Trends in and Predictors of Long-Term Antipsychotic Polypharmacy Use Among Ohio Medicaid Patients with Schizophrenia, 2008–2014

Cynthia A. Fontanella, Ph.D., Danielle L. Hiance-Steelesmith, Ph.D., Hossam Guirgis, M.D., John V. Campo, M.D.

Objective: The study examined trends and patterns in long-term antipsychotic polypharmacy among Ohio Medicaid patients with schizophrenia and predictors of use.

Methods: A study using a retrospective cohort design and Medicaid claims data was conducted for a cohort of 25,062 adults with a schizophrenic disorder receiving antipsychotic medication between 2008 and 2014. Long-term antipsychotic polypharmacy was defined as simultaneous treatment with two or more antipsychotic medications for ≥90 days. Annual trends in antipsychotic polypharmacy were estimated. Multivariate logistic regression was used to identify patient demographic, clinical, and treatment characteristics associated with antipsychotic polypharmacy.

Results: The prevalence of antipsychotic polypharmacy decreased significantly from 29.5% in 2008 (2,715 of 9,211) to 24.9% in 2014 (2,866 of 11,500) (adjusted odds ratio=.98, 99% confidence interval=.97–.99, $p<.001$). Factors significantly associated with antipsychotic polypharmacy included younger age, male sex, disabled status, rural residence, a schizophrenic disorder other than schizoaffective disorder, a greater number of general medical comorbidities, treatment with more psychotropic medication classes, and more outpatient mental health treatment and emergency department visits. Antipsychotic polypharmacy was significantly less likely for African Americans or those from other racial minority groups compared with whites, for those with substance use disorders compared with others, and for those with a greater number of inpatient psychiatric hospitalizations.

Conclusions: Antipsychotic polypharmacy declined for pharmacologically treated individuals with schizophrenia in Ohio Medicaid between 2008 and 2014, but it remained inordinately prevalent given existing treatment guidelines that recommend antipsychotic monotherapy as the standard of care for patients with schizophrenia.

Psychiatric Services 2018; 69:1015–1020; doi: 10.1176/appi.ps.201800052

Treatment guidelines recommend antipsychotic monotherapy as the standard of care for patients with schizophrenia and suggest that the concomitant use of two or more antipsychotics, or antipsychotic polypharmacy, be used only for patients with treatment-resistant illness after multiple trials of antipsychotics, including clozapine (1–3). Antipsychotic polypharmacy is considered acceptable only as a last resort because of limited evidence to support its use (4) and concerns about an elevated risk of adverse side effects, such as extrapyramidal symptoms and cognitive impairment (5–7), overmedication (8,9), long-term safety (for example, risk of diabetes and metabolic syndromes) (10,11), and increased mortality (12,13). Additional concerns include high costs of antipsychotics, especially second-generation antipsychotics, and the negative impact of complicated drug regimens on treatment adherence (14,15).

Despite safety concerns and the paucity of evidence of the efficacy of antipsychotic polypharmacy, the practice is common in real-world clinical settings, with prevalence ranging from 10% to 30%, depending on definition, treatment setting, and patient population (4). Moreover, some evidence suggests that prevalence rates may be increasing. For example, Gilmer and colleagues (16) analyzed 1999–2004 data from Medicaid beneficiaries with schizophrenia (N=15,962) in San Diego County and found that the yearly proportion of beneficiaries receiving second-generation antipsychotic polypharmacy increased from 3.3% in 1999 to 13.7% in 2004. Clark and colleagues (17) examined data from a cohort of 836 Medicaid enrollees with schizophrenia or schizoaffective disorder in New Hampshire and found that antipsychotic polypharmacy increased from 5.7% in 1995 to 24.3% in 1999. Ganguly and colleagues (18) examined trends in antipsychotic polypharmacy among outpatient Medicaid recipients in Georgia and California and found that antipsychotic polypharmacy increased from 32% in 1998 to 41% in 2000.

To the best of our knowledge no recent studies have examined trends in long-term antipsychotic polypharmacy in

a Medicaid population. The few prior studies that have examined trends in antipsychotic polypharmacy have focused on short-term polypharmacy (for example, overlaps of seven, 14, or 30 days), which could reflect cross-titration (transitioning from one antipsychotic to another) rather than deliberate, long-term antipsychotic polypharmacy. Consequently, the proportion of patients receiving persistent, long-term polypharmacy is unknown. The objective of this study was to examine trends, patterns, and predictors of long-term of antipsychotic polypharmacy for a statewide Medicaid population of individuals with a schizophrenic disorder (*ICD-9-CM* code 295.xx), a cluster of diagnoses that includes paranoid schizophrenia, schizoaffective disorder, and unspecified schizophrenia. As in previous research (19,20), we used a conservative operational definition of polypharmacy (≥90 days) to identify the persistent long-term use of antipsychotic combinations.

METHODS

Data Source

This study used Medicaid fee-for-service claims and managed care encounter data obtained from the Ohio Department of Medicaid. The database included demographic and clinical information, inpatient and outpatient utilization data, and outpatient prescription data for Medicaid enrollees. Eligibility files included information on monthly enrollment status, eligibility category (for example, covered families and children or disabled), and demographic characteristics of enrollees. Pharmacy files provided information on prescriptions filled by outpatient pharmacies, including dispense dates, generic name and code, national drug code, dosage, days' supply, and quantity. Antipsychotic medications were identified from pharmacy files by using the dispense date and the generic name codes. The institutional and professional files provided information on service claims for inpatient hospitalizations, physician visits, and other outpatient services and included dates of service, CPT/HCPCS procedure codes, and up to seven *ICD-9-CM* diagnoses. All procedures were approved by the Ohio State University Institutional Review Board.

Study Design and Sample

This observational study employed a retrospective cohort design with administrative claims data. Eligibility for inclusion in the sample was defined by two or more claims for a schizophrenic disorder (*ICD-9-CM* code 295.xx) between January 1, 2008, and December 31, 2014, and ages 18–64. Inclusion in each yearly rate was defined by continuous enrollment in Medicaid during the year and at least one prescription for antipsychotic medication during the year. The final analytic working database included 25,062 unique individuals (N=9,211 in 2008 and N=11,500 in 2014) with 70,993 observations. [A table in an online supplement to this article provides data on the demographic and clinical characteristics of the study sample in 2008 and 2014.] In 2014, the mean±SD age was 45.5±12.3, and the sample included 5,987 (52.1%) males. The same year, a total of 6,746 (58.7%) individuals were white, 10,292 (89.5%) were eligible for Medicaid on the basis of disability, and 6,510 (56.6%) had a diagnosis of a specific schizophrenic disorder (for example, schizophreniform disorder, disorganized schizophrenia, or paranoid schizophrenia) or unspecified schizophrenia rather than schizoaffective disorder (that is, a schizophrenic disorder with a prominent mood component).

Antipsychotic Polypharmacy

Antipsychotic polypharmacy was defined as two or more antipsychotic medications overlapping for ≥90 days at any time during the study period, with an allowable 14-day gap between prescription fills. Antipsychotics were classified as first-generation, second-generation, and clozapine. The first-generation antipsychotic medications included chlorpromazine, fluphenazine, haloperidol, loxapine, molindone, perphenazine, pimozide, prochlorperazine, thioridazine, thiothixene, and trifluoperazine. The second-generation antipsychotics included aripiprazole, asenapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. Clozapine was considered to be a unique agent given that it is typically used for patients with treatment-resistant schizophrenia.

Predictors of Long-Term Polypharmacy

Participants were selected for these analyses on the basis of the following criteria: long-term antipsychotic polypharmacy or antipsychotic monotherapy for ≥90 days between 2008 and 2014; continuous Medicaid enrollment for six months prior to the index prescription date of antipsychotic polypharmacy or monotherapy (referred to hereafter as the preindex period); and at least one claim for a schizophrenic disorder during the preindex period.

Predictor variables were selected on the basis of previous studies of correlates of antipsychotic polypharmacy (21). Patient characteristics included age (18–35, 36–50, and 51–64), race (white, black, and other), sex, area of residence (urban or rural), and Medicaid eligibility based on disability status (yes versus no). Clinical characteristics were identified during the six-month preindex period and included a diagnosis of schizophrenia (rather than schizoaffective disorder) (*ICD-9-CM* code 295), substance use disorder (*ICD-9-CM* codes 304 and 305), any psychiatric comorbidities (all other *ICD-9-CM* codes 290–319), and the Charlson Comorbidity Index (22). Also included were the number of psychotropic medication classes and outpatient, inpatient, and emergency department mental health visits during the preindex period.

Statistical Methods

Trends in demographic and clinical characteristics of study participants are described with frequencies and percentages for 2008 and 2014 [see online supplement]. Patterns of specific antipsychotic use are described by using frequencies

and percentages for each year of the study. Patients could appear in the study any number of times (between one and seven times) between 2008 and 2014. Thus a generalized estimating equation (GEE) population-averaged logistic regression model was used to generate the odds of antipsychotic polypharmacy for ≥90 days for a particular year compared with the prior year. The method of fractional polynomials indicated that the relationship between antipsychotic polypharmacy for ≥90 days and continuous study year was linear. Consequently, the odds ratio (OR) between any two consecutive years is the same. Both the unadjusted and an adjusted OR (AOR) are presented, where the a priori adjustment variables in the GEE logistic regression model are age, gender, race, disabled status, type of primary schizophrenia, any substance abuse, any psychiatric comorbidity, rural versus urban, number of drug classes in the participant's history, Charlson Comorbidity Index score, count of outpatient visits, count of inpatient visits, and count of emergency department visits. When the adjusted GEE model was run, the ORs for the categorical adjustment variables are also presented. In addition, because of the large number of observations over the seven years of the study, statistical significance was set at .01 and 99% confidence intervals (CIs) are presented. All analyses were run with Stata 14.1.

RESULTS

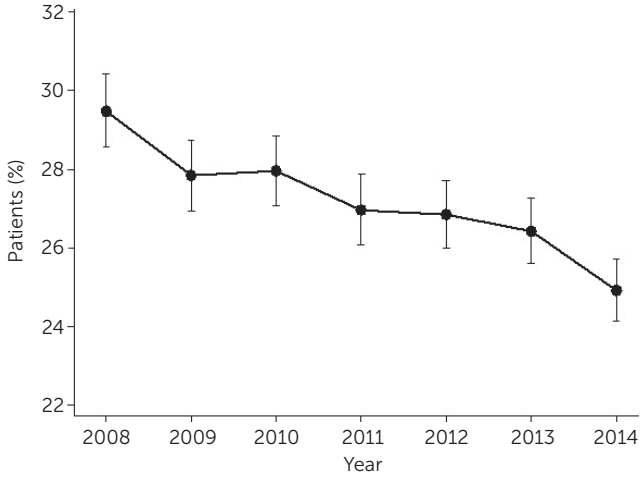
Trends and Patterns of Antipsychotic Polypharmacy

A statistically significant decline was noted in long-term antipsychotic polypharmacy over the study period (Figure 1). The prevalence of antipsychotic polypharmacy decreased from 29.5% in 2008 (2,715 of 9,211) to 24.9% in 2014 (2,866 of 11,500) (AOR=.98, CI=.97–.99, p<.001). Table 1 presents data showing the pattern of long-term polypharmacy from 2008 to 2014 by combination of antipsychotic medications. Of the 2,866 patients receiving antipsychotic polypharmacy in 2014, 88% were prescribed two antipsychotics, 8% were prescribed three, and 4% were prescribed four or more. Among those prescribed two antipsychotics, the most common combination was two second-generation antipsychotics (50%), followed by one second-generation and one first-generation antipsychotic (34%). Twelve percent were prescribed clozapine in combination with another antipsychotic. This pattern was consistent across the study period.

Factors Associated With Long-Term Antipsychotic Polypharmacy

Table 2 presents estimated ORs and CIs from the logistic regression analyses of long-term antipsychotic polypharmacy. Nearly all variables, with the exception of psychiatric comorbidity, were associated with long-term polypharmacy (<.001 for all). Compared with patients ages 18 to 35, those ages 51 to 64 were less likely to receive long-term antipsychotic polypharmacy (OR=.92). Compared with whites, blacks were less likely to receive long-term polypharmacy (OR=.89), as were other racial minority groups (OR=.76). Male gender, being disabled, and living in a rural location were associated with increased odds of receiving long-term polypharmacy (ORs=1.11, 1.73, and 1.18, respectively). Compared with patients with schizophrenia, those with schizoaffective disorder had lower odds of receiving long-term polypharmacy (OR=.89), and patients with a substance use disorder had lower odds of receiving long-term polypharmacy than patients with no such disorder (OR=.87). A 1-unit increase in the Charlson Comorbidity Index score was associated with higher odds of receiving long-term polypharmacy (OR=1.02). Similarly, a 1-unit increase in the number of psychotropic medication classes was associated with higher odds of receiving antipsychotic polypharmacy (OR=1.22). Among the service use variables, higher odds of antipsychotic polypharmacy were associated with increased outpatient and emergency room visits (ORs=1.04 and 1.36, respectively), and lower odds were associated with increased inpatient visits (OR=.95).

FIGURE 1. Trend in long-term antipsychotic polypharmacy among patients with schizophrenia in Ohio Medicaid, 2008–2014[a]



[a] Vertical bars represent 99% confidence intervals.

DISCUSSION

The study findings can be viewed as both encouraging and discouraging from a public health perspective. The observed significant reduction in rates of antipsychotic polypharmacy among Ohio Medicaid patients from 30% in 2008 to 25% in 2014 is encouraging, particularly because studies completed in the 1990s and early 2000s found increasing rates (16,18). This apparent reversal in trend suggests that the reductions in antipsychotic polypharmacy over the study period are likely a result of quality improvement efforts, such as those initiated in 2008 by the Joint Commission in cooperation with the National Association of State Mental Health Program Directors (NASMHPD) and the NASMHPD Research

TABLE 1. Long-term antipsychotic polypharmacy among Ohio Medicaid patients with schizophrenia, 2008–2014[a]

	2008 (N=2,715)		2009 (N=2,682)		2010 (N=2,781)		2011 (N=2,563)		2012 (N=2,798)		2013 (N=2,848)		2014 (N=2,866)	
Pattern	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Combination of 2 antipsychotics	2,373	87	2,337	87	2,428	87	2,229	87	2,423	87	2,483	87	2,523	88
2 second generation	1,317	49	1,303	49	1,366	49	1,255	49	1,350	48	1,407	49	1,437	50
2 first generation	46	2	48	2	40	1	30	1	44	2	44	2	51	2
1 first and 1 second generation	941	35	952	36	952	34	882	34	975	35	962	34	964	34
Clozapine and 1 second generation	256	9	225	8	264	10	242	9	241	9	245	9	239	8
Clozapine and 1 first generation	123	5	117	4	128	5	102	4	118	4	121	4	112	4
Combination of 3 antipsychotics	227	8	228	9	231	8	206	8	227	8	219	8	223	8
2 first and 1 second generation	17	1	21	1	10	<1	9	<1	16	1	11	<1	18	1
2 second and 1 first generation	113	4	121	5	134	5	110	4	120	4	104	4	110	4
3 first generation	0	—	0	—	1	<1	0	—	1	<1	0	—	0	—
3 second generation	65	2	55	2	59	2	48	2	58	2	66	2	69	2
Clozapine and 1 first and 1 second generation	29	1	24	1	26	1	28	1	31	1	28	1	24	1
Clozapine and 2 second generation	29	1	31	1	28	1	24	1	20	1	26	1	24	1
Clozapine and 2 first generation	2	<1	0	—	0	—	1	<1	1	<1	0	—	0	—
Combination of ≥4 antipsychotics	115	4	117	4	122	4	128	5	148	5	146	5	120	4

[a] Percentages may not sum to 100 because of rounding and possible changes in medication type.

institute. These efforts specifically targeted patients being discharged from inpatient psychiatric facilities who were receiving more than one scheduled antipsychotic (23,24). Growing awareness of the lack of proven effectiveness of antipsychotic polypharmacy and education to that effect may also have had some impact, although there were no formal statewide initiatives in Ohio directed toward reducing antipsychotic polypharmacy.

Our finding that rates of antipsychotic polypharmacy remained quite high is nevertheless quite discouraging; one of four pharmacologically treated patients with a schizophrenic disorder met criteria for receiving antipsychotic polypharmacy. This is troubling on several levels. First, treatment guidelines that emphasize the preferability of antipsychotic monotherapy are routinely not followed, despite considerable efforts to raise clinician awareness. Second, this finding calls attention to the reality that standard pharmacological treatments for schizophrenia are often clinically disappointing and that best practices such as clozapine monotherapy are often underutilized. Clozapine is the drug of choice for treatment-resistant schizophrenia because of its greater efficacy and effectiveness compared with other antipsychotics (25–28). Clozapine is also the only antipsychotic recommended for the management of recurrent suicidal behavior (2,29), which affects up to 50% of patients with schizophrenia (30,31). Study findings underscore the importance of efforts to optimize clozapine use among Medicaid-insured patients with treatment-resistant schizophrenia, given that rates of clozapine use remain low in the United States, ranging from 2% to 10% (32).

Consistent with prior research, this study found that the likelihood of antipsychotic polypharmacy was associated with patient, illness, and treatment variables that appear related to greater illness severity (21). This finding suggests that antipsychotic polypharmacy may be related, at least in part, to clinician and patient disappointment with standard antipsychotic monotherapy. Individuals who were younger, male, and disabled and living in rural areas were more likely to receive antipsychotic polypharmacy. Younger age and male sex may influence prescribing behaviors by virtue of their being associated with greater illness severity, poorer outcomes (21), greater concerns about violence, and a perceived greater ability to tolerate medication-related side effects (33). The observed positive association between antipsychotic polypharmacy and disability status is consistent with prior studies (18,19) and likely a proxy for severity of illness. The positive association of rural residence with antipsychotic polypharmacy is consistent with prior research suggesting that adults with serious mental illness in nonmetropolitan areas are less likely to receive guideline-concordant care and regular visits than their metropolitan counterparts (34). Illness characteristics and treatment variables also point toward an association of antipsychotic polypharmacy with greater illness severity; polypharmacy was positively associated with a diagnosis of schizophrenia rather than schizoaffective disorder; a greater number of general medical comorbidities; and use of more psychotropic medication classes, outpatient mental health treatment, and emergency room visits.

Factors associated with lower rates of antipsychotic polypharmacy included a greater number of inpatient psychiatric hospitalizations, which may offer an opportunity to promote treatment guidelines advocating antipsychotic monotherapy; consolidate antipsychotic treatment; and initiate other interventions, such as clozapine or long-acting injectable antipsychotic medication. The presence of a substance abuse disorder was also associated with a lower risk of antipsychotic polypharmacy. Physicians may be less likely to prescribe a second antipsychotic to patients with substance abuse disorders because of an impression that the

patient's substance use may be contributing to the psychotic disorder and thus warrants greater attention than antipsychotic prescribing. In addition, substance abuse has been found to be associated with higher rates of medication nonadherence (35). African Americans and persons from other racial minority groups were also less likely to receive antipsychotic polypharmacy in this study, a finding consistent with some previous investigations (19,36) but not others (37). The impact of race and ethnicity on antipsychotic polypharmacy is difficult to interpret, with some studies reporting higher antipsychotic polypharmacy among white non-Latino patients (38,39), others finding both higher (37) and lower rates among African Americans (19,36), and still others finding no significant differences across racial and ethnic groups (33). The reason for the observed negative association between antipsychotic polypharmacy and African-American and other minority status is unclear, but it may be related to disparities in health service delivery or different cultural beliefs, perceptions, and preferences about psychiatric medications and treatments in these communities (40). Additional research on the relationship between race-ethnicity and antipsychotic polypharmacy is warranted (41,42).

The strengths of this study included a large study sample, examination of long-term polypharmacy versus short-term polypharmacy, longitudinal analysis of antipsychotic polypharmacy use over time, and a wide range of predictor variables. However, several limitations need to be considered. First, because the data are from a single state Medicaid population, findings may not be generalizable to other state programs or to non-Medicaid populations. Second, our use of administrative data precluded an examination of other patient characteristics (for example, positive and negative symptoms and a history of violence) and provider characteristics (for example, specialty and clinical setting) that may be associated with polypharmacy. Third, the comparison between schizophrenia and schizoaffective disorder may be biased by the change in criteria for schizoaffective disorder in *DSM-5*. Finally, absent more reliable diagnostic information than is available in claims data and information about treatment plans and outcomes, it was not possible to gauge the appropriateness of antipsychotic polypharmacy.

CONCLUSIONS

Antipsychotic polypharmacy appears to be declining in prevalence for Ohio Medicaid patients with schizophrenia, suggesting that quality improvement efforts advocating antipsychotic monotherapy may be having an impact. Antipsychotic polypharmacy still remains quite prevalent, with one in four antipsychotic-treated patients in this population being prescribed more than one antipsychotic for 90 or more days. Additional research addressing the underpinnings of risk and protective factors for antipsychotic polypharmacy may inform future efforts to reduce or eliminate antipsychotic polypharmacy.

TABLE 2. Association between long-term antipsychotic polypharmacy and patient characteristics among Ohio Medicaid patients with schizophrenia

Characteristic	OR	99% CI	p
1-year increase in the study period	.98	.97–.99	<.001
Age group (reference: 18–35)			
36–50	.98	.92–1.04	.401
51–64	.92	.86–.98	<.001
Race (reference: white)			
Black	.89	.85–.94	<.001
Other	.76	.62–.93	<.001
Male (reference: female)	1.11	1.06–1.16	<.001
Disabled (reference: no)	1.73	1.55–1.92	<.001
Rural location (reference: urban)	1.18	1.11–1.26	<.001
Primary schizophrenia diagnosis of schizoaffective disorder (reference: schizophrenia)	.89	.85–.93	<.001
Any psychiatric comorbidity (reference: no)	1.00	.95–1.05	.882
Any substance use disorder (reference: no)	.87	.83–.92	<.001
1-unit increase in the Charlson Comorbidity Index score	1.02	1.01–1.04	<.001
1-unit increase in the number of psychotropic medication classes	1.22	1.19–1.25	<.001
10-unit increase in the number of outpatient visits	1.04	1.03–1.04	<.001
1-unit increase in the number of inpatient hospitalizations	.95	.92–.99	<.001
5-unit increase in the number of emergency department visits	1.36	1.21–1.53	<.001

AUTHOR AND ARTICLE INFORMATION

Dr. Fontanella, Dr. Hiance-Steelesmith, and Dr. Guirgis are with the Department of Psychiatry and Behavioral Health, Wexner Medical Center, Ohio State University, Columbus. Dr. Campo is with the Rockefeller Neuroscience Institute, West Virginia University, Morgantown. Send correspondence to Dr. Fontanella (e-mail: fontanella.4@osu.edu).

The authors report no financial relationships with commercial interests.

Received January 31, 2018; revision received April 4, 2018; accepted May 4, 2018; published online July 2, 2018.

REFERENCES

1. Moore TA, Buchanan RW, Buckley PF, et al: The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2006 update. Journal of Clinical Psychiatry 68:1751–1762, 2007
2. Lehman AF, Lieberman JA, Dixon LB, et al: Practice Guideline for the Treatment of Patients with Schizophrenia, Second Edition. American Journal of Psychiatry 161(suppl 2):1–56, 2004
3. IPAP Schizophrenia Algorithm. International Psychopharmacology Algorithm Project, 2006. http://www.ipap.org/pdf/schiz/IPAP_Schiz_flowchart20060327.pdf
4. Correll CU, Rummel-Kluge C, Corves C, et al: Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials. Schizophrenia Bulletin 35:443–457, 2009
5. Jeste DV, Caligiuri MP, Paulsen JS, et al: Risk of tardive dyskinesia in older patients: a prospective longitudinal study of 266 outpatients. Archives of General Psychiatry 52:756–765, 1995
6. Lemmens P, Brecher M, Van Baelen B: A combined analysis of double-blind studies with risperidone vs. placebo and other antipsychotic agents: factors associated with extrapyramidal symptoms. Acta Psychiatrica Scandinavica 99:160–170, 1999

7. Sakurai H, Bies RR, Stroup ST, et al: Dopamine D2 receptor occupancy and cognition in schizophrenia: analysis of the CATIE data. Schizophrenia Bulletin 39:564–574, 2013
8. Procyshyn RM, Honer WG, Wu TK, et al: Persistent antipsychotic polypharmacy and excessive dosing in the community psychiatric treatment setting: a review of medication profiles in 435 Canadian outpatients. Journal of Clinical Psychiatry 71:566–573, 2010
9. Suzuki T, Uchida H, Tanaka KF, et al: Revising polypharmacy to a single antipsychotic regimen for patients with chronic schizophrenia. International Journal of Neuropsychopharmacology 7: 133–142, 2004
10. Correll CU, Frederickson AM, Kane JM, et al: Does antipsychotic polypharmacy increase the risk for metabolic syndrome? Schizophrenia Research 89:91–100, 2007
11. Barnes TRE, Paton C: Antipsychotic polypharmacy in schizophrenia: benefits and risks. CNS Drugs 25:383–399, 2011
12. Waddington JL, Youssef HA, Kinsella A: Mortality in schizophrenia: antipsychotic polypharmacy and absence of adjunctive anticholinergics over the course of a 10-year prospective study. British Journal of Psychiatry 173:325–329, 1998
13. Joukamaa M, Heliövaara M, Knekt P, et al: Schizophrenia, neuroleptic medication and mortality. British Journal of Psychiatry 188:122–127, 2006
14. Miller AL, Craig CS: Combination antipsychotics: pros, cons, and questions. Schizophrenia Bulletin 28:105–109, 2002
15. Fleischhacker WW, Uchida H: Critical review of antipsychotic polypharmacy in the treatment of schizophrenia. International Journal of Neuropsychopharmacology 17:1083–1093, 2014
16. Gilmer TP, Dolder CR, Folsom DP, et al: Antipsychotic polypharmacy trends among Medicaid beneficiaries with schizophrenia in San Diego County, 1999–2004. Psychiatric Services 58: 1007–1010, 2007
17. Clark RE, Bartels SJ, Mellman TA, et al: Recent trends in antipsychotic combination therapy of schizophrenia and schizoaffective disorder: implications for state mental health policy. Schizophrenia Bulletin 28:75–84, 2002
18. Ganguly R, Kotzan JA, Miller LS, et al: Prevalence, trends, and factors associated with antipsychotic polypharmacy among Medicaid-eligible schizophrenia patients, 1998–2000. Journal of Clinical Psychiatry 65:1377–1388, 2004
19. Kreyenbuhl JA, Valenstein M, McCarthy JF, et al: Long-term antipsychotic polypharmacy in the VA health system: patient characteristics and treatment patterns. Psychiatric Services 58: 489–495, 2007
20. Kreyenbuhl J, Valenstein M, McCarthy JF, et al: Long-term combination antipsychotic treatment in VA patients with schizophrenia. Schizophrenia Research 84:90–99, 2006
21. Correll CU, Gallego JA: Antipsychotic polypharmacy: a comprehensive evaluation of relevant correlates of a long-standing clinical practice. Psychiatric Clinics of North America 35:661–681, 2012
22. Charlson ME, Pompei P, Ales KL, et al: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of Chronic Diseases 40:373–383, 1987
23. Hospital-Based Inpatient Psychiatric Services. Chicago, Joint Commission, 2016. http://www.jointcommission.org/hospital-based_inpatient_psychiatric_services/
24. History of HBIPS Core Measure Set. Falls Church, VA, National Association of State Mental Health Program Directors Research Institute, 2012. http://www.nri-inc.org/media/1100/2012-history-of-hbips-bhpms.pdf
25. McEvoy JP, Lieberman JA, Stroup TS, et al: Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. American Journal of Psychiatry 163: 600–610, 2006
26. Leucht S, Komossa K, Rummel-Kluge C, et al: A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. American Journal of Psychiatry 166:152–163, 2009
27. Lewis SW, Barnes TRE, Davies L, et al: Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. Schizophrenia Bulletin 32:715–723, 2006
28. Gören JL, Rose AJ, Smith EG, et al: The business case for expanded clozapine utilization. Psychiatric Services 67:1197–1205, 2016
29. Buchanan RW, Kreyenbuhl J, Kelly DL, et al: The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophrenia Bulletin 36:71–93, 2010
30. Hor K, Taylor M: Suicide and schizophrenia: a systematic review of rates and risk factors. Journal of Psychopharmacology 24 (suppl):81–90, 2010
31. Kasckow J, Felmet K, Zisook S: Managing suicide risk in patients with schizophrenia. CNS Drugs 25:129–143, 2011
32. Olfson M, Gerhard T, Crystal S, et al: Clozapine for schizophrenia: state variation in evidence-based practice. Psychiatric Services 67: 152, 2016
33. Kadra G, Stewart R, Shetty H, et al: Predictors of long-term (≥6 months) antipsychotic polypharmacy prescribing in secondary mental healthcare. Schizophrenia Research 174:106–112, 2016
34. Rost K, Fortney J, Fischer E, et al: Use, quality, and outcomes of care for mental health: the rural perspective. Medical Care Research and Review 59:231–265, 2002
35. Herbeck DM, Fitek DJ, Svikis DS, et al: Treatment compliance in patients with comorbid psychiatric and substance use disorders. American Journal on Addictions 14:195–207, 2005
36. Kreyenbuhl J, Marcus SC, West JC, et al: Adding or switching antipsychotic medications in treatment-refractory schizophrenia. Psychiatric Services 58:983–990, 2007
37. Jaffe AB, Levine J: Antipsychotic medication coprescribing in a large state hospital system. Pharmacoepidemiology and Drug Safety 12:41–48, 2003
38. Leslie DL, Rosenheck RA: Use of pharmacy data to assess quality of pharmacotherapy for schizophrenia in a national health care system: individual and facility predictors. Medical Care 39:923–933, 2001
39. Covell NH, Jackson CT, Evans AC, et al: Antipsychotic prescribing practices in Connecticut's public mental health system: rates of changing medications and prescribing styles. Schizophrenia Bulletin 28:17–29, 2002
40. Puyat JH, Daw JR, Cunningham CM, et al: Racial and ethnic disparities in the use of antipsychotic medication: a systematic review and meta-analysis. Social Psychiatry and Psychiatric Epidemiology 48:1861–1872, 2013
41. Dwight-Johnson M, Sherbourne CD, Liao D, et al: Treatment preferences among depressed primary care patients. Journal of General Internal Medicine 15:527–534, 2000
42. Brody DS, Khaliq AA, Thompson TL 2nd: Patients' perspectives on the management of emotional distress in primary care settings. Journal of General Internal Medicine 12:403–406, 1997