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ORIGINAL ARTICLE

Adherence and outcomes associated with copayment burden in schizophrenia: a cross-sectional survey

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Abstract

Objective: Assess the association of schizophrenia patients' perceived copayment burden with medication adherence and outcomes.

Methods: Patients with schizophrenia (aged 18+) completed self-reported questionnaires. Analyses included those currently using a second-generation antipsychotic (SGA) with no exposure to clozapine or depot formulation antipsychotics. Adherence was assessed using the Morisky Medication Adherence Scale (MMAS). Outcomes included emergency room (ER) use, hospitalization, attempted suicide, missed work due to health, and experiencing severe psychological distress. Logistic regression was used to adjust for demographics, health characteristics, psychotropic medication use, and insurance status.

Results: Of 351 schizophrenia patients, 39% perceived copayment burden. These patients were less than half as likely to have complete adherence [OR = 0.427; 95% CI: 0.257, 0.711; $p = 0.001$]. Copayment burden was associated with greater likelihood of ER use, [OR = 2.157; 95% CI: (1.322, 3.520); $p = 0.002$], hospitalization [OR = 2.512; 95% CI: (1.475, 4.277); $p < 0.001$], attempted suicide [OR = 2.385; 95% CI: (1.156, 4.920); $p = 0.019$], severe psychological distress [OR = 1.833; 95% CI: 1.092, 3.075; $p = 0.022$] and greater likelihood of missing work [OR = 7.193; 95% CI: 2.554, 20.256; $p < 0.001$].

Conclusions: Copayment burden is associated with poorer medication adherence and outcomes. Formularies that reduce copayment burden for SGAs may positively affect medication adherence and outcomes among schizophrenia patients.

Limitations: Patient data were self-reported, which may have introduced additional bias in the study measures. Also, the use of a cross-sectional design precludes causal inference and the use of the current sampling methodology (both interview and Internet panel) might impact the ability to generalize the results to the broader population.

Key words: adherence, antipsychotic agents, copayment, outcomes, schizophrenia

Introduction

Schizophrenia is a chronic psychiatric illness characterized by cognitive, perceptual, behavioral and affective disturbances leading to chronic psychosocial impairment and episodic exacerbations. With a lifetime prevalence between 0.5% and 1.5%^{1,2}, the total cost of schizophrenia in the US has been estimated at \$62.7 billion in 2002^{3,4}.

Atypical antipsychotics are an important aspect of schizophrenia treatment⁵. However, medication adherence rates are generally low in this population^{6–8}, and

poor adherence has been associated with greater likelihood of relapse and hospitalization, with associated incremental healthcare costs^{9–11}.

In order to manage increasing pharmacy costs, payers may institute cost-sharing formulary practices, which provide the payer with revenue to offset the acquisition costs of medications. However, cost-sharing practices and other out-of-pocket costs have been associated with lower treatment adherence in a variety of therapeutic areas, including diabetes¹², dyslipidemia^{13,14}, rheumatoid arthritis¹⁵, and even renal dialysis¹⁶. However, to date, there has

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been little research on the relationship between copayment burden and medication adherence in schizophrenia. A recent study of the effects of introducing copayments for prescription medications showed that subjects with schizophrenia reduced the use of medications not indicated for the treatment of schizophrenia more than medications for schizophrenia¹⁷. However, another study found that increases in copayments by the Department of Veterans Affairs were associated with a 25% reduction in refills of psychiatric medications and a corresponding increase in inpatient utilization likely resulting from non-adherence to medication¹⁸.

Functional impairment associated with schizophrenia may reduce capacity for competitive employment and therefore reduce earning capacity^{19,20}. One study found an employment rate among schizophrenia patients of 17.2%, with only 9.8% working full-time. The mean monthly earnings of the employed sample were less than \$500 per month²⁰. As a result of their marginal income, patients with schizophrenia may be more sensitive to copayment burden than other chronically ill populations.

The primary objective of this study was to assess the association of self-reported copayment burden with medication adherence among patients with schizophrenia treated with antipsychotic medication. A secondary objective was to assess the association of self-perceived copayment burden with clinical and functional outcomes.

Patients and methods

Study design

The current study was an analysis of a cross-sectional survey using a self-administered questionnaire between December 2007 and February 2008. Patients who reported having schizophrenia in an Internet-based consumer panel (Lightspeed Research Ailment Panel) were sent an invitation to participate in a web-based questionnaire via email. An email address was provided for patients to ask any questions they may have had about the survey. Patients were also recruited to interview facilities through panel recruiting, grassroots campaigns, and newspaper advertising. Once enrolled, a facilitator at each interview site provided the respondent with a paper copy of the questionnaire. All responses were self-reported. However, the facilitator was available during all of the interviews to answer any questions posed by the respondent and to ensure completion of the survey instrument.

The study protocol and questionnaire were reviewed and approved by Essex IRB (Lebanon, NJ). A statement of informed consent was provided to potential respondents prior to participation in the study. Patients who

explicitly agreed to participate in the study were then enrolled.

Study population

Inclusion criteria for participation in the primary survey were: aged 18 or older, reporting that they were diagnosed with schizophrenia by a healthcare professional, residing in the US, able to read and write English, and consenting to participate in the study. In order to be eligible for inclusion into the analytic sample, subjects were required to be currently taking at least one second-generation antipsychotic (SGA) which included aripiprazole, olanzapine, paliperidone ER, quetiapine, oral risperidone, and ziprasidone. Patients were excluded from the analytic sample if they reported ever using clozapine or a long-acting injectable antipsychotic medication. Figure 1 illustrates the criteria for inclusion in the study sample.

Study measures

Copayment burden. Patients were asked, 'Is a co-pay for antipsychotic medication a burden for you?' Patients who responded, 'Yes' were classified as experiencing copayment burden, and those who responded, 'No' were classified as not experiencing a copayment burden.

Adherence. Adherence was assessed using the Morisky Medication Adherence Scale (MMAS)^{21,22}. The MMAS consists of four yes/no questions that assess adherence to prescribed medication. These questions assess forgetfulness about taking medication, carelessness about taking medication, stopping medication when feeling better, and stopping medication when feeling worse. The score is the sum of 'yes' responses, with a range of 0–4. The MMAS was first validated for patients using antihypertensives, but has since been used across a variety of therapeutic areas²¹. A score of ≥ 2 is associated with a high likelihood of medication non-adherence²². Throughout the analyses, respondents with a score ≥ 2 were classified as non-adherent and those with a score of 0 or 1 were classified as adherent. In addition, complete adherence was defined as a score of zero.

Clinical outcomes. Patient outcomes assessed in this study included emergency room use, hospitalization, and attempted suicide in the past 6 months. In addition, missing work for any health-related reason (mental or medical) was assessed for the past 6 months among patients who were employed either full-time or part-time. Each of these outcomes was defined as a dichotomized variable, where yes = 1 and no = 0.

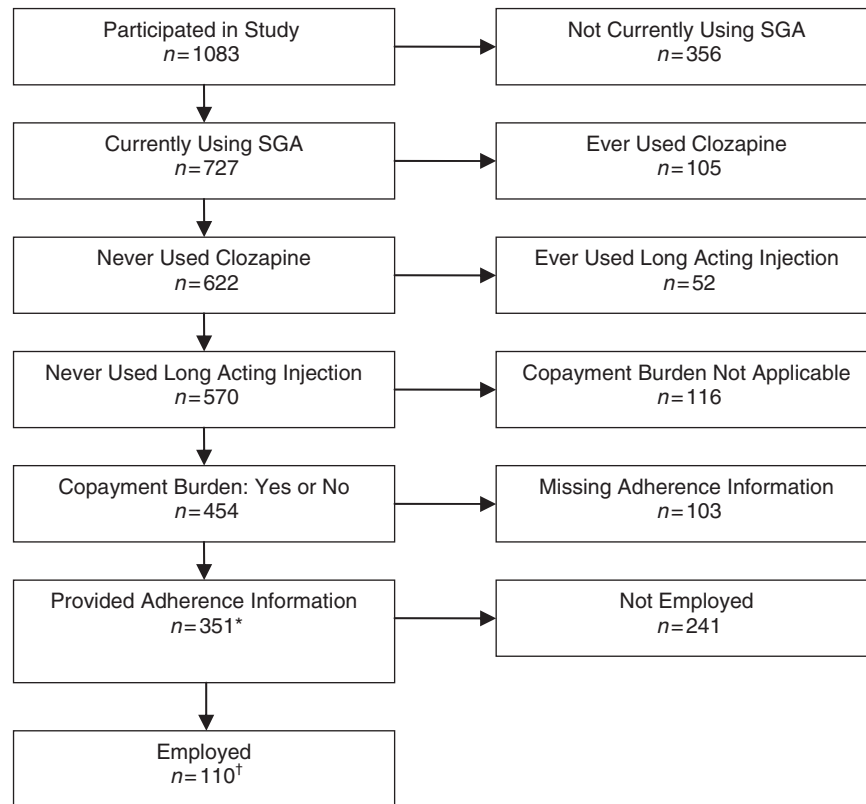


Figure 1. Patient flow. *Total sample included in the current study (including analyses of adherence, ER use, hospitalization, attempted suicide, and severe distress). †Subsample included for analyses of missed work (since the 241 patients who were not employed had missing data for employment metrics).

Psychological distress in the past month was assessed using the Psychological General Well Being Scale (PGWB)^{23,24}. The PGWB is a self-administered 22-item questionnaire assessing anxiety, depression, vitality, positive well-being, self-discipline and general health with scores ranging between 0 and 110. Severe distress was classified as a score of 60 or lower.

Demographics, health characteristics, and psychotropic medication use. Demographics except age were assessed as categorical variables and included: gender (female vs. male), marital status (single, never married vs. ever married), education (some college or higher vs. no college), employment status (employed or student vs. not employed or retired), and poverty (annual household income less than \$20,000 vs. income \$20,000 or greater).

Health characteristics included tobacco use (yes vs. no), alcohol or substance use (yes vs. no), and the total number of comorbid medical conditions, which included type I and type II diabetes, high blood pressure, high cholesterol, heart disease, migraine, liver disease, and HIV. Also, total number of psychotropic medications was assessed as a count of the following medications:

antipsychotics, non-antipsychotic mood stabilizers, antidepressants, and anxiolytics.

Insurance status. Health insurance was assessed using the following dummy variables: Veteran's Administration (VA) with or without other sources; managed care without VA, Medicare, or Medicaid; Medicare or Medicaid without VA or managed care; Medicare or Medicaid and managed care without VA. The reference group was none of these, which included the uninsured as well as patients who did not know their insurance type.

Statistical analyses

Bivariate statistics were used to compare adherence, patient outcomes, demographics, health characteristics, psychotropic medication use, and insurance status, across patients with and without copayment burden. Chi-square tests were used to assess significant differences in categorical variables, and *t*-tests were used to assess significant differences in continuous variables.

Table 1. The effect of demographics and patient characteristics on the perception of a copayment burden among patients with schizophrenia.

Demographics and characteristics	Total (<i>n</i> = 351)	With copayment burden (<i>n</i> = 137)	Without copayment burden (<i>n</i> = 214)	<i>p</i> -value
Female, %	55.6%	56.2%	55.1%	0.845
Age, mean (SD)	43.4 (11.7)	44.3 (11.6)	42.8 (11.8)	0.235
White, %	63.5%	67.2%	61.2%	0.260
Single, never married, %	46.3%	40.4%	50.0%	0.080
Some college or higher, %	55.3%	62.8%	50.5%	0.024
Employed, %	34.3%	34.6%	34.1%	0.932
Poverty (income < \$20,000), %	56.1%	52.6%	58.4%	0.281
Used tobacco, %	70.0%	73.7%	67.6%	0.223
Used alcohol or substance, %	84.6%	85.4%	84.1%	0.744
Number of comorbid conditions, mean (SD)	1.3 (1.3)	1.6 (1.4)	1.2 (1.2)	0.004
Number of psychotropic medications, mean (SD)	3.3 (1.5)	3.5 (1.7)	3.2 (1.3)	0.054
Health insurance, %				
Veterans Administration (VA)	5.4%	4.4%	6.1%	0.494
Managed care (no VA, Medicare, Medicaid)	23.9%	27.0%	22.0%	0.280
Medicare/Medicaid (no managed-care)	59.3%	52.6%	63.6%	0.041
Managed care & Medicare/Medicaid	4.3%	6.6%	2.8%	0.089
Online sample, %	16.8%	18.3%	15.9%	0.564

Method: Chi-square for comparisons of percentages and *t*-tests for comparisons of means.

The independent associations of copayment burden with treatment adherence and patient outcomes were assessed using logistic regression analysis. To assess adherence, models were developed for each of the following dependent variables: adherence, complete adherence, and each of the four MMAS items. To assess outcomes, models were developed for each of the following dependent variables: visiting the ER, hospitalization, attempted suicide, severe distress, and missing work (among the subgroup of employed patients). Covariates included in all models included demographics, health characteristics, number of psychotropic medications, insurance status, and recruitment site (interview vs. Internet). A post hoc mediational analysis was also performed, examining whether non-adherence explains the relationship between copayment burden and health outcomes. Mediation was tested using the Sobel *z*-test, which tests the significance of the indirect effect²⁵. All analyses were run using SAS software.

Results

Sample characteristics

The survey population consisted of 1083 patients reporting a diagnosis of schizophrenia. Of these, 157 were internet participants and 926 were on-site participants. A total of 351 patients met inclusion criteria for analysis. Sample characteristics for the analytic sample as well as patients

with and without copayment burden are presented in Table 1.

Of the 351 patients who met criteria for inclusion in the analysis, 137 (39.0%) reported experiencing copayment burden and 214 (61%) reported no copayment burden. More patients with copayment burden reported at least some college education and had a greater number of physical comorbid conditions than patients without perceived copayment burden. Other patient characteristics, including tobacco use and substance use, did not significantly vary by level of copayment burden.

The largest portion of the sample (59.3%) was covered by Medicare and/or Medicaid. Of the sample covered by Medicare and/or Medicaid, 38.5% of patients were covered by both. Managed-care insurance without additional public sector coverage was reported by 23.9% of the sample, and an additional 4.3% had both public sector and managed-care coverage. Consistent with state-mandated caps on copayments, fewer patients with copayment burden had public sector coverage alone.

Copayment burden and medication adherence

Unadjusted bivariate analysis revealed a significant positive relationship between copayment burden and lower rates of adherence (MMAS < 2, *p* = 0.049) and a negative relationship between copayment burden and complete adherence (MMAS = 0, *p* = 0.001). In addition, rates of forgetting to take medication and stopping medication when

Table 2. Unadjusted association of copayment burden with medication adherence and patient outcomes.

Association	Total (<i>n</i> = 351)	With copayment burden (<i>n</i> = 137)	Without copayment burden (<i>n</i> = 214)	<i>p</i> -value
Adherence				
Adherence (Morisky Medication Adherence Scale <2)	64.7%	58.4%	68.7%	0.049
Complete adherence (Morisky Medication Adherence Scale = 0)	39.6%	28.5%	46.7%	0.001
Careless about taking medication	31.1%	35.8%	28.0%	0.127
Forget to take medication	50.4%	61.3%	43.5%	0.001
Stop medication when feel better	25.1%	29.9%	22.0%	0.093
Stop medication when feel worse	23.4%	30.7%	18.7%	0.001
Outcomes				
Visited emergency room (ER) in past 6 months	40.7%	52.6%	33.2%	<0.001
Hospitalized in past 6 months	30.8%	40.9%	24.3%	0.001
Suicide attempt in past 6 months	12.5%	17.5%	9.4%	0.024
Severe distress (≤ 60 on the Psychological General Well Being Scale)	65.7%	74.4%	60.1%	0.006
Of employed . . .	(<i>n</i> = 110)	(<i>n</i> = 44)	(<i>n</i> = 66)	
Missed work in past 6 months due to health	34.6%	56.8%	19.7%	<0.001

Method: Chi-square for comparisons of percentages.

feeling worse were significantly higher among patients with self-reported copayment burden. Stopping medication when feeling better and being careless about taking medication did not significantly vary by copayment burden status (Table 2).

Logistic regression adjusting for covariates revealed a trend association between copayment burden and adherence (MMAS < 2) (OR 0.627, $p = 0.060$). Patients with copayment burden were less than half as likely (OR = 0.43, $p = 0.001$) to report complete adherence compared to patients without copayment burden. Also, VA insurance was negatively associated with complete adherence. Payer type was not significant in any other adherence model. In the logistic regression models assessing individual MMAS items, copayment burden was significantly associated with greater likelihood of forgetting to take medication (OR = 2.06, $p = 0.003$) and stopping medication when feeling worse (OR = 2.00, $p = 0.016$), but not being careless about taking medication or stopping medication when feeling better (Table 3).

Association of copayment burden and patient outcomes

Unadjusted bivariate analysis revealed higher rates of emergency room visits, hospitalizations, and suicide attempts in the prior 6 months among those with copayment burden. In addition, more patients with copayment burden were characterized as in severe distress according to the PGWB. Among employed patients ($n = 110$), more patients with copayment burden missed work due to mental health or other medical reasons in the prior 6 months (Table 2).

Logistic regression adjusting for covariates revealed that copayment burden was associated with a greater likelihood of visiting the emergency room, hospitalization, attempted suicide, and experiencing severe distress. Among employed patients, those with reported copayment burden were significantly more likely to miss work due to mental health or other medical reasons. (Table 3)

Mediation of copayment burden and patient outcomes

As a final post hoc analysis, complete adherence was examined as a potential mediator of the relationships observed between copayment burden and outcomes (emergency room visits and hospitalizations). In other words, it was tested whether complete adherence was the reason for the association between burden and resource use (i.e., copayment burden lead to reduced adherence which, in turn, lead to increased number of emergency room visits and hospitalizations). To test this hypothesis, two mediational analyses were conducted and whether the path of the indirect effect (copayment burden to adherence to emergency room/hospitalization) was significantly greater than zero examined.

As reported above, copayment burden was significantly associated with an increased likelihood of an emergency room visit ($b = 0.77$, $p = 0.002$) and hospitalization ($b = 0.92$, $p = 0.001$). When adding complete adherence to each model, the strength of relationship of copayment burden and emergency room remained unchanged ($b = 0.77$, $p = 0.002$) however the relationship of copayment burden and hospitalization slightly weakened ($b = 0.81$, $p = 0.003$). Although a significant indirect effect was observed for hospitalization (Sobel $z = 2.11$,

Table 3. Adjusted association of copayment burden with medication adherence and patient outcomes.

Association	Odds ratio	95% confidence interval		<i>p</i> -value
		Low	High	
Adherence				
Adherence (Morisky Medication Adherence Scale <2)	0.627	0.386	1.021	0.060
Complete adherence (Morisky Medication Adherence Scale = 0)	0.427	0.257	0.711	0.001
Careless about taking medication	1.450	0.880	2.390	0.145
Forget to take medication	2.058	1.270	3.335	0.003
Stop medication when feel better	1.592	0.930	2.725	0.090
Stop medication when feel worse	2.000	1.140	3.507	0.016
Outcomes				
Visited emergency room (ER) in past 6 months	2.157	1.322	3.520	0.002
Hospitalized in past 6 months	2.512	1.475	4.277	<0.001
Suicide attempt in past 6 months	2.385	1.156	4.920	0.019
Severe distress (≤60 on the Psychological General Well Being Scale)	1.833	1.092	3.075	0.022
Missed work in past 6 months due to health*	7.193	2.554	20.256	<0.001

Method: Logistic regression adjusting for gender, age, race, marital status, education, employment, poverty, tobacco use, alcohol/substance use, comorbid conditions, count of psychotropic medications, insurance status, and interview site.

*Analysis limited to eligible subjects who were employed full-time or part-time ($n = 110$).

$p = 0.035$), none was observed for emergency room visits (Sobel $z = -0.13$, $p = 0.90$).

Discussion

This cross-sectional survey demonstrated a significant relationship between copayment burden and medication adherence, which was consistent with prior research in therapeutic areas such as diabetes¹², dyslipidemia^{13,14}, rheumatoid arthritis¹⁵, and renal dialysis¹⁶, as well as schizophrenia^{17,18}. This study investigated the relationship between patient-reported copayment burden and adherence, in contrast to Zeber *et al.*, who assessed the relationship between actual copayment amount and refill rates in a VA population with schizophrenia. Yet, the consistency of these results suggests that patients with schizophrenia are sensitive to both absolute and perceived economic burden associated with their prescription medications. Of course, it should be noted that the current study was limited to patients currently taking antipsychotic medications and therefore cannot estimate the impact of copayment burden on medication discontinuation.

Perceived copayment burden was also associated with poorer outcomes, including greater likelihood of ER use, hospitalization, suicide attempts, severe distress, and missed work. Previous research has suggested that these effects may be mediated by medication non-adherence, which is associated with poor outcomes^{9–11,18}. However, our mediational analysis was inconsistent. Although there was evidence that non-adherence is a driving force of the relationship between burden and outcomes, this was only true for hospitalization. Further research is need to investigate the cascade of effects when copayment burden is

present. Nevertheless, this study observed a greater likelihood of ER use and hospitalization associated with copayment burden, which may offset any economic advantages associated with cost-sharing strategies. Since employers have a role in defining formulary benefit design, the finding that copayment burden is associated with work absenteeism also raises questions regarding the practicality of cost-sharing in this area.

Another finding is that, while Medicaid copayment caps are designed to minimize economic burden among low-income beneficiaries, and in fact fewer subjects with burden reported having public sector health coverage, the subjective experience of economic burden was strongly associated with incomplete adherence independent of payer type. This suggests that any type of medication cost sharing, however small, may pose a risk for non-adherence in persons with schizophrenia.

Because adherence is necessary to receive the full benefits of antipsychotic treatment, physicians consider multiple factors that effect adherence when making treatment decisions. Among these are increasing patient health literacy, setting personalized and meaningful treatment goals, and individualizing medication regimens to meet the specific needs of each patient. There are a number of atypical antipsychotic treatment options for schizophrenia, and recent studies have suggested no significant differences in efficacy^{26,27}. However, biological heterogeneity of tolerability and response among psychiatric disorders leads to a need for more diverse pharmacologic options in order to optimize treatment for individual patients^{28,29}. The ability to individualize a medication regimen may be restricted by copayment burden that reduces the patient's ability or motivation to be fully adherent even if it is quite suitable for the patient. On the other hand, limited prescribing

options purely based on costs may reduce the ability of a physician to match the medication regimen to the patient's unique needs and limitations.

The finding that copayment burden was associated with some, but not all, responses on the MMAS warrants further discussion. The items significantly associated with copayment burden included 'forgetting to take medication' and 'stopping medication when feeling worse.' Forgetting to take medication may be a proxy for measuring reduced motivation. In other words, the burden of copayment may make patients less motivated to take their medication regularly, thus a higher likelihood of 'forgetting'. Burden was also associated with discontinuing medication 'when feeling worse'. This may suggest that with a greater burden, patients are less likely to tolerate side-effects. However, it is curious that burden was not also associated with 'stopping medication when feeling better' (though the trend was in the expected direction). Though speculation, it is possible that the burden is more tolerable if it is believed that the economic investment is resulting in better health. Even more puzzling is the lack of a significant effect between burden and being careless about medications. Surely, if burden is associated with forgetfulness, it would be reasonable to expect a similar relationship with carelessness. Certainly, future research should seek to replicate these findings and better understand how patients conceptualize copayment burden. The aim of the current study was to focus on patients' perceptions of copayment burden in a general sense. However, further research investigating the issues surrounding copayment burden are warranted especially given the pattern of results with the individual adherence items.

Limitations of this study include its cross-sectional design, which precludes causal inference. It is possible, for instance, that patients were more likely to experience their cost-sharing as burdensome as rationalization for their non-adherence. Or, alternatively, patients with more severe forms of the condition may be more likely to be forgetful in taking their medications, and report worse outcomes, suggesting that the burden-to-adherence relationship is not causal. Similarly, other variables not assessed in this study may explain the observed relationships. For example, household size was not assessed which may interact with household income to explain some of the observed relationships. Future research should rely on prospective or longitudinal designs.

Data were collected via the internet and on-site in metropolitan areas, and therefore, the sample may not be representative of people without internet access or who live in more rural areas. The self-report nature of the study might have either excluded patients with cognitive difficulties, or resulted in invalid results. Moreover, diagnoses, treatments, and health resource utilization were not

confirmed by clinicians, patient records, or administrative claims data.

Another important limitation is the assessment of burden. The aim of the current study was to determine the relationship between perceived copayment burden (however a patient defines the term without the researchers imposing an *a priori* definition or relying on purely dollar amounts) and adherence and outcomes. Because of this broad approach, it remains unclear precisely the aspects of copayments that were perceived as burdensome. Indeed, subsequent research should validate this methodology and determine what constitutes a burden in this population.

Conclusions

These results demonstrate that self-reported copayment burden in patients with schizophrenia is associated with reduced medication adherence and negative clinical and economic consequences. Although preliminary evidence suggests that copayment burden may lead to non-adherence which, in turn, leads to increased hospitalization, more research is necessary to replicate this finding.

Transparency

Declaration of funding: The Schizophrenia Study was conducted and wholly owned by Consumer Health Sciences/Kantar Health, Princeton, NJ. Bristol-Myers Squibb, Plainsboro, NJ licensed access to the study and funded the analysis presented in this paper.

Declaration of financial/other relationships: E.K., C.C.C., and J.A.B. have disclosed that they are employees of Bristol-Myers Squibb; S.B. and S.G. have disclosed that they are employees of Kantar Health; R.W. has disclosed that he is an employee of Otsuka America Pharmaceutical.

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