

The Economic Impact of Cognitive Impairment and Negative Symptoms in Schizophrenia:

A Targeted Literature Review With a Focus on Outcomes Relevant to Health Care Decision-Makers in the United States

Christoph U. Correll, MD; Pin Xiang, PharmD, MS; Kaushik Sarikonda, PharmD, MS; Nikhil Bhagvandas, MS; and Matthew Gitlin, PharmD

Abstract

Objective: To conduct a targeted literature review (TLR) to examine the impact of cognitive impairment and negative symptoms among patients with schizophrenia treated in the United States across a range of outcomes pertinent to the US health care system decision-makers, such as payers and policy-makers.

Data Sources: The authors searched EMBASE and PubMed from January 2012 to January 2024. Search terms included schizophrenia, cognitive impairment and negative symptoms, and direct medical and nonmedical, indirect, and societal outcomes.

Study Selection: Considered for inclusion were US-based studies reporting on the relationship between cognitive

impairment or negative symptoms and direct medical and nonmedical, indirect, and societal outcomes in patients with schizophrenia. A total of 4,212 articles were initially identified for screening.

Data Extraction: One reviewer extracted data and another reviewer ensured studies met Population, Intervention, Comparison, Outcomes, Study Design-Time Period (PICOS-T) criteria for inclusion and exclusion.

Results: Eight studies (n = 262,683) were included that reported specifically on associations between cognitive impairment or negative symptoms and targeted outcomes. Patients with schizophrenia and moderate/severe cognitive impairment had a 100% increase in relapse-related hospitalizations (0.6 vs 0.3, adjusted incidence rate

ratio = 1.85, $P < .05$) and ER visits (0.4 vs 0.2, adjusted odds ratio = 1.77, $P < .05$) vs patients with no/mild cognitive impairment. Additionally, there was an almost 50% increase in outpatient visits (8.4 vs 5.5, $P < .001$) and inpatient admissions (6.8 vs 4.5, $P < .001$) over the study period (2014 Q1–2017 Q4) for patients with negative symptoms vs without negative symptoms. Direct nonmedical, indirect, and societal outcomes are described.

Conclusions: This review highlights the economic burden of cognitive impairment and negative symptoms by focusing on outcomes relevant to health care decision-makers in the United States.

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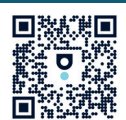
Author affiliations are listed at the end of this article.

Schizophrenia is a chronic mental health condition that can occur at any age, with the average age of diagnosis for men in the late teens to early 20s and for women between their late 20s to early 30s.¹ The annual prevalence of schizophrenia among US adults is around 1%,² which equates to around 3 million adults in the US aged 18 or older.³ Approximately 100,000 Americans are newly diagnosed with schizophrenia each year.⁴

Schizophrenia is characterized by positive, cognitive, and negative symptoms,¹ and these symptoms contribute

to suboptimal functional outcomes.^{5–7} Positive symptoms, which constitute hallucinations, delusions, disorganized thinking, and behavior,⁸ are treated with antipsychotic medications to ensure patients achieve clinical stability and avoid relapses.⁹ Cognitive symptoms affect essentially all domains of cognition, with most salient impairments in processing speed, attention, working, and episodic memory as well as executive functioning and social cognition.¹⁰ Negative symptoms include loss of motivation, interest, and enjoyment in daily activities as well as social withdrawal and difficulties in displaying emotions.¹¹

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Clinical Points

- From a US health care perspective, limited literature of high quality indicates a relevant economic burden of cognitive impairment and negative symptoms in patients with schizophrenia with respect to relevant health care utilization and personal as well as societal cost outcomes.
- For example, presence of moderate/severe cognitive dysfunction almost doubled relapse-related hospitalizations and emergency room visits, while presence of relevant negative symptoms increased inpatient admissions and outpatient visits by about 50%.
- This study reiterates the importance of cognitive impairment and negative symptoms and related outcomes of interest and the need for future research on nonpharmacologic and novel-mechanism pharmacologic interventions that can specifically address these symptom domains of schizophrenia and help alleviate this burden.

The prevalence of cognitive impairment and negative symptoms in the schizophrenia population is quite high with more than 80% of patients experiencing significant cognitive impairment¹² and up to 60% of patients showing clinically relevant negative symptoms.¹¹ Despite substantial advancement in the scientific understanding of the illness and in the treatment of positive symptoms, cognitive and negative symptoms still have no approved treatments.^{12,13} Cognitive impairment is a significant factor in functional disability.¹² Functional disability is mediated by factors such as functional capacity, defined as the ability to perform critical everyday living skills.^{14–19} Additionally, a lower treatment response and poor functional outcomes are predicted by a significant negative symptom burden.¹¹

The chronic, long-term nature of schizophrenia is relevant to patients, caregivers and family members, society, medical providers, policy-makers, and payers. Although achieving clinical stability is currently the primary goal due to the nature of available treatments, direct medical outcomes (inpatient, outpatient, and emergency room [ER] costs, and utilization), direct nonmedical outcomes (costs and utilization associated with the criminal justice system), and indirect outcomes (lost productivity) are of additional importance to stakeholders.²⁰ There are additional, harder-to-quantify societal outcomes that are crucial in assessing functional disability related to schizophrenia.¹² Putting these pieces together, we developed a conceptual framework (Figure 1) to demonstrate the potential association between cognitive and negative symptoms and outcomes of interest in a variety of functional domains.

The association between negative symptoms and health care costs and resource utilization (HCRU) has been conducted in an earlier systematic literature review by

Weber et al²¹ Our review adds additional outcomes of interest as well as focuses on both cognitive impairment and negative symptoms from a US perspective. The primary objective of this literature review was to examine the effect of cognitive impairment and negative symptoms associated with schizophrenia on a wide range of outcomes beyond endpoints used in evaluating efficacy in clinical trials.

METHODOLOGY

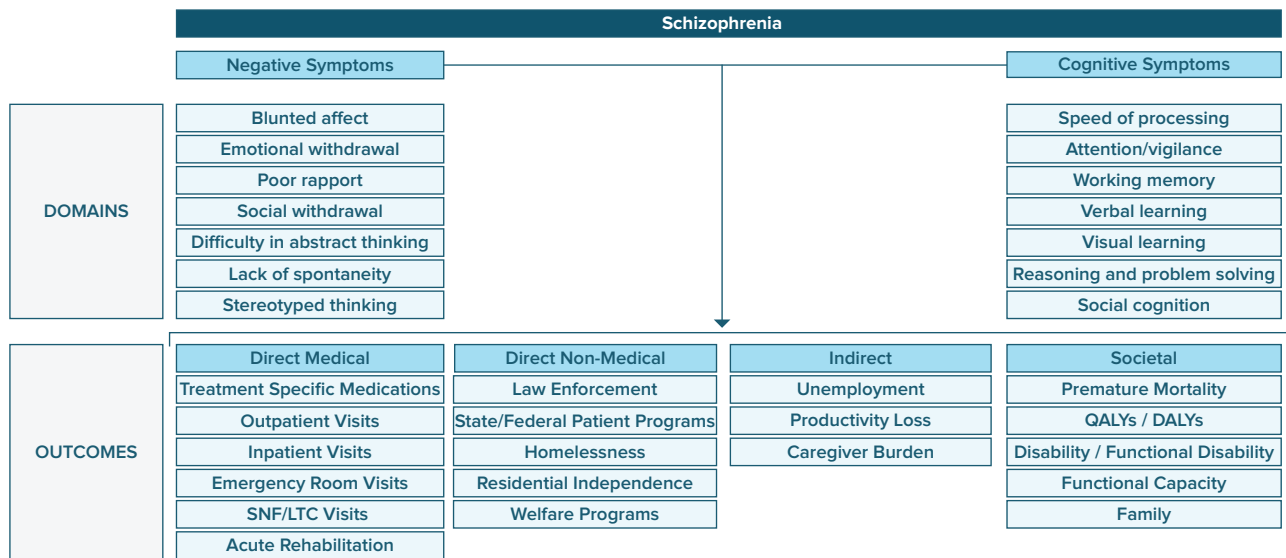
The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines for conducting systematic reviews and meta-analyses.²² The search was conducted in EMBASE and PubMed. When this review began, a 10-year time horizon (January 2013–December 2022) was chosen to ensure the outcomes of interest such as health care resource use and costs were still applicable to the schizophrenia population today. However, during the finalization of our review, new evidence was identified in 2023. To ensure our review reflected the most recent data, we chose to update the review to cover evidence published between January 2012 and January 2024. Additional desktop searches were conducted in Google and Google Scholar for any grey literature including conference proceedings or abstracts. The review ensured selected studies matched the Population, Intervention, Comparison, Outcomes, Study Design–Time Period (PICOS-T) criteria²³ for inclusion and exclusion.

Eligibility Criteria

Inclusion of eligible studies followed PICOS-T criteria:

1. Population: Patients diagnosed with schizophrenia and cognitive impairment or negative symptoms
2. Intervention: Any
3. Comparison: Any
4. Outcomes:
 - a. Outcomes focusing on direct medical, direct nonmedical, indirect, and societal impact, specifically any mention of their rates, HCRU, and costs.
 - b. Costs include direct costs of treatment and other expenses directly induced by the illness, including the legal system, indigent assistance including public assistance payments (supplementary security income or food stamps), homelessness or residential support costs, vocational assistance services, as well as direct (Veterans Affairs or social security) payments for disability compensation.
5. Study Design: US-specific prospective and retrospective cohort and cross-sectional studies were included. Randomized controlled trials, case reports, and case series were excluded.
6. Time Horizon: January 2012–January 2024.

Figure 1.
Conceptual Framework



Abbreviations: DALY = disability-adjusted life year, LTC = long-term care, QALY = quality-adjusted life year, SNF = skilled nursing facility.

Search Terms/Strategy

The following search items were used, which were all combined using the logic operator AND:

- Terms that identify study population: Schizophrenia AND cognitive impairment OR negative symptoms.
- Terms that identify outcomes: Cost OR economic OR resource OR law enforcement OR incarceration OR violence OR crime OR judicial OR legal OR police protection OR state program OR federal program OR patient support OR job program OR homelessness OR homeless status OR residential independence OR independence in residence OR independent living OR assisted living OR housing OR food assistance OR food stamp program OR food stamp OR welfare OR tax credit OR unemployment OR productivity OR suicide OR caregiver OR societal OR intangible OR quality-adjusted life year OR disability-adjusted life year OR disability OR disability compensation OR functional disability OR functional capacity OR social stigma OR relationship.
- Term that identifies the country: United States.
- Filters applied: Classical Article, Clinical Study, Comparative Study, Multicenter Study, Observational Study, Humans, English.

Study Selection and Data Extraction

The review began with screening of titles and abstracts. Screening criteria included patient population (patients with schizophrenia and cognitive impairment or negative symptoms), outcomes of

interest (any publication evaluating key outcomes of interest in the schizophrenia population was included), and study design (prospective and retrospective cohort studies, cross-sectional studies were included; randomized controlled trials, case reports, and case series were excluded). Another reviewer independently assessed the studies that were selected after initial screening of titles and abstracts to ensure they matched the PICOS-T criteria for inclusion and exclusion.

Data on the variables listed below were extracted by a single reviewer and checked by a second independent reviewer for accuracy and quality:

- Study characteristics: study design, data source, study period, population of interest, inclusion/exclusion criteria, and number of patients.
- Definitions of outcomes of interest: we included a total of 18 outcomes of interest and the definitions are described below:
 - Direct Medical Outcomes:** any rates, utilization, and costs associated with the following 6 outcomes:
 - Medications (for illness-specific medications, we focused on the number of prescriptions per year and associated costs to treat schizophrenia).
 - Outpatient
 - Inpatient
 - Emergency room or urgent care
 - Skilled nursing facility or long-term care

- Acute rehabilitation
- **Direct Nonmedical Outcomes:** Any rates, utilization, and costs associated with the following 5 outcomes:
 - Law enforcement or incarceration
 - State or federal programs (focused on the costs of incorporating these programs)
 - Homelessness
 - Residential independence
 - Welfare programs (focused on the costs of incorporating these programs)
- **Indirect Outcomes:** Any rates and costs associated with the following 3 outcomes:
 - Unemployment or reduced wages
 - Productivity loss
 - Caregiving or unpaid labor for caregiver
- **Societal Outcomes:** Any rates and costs associated with the following 4 outcomes:
 - Premature mortality or suicide (suicide and suicide attempt were included but not suicidal behavior or suicidal ideation).
 - Quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs).
 - A person's health status is evaluated using a QALY, in which the benefits of a longer life are modified to consider the quality of that life. The calculation of DALYs is based on the total number of years lost to premature death and years lost to disability.²⁴ For QALYs and DALYs, the review focused on total life years.
 - Disability or functional disability or functional capacity and its predictors.
 - Family-related issues such as divorce and custody of children.

Quality Assessment

Given the assumption that a limited number of studies would be identified, we included all studies regardless of quality. However, when interpreting the data and results, the strengths and weaknesses of the included studies were taken into consideration.

RESULTS

Study Inclusion

Using predetermined search criteria, we identified 49 studies reporting on the outcomes of interest in the schizophrenia population. After excluding 41 studies that reported on association between the outcomes of interest and schizophrenia in general or symptoms other than cognitive impairment or negative symptoms, 8 studies (n = 262,683, mean age = 46 years, and male = 66%) were included that specifically reported on associations between outcomes of interest and cognitive impairment or negative symptoms (Figure 2).

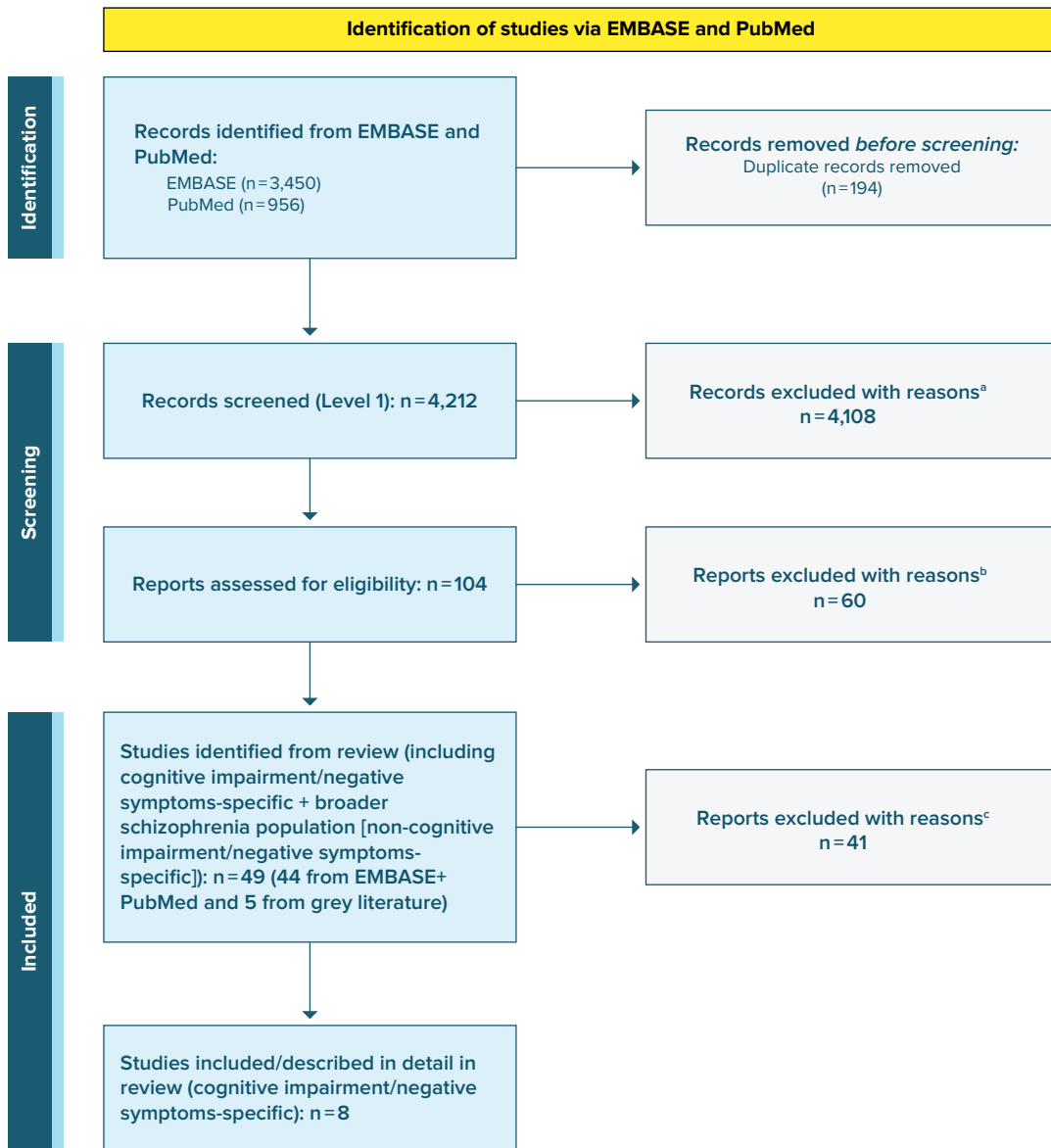
Table 1 summarizes the 8 publications^{25–32} that reported on associations between outcomes of interest and cognitive impairment or negative symptoms. Among these, 5 studies^{25–29} reported on associations between outcomes of interest (outpatient visits, inpatient admissions, ER visits, unemployment, homelessness, and suicide) and cognitive impairment. Four studies^{27,30–32} reported on associations between outcomes of interest (outpatient visits, inpatient admissions, unemployment, caregiver burden, and suicide) and negative symptoms. The study by Correll et al²⁷ was the only study that reported on associations between outcomes of interest in patients with cognitive impairment and negative symptoms and schizophrenia. An assessment of these studies was conducted to determine the distribution and availability of evidence across the outcomes of interest. Based on the 18 outcomes of interest described above, 6 outcomes of interest were available for patients with cognitive impairment and 5 outcomes of interest were available for patients with negative symptoms. The following section provides a detailed summary on the associations of outcomes of interest in patients with cognitive impairment and negative symptoms, respectively.

Studies With Associations With Cognitive Impairment

Five studies (n = 1,846, mean age = 44 years, and male = 67%) reported on the association between some of the relevant outcomes of interest and cognitive impairment in patients with schizophrenia.^{25–29}

Direct medical outcomes. Health care resource utilization. Kadakia et al²⁵ assessed the relationship between cognitive impairment (not at all cognitively impaired, borderline, or mild cognitive impairment were classified as no/mild; moderate, marked, severe, or among the most extreme were classified as moderate/severe) and HCRU among patients with schizophrenia (n = 1,135, mean age = 40.0 years, and male = 58.6%) and found statistically significant differences in patients whose cognitive impairment was moderate/severe vs those who had no/mild cognitive impairment. Patients with schizophrenia and moderate/severe cognitive impairment showed a 100% increase in resource utilization for relapse-related hospitalizations (0.6 vs 0.3, adjusted incidence rate ratio = 1.85, $P < .05$) and ER visits leading to hospitalization (0.4 vs 0.2, adjusted odds ratio (aOR) = 1.77, $P < .05$) (Table 2).²⁵ Casso et al's²⁶ study in 2017 analyzed the relationship between cognitive impairment associated with schizophrenia and HCRU (n = 65, mean age = 43 years, and male = 59%). The findings revealed a trend where patients with cognitive impairment had twice as many ER visits compared to nonimpaired patients, although the results were not statistically significant (0.15 vs 0.08 per patient per month).²⁶ In their 2019 study,²⁷ Correll et al investigated the HCRU in treatment-resistant schizophrenia (TRS)

Figure 2.
PRISMA Diagram



^aReasons for exclusion: Level 1 (population: 1,744, outcomes: 1,774, comparators: 263, review: 59, duplicates: 24, others: 244).

^bReasons for exclusion: Level 1 (population: 14, outcomes: 30).

^cReasons for exclusion: Level 1 (population: 41).

Abbreviation: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

patients, categorized by their hospitalization history: those with ≥ 2 hospitalizations (n = 322, mean age = 39.7 years, and male = 73.9%) and ≤ 1 hospitalization (n = 79, mean age = 37.7 years, and male = 69.6%). Cognitive impairment severity was assessed based on a scale ranging from 1 (minimal) to 6 (extreme) in patients with cognitive impairment. The study found that patients with schizophrenia who experienced any cognitive impairment had more ≥ 2 hospitalizations than ≤ 1 hospitalization (41.3% vs 22.8%, $P < .01$). Additionally, patients who experienced cognitive impairment daily had

more ≥ 2 hospitalizations than ≤ 1 hospitalization (65.4% vs 27.8%), although the results were not statistically significant.²⁷

Direct nonmedical outcomes. Homelessness. Kadakia et al²⁵ also assessed the relationship between cognitive impairment and homelessness among patients with schizophrenia and found statistically significant differences in patients with moderate/severe cognitive impairment vs those with no/mild cognitive impairment. The proportion of patients with moderate/severe cognitive impairment who lived in supported housing was approximately 90% greater

Table 1.
Publications With Association With Cognitive Impairment/Negative Symptoms

Publication name	Type of publication	Sample size	Population	Cognitive impairment or negative symptoms assessed	Method of assessment of cognitive impairment or negative symptoms	Outcomes assessed
Basimallik et al 2023 ²²	Retrospective claims study	RNS patients: 5,691 Non-RNS patients: 236,895	Patients with RNS and non-RNS	Negative symptoms	Using ICD-10-CM = F20.5 codes	<ul style="list-style-type: none"> Inpatient Outpatient
Cassio et al 2017 ²⁶	Retrospective claims study	All SCZ patients: 65 CIAS patients: 39	Patients with CIAS	Cognitive impairment	Two independent expert reviewers assessed mental status exam and classified patients as “clearly impaired” or “not impaired”	<ul style="list-style-type: none"> Outpatient Inpatient ER
Correll et al 2019 ²⁷	Online survey	TRS patients: 408	Patients with TRS	Cognitive impairment and negative symptoms	Psychiatrists completed patient records and collected clinical characteristics (cognitive impairment/negative symptoms) for patients	<ul style="list-style-type: none"> Inpatient Unemployment Suicide
Kadakia et al 2021 ²⁵	Point-in-time survey	SCZ patients with no/mild cognitive impairment: 651 SCZ patients with moderate/severe cognitive impairment: 484	Adult patients with schizophrenia	Cognitive impairment	Psychiatrists described patients’ cognitive impairment as “no/mild” or “moderate/severe”	<ul style="list-style-type: none"> Inpatient ER Unemployment Homelessness
Lavallee et al 2019 ³⁰	Retrospective database study	NSS patients: 8,402 NNSS patients: 8,402	Patients with NSS and NNSS	Negative symptoms	Using DSM-IV/ICD-9 codes, NSS and NNSS patients were defined as having either ≥2 negative symptom codes or no negative symptoms	<ul style="list-style-type: none"> Inpatient Outpatient
Llerena et al 2018 ²⁸	Longitudinal study	76	Homeless participants with a history of a psychotic diagnosis	Cognitive impairment	MCCB	<ul style="list-style-type: none"> Homelessness
Rabinowitz et al 2013 ³¹	Post hoc analysis	Neither prominent positive nor prominent negative: 575 Only prominent negative: 274 Only prominent positive: 295 Both prominent positive and negative: 303	Patients with neither prominent positive nor prominent negative symptoms, only prominent negative symptoms, only prominent positive symptoms, or both prominent negative and positive symptoms	Negative symptoms	PANSS	<ul style="list-style-type: none"> Caregiver
Villa et al 2018 ²⁹	Cross-sectional study	162	Adults with schizophrenia or schizoaffective disorder	Cognitive impairment	MCCB	<ul style="list-style-type: none"> Suicide

Abbreviations: CIAS = cognitive impairment associated with schizophrenia, DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, ER = emergency room, HCRU = health care resource utilization, ICD = *International Classification of Diseases*, Ninth Revision, MCCB = MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery, NNSS = nonnegative symptom of schizophrenia, NSS = negative symptoms of schizophrenia, PANSS = Positive and Negative Syndrome Scale, RNS = residual negative symptoms, SCZ = schizophrenia, TRS = treatment-resistant schizophrenia.

Table 2.
Results Among Patients With Cognitive Impairment

Outcomes	Estimate(s)		P-value
	Patients with moderate/severe cognitive impairment (n = 484) ^{24,a} or clearly impaired patients (n = 39) ^{25,b}	Patients with no/mild cognitive impairment (n = 651) ^{24,a} or not impaired patients (n = 39) ^{25,b}	
Direct medical outcomes			
HCRU			
Hospitalizations related to schizophrenia relapse, mean ^a	0.6 (n = 322)	0.3 (n = 499)	<.05
Days hospitalized, mean ^a	3.4 (n = 297)	1.8 (n = 484)	<.05
Number of hospitalizations since diagnosis, mean ^a	1.8 (n = 139)	1.1 (n = 304)	<.05
Hospitalizations, PPPM ^b	0.08	0	N/A
ER visits resulting in hospitalization, mean ^a	0.4 (n = 309)	0.2 (n = 495)	<.05
ER visits, PPPM ^b	0.15	0.08	N/A
Direct nonmedical outcomes			
Homelessness			
Living with partner or spouse, proportion ^a	11.7%	21.4%	<.05
Supported housing, proportion ^a	8.5%	4.5%	<.05
Indirect outcomes			
Unemployment			
Due to disability, proportion ^a	50%	29.7%	<.05
Full-time, proportion ^a	1.6%	6.1%	<.05
Part-time, proportion ^a	13.2%	22.3%	<.05
Societal outcomes			
Quality of life			
EQ-5D Health Index, mean ^a	0.73 (n = 133)	0.82 (n = 287)	<.05
EQ-5D VAS, mean ^a	66.9 (n = 140)	73.9 (n = 282)	<.05
Average life satisfaction, mean ^a	46.5 (n = 104)	54.9 (n = 229)	<.05

^aKadakia et al 2021²⁵ reported HCRU related to schizophrenia relapse in the previous 12 mo.
^bCasso et al 2017.²⁶
Abbreviations: ER = emergency room, HCRU = health care resource utilization, N/A = not available, PPPM = per patient per month, VAS = visual analog scale.

than patients with no/mild cognitive impairment (8.5% vs 4.5%, aOR = 1.99, and $P < .05$) (Table 2). In another study by Llerena et al,²⁸ the authors found that almost half of patients with schizophrenia (n = 30, mean age = 49.33 years, and male = 100%) were susceptible to unsheltered homelessness with days unsheltered being significantly correlated with overall cognition such that poorer cognition was associated with more days unsheltered.

Indirect outcomes. Unemployment. Kadakia et al²⁵ also assessed the relationship between cognitive impairment and unemployment among patients with schizophrenia and found statistically significant differences in patients with moderate/severe cognitive impairment vs those with no/mild cognitive impairment. Patients with no/mild cognitive impairment were almost twice (13.2 vs 22.3%, aOR = 0.53, $P < .05$) and 4 times (1.6 vs 6.1%, aOR = 0.25, $P < .05$) more likely to have part-time and full-time employment compared to patients with moderate/severe cognitive impairment, respectively (Table 2). Correll et al's²⁷ described unemployment in TRS patients (not employed or not in education [n = 304, mean age = 40.6 years, and male = 74.3%] vs employed or in education [n = 96, mean age = 35.6 years, and male = 68.8%]) who had cognitive

impairment. The study found that patients with schizophrenia who experienced cognitive impairment were more likely to be unemployed or not in education than be employed or in education (41.8% vs 25%, $P < .01$). Additionally, patients who experienced cognitive impairment daily were more likely to be unemployed or not in education than be employed or in education (68.5% vs 20.8%), although the results were not statistically significant.

Societal outcomes. Suicide. Results from Villa et al²⁹ in chronic and treated patients with schizophrenia (n = 162, mean age = 50.6 years, and male = 53%) showed that 41% of the patients attempted suicide (41%). However, the study found no meaningful relationship between cognition and suicide-related history. The study by Correll et al²⁷ described suicide in TRS patients with at least 1 suicide attempt (≥ 1 suicide attempt [n = 153, mean age = 38.3 years, and male = 72.5%] vs 0 suicide attempt [n = 204, mean age = 39.8 years, and male = 74.5%]) who had cognitive impairment. The study found that patients with schizophrenia who experienced cognitive impairment were more likely to attempt suicide than not attempt one (37.3% vs 36.8%), although the results were not statistically

significant. Additionally, patients who experienced cognitive impairment daily were more likely to attempt suicide than not attempt one (59.6% vs 57.3%), although the results were not statistically significant.²⁷

Quality of life. Kadakia et al²⁵ assessed the relationship between cognitive impairment and quality of life (QOL) among patients with schizophrenia and found statistically significant differences in patients with moderate/severe cognitive impairment vs those with no/mild cognitive impairment. Patients with moderate/severe cognitive impairment had significantly lower QOL vs those with no/mild cognitive impairment (EQ-5D Health Index: 0.73 vs 0.82, difference = -0.09, $P < .05$; EQ-5D visual analogue scale: 66.9 vs 73.9, difference = -7.0, $P < .05$) (Table 2).

Studies With Associations With Negative Symptoms

Four studies (n = 261,245, mean age = 46 years, and male = 66%) reported on the association between some of the relevant outcomes of interest and negative symptoms in patients with schizophrenia.^{27,30–32}

Direct medical outcomes. Health care resource utilization. Lavalley et al³⁰ investigated whether patients with negative symptoms utilized more HCRU (and the associated expenditure) than patients without negative symptoms (n = 8,402 for negative symptoms and n = 8,402 for those without negative symptoms, mean age = 54 years, and male = 59%). Using the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* and *International Classification of Diseases, Ninth Revision (ICD-9)* code for Schizophrenia Residual Type or with the specifier With Prominent Negative Symptoms, patients with and without negative symptoms were defined as having either ≥ 2 negative symptoms codes or no negative symptoms, respectively. There was almost a 50% increase in outpatient visits (8.4 vs 5.5, $P < .001$) and inpatient admissions (6.8 vs 4.5, $P < .001$) which were statistically significant for patients with negative symptoms compared to patients without negative symptoms (Table 3). Additionally, there was almost 40% and 30% statistically significant increases in annual inpatient (\$45,410 vs \$33,049, $P < .001$) and total (\$55,864 vs \$43,385, $P < .001$) cost of care in patients with negative symptoms compared to patients without negative symptoms (Table 3).³⁰ Correll et al's²⁷ study described the utilization of resources in TRS patients (≥ 2 hospitalizations [n = 322, mean age = 39.7 years, and male = 73.9%] vs ≤ 1 hospitalization [n = 79, mean age = 37.7 years, and male = 69.6%]) who had negative symptoms which was assessed based on severity levels. The study found that patients with schizophrenia who experienced any negative symptoms had more ≥ 2 hospitalizations than ≤ 1 hospitalization (75.8% vs 67.1%), although the results were not statistically significant. Additionally, patients who experienced negative symptoms daily had more ≥ 2 hospitalizations

than ≤ 1 hospitalization (50.8% vs 20.8%, $P \leq .001$). A more recent 2023 retrospective claims database study by Basumallik et al,³² which estimated the HCRU and health care costs among patients with residual negative symptoms, found that patients with residual negative symptoms (n = 5,691, mean age = 50 years, and male = 60.7%) had significantly greater all-cause inpatient admissions (5.2 vs 4.2, $P < .001$) and greater outpatient ER visits (2.8 vs 2.0, $P < .001$) compared to patients with nonresidual negative symptoms (n = 236,895, mean age = 47.7 years, and male = 57.3%). Additionally, the residual negative symptoms cohort had greater average schizophrenia-related inpatient stay costs (\$15,492 vs \$12,842, $P < .001$) and greater ER costs (\$864 vs \$570, $P < .001$) compared to the nonresidual negative symptoms' cohort (Table 3).³²

Indirect outcomes. Unemployment. Correll et al's²⁷ study described unemployment in TRS patients (not employed or not in education [n = 304, mean age = 40.6 years, and male = 74.3%] vs employed or in education [n = 96, mean age = 35.6 years, and male = 68.8%]) who had negative symptoms. The study found that patients with schizophrenia who experienced any negative symptoms were more likely to be unemployed or not in education than be employed or in education (75.3% vs 70.8%), although the results were not statistically significant. Additionally, patients who experienced negative symptoms daily were more likely to be unemployed or not in education than be employed or in education (52.0% vs 23.5%, $P \leq .001$).

Caregiver burden. Using the Family/Caregiver Baseline Interview, Rabinowitz et al³¹ assessed the number of lost workdays outside or within the household in the past month due to a family member's illness. They estimated that caregivers taking care of patients with prominent negative symptoms (n = 274) experienced more lost workdays compared to caregivers responsible for patients with neither prominent positive nor prominent negative symptoms (n = 575) (1.81 vs 1.73, overall P -value $< .001$).

Societal outcomes. Suicide. The 2019 study by Correll et al²⁷ described suicide in TRS patients [≥ 1 suicide attempt (n = 153, mean age = 38.3 years, and male = 72.5%) vs 0 suicide attempt (n = 204, mean age = 39.8 years, and male = 74.5%)] who had negative symptoms. The study found that patients with schizophrenia who experienced any negative symptoms had similar results with respect to attempting suicide than not attempting one (75.2% vs 75.5%).

QOL. Rabinowitz et al³¹ analyzed Short Form-12 mental health scores as well as functioning items using Lehman's and Heinrich's health-related QOL scales. The study found that caregivers taking care of patients with prominent negative symptoms (n = 274) had lower scores on both instruments compared to caregivers responsible for patients with neither prominent positive nor prominent negative

Table 3.
Results Among Adult Patients With Negative Symptoms

Outcome	Estimate(s)		P- value
	Patients with negative symptoms (n = 8,402) ^{29,a} or residual negative symptoms (n = 5,691) ^{32,b}	Patients without negative symptoms (n = 8,402) ^{29,a} or nonresidual negative symptoms (n = 236,895) ^{32,b}	
Direct medical outcomes			
HCRU			
Psychiatric visits, mean ^a	7.5	5.5	<.001
Psychologist visits, mean ^a	5	4	<.04
Outpatient visits, mean ^a	8.4	5.5	<.001
Outpatient ER visits, mean ^b	2.8	2.0	<.001
Inpatient admissions, mean ^a	6.8	4.5	<.001
Inpatient admissions, mean ^b	5.2	4.2	<.001
Inpatient stays, mean ^a	74.6 days	66.3 days	.001
Annual inpatient cost of care, mean ^a	\$45,410	\$33,049	<.001
Annual total cost of care, mean ^a	\$55,864	\$43,385	<.001
Inpatient costs, PPPY	\$15,492	\$12,824	<.001
Outpatient costs, PPPY	\$864	\$570	<.001

^aLavallee et al 2019.³⁰

^bBasumallik et al 2023.³²

Abbreviations: ER = emergency room, HCRU = health care resource utilization, PPPY = per patient per year.

symptoms (n = 575) (SF-12 Mental Health [40.5 vs 43.3, overall *P*-value < .001] and Lehman's and Heinrich's health-related quality of life Scale [−0.75 vs 0.99, overall *P*-value < .001]).

DISCUSSION

To our knowledge, this is the first literature review that summarizes outcomes that are relevant to the US health care system and assess the impact of cognitive impairment and negative symptoms on these outcomes of interest in patients diagnosed with schizophrenia. A systematic literature review conducted by Weber et al²¹ identified 6 studies with literature on HCRU and costs associated with negative symptoms of schizophrenia and was not country-specific. Our US-centric review contributes to the literature by expanding on additional outcomes of interest and focusing both on cognitive impairment and negative symptoms. Putting the burden of cognitive impairment and negative symptoms into the context to that of positive symptoms, Correll et al²⁷ observed that a greater proportion of patients with schizophrenia who experienced cognitive impairment and negative symptoms daily had >2 hospitalizations (65.4% and 50.8%, respectively) compared to those patients who experienced positive symptoms daily (32.5%).²⁷ While positive symptoms are generally responsible for hospitalization and are also related to caregiver burden and cost, negative and cognitive symptoms, alone or in combination with positive symptoms, are related to HCRU, caregiver burden, and

cost even more than positive symptoms^{21,31,33,34} for which targeted treatments currently exist.

Compared to positive symptoms, cognitive impairment and negative symptoms generally receive much less attention and are also less responsive to currently available pharmacotherapeutic agents, such as dopamine D2 antagonists and D2 partial agonists,¹¹ including various psychopharmacologic augmentation strategies.³⁵ The few impactful studies that evaluated some of these outcomes found that patients with schizophrenia with more severe cognitive impairment had worse outcomes compared to patients with no/mild cognitive impairment.²⁵ With regard to negative symptoms, there was a significant increase in HCRU and direct costs in patients with schizophrenia who had negative symptoms compared to those who did not.³⁰

There was a lack of research regarding the association between cognitive impairment and negative symptoms on other direct medical (medications and long-term care), direct nonmedical (law enforcement and residential independence), indirect (disability-related unemployment and caregiver burden), and societal outcomes (family issues such as divorce and public stigma). However, a few studies reported on these associations among the general schizophrenia population. Bessonova et al³⁶ evaluated the treatment costs of second-generation oral antipsychotics and found mean annual direct medical costs ranging between \$17,115 and \$28,101. Pilon et al³⁷ assessed the economic burden in recently relapsed Medicaid patients with schizophrenia and found that recently relapsed patients had \$21,862 higher mean total health care costs compared to patients without

schizophrenia (\$37,424 vs \$15,563, $P < .001$), driven by \$8,486 higher mean long-term care costs ($P < .001$). Lin et al³⁸ assessed incarceration rates among US veterans who had a schizophrenia relapse and found patients in the relapse cohort having greater incarceration (0.6% vs 0.4%) compared to patients in the nonrelapse cohort. In another study, a greater proportion of remitted patients lived in independent housing compared to nonremitted patients (72% vs 65%, $P < .05$).³⁹ In a survey analysis, relapsed patients with schizophrenia were 38% more likely to experience disability-related unemployment compared to patients in remission.⁴⁰ In a study that evaluated caregiver burden of patients with TRS ($n = 27$, mean age = 48 years, and male = 22%), Brain et al⁴¹ found caregivers administering direct care for an average of 37 hours per week. Almost 80% reported being on call the whole day. In a study on primary caregivers, Csoboth et al⁴² estimated the schizophrenia caregiver group had higher direct (\$28,314 vs \$19,750), indirect (\$8,999 vs \$8,085), and total costs (\$32,905 vs \$23,930) compared to the nonschizophrenia caregiver group. Lin et al³⁸ observed divorce rates in US veterans with schizophrenia and a history of relapse, finding similar rates of separation (36% vs 34%) in the relapse ($n = 16,862$, mean age = 56.4 years, and male = 91.95) vs nonrelapse cohort ($n = 16,862$, mean age = 56.6 years, and male = 92.1). Pescosolido et al⁴³ evaluated public perceptions of violence and support for coercive treatment over 2 decades and found over 60% of people felt that patients with schizophrenia were dangerous, and 44%–59% were in support of using coercive treatment.

Most of the data from ex-US countries on cognitive impairment and negative symptoms align with what we have found in our review of US-specific data, in that the focus is on the impact of cognitive impairment and negative symptoms in patients with schizophrenia on direct medical outcomes. A study by Millier et al⁴⁴ which explored HCRU by health states (defining health states by the level of impairment across positive, cognitive, and negative symptoms) found that the highest burden was for the use of day clinics for those with a predominance of positive and cognitive symptoms. In another population-based, retrospective review of medical records in Spain, patients with negative symptoms had significantly higher average/unit health care costs than patients without negative symptoms (€2,170.00 vs €1,765.30, respectively; $P < .001$).⁴⁵

Limitations

This review has several limitations. First, despite the employed systematic search strategy, it is possible that not all eligible studies were included owing to some not being captured by the selected inclusion criteria and/or search terms. For example, we may have missed studies (unpublished reports or grey literature) owing to the

wide variation in how cognitive impairment is defined. Second, the generalizability of our findings may be limited since our review focused only on US-based studies. Nevertheless, this restriction was the result of an explicit focus on the US health care system, as it also has unique features that make a focused review relevant, such as ethnic and socio-economic characteristics, payer and payer system characteristics, and funding as well as access to care barriers. Third, since the primary focus of our review was to address the economic burden of cognitive impairment and negative symptoms in patients with schizophrenia, we were unable to identify data on missed appointments and frequency of outpatient visits scheduled or attended. These outcomes should be investigated in future studies, as they could be crucial in understanding potential downstream associations between visit frequency, adherence to visits, and the total cost of care for schizophrenia patients. Fourth, the included studies were heterogeneous and often reported only partial data. For example, 5 of the 8^{25–32} studies that we identified and relied heavily on in this review did not use validated instruments to assess either cognitive impairment or negative symptoms. Three studies utilized opinions or judgments from expert reviewers²⁶ or psychiatrists^{25,27} to assess cognitive impairment and/or negative symptoms. Two studies^{30,32} evaluated negative symptoms by using *DSM-IV/ICD-9/ICD-10* codes, which has reliability and validity issues. Although cognitive impairment is one of the core symptoms of schizophrenia, neither the ICD nor the *DSM* have included cognitive impairment in their diagnostic criteria for schizophrenia to date. Fifth, although some studies controlled for baseline patient characteristics,^{25,29,30,32} they did not assess and control for other potentially relevant confounders, such as medication side effects or nonadherence, potential collinearity between cognitive impairment and negative symptoms, illness chronicity, and protracted psychosocial impairment. It is possible that patients with schizophrenia experience cognitive impairment and negative symptoms due to side effects from the antidopaminergic and anticholinergic medications they are on.^{11,46} Moreover, although less illness insight and knowledge about schizophrenia have been associated with higher medication nonadherence in schizophrenia,^{47–49} negative and cognitive symptoms have also been identified as factors driving antipsychotic nonadherence,^{49–53} with cognitive dysfunction even potentially being related to poor illness insight.⁵⁴ Despite these relationships, none of the identified studies included medication nonadherence in their analyses. Furthermore, there could also be interactions between the various symptom domains of schizophrenia. In this context, 4 studies only assessed the burden caused due to cognitive impairment;

3 studies only evaluated the burden caused due to negative symptoms. Only one study²⁷ covered the burden of all symptom domains. None of the studies controlled for any collinearity that could potentially exist between positive symptoms, cognitive impairment, and negative symptoms. Regarding illness chronicity, only Correll et al²⁷ in their study investigated whether time of onset of TRS had any impact on outcomes and found that patients with late-onset TRS (TRS after >5 years of treatment) were associated with poorer outcomes compared to patients with early-onset TRS (TRS within the first 5 years of treatment). The other studies only assessed outcomes in the prevalent population and did not mention or control for chronicity. Therefore, it is difficult to gauge whether outcomes are equally robust in patients with early-episode vs later-episode schizophrenia. Similarly, despite potential interactions between negative and cognitive symptoms and health care cost with psychosocial impairment, none of the 8 reviewed studies looked at confounding effects of protracted psychosocial impairment, such as loss of social supports and occupational disability. Finally, there is currently no clinically useful bedside test for cognitive impairment. While the Montreal Cognitive Assessment and Mini-Mental Status Examination have been tested as quick screening tools for severe cognitive dysfunction in schizophrenia,^{55,56} these tests by no means assess the breadth and depth of the cognitive dysfunction that is mostly much below the profound level as found in patients with dementia where these tests are generally used.⁵⁷⁻⁵⁹ Similarly, negative symptoms are often not measured or quantified. Therefore, the classification of patients with vs without cognitive impairment, or with prominent/predominant negative symptoms¹¹ in clinical care settings and population, is difficult or impossible. This complexity makes the identification of such subpopulations and understanding their impact on HCRU outcomes a challenging task.

Implications for Future Research

Positive, cognitive, and negative symptoms are distinct domains of schizophrenia. Despite some correlation, cognitive impairment and negative symptoms often persist even after positive symptoms stabilize during antipsychotic treatment, as negative symptoms and cognitive impairment are less responsive to current treatment options.⁶⁰ Additionally, treatment with current antipsychotic medications may cause or exacerbate cognitive impairment and secondary negative symptoms.⁴⁶ Future research focusing on or controlling for these confounding effects as well as focusing on factors, such as the potential associations between various symptom domains, and between various symptom domains and nonadherence and illness chronicity, would be highly valuable. Additionally, the

relationship between symptom domains and scheduled, but missed appointments should be investigated. Nonpharmacologic interventions, such as cognitive behavioral therapies, social skills groups, cognitive remediation, and exercise interventions, have been shown to improve cognitive impairment, negative symptoms, and overall functioning to varying degrees, especially when combined with rehabilitation methods.⁶¹⁻⁶⁶ However, several barriers toward the widespread implementation and consistent use of these nonpharmacologic options remain, including a lack of capacity to support training, inconsistent providers' abilities within organizations, and time constraints.⁶⁶⁻⁶⁸ Finally, clinicians continue to primarily assess and diagnose schizophrenia without using scales to measure cognitive impairment and negative symptoms. These instruments can be used to measure treatment efficacy and track the severity of cognitive impairment and negative symptoms in the schizophrenia population. In our review, the MATRICS Consensus Cognitive Battery (MCCB), the Beck Cognitive Insight Scale, and the Clinical Assessment Interview for Negative Symptoms have been utilized as assessment tools by Llerena et al²⁸ and Villa et al²⁹ for cognitive impairment and negative symptoms, respectively. Outcomes that capture functioning are also rarely or insufficiently employed in clinical care and are only beginning to gain traction in research on patients with schizophrenia. In general, accurate, valid, and effective assessment methodologies are needed to evaluate cognitive impairment and negative symptoms and to measure the functional and health care utilization outcomes in patients with schizophrenia and of different treatment modalities.¹⁰ Research into appropriate nonpharmacologic and novel-mechanism of action pharmacologic treatment options¹³ that target domains specific to cognitive impairment and negative symptoms should be an area of active investigation.

CONCLUSION

This review highlights the importance of cognitive impairment and negative symptoms in people with schizophrenia, focusing on outcomes that are relevant to health care decision-makers in the United States. While not substantial, some literature exists that points to the increasing burden associated with cognitive impairment and negative symptoms, which is also in line with international publications. Additional studies with more recent and different cohorts are needed to reiterate the clinical and economic burden of cognitive impairment and negative symptoms. There is an ever-growing need for future research that focuses on pharmacologic and nonpharmacologic interventions that can help alleviate the important cognitive impairment and negative symptom domains of schizophrenia.

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Author Affiliations: Department of Psychiatry, The Zucker Hillside Hospital, Northwell Health, Glen Oaks, New York; Department of Psychiatry and Molecular Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York; Department of Child and Adolescent Psychiatry, Charité–Universitätsmedizin Berlin, Berlin, Germany; German Center for Mental Health (DZPG), Partner Site Berlin, Berlin, Germany (Correll); Boehringer Ingelheim, Ridgefield, Connecticut (Xiang); BluePath Solutions, Los Angeles, California (Sarikonda, Bhagvandas, Gitlin).

Corresponding Author: Christoph U. Correll, MD, Psychiatry Research, The Zucker Hillside Hospital, 75-59 263rd St, Glen Oaks, NY 11004 (ccorrell@northwell.edu).

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