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# **Antipsychotic Prescribing Pathways, Polypharmacy, and Clozapine Use in Treatment of Schizophrenia**

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Objective: To ensure optimal care for patients with schizophrenia, antipsychotic medications must be appropriately prescribed and used. Therefore, the primary objectives of this study were to identify and describe pathways for antipsychotic prescribing, assess the consistency of observed pathways with treatment guidelines, and describe variability across facilities.

Methods: Data from Veterans Affairs administrative data sets from fiscal year (FY) 2003 to FY 2007 were gathered for analysis in this retrospective cohort study of antipsychotic prescribing pathways among 13 facilities across two regional networks. Patients with a new episode of care for schizophrenia or schizoaffective disorder in FY 2005 were identified, and antipsychotic prescribing history was obtained for two years before and after the index diagnosis.

Demographic characteristics and distribution of comorbidities were assessed. Median medical center rates of polypharmacy were calculated and compared with Fisher's exact test.

Results: Of 1,923 patients with a new episode of schizophrenia care, 1,003 (52%) had complete data on prescribing pathways. A majority (74%) of patients were prescribed antipsychotic monotherapy, and 19% received antipsychotic polypharmacy. Of patients receiving antipsychotic polypharmacy, 65% began polypharmacy within 90 days of starting any antipsychotic treatment. There was a fourfold difference in polypharmacy across facilities. Antipsychotic polypharmacy was not associated with geographic location or medical center patient volume. Clozapine utilization was low (0%–2%).

Conclusions: Retrospective examination of longitudinal prescribing patterns identified multiple antipsychotic prescribing pathways. Although most patients received guideline-concordant care, antipsychotic polypharmacy was commonly used as initial treatment, and there was substantial variability among facilities. Study findings suggest the utility of secondary data to assess treatment adaptation or switching for practical clinical trials.

Although antipsychotics are effective for the treatment of schizophrenia, many patients do not respond to the first antipsychotic prescribed (1–3). Patients without a response on a second antipsychotic trial are typically considered treatment resistant (4–10). Because clozapine is the only antipsychotic proven effective for treatment-resistant schizophrenia, it is widely recognized as the preferred treatment option for patients who have not responded to two antipsychotic

monotherapy trials (4–10). This approach is reflected in evidence-based treatment guidelines, which recommend that such patients be offered clozapine (6–10).

With these evidence-based treatment guidelines, one can conceptualize guideline-concordant treatment as an antipsychotic (AP) prescribing pathway, whereby AP1→AP2→clozapine. However, studies indicate that adherence to this guideline is low (11–25). Increasingly, long-term use of two or more regularly scheduled antipsychotics (polypharmacy) is prescribed, often before clozapine (11,15,17–19,23–25). This practice is inconsistent with evidence-based guidelines, which do not endorse long-term antipsychotic polypharmacy and recommend it only as a last-line treatment when clozapine has failed (6–10).

Rates of clozapine and antipsychotic polypharmacy use vary by treatment setting (11–25). However, most studies to date on antipsychotic prescribing have been cross-sectional even though longitudinal assessment is required to characterize appropriate use of polypharmacy. Cross-sectional studies cannot make the important distinction between antipsychotic polypharmacy use for treatment-resistant individuals (such as after a failed clozapine trial) and for other, less discriminating use. Also, findings from cross-sectional studies do not provide necessary information to assess which patients may be eligible for clozapine (11,16,20). This is of particular importance because the longitudinal studies that have been conducted indicate that clozapine is started after the failure of an average of six antipsychotic trials, including a period of antipsychotic polypharmacy, suggesting that the most effective treatment for treatment-resistant patients is delayed or not used (17–19,24,25).

Longitudinal studies of large administrative data sets are becoming increasingly important. The development of more cost-efficient adaptive and practical clinical trials could be informed by data from existing sources. Also, studies examining the impact of policy or implementation strategies on prescribing pathways can be done in a naturalistic setting, guiding development of interventions that may be successful in real-world applications. Ultimately these studies may improve use of guideline-based treatment and outcomes in mental health.

Therefore the goals of this descriptive retrospective cohort study were to use administrative data to develop a systematic method for describing longitudinal antipsychotic prescribing pathways and to describe the observed sequence of antipsychotic trials as related to evidence-based guideline recommendations.

## **Methods**

### ***Setting and data sources***

The Veterans Health Administration (VHA) is a national health care system treating >87,000 veterans with schizophrenia or schizoaffective disorder annually. Because the VHA has used electronic records for clinical care for many years, readily available administrative data sets can be used to identify and describe longitudinal antipsychotic prescribing pathways. Administrative data have been used extensively in other antipsychotic studies (11,20,26–28).

We focused on 13 medical centers across two Veterans Affairs (VA) Integrated Service Networks (VISNs). We chose two VISNs in different regions of the United States that serve a large number of veterans with schizophrenia or schizoaffective disorder. Data to identify our target sample and characterize individuals' medication history were obtained from the VA National Patient Care Database (NPCD), which contains information on inpatient and outpatient visits, *ICD-9-CM* diagnoses and procedure (CPT-4) codes, dispensed medication, and patient demographic characteristics. Data on average patient volume were derived from the fiscal year (FY) 2004 VA National Psychosis Registry (NPR) report, which includes data from multiple sources for all veterans treated for psychoses within the VHA.

### ***Study sample***

We identified all patients from two VISNs who received a prescription for an antipsychotic and were actively engaged in ongoing treatment, with a new episode of care for spectrum disorders in FY 2005. We focused on new episodes of care because treatment recommendations begin with the first treatment chosen for an episode of illness.

A new episode of care was defined as an *ICD-9-CM* schizophrenia-related diagnosis (codes 205.0–295.9) in at least one inpatient or two outpatient encounters in FY 2005, no schizophrenia-related diagnosis in the previous two years, initiation of an index antipsychotic prescription, and no antipsychotic prescription for daily use >90 days in the year before the diagnosis. Patients with multiple psychiatric disorders coded on the diagnosis date were included if the number of schizophrenia-related diagnoses exceeded or equaled the number of other psychiatric disorders (20). Patients had to be actively engaged in VHA treatment, as evidenced by at least one VHA

outpatient visit for any medical or psychiatric disorder in both FY 2006 and FY 2007. The Boston VHA institutional review board approved this study.

### ***Antipsychotic use***

Antipsychotic use was defined as any dose of an antipsychotic (American Hospital Formulary Service class 28:16.08) for daily use dispensed from an outpatient VHA pharmacy for  $\geq 90$  days in FY 2005. The 90-day criterion was chosen on the basis of previous studies in which discontinuation of treatment due to adverse events versus inefficacy occurred earlier in treatment (25).

The index antipsychotic prescription was defined as the first antipsychotic prescribed for daily use in FY 2005. To minimize the likelihood of falsely categorizing as polypharmacy transitions from one antipsychotic to another, we defined polypharmacy as concomitant prescription of two antipsychotics for daily use for  $>90$  days (11). Intermittent exposures of  $\leq 90$  days were considered noninformative.

### ***Informative sample***

Each patient's prescribing pathway was characterized according to the antipsychotic trials received during the two years after the index antipsychotic trial. As summarized in Figure 1, receipt of a single antipsychotic other than clozapine for daily use (pathway 1) or two sequential prescriptions for regularly scheduled nonclozapine antipsychotics (pathway 2) with no gaps  $>90$  days for the duration of the study was categorized as monotherapy. Receipt of two prescriptions concomitantly for  $>90$  days was categorized as polypharmacy. Antipsychotic polypharmacy could occur at various points in the treatment sequence (pathways 3–6). Patients who received clozapine for daily use as the second or third monotherapy trial were categorized as receiving early clozapine (pathway 8) or clozapine (pathway 7), respectively. Patients who received three or more sequential nonclozapine antipsychotics were categorized as delayed use of clozapine (pathway 9). Because prescription history data were available to definitively characterize pathways 1–9, we refer to them collectively as informative cases.

### ***Noninformative cases***

Some observed pathways were noninformative because incomplete information made a categorization ambiguous or uncertain. For example, some cases received a single trial (pathway

11) or sequential trials of antipsychotics (pathway 10) but no further antipsychotic prescriptions during the observation period. Thus it was not possible to characterize these pathways.

### ***Characterization of antipsychotic pathways***

Pathways 1, 2, and 7 represent guideline-endorsed antipsychotic prescribing pathways and thus were characterized as guideline concordant. In cases of extreme suicidality or aggression, guidelines endorse using clozapine as the second antipsychotic, so pathway 8 was categorized as guideline concordant (6). Pathways 3–6 all involved polypharmacy before clozapine was prescribed, and these pathways were categorized as guideline nonconcordant. Antipsychotic polypharmacy including clozapine was considered guideline nonconcordant because clozapine monotherapy was not used before polypharmacy was initiated. Pathway 9 involved use of a nonclozapine antipsychotic after two failed antipsychotic trials and was categorized as nonconcordant with guidelines. Pathways with clozapine as the first antipsychotic were excluded from the study because these likely reflect treatment-resistant patients for whom standard guideline-concordant care may not be appropriate.

### ***Analytic sample***

Previous studies have demonstrated that antipsychotic monotherapy and polypharmacy are the most common forms of antipsychotic treatment (12–14). These antipsychotic prescribing pathways also have the clearest relationship to guideline recommendations. Hence these groups formed the analytic sample and were used to address the second major aim of the study, comparison of prescribing practices with treatment guidelines. Because patients requiring clozapine treatment represent either more severely ill or treatment-resistant populations, they were excluded from the analytic sample.

### ***Measures and analyses***

Our measures and analyses proceeded at both the patient and facility center levels. At the patient level, our primary dependent variable was pathway assignment. Using the *ICD-9-CM* diagnosis codes associated with each medical encounter during the study, we created presence and absence variables for the antipsychotic-related comorbidities diabetes and hyperlipidemia. From the NPCD we obtained five demographic characteristics: age at time of the index visit, marital status

(four categories), gender, self-reported race (U.S. Census categories), and self-reported ethnicity (whether, yes-no, patients considered themselves Hispanic, Latino, or Spanish).

We used basic frequencies, central tendency, and variance statistics to describe the number of cases in each of the antipsychotic pathway groups as well as the demographic and comorbidity profiles of all informative cases and the analytic sample. Within the analytic sample, we compared the demographic characteristics and distribution of comorbidities between monotherapy and polypharmacy groups by computing chi square statistics on the cross-tabulation of antipsychotic pathway (monotherapy and polypharmacy) by those categorical variables. For age, we computed independent-groups t tests between monotherapy and polypharmacy.

At the medical center level, we computed a polypharmacy rate as the percentage of cases in the analytic sample at that medical center that fell into the monotherapy and polypharmacy pathways. The denominator for this rate was the total number of cases in our analytic sample: the combined monotherapy and polypharmacy groups. As a measure of the total volume of patients with severe mental illness (psychotic and bipolar disorders), we obtained counts of such cases for each medical center from the NPR. Finally, because facilities were located in two geographically diverse VISNs, a dichotomous categorical location code was created to represent region (designated A or B). For analyses at the medical center level, we used basic descriptive statistics to describe the distribution of polypharmacy rates.

To examine the association between polypharmacy rate and geographic region, we computed the median polypharmacy rate at the medical center level, classified facilities as above or below that rate, and computed the Fisher exact probability test on the cross-tabulation of polypharmacy rate (below or above median) by region. Finally, to examine the association between polypharmacy rate and volume of patients with severe mental illness, we computed the facility median for volume of these patients, classified facilities as being above or below that volume, and then computed the Fisher exact probability test on the cross-tabulation of polypharmacy rate (below or above median) and volume of patients with severe mental illness (below or above median).

## **Results**

We identified 1,923 new treatment episodes of schizophrenia and schizoaffective disorders in FY 2005 and their distribution across nonredundant pathway groups (Table 1). Of the total, 310 (16%) veterans did not utilize VHA outpatient services in FY 2006 and FY 2007. Another 338 (18%) utilized VHA services but did not receive antipsychotic medications from an outpatient VHA pharmacy in FY 2005, and 272 (14%) did not receive a sufficient number of antipsychotic prescriptions to allow reasonable judgment about appropriate pathway assignment. These 920 noninformative cases (48%) were not included in further analyses. There was no difference in median age between the informative and noninformative groups.

The remaining 1,003 informative cases involved patients who entered a new treatment episode for schizophrenia or schizoaffective disorder, were treated with an antipsychotic in FY 2005–FY 2007 and had one or more outpatient clinic visits in FY 2006 and FY 2007. Within the informative sample, 763 patients (76%) received care consistent with treatment guidelines (Table 1). The most common guideline-concordant prescribing pathway was monotherapy (N=745, 74%), followed by early use of clozapine (N=17, 2%). One patient received clozapine after two antipsychotic trials. The remaining 24% (N=240) of informative cases followed prescribing pathways that were nonconcordant with guidelines, with nonclozapine polypharmacy being the most common path (N=188, 19%). Notably, of patients receiving antipsychotic polypharmacy, 65% (N=127) received polypharmacy as their first antipsychotic treatment and 4% (N=45) received polypharmacy in place of clozapine.

A total of 933 informative cases (93%) qualified for the analytic sample, which for reasons discussed above consisted of the (nonclozapine) antipsychotic monotherapy (N=745) and (nonclozapine) polypharmacy (N=188) pathway groups. Self-reported race and ethnicity were missing in 49% and 51% of cases, respectively. The descriptive statistics for these variables and the chi square analyses were based, respectively, on persons whose race (N=474) or ethnicity (N=454) was known. The analytic sample was predominantly single (45%), Caucasian (54%), and male (93%) (Table 2), with a mean±SD age of 50.7±12.2. The incidence of diabetes and hyperlipidemia was 16% and 17%, respectively.

There were no statistically significant associations between pathway group and demographic characteristics or comorbidities, with three exceptions. Six percent of the nonclozapine monotherapy sample was female compared with 13% of the nonclozapine polypharmacy group

( $\chi^2=9.39$ ,  $df=1$ ,  $p<.01$ ), and 52% of the monotherapy group was Caucasian compared with 65% of the polypharmacy group ( $\chi^2=8.54$ ,  $df=3$ ,  $p<.05$ ). A significant association was observed with a higher proportion of hyperlipidemia in the polypharmacy group (22%) compared with the monotherapy group (15%;  $\chi^2=4.38$ ,  $df=1$ ,  $p<.05$ ).

We observed a more than fourfold difference in antipsychotic polypharmacy rates between the medical centers (Figure 2). The median medical center polypharmacy rate was 21%, and the likelihood of being above that rate was no greater in region A compared with region B ( $p=.59$ , by Fisher exact test). The median annual medical center volume of cases of severe mental illness was 1,616, and the likelihood of being above or below the median polypharmacy rate for a facility was no greater at lower-volume facilities compared with higher-volume facilities ( $p=.10$ , by Fisher exact test).

## **Discussion**

Using retrospective data of longitudinal antipsychotic prescribing, we classified 1,003 of 1,923 patients (52%) with new treatment episodes of schizophrenia into one of 11 antipsychotic prescribing pathways. Of these informative cases, 74% were treated along antipsychotic monotherapy pathways, consistent with treatment guidelines. This is consistent with estimates that 70%–80% of patients with schizophrenia are responsive to treatment (1,2).

We found that 24% of patients received care nonconcordant with guidelines, primarily involving antipsychotic polypharmacy. A total of 13% of informative cases received polypharmacy before receiving a monotherapy antipsychotic trial. This rate is 3.5 times higher than previously reported in the California Medicaid population (29). This discrepancy is most likely related to methodological differences. Whereas the Medicaid study reported antipsychotic polypharmacy as the initial treatment for patients who received prescriptions for two antipsychotics at the first fill, our study defined polypharmacy as initial treatment when patients did not receive an adequate monotherapy trial of antipsychotic before receiving antipsychotic polypharmacy. Thus, for our population, initial treatment with antipsychotic polypharmacy included patients who received polypharmacy within the first 90 days of treatment. The fact that 65% of patients treated with polypharmacy started antipsychotic polypharmacy within the first 90 days of treatment indicates that a majority of patients on polypharmacy were not treated with a single evidence-based treatment. In summary, both studies suggest that antipsychotic

polypharmacy is often being used as the initial treatment, contravening all evidence-based guidelines.

Similar to other studies, our study showed a significant difference among medical centers in utilization of antipsychotic polypharmacy, and this variability was not associated with geographic region or volume of patients with severe mental illness. Previous studies indicated that clinicians reserve antipsychotic polypharmacy for patients with more severe illness. However, it seems unlikely there would be a fourfold difference in the number of severely ill patients between facilities and that 65% of patients receiving polypharmacy were so sick that they required antipsychotic polypharmacy as first-line treatment (30). Thus future research should investigate whether organizational characteristics account for some variability in antipsychotic prescribing. For example, differences in availability of resources, staffing, quality improvement capability, program implementation, care coordination, and communication may affect provision of care (26,31–33). The organization and provision of care have been shown to vary among VHA mental health programs, which may contribute to the observed variation (31,33).

Medical centers with lower volume of patients with severe mental illness trended toward higher rates of polypharmacy. Whereas five of six low-volume medical centers had higher rates of polypharmacy, five of seven high-volume medical centers had lower rates of polypharmacy, suggesting that more experience with severe mental illness may be related to increased adherence with treatment guidelines.

Clozapine underutilization is an issue in the treatment of schizophrenia and schizoaffective disorders, possibly because of increased prescribing burden, including prescriber and patient registration requirements; significant side-effect burden; and frequent laboratory testing to monitor for side effects. In this study, only about 2% (N=18) of patients in the informative sample received clozapine consistent with evidence based guidelines, whereas 45 patients who fared poorly on two antipsychotic trials did not receive clozapine. Some of these cases may reflect antipsychotic intolerance rather than clozapine nonresponse. However, given that up to 20% of patients with schizophrenia are treatment resistant whereas under 2% of patients received clozapine and almost 19% received antipsychotic polypharmacy, it seems unlikely that use of

clozapine is optimized. It is concerning that patients may be receiving polypharmacy in place of clozapine or that initiation of clozapine is delayed.

Consistent with other studies, receipt of antipsychotic polypharmacy was more common with women and Caucasian patients (29,34). Our finding that patients receiving antipsychotic polypharmacy were more likely to have hyperlipidemia is contrary to at least one previous study (35). However, antipsychotic polypharmacy may be a marker for factors such as body mass index and concomitant medications that were not controlled for in this study.

It is interesting to note that 338 patients diagnosed as having schizophrenia or schizoaffective disorder received care within the VHA but did not receive antipsychotics. Some of these patients may fill their prescriptions outside the VHA. It is also possible that these patients had less severe illness or chose not to fill antipsychotic prescriptions and therefore represent a population in need of outreach.

## **Conclusions**

To our knowledge, this study is unique in its description and categorization of antipsychotic prescribing pathways. Our method allowed for identification of justified deviations from treatment guidelines and of patients possibly eligible for a clozapine trial. Nonetheless, there are some limitations that should be noted. Data derived from prescription files do not account for nonadherent patients, and the filling of a prescription does not necessarily mean that the medications were taken how and when they should have been. Given that this study did not focus on treatment outcomes, however, this limitation is not a critical concern. Also, such data cannot account for patient and clinician preferences. Medication changes may have been secondary to drug intolerance rather than inefficacy, and thus all 45 patients with two unsuccessful sequential trials of monotherapy may not have been appropriate for a clozapine trial. However, the use of the 90-day minimum to identify an antipsychotic trial in this study makes this somewhat less likely.

Consistent with prior cross-sectional analyses, we observed that 19% of patients with schizophrenia treated within the VHA received polypharmacy, and the utilization of clozapine was several-fold lower. A large portion of patients started with polypharmacy as the initial antipsychotic trial. In addition, there was unexplained variability between medical centers in use of antipsychotic polypharmacy. Future research should consider the causes of variability and its

impact on patient outcomes. Pathways analysis is a useful way to use secondary data to inform practical clinical trials and effectiveness of prescribing policies.

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The authors report no competing interests.

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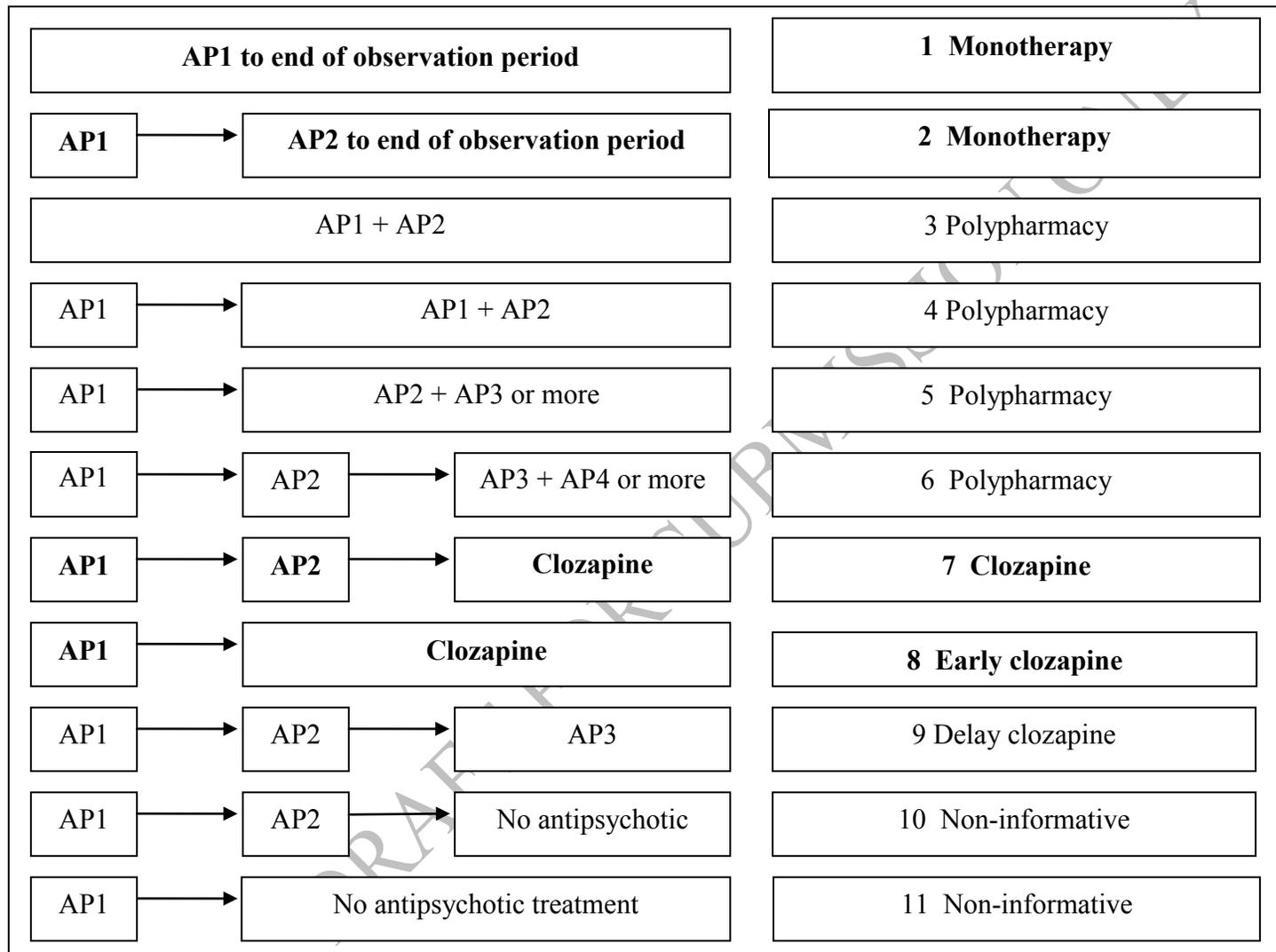
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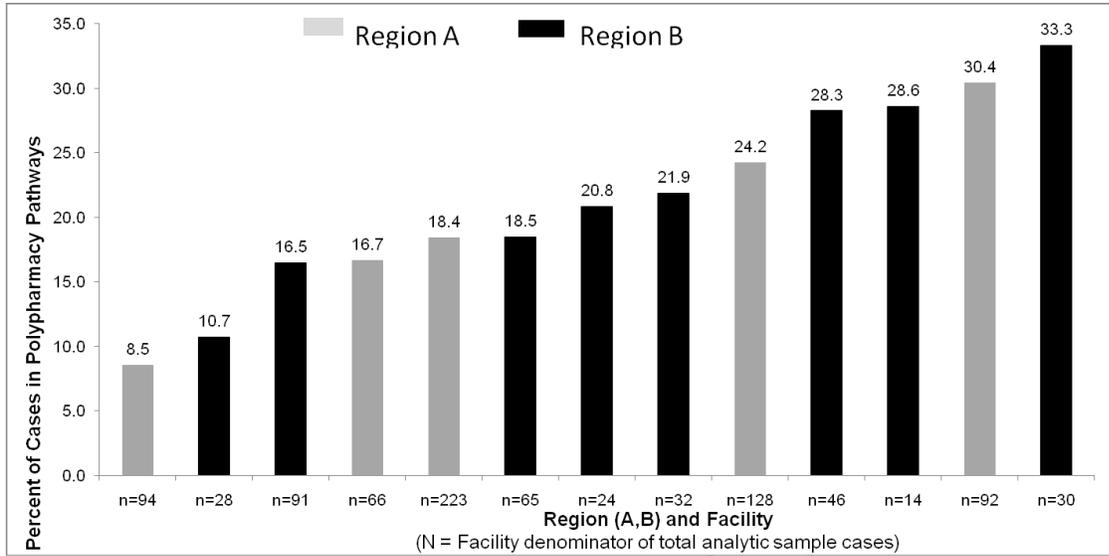
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Figure 1 Antipsychotic (AP) prescribing pathways among veterans with schizophrenia or schizoaffective disorder<sup>a</sup>



<sup>a</sup>Guideline-concordant pathways are in boldface.

Figure 2 Rates of polypharmacy for treatment of schizophrenia or schizoaffective disorder, by VHA facility<sup>a</sup>



<sup>a</sup>N indicates the facility denominator of total analytic sample cases. VHA, Veterans Health Administration

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Table 1 Observed distribution of antipsychotic prescribing pathways for VHA patients with schizophrenia or schizoaffective disorder<sup>a</sup>

Pathway	N	% total cases (N=1,923)	% informative cases (N=1,003)
Informative cases			
Concordant with guidelines			
Monotherapy without clozapine	745	39	74
Early use of clozapine	17	1	2
Clozapine	1	<1	<1
Subtotal	763	40	76
Nonconcordant with guidelines			
Polypharmacy without clozapine	188	10	19
Polypharmacy with clozapine	7	<1	<1
Delayed use of clozapine	45	2	5
Subtotal	240	13	24
Total	1,003	52	100
Noninformative cases			
Insufficient VHA antipsychotic trials	272	14	
No VHA utilization	310	16	
VHA utilization but no antipsychotics dispensed	338	18	
Total	920	48	
Total	1,923	100	

<sup>a</sup> VHA, Veterans Health Administration

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Table 2 Demographic and clinical characteristics of VHA patients with schizophrenia or schizoaffective disorder<sup>a</sup>

Characteristic	Total analytic sample (N=933)		Nonclozapine monotherapy (N=745)		Nonclozapine polypharmacy (N=188)	
	N	%	N	%	N	%
Caucasian	258	54	193	52	65	65
Hispanic	50	11	36	10	14	15
Male	863	93	699	94	164	87
Not married	417	45	332	45	85	46
Comorbidity <sup>b</sup>						
Diabetes	152	16	123	17	29	15
Hyperlipidemia	156	17	115	15	41	22

<sup>a</sup>VHA, Veterans Health Administration. Because of missing data, the denominator for percentages is not the group maximum for all variables.

<sup>b</sup>Patients may appear in more than one category.

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