis of epilepsy, other psychoses, and other mental disorders was also positively associated with long-term antipsychotic polypharmacy.

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

All antipsychotic drugs selected in the model were strongly associated (ORs of 5 to 28, p < .0001) with a higher likelihood of long-term antipsychotic polypharmacy. Among the atypical antipsychotics, quetiapine had the highest positive association with long-term antipsychotic polypharmacy (OR = 18.32, 95% CI = 13.07 to 25.68), followed by olanzapine (OR = 14.45) and risperidone (OR = 9.18). Among the conventionals, chlorpromazine (OR = 28.87, 95% CI = 21.14 to 39.42), followed by thioridazine (OR = 18.61) and thiothixene (OR = 8.44), had the highest positive associations. Clozapine (OR = 11.77) was also associated with long-term antipsychotic polypharmacy.

Among the prior utilization variables, regular antipsychotic use (1 antipsychotic prescription filled every 2 months) was associated (OR = 4.8) with long-term antipsychotic polypharmacy. Among the temporal variables, index dates in the fourth quarter (October, November, December) had a higher association with antipsychotic polypharmacy (OR = 2) compared with those in the first quarter. Also, the years 1999 (OR = 5.53) and 2000 (OR = 9.67) had a higher association with long-term antipsychotic polypharmacy compared with 1998.

Diagnosis of acquired immunodeficiency syndrome (AIDS) (OR = 0.52), alcohol abuse (OR = 0.58), and personality disorders (OR = 0.71) and drug use for cardiac conditions (OR = 0.81) were negatively associated with long-term antipsychotic polypharmacy, although the strength of association was low (p ~ .05) for AIDS and drug use for cardiac conditions.

No additional factors were identified in the clozapine polypharmacy versus clozapine monotherapy analysis. However, in the nonclozapine groups, arrhythmia (OR = 2.0, 95% CI = 0.97 to 4.33), chronic obstructive pulmonary disease (COPD) (OR = 1.7, 95% CI = 1.14 to 2.57), asthma (OR = 2.3, 95% CI = 1.18 to 4.60), and complicated diabetes (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

The *Journal of Clinical Psychiatry* treatment guideline[28] and some review articles on antipsychotic usage[1,2,31] recognize antipsychotic polypharmacy as a possible option in 2 specific situations: short-term or p.r.n. use for "symptom control" and as a short-term tactic while switching from one monotherapy to another. The *Journal of Clinical Psychiatry* guideline is the only one that defines this short-term usage period, placing it at 2 months. However, the authors also acknowledge the lack of published evidence and potential for adverse events with antipsychotic polypharmacy. Therefore, it is of concern to see that 23% of patients received polypharmacy for more than 2 months and the mean duration of use was almost 8 months.

We found no previous studies that report prevalence data for Medicaid-eligible schizophrenia patients or any that report prevalence of long-term polypharmacy for any population. However, the overall combined prevalence rate of long-term and short-term polypharmacy in our study was similar to that reported in a 1985 survey of 768 patients in 8 countries (overall prevalence = 40%, U.S. prevalence = 36%)[1] but was considerably higher than the prevalence reported in a more recent Veterans Affairs (VA) study looking at data over a short 4-month time period (6.8%)[32] and was also higher than those in a 1-year prevalence study using physician office–based data from 1997 (16.7%)[33] and a Canadian study of hospital outpatients (27.5%).[34] Some of the factors responsible for a higher prevalence estimate in our study could be a longer study time frame (the VA study captured prescription records during a 1-week period), a more recent year of study (the physician office–based study was performed in 1997), Medicaid system-specific policies (California and Georgia Medicaid had removed a prior authorization rule

restricting newer antipsychotic use in 1997, which may have increased antipsychotic switches, inflating our prevalence estimates), and analysis of a Medicaid population, which is considered a more ill group of patients than non–Medicaid-eligible persons with schizophrenia.

The 11% difference in prevalence of long-term polypharmacy between California and Georgia is interesting. Additionally, the rate of increase in the prevalence of long-term antipsychotic polypharmacy from 1998 to 2000 was notably higher in California (19%) than in Georgia (6%). There are several potential reasons for this occurrence. First, these findings could be a result of differences in reimbursement policies. We compared the prescription and inpatient reimbursement policies between the 2 states and found no substantial difference. Both states had rules requiring prior authorization for atypical agents before 1998, reimbursed mental health hospitalizations, had state psychiatric hospitals that bill Medicaid, and had similar treatment authorization procedures. However, we cannot discount the fact that there could have been policy changes between 1998 and 2000 that we are not aware of that could have driven these prevalence rates. Second, the difference in prevalence rate could be a reflection of dissimilar prescribing habits in the 2 states. However, among schizophrenia patients who received at least 1 prescription for an antipsychotic, antipsychotic prescribing rates, which are a marker for prescribing habits, were similar in the 2 states (atypicals: Georgia, 49%; California, 48%; conventionals: Georgia, 47%; California, 44%) except for clozapine (Georgia, 4%; California, 7%). Other process-related measures, for example, the average number of physicians seen by California subjects compared with Georgia subjects, could be responsible for the difference in long-term polypharmacy rates. These are, however, speculations and cannot be confirmed through our analysis.

The rising trend for all atypical polypharmacy combinations (atypical + atypical, atypical + conventional, atypical + clozapine) may be because of increased availability of newer antipsychotics or changing prescribing habits. As newer antipsychotics become available, there is a higher probability of receiving antipsychotic polypharmacy as patients on treatment with older antipsychotics are switched to newer medications. The rise in atypical polypharmacy could also be due to changing prescribing habits among physicians as they find success and a growing confidence in treating patients with antipsychotic polypharmacy.

Long-term clozapine polypharmacy episodes had a mean duration of 301 days (95% CI = 281 to 320) and lasted longer than nonclozapine episodes (225 days, 95% CI = 219 to 231); this may be explained by the fact that clozapine is reserved for treatment-refractory patients who require longer durations of treatment than the relatively better controlled nonclozapine patients. 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 (31%), suggesting refractory patients and less control with monotherapy in the clozapine group.

The long-term nonclozapine atypical + conventional group had the highest prevalence, 16%. The therapeutic actions of conventional antipsychotic drugs are due to blockade of dopamine (D_2) receptors, whereas the atypical antipsychotics block both D_2 and serotonin 5-HT_{2A} receptors.[35] Due to the differing receptor profiles, there may be a pharmacologic justification for combining atypicals with conventionals and using them for a long duration, but there are no clinical studies that provide evidence for such use. Individuals in the atypical + conventional group in our study could have been patients receiving treatment on a switchover or p.r.n. basis who were started on a short-term combination therapy and then remained on it for some reason. For example, the therapy may have been continued if a patient was stable and the physician did not want to risk a relapse; this has been quoted as a reason in a study of antipsychotic polypharmacy.[36] Physicians may also be observing that their patients are stabilized on atypical + conventional combination treatment and that there is real merit to such therapy.

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 conditions may induce a physician to switch to a better-tolerated treatment. However, since our study did not have a medication-free washout period (49% of the antipsychotic polypharmacy patients had received polypharmacy in some prior period), these could be side effects of prior treatment with antipsychotic polypharmacy or monotherapy. The association between diagnosis of cardiac arrhythmia and nonclozapine atypical + atypical polypharmacy (OR = 2.0) was as expected, given that cardiovascular side effects such as tachycardia are common with atypical monotherapy. Although a causal relationship cannot be established from our analysis, this association may reflect an increased risk of cardiac side effects with atypical polypharmacy. At the same time, this association may be indicative of an effort to reduce cardiovascular side effects by titrating the patient to a better-tolerated therapy. However, in the absence of any other information on this association, it might be prudent to exercise caution, e.g., regular electrocardiogram monitoring, especially while adding one atypical to another. Similarly, Parkinson's disease was strongly associated ($p < .0001$) with nonclozapine polypharmacy involving conventional antipsychotics (OR > 3.5). The positive association between complicated diabetes and atypical + atypical polypharmacy may reflect recent concerns about the occurrence of diabetes associated with the use of olanzapine.[37] The positive association between asthma/

COPD and atypical + atypical polypharmacy may be explained through evidence in the medical literature that suggests noncausal mechanisms such as noncompliance to asthma therapy in this population and causal mechanisms such as depression of the central nervous system and impaired respiratory drive during asthma attacks.[38]

The odds ratios for all of the antipsychotic drugs were high because we included only antipsychotics that were highly prevalent in the long-term polypharmacy cohort. We did this because we were interested in understanding the relative effects of being prescribed these 10 drugs, which are evident from the odds ratios. One of the interesting findings was that being placed on more recently marketed atypical antipsychotics was associated with an increased likelihood of being exposed to long-term polypharmacy; for example, for quetiapine, launched in 1997, OR = 18.32; for olanzapine, launched in 1996, OR = 14.45; and for risperidone, launched in 1994, OR = 9.18. One explanation for this could be that more people on treatment with the most recent atypical compared with other medications are in a switchover stage. This trend was similar across all the groups. Also, use of low-potency antipsychotic medications such as quetiapine or chlorpromazine was strongly associated with long-term antipsychotic polypharmacy.

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 clozapine + atypical and atypical + atypical combinations are especially expensive, and the atypical + atypical combinations have been mentioned as cost drivers and a concern in the California Medicaid system.[39] Using the estimates for mean length of episode, number of episodes, prevalence by type of polypharmacy and a per-day average cost of antipsychotic,[40] we calculated a rough speculative estimate* for the excess antipsychotic cost per year to Medicaid due to long-term polypharmacy. The annual cost to the Medicaid systems of adding a second antipsychotic in 2000 U.S. dollars was $494,877 for Georgia and $6,032,775 for California. From a policy perspective, if Medicaid considered implementing a prior authorization rule for long-term polypharmacy (usage beyond 60 days), the Medicaid systems could save $412,397 and $5,027,312 per year in antipsychotic prescription costs in Georgia and California, respectively. These estimates are based only on the incremental cost of the additional antipsychotic drugs when used concurrently with another antipsychotic and do not include any administrative or indirect costs (savings) such as drug level monitoring costs or additional or reduced hospitalizations that may be associated with polypharmacy.

The higher cost in California was driven by the fact that California has a larger Medicaid population, higher prevalence of clozapine + atypical and atypical + atypical polypharmacy, and longer durations of polypharmacy. It is also important to note that in California there was a 9-fold increase in the likelihood of atypical + atypical long-term polypharmacy in 1999 over 1998 and that there was a 21-fold increase in 2000. This change was the highest among all other antipsychotic polypharmacy groups. While evaluating these speculative cost estimates, it is important to bear in mind that they are based on average wholesale prices and recommended daily dosing, which act as proxy measures for Medicaid-specific drug prices and actual average prescribed doses, respectively.

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, we singled out the longest episodes in our analysis to identify factors associated with polypharmacy. The identified longest episode may not be the first episode 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 polypharmacy therapy.

Unless specifically mentioned, prevalence data reported here have not been adjusted for the fact that total months of Medicaid eligibility over the 3-year period varied between recipients. However, this may have affected the results marginally, because over 90% of polypharmacy subjects were continuously eligible for more than 2 years and 79% were continuously eligible for all 3 years. Additionally, the eligibility profile was very similar (California vs. Georgia, 78% vs. 80% continuously eligible for 3 years) for both states and would not have affected between-state comparisons.

*Drug cost per day was calculated as the unit cost (average wholesale price) of each drug multiplied by the average maintenance phase daily dose (mg/day) of the drug as derived from the *Journal of Clinical Psychiatry* treatment guideline. The average maintenance phase daily doses for commonly prescribed agents were olanzapine 10 mg, risperidone 4 mg, quetiapine 300 mg, haloperidol 5 mg, fluphenazine 5 mg, and thioridazine 300 mg. A weighted average daily cost of atypicals (~ $8) and conventionals (~ $0.23) was obtained using the product-specific drug cost per day and the utilization of the different atypical and conventional drugs observed in Georgia and California Medicaid. The annual cost of adding a second antipsychotic was calculated separately for each polypharmacy group by multiplying the weighted average daily cost for atypical or conventional, multiplied by the average duration of polypharmacy, multiplied by the number of episodes of that polypharmacy combination. It was assumed that when there were combinations using conventional drugs, the conventional drug would be the drug discontinued and represent the incremental cost (atypicals and clozapine were assumed to be the drugs that would be kept if the patient had to be treated with only 1 antipsychotic), and atypical costs were counted only for atypical + atypical or clozapine + atypical polypharmacy episodes.

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 Positive and Negative Syndrome Scale scores that may be important predictors of antipsychotic polypharmacy. Our results are specific to Medicaid-eligible schizophrenia patients and may not be generalizable to other patient populations.

CONCLUSION

Long-term antipsychotic polypharmacy is widely prevalent (23%), is prescribed for long durations (~ 8 months), and is an increasing phenomenon among Medicaid-eligible schizophrenia patients, indicating a significant discrepancy with practice guidelines. Effectiveness research is needed to define the full scope and potential for prescribing antipsychotic polypharmacy. In the absence of this information, clinicians have little or no prescribing guidance to treat schizophrenia patients who have had a partial response or nonresponse to adequate doses of single antipsychotics.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Tegretol, and others), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Fazaclo, Clozaril, and others), fluphenazine (Prolixin, Permitil, and others), gabapentin (Neurontin and others), haloperidol (Haldol and others), lamotrigine (Lamictal), levetiracetam (Keppra), lithium (Eskalith, Lithobid, and others), loxapine (Loxitane and others), mesoridazine (Serentil), molindone (Moban), olanzapine (Zyprexa), perphenazine (Trilafon and others), pimozide (Orap), prochlorperazine (Compazine, Compro, and others), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane and others), tiagabine (Gabitril), topiramate (Topamax), trifluoperazine (Stelazine and others), valproic acid (Depakene and others), ziprasidone (Geodon).

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