Use Of Atypical Antipsychotic Drugs For Schizophrenia In Maine Medicaid Following A Policy Change

Discontinuities in use of these critical drugs became apparent after Maine Medicaid instituted prior authorization and step therapy.

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ABSTRACT: More than one-third of Medicaid programs and Medicare Part D plans use prior authorization (PA) policies to control the use of atypical antipsychotics (AAs). We used Medicaid and Medicare claims data to investigate how Maine's PA policy affected AA use, treatment discontinuities, and spending among schizophrenia patients initiating AA therapy. Patients initiating AAs during Maine's policy experienced a 29 percent greater risk of treatment discontinuity than patients initiating AAs before the policy took effect; no change occurred in a comparison state. AA spending was slightly lower in both states. Observed increases in treatment discontinuities without cost savings suggest that AAs should be exempt from PA for patients with severe mental illnesses. [Health Affairs 27, no. 3 (2008): w185–w195 (published online 1 April 2008; 10.1377/hlthaff.27.3.w185)]

IN RESPONSE TO INCREASING SPENDING FOR psychotropic drugs, utilization management policies have been applied with increasing frequency.[1] Access to atypical antipsychotics (AAs) is restricted through prior authorization (PA) policies by approximately 40 percent of state Medicaid programs and approximately one-third of Medicare Part D (prescription drug) plans.[2] These policies rarely distinguish between questionable (such as dementia) and appropriate clinical use (such as schizophrenia or bipolar disorder) and are often based on

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medication acquisition cost.[3] The potential clinical and economic consequences of such policies for the severely mentally ill are unknown.

Schizophrenia is a disabling and costly illness.[4] Without antipsychotic treatment, about 80 percent of patients experiencing a schizophrenic episode have a recurrence within a year.[5] However, medication adherence problems are common, resulting in more frequent acute psychotic episodes and hospitalization, with newly treated patients at greatest risk of acute episodes following nonadherence.[6] Responses to specific AAs and risks of adverse events (such as extrapyramidal symptoms [EPS], weight gain, tardive dyskinesia, and diabetes) vary.[7] Thus, if certain patients are sensitive to adverse events associated with preferred agents, the PA policy could increase the incidence of unfavorable outcomes and contribute to medication discontinuation.[8]

In July 2003 the Maine Medicaid program expanded its preferred drug list (PDL) by implementing a PA and step-therapy policy affecting new AA users. Use of a nonpreferred medication (olanzapine or aripiprazole) was permitted only after (1) failure of both an initial preferred agent (risperidone) and a subsequent preferred agent (ziprasidone or quetiapine), each used at full therapeutic doses for at least two weeks; or (2) submitting a form requesting PA by documenting (with supporting office notes) medical necessity for the nonpreferred medication. The MaineCare Medicaid program suspended the policy on 1 March 2004 and replaced it with a provider education program following numerous case reports of adverse effects associated with the policy.[9] We investigated the impact of the PA policy in Maine on AA use, spending, and treatment discontinuities among nonelderly Medicaid patients with schizophrenia.

Study Data And Methods

■ **Study and comparison states.** Maine Medicaid implemented the PA policy in July 2003. New Hampshire was chosen as the comparison state because of its geographic proximity, similar demographic characteristics, and lack of PA requirements for AAs when the Maine policy was in effect.

■ **Data sources.** We obtained complete Medicaid claims files for 2001–2004 from the Centers for Medicare and Medicaid Services (CMS) to measure AA use and other health care services provided to Medicaid enrollees. In each state, we identified all patients with study diagnoses and extracted their encounter and enrollment data. For patients dually enrolled in Medicaid and Medicare, we also obtained and linked Medicaid and Medicare data.

From medication claims in the Medicaid Statistical Information Systems (MSIS) of the two study states, we extracted reliable data on patient identifiers, National Drug Code (NDC), dispensing date, number of units provided (for example, tablets), days' supply, and amount reimbursed.[10]

■ **Identification of continuously enrolled cohort.** Study inclusion criteria were (1) continuous enrollment in Maine or New Hampshire Medicaid from Janu-

ary 2001 to December 2004, (2) ages 18–63 in 2001, and (3) at least one inpatient or two outpatient diagnoses of schizophrenia or schizoaffective disorder (ICD-9-CM 295) during the study period.[11] The continuously enrolled cohort contained 4,600 patients meeting all inclusion criteria.

■ **Identification of patients with new treatment episodes.** Because the policy exempted existing AA users, we restricted analyses of treatment discontinuities to patients with schizophrenia who were newly receiving AA treatment (except clozapine, which was unaffected by the policy). We identified two cohorts of newly treated patients in each state. The policy cohort included those who filled an AA prescription between July 2003 and February 2004 but without AA use in the ninety days before initiation of therapy. The prepolicy cohort included those who initiated AA therapy between July 2002 and February 2003, an identical eight-month period in the year before policy implementation. Patients with forty-five or more days in an institution during the ninety days before treatment initiation were excluded from both cohorts.

The date of AA initiation was the index date for follow-up of treatment discontinuities. To examine usage over time, we required cohort members to be continuously enrolled for ten months before and ten months after initiation of therapy.[12]

■ **Measures.** *Use of antipsychotic medications.* We calculated the prevalence of use (prescription fill) of each AA for eight months before, during, and after the policy among newly treated patients. Only Maine had enough patients to analyze utilization trends by preferred and nonpreferred categories.

Discontinuities in therapy. The primary effectiveness measure in a recent large trial of antipsychotic therapy for schizophrenia was the time until a patient discontinued initial therapy, as measured by discontinuation or a switch in pharmacotherapy. Such changes occur commonly and indicate attempts to treat schizophrenic symptoms.[13] We decided a priori to use a similar composite end point, with *discontinuity* defined as evidence of a gap in therapy or switching to or augmentation with another antipsychotic.

Using information on days supplied from pharmacy claims data, we allocated medication in daily amounts until the supply was exhausted. We defined a *meaningful gap in therapy* as thirty days or more without any antipsychotic medication, and we conducted sensitivity analyses for two alternative gap periods: fifteen days or more, and forty-five days or more. We defined *switching* as changing the initial AA to a second AA or typical antipsychotic (TA), or both, and *augmentation* as adding another AA or TA to the index medication. We censored all observations after the end of February 2004 (last policy month) for the policy cohort and February 2003 for the prepolicy cohort.

■ **Demographic and utilization covariates.** Enrollment data included monthly eligibility, sex, race, age, and whether dually enrolled in both Medicaid and Medicare. Pre-initiation utilization characteristics included psychoactive medication use, number of different medications dispensed, number of physician visits, and

number of inpatient admissions.[14]

■ **Statistical analysis.** Baseline comparisons between states for most variables were made using chi-square tests; nonparametric tests were used to compare the number of different medications dispensed.[15]

We used Kaplan-Meier survival curves and Cox proportional-hazards regression to compare the risk (hazard) of treatment discontinuity in the policy versus prepolicy cohorts of newly treated patients in each state, controlling for age, sex, number of hospital admissions, number of physician visits, and dual enrollment in Medicaid and Medicare at baseline. Change in the risk of treatment discontinuity was estimated by state as a relative risk with 95 percent confidence interval (CI). The proportional-hazards assumption was satisfied.[16] We also compared pre-post changes in both states in a single proportional-hazards model.

We measured changes in drug spending for AAs in the continuously enrolled cohort using segmented time-series regression models.[17] These models estimated changes in level and trend (slope) of AA use by comparing the respective eight-month policy, prepolicy, and postpolicy periods. We controlled for all significant autocorrelation terms.[18]

Study Results

■ **Background characteristics of study cohorts.** The baseline demographic and treatment characteristics of Maine and New Hampshire enrollees were similar (Exhibit 1). About half of patients were male, and less than 15 percent were ages 55–63 in 2001.

■ **Changes in AA use after the PA policy.** Among continuously enrolled patients there was an absolute 3 percent increase in preferred AA use and a 5.6 percent decline in nonpreferred AAs during the policy period.[19]

Changes in initial medication choice in Maine were pronounced among the target group initiating treatment with AAs during the policy.[20] The proportion of newly treated patients started on nonpreferred agents decreased abruptly from 39.9 percent before the policy (95 percent CI: 33.8, 46.0) to 28.6 percent during the policy (95 percent CI: 22.8, 34.5), but increased to 34.7 percent (95 percent CI: 29.5, 39.9) after the policy. Use of the first-preferred agent increased by a similar magnitude from 32.7 percent (95 percent CI: 26.8, 38.5) to 41.9 percent (95 percent CI: 35.4, 48.3) during the policy, but remained high at 39.1 percent (95 percent CI: 33.7, 44.5) after discontinuation of the policy. There were no significant changes in initiation of second-preferred agents.

■ **Changes in rates of antipsychotic treatment discontinuities.** There was a clear separation in Maine of the prepolicy versus policy hazard curves for treatment discontinuity (Exhibit 2), especially after thirty days of follow-up (that is, the start of thirty-day treatment gaps). This suggests greater risk for treatment discontinuities after AA initiation in the policy period. Among 151 discontinuities identified in the Maine policy cohort, there were 104 gaps in therapy longer than thirty days,

EXHIBIT 1
Baseline Characteristics Of The Study (Maine) And Comparison (New Hampshire) Cohorts

Characteristic	Continuously enrolled		Newly treated	
	Study cohort (ME) (N = 3,104)	Comparison cohort (NH) (N = 1,496)	Study cohort (ME) (N = 450)	Comparison cohort (NH) (N = 134)
Female	45.4%	44.4%	42.2%	50.0%
Age group (years)[a]				
18–34	26.0%	21.1%[b]	38.7%	26.1%[b]
35–54	61.5	64.7	53.8	59.0
55–63	12.5	14.2	7.6	14.9
White race	96.9	96.9	95.3	93.2
Medicare/Medicaid dually eligible	64.3	73.1[b]	50.7	59.7
Psychoactive drugs used				
Atypical antipsychotic (AA)	73.9%	74.7%	42.7%	44.0%
Typical antipsychotic (TA)	34.0	31.4	17.6	25.4[b]
Antidepressant	57.1	53.7[b]	56.0	58.2
Lithium	10.5	11.1	9.3	10.5
Anxiolytic and hypnotic	31.9	32.1	27.6	28.4
No. of different medications dispensed[c]	8.3 (±5.6)	8.5 (±5.9)	6.4 (±4.9)	7.5 (±5.5)
Percent with hospital admission	28.9%	25.7%[b]	42.4%	43.3%

SOURCE: Authors' calculations using data from the Centers for Medicare and Medicaid Services, 2001–2004 ME/NH Medicaid and Medicare claims and enrollment data.

NOTES: All values are based on nonmissing information. The baseline period was 2002 for the continuously enrolled cohort and the ten-month period before AA initiation for the newly treated cohort.

[a] Age group as of January 2001.

[b] Significant difference between the two states, $p < 0.05$.

[c] Determined by American Hospital Formulary Service (AHFS) Class.

eleven medication switches, and thirty-six augmentations. Among the thirty-five discontinuities identified in the smaller New Hampshire policy cohort, there were fifteen similar gaps in therapy, three medication switches, and seventeen augmentations. There was no observed difference in the hazard rates for discontinuity in the prepolicy versus policy cohorts in New Hampshire (Exhibit 3).

Exhibit 4 presents risk ratios from the Cox models after adjusting for all covariates, comparing between state changes in risk of discontinuity. The policy cohort in Maine had 1.29 (95 percent CI: 1.02, 1.63; $p = 0.036$) times the risk of treatment discontinuity relative to the prepolicy cohort, and 1.18 for gaps alone (95 percent CI: 0.89, 1.57; $p = 0.245$). The risk of treatment discontinuities did not change (prepolicy versus policy) in the comparison state. The ratio of study-state versus comparison-state changes in the hazard ratio of treatment discontinuities (Exhibit 4) was 1.55 (95 percent CI: 0.94, 2.56; $p = 0.09$) for gaps of thirty or more days; and 1.94 (95 percent CI: 1.14, 3.29; $p = 0.01$) for gaps longer than forty-five days. Consistent estimates across all discontinuity cut-off values were observed with each analytic method.

■ **Spending on AAs.** After health care inflation was adjusted for, the average

EXHIBIT 2
Time To Treatment Discontinuity Among Newly Treated Members Of The Study Cohort (Maine) During The Prepolicy And Policy Observation Periods, 2002-2004
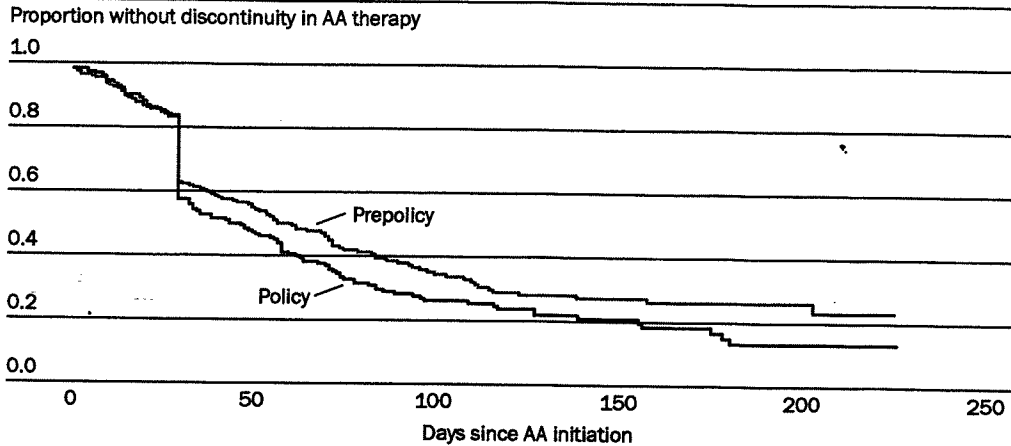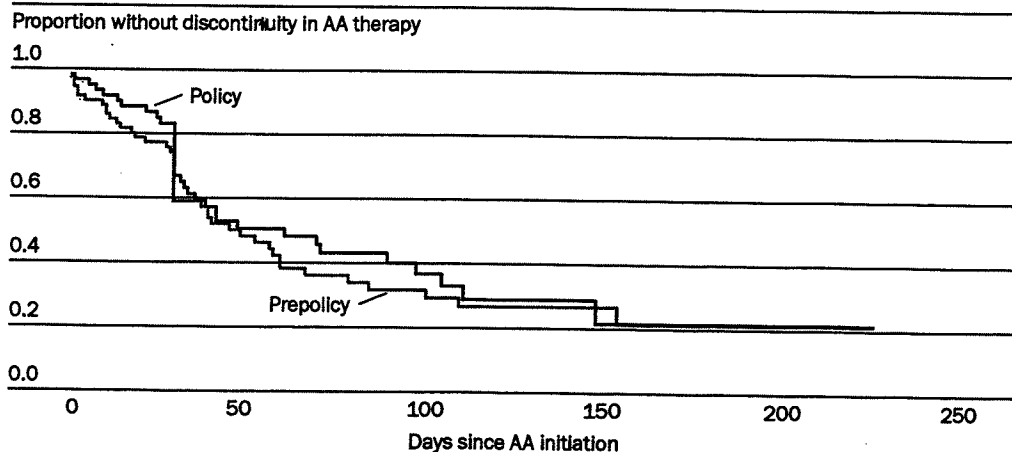
Proportion without discontinuity in AA therapy

Days since AA initiation

SOURCE: Authors' calculations using data from the Centers for Medicare and Medicaid Services, 2001-2004 ME/NH Medicaid and Medicare claims and enrollment data.
NOTES: Treatment discontinuity denotes either thirty or more days without therapy after initiation of an atypical antipsychotic (AA) or switching or augmentation of the initiation therapy. The prepolicy period was July 2002-February 2003 (n = 228); the policy period was July 2003-February 2004 (n = 222).

monthly AA medication costs in Maine rose from an estimated $200.21 to $226.66 per patient per month during the pre-policy period (Exhibit 5). The policy was as-

EXHIBIT 3
Time To Treatment Discontinuity Among Newly Treated Members Of The Comparison Cohort (New Hampshire) During The Prepolicy And Policy Observation Periods, 2002-2004

Proportion without discontinuity in AA therapy

Days since AA initiation

SOURCE: Authors' calculations using data from the Centers for Medicare and Medicaid Services, 2001-2004 ME/NH Medicaid and Medicare claims and enrollment data.
NOTES: Treatment discontinuity denotes either thirty or more days without therapy after initiation of an atypical antipsychotic (AA) or switching or augmentation of the initiation therapy. The prepolicy period was July 2002-February 2003 (n = 71); the policy period was July 2003-February 2004 (n = 63).

EXHIBIT 4

Change In Hazard Rate Of Treatment Discontinuity In The Study (Maine) And Comparison (New Hampshire) States Among Newly Treated Patients, Comparing The Policy And Prepolicy Periods

	Adjusted hazard ratio: policy vs. prepolicy hazard (95% CI)		Combined model:[a] relative change in hazard ratio for study cohort vs. comparison cohort
	Study cohort (ME)[b]	Comparison cohort (NH)[c]	
Time until treatment discontinuity[d]	1.29 (1.02, 1.63)**	0.71 (0.44, 1.13)	1.55 (0.94, 2.56)
Sensitivity analysis			
≥15 days	1.24 (1.00, 1.56)	0.68 (0.43, 1.07)	1.47 (0.91, 2.38)
≥45 days	1.30 (1.02, 1.66)**	0.54 (0.33, 0.89)**	1.94 (1.14, 3.29)**

SOURCE: Authors' calculations using data from the Centers for Medicare and Medicaid Services, 2001–2004 ME/NH Medicaid and Medicare claims and enrollment data.

NOTES: Index date for survival analysis was date of initial treatment with index atypical antipsychotic (AA) drug. Models were adjusted for the following baseline (pretreatment) variables: age, sex, number of days of hospitalization, average number of physician visits, number of different medications dispensed, and any dual enrollment (Medicaid and Medicare); all follow-up time was censored at date of policy discontinuation (1 March 2004) or the equivalent date for the prepolicy cohort (1 March 2003). CI is confidence interval.

[a] The ratio of study- versus comparison-group changes in the hazard ratio of treatment discontinuities resulting from a combined model with an interaction term for policy and state.

[b] Prepolicy N=228; during policy N=222.

[c] Prepolicy N=71; during policy N=63.

[d] Occurrence of either thirty or more days without therapy following initiation of an atypical antipsychotic (AA) or switching/augmentation of the initiation therapy.

**p < 0.05

sociated with a decrease in trend of $2.33 per patient per month (95 percent CI: –3.56, –1.10), or an average reduction of $18.63 per patient at the end of the eight-month policy period. In New Hampshire, there was a corresponding decrease of $3.58 per patient per month (95 percent CI: –5.81, –1.35) after the eight-month baseline period.

Discussion And Policy Implications

Our findings provide strong evidence of both intended and unintended consequences of the Maine PA policy. The most frequent adverse clinical outcome was treatment discontinuation, a strong predictor of acute psychotic episodes, hospitalization, and other negative clinical and economic outcomes.[21] Pharmacy savings were minimal.

■ **Study limitations.** Despite the consistent pattern of effects observed, the study had several limitations. The termination of Maine's PA policy after our study began resulted in limited follow-up, reducing our statistical power to detect treatment discontinuities among newly treated patients. More than 60 percent of treatments were initiated with the first-preferred AA in the last two months of the PA policy. As a result, we may have underestimated the effects of the policy on treatment discontinuities. The policy period was also insufficient to measure important potential changes in adverse events, such as development of diabetes.[22] Neverthe-

EXHIBIT 5

Time Series Of Average Monthly Medicaid Spending For Atypical Antipsychotic (AA) Agents Per Continuously Enrolled Patient In The Study (Maine) And Comparison (New Hampshire) Cohort, November 2002–October 2004
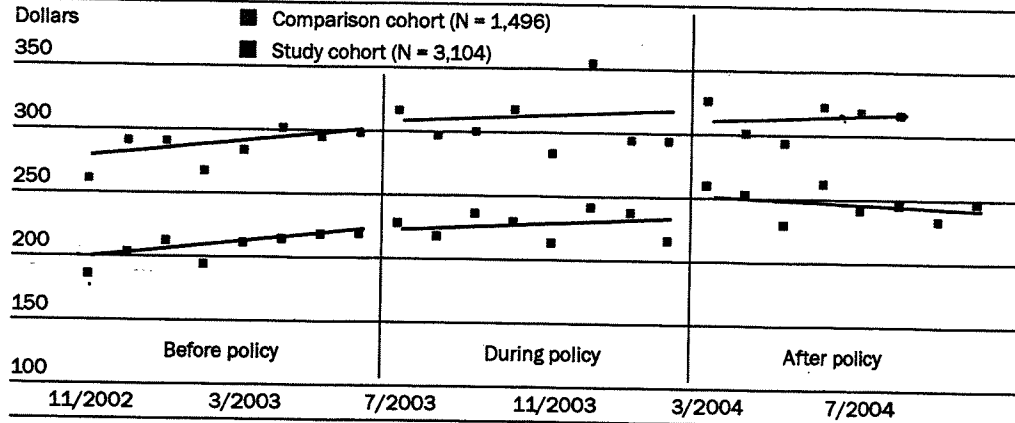
SOURCE: Authors' calculations using data from the Centers for Medicare and Medicaid Services, 2001–2004 ME/NH Medicaid and Medicare claims and enrollment data.
NOTES: All payments were adjusted to 2004 dollars using the Medical Care Consumer Price Index. The fitted trend lines for the study cohort show predicted values from segmented time-series regressions. Follow-up was truncated after August 2004 in the comparison cohort when New Hampshire implemented a prior authorization policy for certain AA agents.

less, the consistent PA effects on rates of treatment discontinuities observed in sensitivity analyses and the lack of effects in the comparison cohorts provide additional support for our findings. Our findings are also consistent with previous studies of the effects of other policies on discontinuation of antipsychotic agents among patients with severe mental illnesses.[23]

The individual components of our discontinuity measure do not represent equivalent risk to patients with schizophrenia. Switching and augmentation may represent a fine-tuning of therapy or may indicate poor clinical response. However, increases in risk of discontinuities associated with a policy change represent markers of reduced functioning or increased symptoms.[24] Importantly, more than two-thirds of the discontinuities observed were medication gaps, an outcome associated with increased risk of hospitalization.[25]

Finally, we were unable to adjust our estimates of expenditures to account for rebates paid to Medicaid by the respective AA manufacturers.

■ **Policy Implications.** Maine introduced a different PA program in 2007 for patients newly starting nonpreferred AAs; two AAs remained subject to PA as of January 2008.[26] An additional fifteen states have implemented PA programs for AAs in the past few years.[27] Furthermore, although the CMS includes AAs in the six medication classes entitled to extra protections in Part D, new users of AAs may nevertheless be subject to PA, unlike new users of HIV/AIDS medications, who are exempt.[28] Our results indicate that PA and step-therapy requirements for new users of AAs may result in problematic disruptions in therapy among patients with schizophrenia.

Previous reports have expressed concern regarding the use of PA for psychotropic medicines because of variations in adverse events and efficacy, idiosyncratic differences in response to therapy, and the general vulnerability of the seriously mentally ill.[29] A MaineCare Advisory Committee report examining PA listed similar issues concerning medication access and patient care.[30] A 2006 national survey of psychiatrists reported substantial rates of medication discontinuation associated with Medicare drug coverage issues.[31] Another Part D survey reported that dually eligible enrollees experienced PA twice as frequently as those not eligible for low-income subsidies.[32]

PA and step therapy clearly have a place as utilization management tools in Medicaid and Medicare. Medication classes such as nonsteroidal anti-inflammatory drugs (NSAIDs) or angiotensin-converting enzyme (ACE) inhibitors may have more homogeneous effects, providing better opportunities for savings through use of PA policies with lower risk of adverse outcomes.[33] However, caution is required when applying these tools for antipsychotics and other mental health drugs.

Our findings may also reflect problems in how PA programs are implemented, and how they might unintentionally but selectively affect vulnerable patients. Physicians may tend to switch to prescribing preferred medications because requesting a PA is a time-consuming process, even if they have concerns about the appropriateness of the medication for a specific patient.[34] In addition, some study patients in Maine who went to the pharmacy with an unapproved prescription might not have understood that they had the option to seek PA and thus might have failed to obtain the medication (an unmeasurable outcome in this study). Because patients with chronic mental illnesses are more likely than others to be confused by administrative barriers to care and have multiple comorbidities, they are likely to be disproportionately affected by multiple PAs for different classes of medication.[35]

Whatever may have contributed to the increased treatment discontinuities we observed, our findings suggest that step therapy and PA of AAs for patients with schizophrenia may result in suboptimal use of essential medications. These findings contrast with CMS guidance to state Medicaid directors that "because nonpreferred drugs remain available to beneficiaries through prior authorization, a PDL allows states to ensure appropriate patient access to needed medications and maintain continuity of patient therapy."[36] Our data suggest the need for additional research on the potential negative effects of PA policies in especially vulnerable populations. Our findings also indicate the importance of exempting essential psychoactive medications from PA and step-therapy requirements in Medicaid and Medicare until more is known about the clinical and economic consequences of such policies for vulnerable patients with schizophrenia.

NOTES

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