

Schizophrenia: Opportunities to Improve Outcomes and Reduce Economic Burden Through Managed Care

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Economic Impact of Schizophrenia

Direct and Indirect Costs

Schizophrenia represents a significant economic burden for patients, payers, and society, and the total costs related to the illness appear to be disproportionate to the disease prevalence. A study published in 2016 elucidated current medical costs, including both direct and indirect costs of schizophrenia in the United States.¹ Using the prevalence rate of 1.1% from 2013, the study estimated the number of patients diagnosed with schizophrenia in the United States to be 3.5 million, which translated to an annual economic burden of approximately \$155.7 billion. Direct healthcare costs amounted to \$37.7 billion, or 24% of the total cost, and included medication use, outpatient and inpatient services, emergency department (ED) visits, long-term care utilization, and other medical services. Of the drivers of direct healthcare costs, inpatient visits and medications were found to be the largest contributors to spending, accounting for 10% and 6% of the total cost, respectively. Indirect costs were estimated at \$117.3 billion and contributed to 76% of the total economic cost. Of the drivers of indirect costs related to schizophrenia, high unemployment rates and caregiver burden were found to be the largest contributors to spending, accounting for 38% and 34% of the total cost, respectively. Based on the findings from the study, the total average annual cost per patient diagnosed with schizophrenia was estimated to be \$44,773.¹

Medicare and Commercially Insured Costs of Care Estimates

A study by Feldman et al compared the cost of care for 2 groups of Medicare beneficiaries: those who were diagnosed with nonschizoaffective schizophrenia in a sample collected from 2003 to 2007, and the general Medicare population, for whom cost estimates were determined from 2001 to 2009.² Medicare patients with diagnosed schizophrenia had a cost of care that was approximately 80% higher than the general Medicare population per year in 2010 dollars. Overall, more than 50% of the annual cost was due to psychiatric and medical hospitalizations, occurring in approximately 30% of the patients with schizophrenia.²

ABSTRACT

Schizophrenia is a complicated chronic disease affecting approximately 3.5 million people in the United States, and its annual healthcare costs exceed \$155 billion. People living with schizophrenia often experience a reduced quality of life (QOL) and are more likely to be homeless, unemployed, or living in poverty compared with the general population. Life expectancy for patients with schizophrenia is 15 to 20 years below the average and is complicated by numerous comorbidities, such as weight gain, increased cardiovascular risk, and changes in mood and cognition. Treatment nonadherence can increase the risk of relapse, rehospitalization, and self-harm, leading to a reduced QOL and increased economic burden. Managed care professionals are positioned to improve adherence and outcomes through various drug utilization strategies. Clinicians may also empower patients with schizophrenia through shared decision making and the creation of a therapeutic alliance. Careful monitoring of medication-related adverse effects and offering potential medication alternatives and routes of administration when indicated may also improve adherence to treatment regimens, resulting in improved outcomes and reduced healthcare costs.

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Cost comparison studies have also been conducted in commercially insured patients. A study by Fitch et al evaluated the average cost per patient per month (PPPM) for patients with diagnosed schizophrenia compared with a demographically adjusted population without schizophrenia.³ On average, the total claim cost per patient with schizophrenia was more than 4 times the average total claim cost for a demographically adjusted population without schizophrenia. In a breakdown of cost, the PPPM cost for patients with diagnosed schizophrenia was \$1806, with 42% used for inpatient resources, 33% for outpatient resources, and 25% for prescription medications. Authors also determined that PPPM costs are highest in the month of diagnosis, labeled as the index month, with an average of \$6601 owing mainly to the high cost of inpatient care.³

Additionally, a retrospective claims-based study published in 2018 by Huang et al investigated healthcare resource utilization (HRU) and costs of care in young adults aged 18 to 64 years with diagnosed schizophrenia.⁴ The study included 9889 patients and compared them with a control cohort of patients who did not have schizophrenia. Additionally, younger adults with schizophrenia aged 18 to 35 years were compared with older adults aged 36 to 64 years, also diagnosed with schizophrenia. Those aged 18 to 35 years with schizophrenia had significantly lower rates of comorbid conditions but significantly higher rates of depressive disorders, anxiety, bipolar disorder, attention-deficit/hyperactivity disorder, and personality disorder as compared with the older group. Total costs of care were also significantly higher for younger patients with schizophrenia as compared with the older group (\$22,578 vs \$28,857; $P < .0001$). When compared with controls who did not have schizophrenia, patients with schizophrenia had higher all-cause HRU (inpatient admissions, outpatient office visits, ED visits, pharmacy visits) as compared with controls. HRU costs per patient per year (PPPY) were also significantly higher for patients with schizophrenia compared with those who did not have a diagnosis of schizophrenia (\$22,338 vs \$7332; $P < .0001$).⁴

Cost of Treatment Resistance

Treatment resistance has been broadly defined in previous studies as when 2 or more adequate trials of an antipsychotic therapy have been administered for 4 or more weeks at appropriate doses, and they fail to elicit a response.^{5,6} Up to 30% of patients with chronic schizophrenia meet these criteria for treatment-resistant schizophrenia.⁷ Patients with treatment-resistant schizophrenia face a disease burden that includes a reduced quality of life (QOL), presence of disease-associated and treatment-associated adverse effects (AEs), increased medical costs, increased rates of serious comorbidities, and increased suicide risk compared with patients who are not considered treatment resistant. Annual costs associated with treatment resistance range from \$66,360 to \$163,795, or 3- to 11-fold higher than the annual cost of patients with schizophrenia

that is not considered treatment resistant. Although estimates in the literature vary, treatment resistance in schizophrenia conservatively adds more than \$34 billion in annual direct medical costs as a result of HRU, including hospitalizations and outpatient costs.⁸

QOL in Schizophrenia

Patients diagnosed with schizophrenia experience a reduced QOL that is multifactorial. Some contributors to reduced QOL include homelessness, unemployment, and poverty.⁹ Unemployment rates have been reported to be as high as 80% to 90% in this population and pose an ongoing challenge.¹⁰ Nearly 50% of patients have long-term psychiatric problems and approximately 20% have chronic symptoms and disability.¹⁰ QOL measures have been shown to aid in predicting likelihood of relapse in patients with schizophrenia. In a study by Boyer et al ($n = 1024$), relapse was defined by the following criteria: (1) hospitalization due to worsening of psychotic symptoms or of such magnitude that hospitalization appeared imminent; (2) a re-emergence of florid psychotic symptoms such as delusions, hallucinations, or bizarre behavior; or (3) a thought disorder lasting 7 days or longer. Results of the study showed that a higher QOL score predicts a lower rate of relapse at 24 months (hazard ratio [HR], 0.82; 95% CI, 0.74-0.91; $P < .001$) for the SF36-Physical Composite Score; (HR, 0.88; 95% CI, 0.81-0.96; $P = .002$) for the SF36-Mental Composite Score).¹¹ With the evidence showing that reduced QOL results from many different disease aspects, it is important to address areas of reduced QOL in order to limit the chances of relapse.

Nonpharmacologic interventions, such as exercise, may improve QOL and be beneficial for patients with schizophrenia. A meta-analysis conducted in the Netherlands evaluated the relationship between physical fitness and functionality in 1109 patients with schizophrenia.¹² Studies in patients with schizophrenia in which effects of exercise were assessed were pooled and compared with a control group who did not exercise. The meta-analysis findings were that exercise improved clinical symptoms, QOL scores, symptoms of depression, and global functioning. Exercise was superior to control conditions in improving total symptom severity; positive, negative, and general symptoms; QOL scores; global functioning; and depressive symptoms. Yoga, specifically, was found to have a positive effect on cognition, but more research is needed to elucidate this connection. Physical exercise, including aerobic exercise and yoga, should be considered as a potential adjunct to pharmacologic treatment to improve overall well-being in patients with schizophrenia.¹²

Morbidity and Mortality

A diagnosis of schizophrenia has been associated with a reduced life expectancy of 10 to 20 years as well as an increased risk of premature mortality. One meta-analysis evaluating more than 1 million participants found that increased morbidity and mortality

for patients with schizophrenia is related to social factors such as alcohol or tobacco use,¹³ while another meta-analysis¹⁴ demonstrated the increased rates of metabolic syndrome were partly attributable to the medications themselves. Patients with severe mental illness, including schizophrenia, are often heavy smokers, and healthcare professionals are uniquely equipped to assess smoking status and offer support in smoking cessation.¹⁵

Patients with schizophrenia are at an increased risk for several comorbid conditions, such as dementia, liver disease, AIDS, heart failure, and type 2 diabetes. Cardiovascular (CV) morbidity and mortality in schizophrenia often occur before age 50 years. In a meta-analysis, the schizophrenia mortality rate (2.5) was at least as high as in individuals with heavy smoking status (RR, 2.4-2.7).¹⁶ Further, the main causes of death in patients with schizophrenia are suicide, cancer, and CV disease.¹⁷ Suicide in patients with schizophrenia is estimated to be more than 12 times greater (median standardized MR, 12.86) than in the general population.¹⁸ Depression is another common comorbid illness in patients with schizophrenia. In a study of 2228 participants, almost 40% of patients with schizophrenia were deemed to have depression.¹⁹ Over the course of the 3-year study period, the cohort with depression was more likely to use mental health services, present safety concerns, have greater substance use, and report lower overall QOL (Table).¹⁹

A US study evaluating the risk of premature death in adult Medicaid patients with mental illness from 2001 to 2007 found that adults with schizophrenia die at approximately 3.5 times the rate of the general population (standardized MR, 3.7; 95% CI, 3.7-3.7).²⁰ Deaths were attributed to several comorbid illnesses, with CV disease representing

the highest mortality rate (403.2 per 100,000 person-years) and a standardized MR of 3.6 (95% CI, 3.5-3.6). Various cancers were also evaluated; lung cancer was found to have the highest mortality rate (74.8 per 100,000 person-years) and a standardized MR of 2.4 (95% CI, 2.4-2.5) in this patient population. Other comorbidities contributing to mortality include chronic obstructive pulmonary disease (standardized MR, 9.9; 95% CI, 9.6-10.2) as well as influenza and pneumonia (standardized MR, 7.0; 95% CI, 6.7-7.4).²⁰

Substance Use in Schizophrenia

Substance use can have a negative effect on QOL and impact disease progression in patients with schizophrenia. Substance use has been linked to higher conversion rates from schizotypal disorder to schizophrenia. More specifically, cannabis, amphetamine, and opioid use disorders may be associated with conversion. In one study, 2539 participants with schizotypal disorder were identified and followed over several decades.²¹ After 2 years, 16.3% of participants experienced conversion to schizophrenia. After 20 years, the conversion rate was 33.1% (95% CI, 29.3%-37.3%) overall, 58.2% (95% CI, 44.8%-72.2%) among those with cannabis use disorders, and 47.0% (95% CI, 35.3%-60.2%) among those with alcohol use disorder compared with 30.6% (95% CI, 27.7%-34.5%) in those without substance use disorders.²¹

Impact of Medication-Related AEs

Antipsychotics are considered effective for both acute and maintenance management of schizophrenia, but numerous AEs, including weight gain, metabolic disturbances, hyperprolactinemia, impaired

TABLE. Functional Outcomes Variables for Cohorts Without and With Depression at Enrollment and Across the 3-Year Study¹⁹

Outcome ^a	Assessed at Enrollment		3-Year Outcomes	
	No depression	Depression	No depression	Depression
HRU				
Emergency psychiatric services	5.4	15.3	4.1	12.4
ED visits	15.5	24.2	7.4	14.5
Psychiatrist contacts (mean)	3.8	4.9	3.3	4.0
Safety to self and others				
Violent behavior	3.3	12.4	3.5	10.3
Arrested or jailed	5.6	8.6	3.8	6.2
Victim of crime	8.2	15.7	6.7	14.5
Suicidal ideations	4.6	33.3	4.3	30.1
Suicide attempts	0.7	6.0	0.7	4.7
Substance use	25.2	32.2	21.4	28.8
QOL, overall (mean)	64.9	52.9	64.3	52.3

ED indicates emergency department; HRU, healthcare resource utilization; QOL, quality of life.

^aFigures are percentages unless otherwise noted.

Adapted from: Conley RR, Ascher-Svanum H, Zhu B, Faries DE, Kinon BJ. The burden of depressive symptoms in the long-term treatment of patients with schizophrenia. *Schizophr Res.* 2007;90(1-3):186-197. doi: 10.1016/j.schres.2006.09.027.

cognition, extrapyramidal symptoms, sedation, QTc prolongation, and sexual dysfunction have been well documented.²²⁻²⁶ Antipsychotic polypharmacy increases the frequency of AEs, and a longer duration of treatment translates to greater severity of AEs.²⁶ Second-generation antipsychotics (SGAs), especially clozapine and olanzapine, may contribute to weight gain in patients with schizophrenia by stimulating higher caloric intake and lowering energy expenditures. Behavioral intervention recommendations have been made for the management of weight gain and obesity in patients with schizophrenia through caloric intake reduction, dietary restructuring, and moderate-intensity physical activity.²⁷

Dyslipidemia may occur in patients with schizophrenia as a consequence of medication use and poor dietary and lifestyle habits.²⁸ The degree of effect on lipid levels varies for each antipsychotic; Yogarathnam et al evaluated several SGAs and determined that clozapine, olanzapine, and quetiapine were more likely to increase triglyceride levels and olanzapine and quetiapine were more likely to increase total cholesterol levels. Alternatively, risperidone, aripiprazole, and ziprasidone were associated with either minimal effects or decreases in cholesterol and triglyceride levels.²⁹ Treatment for schizophrenia should be individualized for patients, and management of potential medication AEs, such as dyslipidemia, should be part of an integrated care team approach. Given the numerous AEs related to SGAs, careful screening and monitoring of blood glucose, cholesterol, and weight are of the utmost priority in identifying and preventing metabolic syndrome. Managed care professionals and the care teams are positioned to help provide management of potential AEs and improve QOL for patients with schizophrenia through case management and medication therapy management programs.

Impact of Negative Symptoms in Schizophrenia

Negative symptoms and cognitive impairment associated with schizophrenia tend to be chronic and are associated with long-term effects on social function. This is in contrast with positive symptoms, which tend to relapse and remit, although some patients experience residual long-term positive symptoms.¹⁰ Negative symptoms contribute to poor functional outcomes, including reduced interpersonal relations, instrumental role functioning, and use of common objects and activities.³⁰ None of the currently approved agents specifically target negative symptoms of schizophrenia.

Impact of Medication Nonadherence

Nonadherence is a challenge in schizophrenia and can occur due to various factors, such as social isolation, disease stigma, and substance abuse. In addition, the symptoms of the illness itself may cause a lack of disease awareness, depression, and cognitive impairment, making medication adherence more difficult. From a societal perspective, many patients face challenges in accessing

much needed mental health services, which also can be fragmented and difficult to navigate.³¹ Managed care formularies should be designed in such a manner to ensure there is adequate access to therapy and to limit the barrier of medication coverage.

In the setting of nonadherence, patients previously in remission may experience relapse, and those with existing symptoms may experience symptom persistence. Nonadherence leads to increases in both patient and service costs. For patients, nonadherence may manifest in several ways, including impaired functioning, decreased QOL, self-neglect, self-harm, vulnerability, aggression, and substance misuse. A study conducted in the United States estimated the cost of rehospitalization due to antipsychotic medication nonadherence at about \$1.5 billion per year.³² Unrecognized nonadherence may result in unnecessary medication changes for patients or a misdiagnosis of treatment resistance.³¹ Improving medication adherence can reduce hospitalizations, rehospitalizations, and hospital length of stay. Initiatives and strategies to improve adherence have the potential to improve outcomes in this population.^{33,34}

Strategies to Improve Management and Outcomes Reducing Medication-Related AEs

Although all medications can cause AEs, clinicians are charged with carefully selecting the most appropriate treatment option for each individual patient to achieve the best possible outcome. Practical strategies to improve patient care include shared decision making, regularly assessing adherence, selecting manageable regimens, and providing adequate counseling regarding possible AEs and expected therapeutic benefit. To mitigate AEs, clinicians can use the following techniques³¹:

- Titrate doses gradually.
- Set realistic expectations for patients if AEs might resolve with time.
- Use a checklist of possible AEs for patients to complete.
- Alter the timing of administration.
- Conduct a dose reduction with shared decision making regarding potential for relapse.
- Offer treatment options to address an AE.
- Switch to an alternative antipsychotic medication.

Shared Decision Making and the Therapeutic Alliance

Shared decision making involves the patient in all aspects of disease treatment and management. It is one way to empower patients with severe mental illness such as schizophrenia to self-manage their illness and actively participate in their healthcare. In a study by Delman et al, young patients with severe mental illness who actively participated in treatment decisions demonstrated reduced

symptoms, improved self-esteem, increased service satisfaction, and improved treatment adherence.³⁵ Use of patient preferences through a discrete choice experiment, which helps to define stated preferences, is one way to improve patient understanding of risks and benefits and involve patients in the selection of their treatment.³⁶ More research is needed to identify and develop tools to improve shared decision making. Taking patient-specific factors into consideration and working with the patient to understand various treatment options can help avoid excessive HRU and unnecessary stress for the patient.

Improving Adherence and Comorbidity Management

When SGAs were introduced as a replacement for first-generation antipsychotics, cost was a concern as most new brand-only agents initially cost 10 to 100 times more than older medication options.³⁷ The strategy for cost containment included initiating step therapy, allowing exceptions with prior authorization, and giving preference to generic drugs with low risk of AEs.³⁷ Ideally, in addition to cost, policies and utilization management strategies should take into account safety, efficacy, outcomes, and health indicators. As new treatments enter the market, the opportunity to evaluate HRU and healthcare costs for various treatment options materializes. Support services, such as electronic reminders via text messages and telephones, cognitive-behavioral and motivational strategies, and financial incentives, may also be used to address medication adherence; however, these have mixed results and should be tailored to specific patient needs.³⁸

FIGURE. The STAY Initiative⁴¹

- 1 Recognizing that most patients with schizophrenia are at risk of partial adherence/nonadherence at some time during the course of their illness
- 2 The benefits of good therapeutic alliance and nonjudgmental atmosphere for identifying potential adherence issues
- 3 Tailored treatment plans to meet an individual's needs, including the most suitable route of delivery of antipsychotic medication
- 4 Involving family/key persons in care and psychoeducation of the patient, assuming the patient agrees to this
- 5 Ensuring optimal effectiveness of care
- 6 Ensuring continuity in the care of patients with schizophrenia

STAY indicates Six principles to improve Treatment Adherence in Your patient.

Long-term medication adherence in patients with schizophrenia is associated with positive outcomes, including improved clinical status, improved QOL and functioning, and reduced risk of relapse and rehospitalization.^{39,40} Focusing on the importance of adherence can help patients achieve their treatment goals. The Six principles to improve Treatment Adherence in Your patient (STAY) initiative was developed and designed to address the concern of partial adherence/nonadherence of antipsychotic medication use in schizophrenia. These principles are outlined in the **Figure**.⁴¹

Healthcare Effectiveness Data and Information Set (HEDIS) measures were developed by the National Committee for Quality Assurance and released in 2013 to improve management of schizophrenia and help identify potential gaps in care for this population using standardized performance measures. The HEDIS measures include follow-up care after hospitalization or ED visit, diabetes and CV disease screening and monitoring, and adherence to antipsychotic medications.⁴² As part of the HEDIS measures of performance where effectiveness of care can be evaluated, the measure assesses adults aged 18 to 64 years with schizophrenia enrolled in Medicaid and who were dispensed and remained on an antipsychotic medication for at least 80% of their treatment period.⁴³ For 2020, adherence to antipsychotics has expanded to include commercial and Medicare product lines and patients 19 years and older.⁴⁴

In a large, prospective, noninterventional trial of more than 2000 patients with schizophrenia, authors found that medication adherence led to lower HRU and increased utilization of group therapy.⁴⁵ Psychiatric hospitalization rates were significantly lower ($P < .001$) among adherent patients; however, formulation of antipsychotic was not described.⁴⁵ Authors have also attempted to model potential direct medical cost savings, including routine care as well as inpatient and outpatient costs, if low-frequency administration (LFA) products could be developed to help guarantee adherence over longer intervals. Administration of risperidone long-acting injectable (LAI) every 3 months was estimated to reduce expensive inpatient relapses and be less costly than both monthly risperidone LAI and daily risperidone oral therapy based on the model. Further extending the interval to 6 months or 9 months resulted in additional cost savings, although the specific cost of medication therapy for LFA formulations was not part of the estimation.⁴⁶ Whereas longer-lasting products used in the model have yet to be developed, the potential for reducing expensive hospitalizations and improving relapse rates could be a significant driver in changing the management of schizophrenia, if these products are available in the future.

Role of LAI Antipsychotics

LAI antipsychotics provide a treatment option with the potential to improve adherence and overall healthcare costs. One study evaluated HRU for 435 patients with schizophrenia who were started on LAI antipsychotics.⁴⁷ A significant decrease ($P < .001$) in the number

of hospitalizations and ED visits was observed. As a breakdown, hospitalization for any reason or for psychiatric reasons decreased by 41% and 56%, respectively, and overall ED visits decreased by 40%.⁴⁷ Recent studies have also evaluated the impact of various treatment options on mortality in patients with schizophrenia. In a nationwide cohort of 29,823 patients in Sweden, researchers determined that LAI antipsychotics were associated with a 32% lower risk of all-cause mortality as compared with oral agents. Additionally, second-generation LAIs and oral aripiprazole were associated with the lowest mortality.⁴⁸

A study by Lin et al compared the effect of initiating treatment with LAI antipsychotics versus with a broad range of oral antipsychotics by measuring healthcare costs and adherence in a Medicare database.⁴⁹ Drug costs were significantly higher ($P < .001$) with LAI antipsychotic use. However, inpatient and outpatient healthcare costs were significantly lower ($P < .001$) and medication adherence was significantly higher ($P < .001$) in the LAI antipsychotic group versus the oral antipsychotic group.⁴⁹ The higher cost of LAI antipsychotic medications was factored in to estimate the potential costs savings to health systems as a result of reduced schizophrenia-related hospitalizations when LAIs are used versus oral agents. Authors estimated that for every 5000 patients treated with an LAI antipsychotic, there would be a savings of more than \$15 million for Medicare beneficiaries and more than \$18 million annually for commercially covered patients.⁴⁹

Researchers studying Medicaid patients with schizophrenia who started treatment with an LAI antipsychotic found significantly reduced ($P < .001$) overall and schizophrenia-related hospitalizations, length of stay, and hospital charges. Annual total schizophrenia-related costs were lowered by \$5576 PPPY and hospital costs were lowered by \$7744 PPPY after starting the LAI antipsychotic.⁵⁰ Similar results were described in a study of a commercial patient population with schizophrenia, in which researchers evaluated changes in hospitalization and costs of care from 6 months before to 6 months after initiating depot antipsychotics in patients with schizophrenia. Results in this study demonstrated a significant reduction ($P < .001$) in psychiatric hospitalizations, from 49.7% before depot antipsychotic use to 22.4% after initiating depot antipsychotic use. Mean hospitalization duration for psychiatric purposes was reduced from 7.3 to 4.7 days ($P = .05$). Depot antipsychotic use represented a significant reduction in total healthcare costs, which declined from \$11,111 to \$7884 ($P < .05$); the reduction in costs for psychiatric hospitalizations from \$5384 to \$2538 was also significant ($P < .05$).⁵¹ Evaluating total costs related to schizophrenia care represents an opportunity for payers to capture cost savings by focusing on drug utilization management strategies, including formulary options that promote adherence. These studies demonstrate the opportunity for managed care organizations to identify and engage those who begin to demonstrate nonadherence to oral therapy. Increased adherence

to prescribed treatment options translates to reduced hospitalizations and improved outcomes, thereby ensuring the best chance of optimal and sustainable healthcare for patients with schizophrenia.

Conclusions

Schizophrenia is a complex chronic illness with multiple comorbidities and high mortality rates. The development of LAIs and generic medication options have significantly improved patient adherence and reduced costs for care in patients with schizophrenia. Despite these advances, schizophrenia has a high economic burden for patients and society. Providers caring for patients with schizophrenia are charged with a complicated task of ensuring individualized care while managing numerous AEs that may occur with recommended therapy. Carrying out shared decision making and careful monitoring as part of a therapeutic alliance can improve the QOL and outcomes for patients living with schizophrenia. Payers need to be aware of the difficulties that exist with managing schizophrenia and engage in strategies to ensure improved outcomes for this challenging population. ■

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