Systematic Review of Real-World Treatment Patterns of Oral Antipsychotics and Associated Economic Burden in Patients with Schizophrenia in the United States

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ABSTRACT

Background: Schizophrenia is a chronic mental disorder associated with substantial morbidity and mortality affecting 0.25–1.6% of adults in the USA. Antipsychotic treatment is the standard of care for schizophrenia, but real-world treatment patterns and associated costs have not been systematically reviewed.

Objective: We conducted a systematic review to summarize treatment patterns and associated costs related to oral antipsychotic treatment of patients with schizophrenia in the USA.

Data Sources: We searched Medline (via PubMed) and Embase to identify relevant observational studies published from January 1, 2008, to June 1, 2018; costs were converted to 2018 US dollars.

Study Eligibility: Observational, real-world studies reporting on patterns of treatment and/or associated costs for adult patients with schizophrenia treated with oral antipsychotics in the USA were included.

Results: Eighty-one studies were identified. Frequently prescribed oral second-generation antipsychotics were olanzapine (up to 50.9%), risperidone (up to 40.0%), and quetiapine (up to 30.7%). Suboptimal adherence was common across studies. Antipsychotic switching occurred in about half of patients, while antipsychotic combination therapy occurred in nearly 30%; all were associated with increased medication-related costs. Mean annual direct medical costs differed by treatment, with reported costs of $17,115 to $26,138 for patients treated with olanzapine, $18,395 for risperidone, and $17,656 to $28,101 for quetiapine.

Limitations: This systematic review is limited by the variations in definitions of schizophrenia-related clinical terms used between studies and by the inclusion of studies focused on only the US health care system.

Conclusions: In the treatment of schizophrenia, suboptimal adherence, antipsychotic switching, and antipsychotic augmentation were all associated with high costs of care in comparison to patients who were adherent and did not require antipsychotic switching or augmentation. These findings illustrate the need for the development of new treatments

that address efficacy and adherence challenges of currently available therapies.

PLAIN LANGUAGE SUMMARY

Schizophrenia is a debilitating mental disorder that affects up to 1.6% of adults in the USA. Antipsychotic medications reduce symptoms of the disease, but many patients with schizophrenia are not fully adherent or choose to discontinue treatment entirely, increasing their risk of hospitalization. In others, efforts to achieve better symptom control or to avoid intolerable side effects may result in switching antipsychotic medications or adding additional medications, leading to higher medical treatment costs. The magnitude of these cost increases is unclear. This study sought to assess medical costs associated with antipsychotic treatment adherence, switching, and adding additional antipsychotics. We reviewed 81 studies published from January 2008 through June 2018 examining treatment adherence in patients with schizophrenia. We calculated rates of adherence, switching, and adding antipsychotics, as well as associated medical costs. Overall adherence to antipsychotic treatment was less than 50%, with up to 50% of patients switching medications and up to 29% adding an additional antipsychotic medication to their current treatment. Patients who were not treatment adherent incurred annual medical costs of $10,316 compared with $5723 in patients who were adherent. The costs of immediate or delayed switching of antipsychotic medications ranged from $21,922 to $28,232, while costs of adding an additional antipsychotic ranged from $24,045 to $29,344. These data suggest that suboptimal medication adherence, along with high rates of patient discontinuation and medication switching, lead to higher treatment costs in the management of patients with schizophrenia.

Keywords: Antipsychotics; Costs; Mental health; Standard of care; Treatment adherence

Key Summary Points

The objective of this systematic review was to summarize oral antipsychotic treatment patterns (e.g., switching, discontinuing, or augmenting antipsychotic medications) and associated costs among patients living with schizophrenia in the USA from real-world evidence.

Oral antipsychotic medication costs are a significant proportion of the economic burden of schizophrenia, contributing 28–44% of total direct medical costs annually.

Suboptimal adherence to oral antipsychotic medications was common: adherent patients had three times higher annual medication costs, whereas patients with suboptimal adherence had 50% higher annual inpatient costs.

Switching or combining oral antipsychotic medications was also common, with total direct costs as high as $28,232 for patients who switched treatments and $29,344 for those who augmented their treatment.

There remains an unmet need for new, efficacious antipsychotic medications that may improve adherence, decrease health care resource utilization, and lessen the cost burden associated with schizophrenia.

INTRODUCTION

Schizophrenia is a serious, chronic mental health disorder that impacts individuals and society as a whole. Among adults in the USA, the estimated prevalence of schizophrenia and related psychotic disorders ranges from 0.25% to 1.6% of the population [1–4]. Previous reviews have found that schizophrenia is associated with a substantial economic burden on

the US health care system that is estimated to be as high as $174 billion annually [5]. Drivers of the excess costs of schizophrenia include direct medical costs such as pharmacotherapy and inpatient and outpatient care, as well as indirect costs associated with unemployment and caregiving [3, 5].

Antipsychotic medications are the first-line treatment for schizophrenia and are effective at reducing the symptoms of the disease [6]. As such, antipsychotic pharmacotherapy comprises a substantial proportion of direct medical costs within the US health care system [3, 5]. However, many patients with schizophrenia are not fully adherent to their medications or choose to discontinue treatment entirely, increasing their risk of relapse and hospitalization [7, 8]. In other patients, efforts to achieve better symptom control or avoid intolerable side effects may result in switching antipsychotic medications or adding additional medications [8–10], leading to higher medical costs [11]. The magnitude of costs associated with these antipsychotic treatment outcomes within the US health care system is unclear.

While individual studies have assessed treatment patterns with the use of antipsychotic medications among patients with schizophrenia in the USA, the economic implications associated with different treatment patterns have not been reported in the literature. Previous systematic reviews have focused on specific subpopulations of patients living with schizophrenia (e.g., privately insured patients [12]) and have not assessed treatment patterns and costs for broader populations.

Objective

The objective of this systematic review was to identify and summarize real-world evidence for oral first-generation and second-generation antipsychotic (FGA and SGA, respectively) treatment patterns and associated costs among patients living with schizophrenia in the USA.

METHODS

Data Sources and Search Strategy

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [13]. The PRISMA checklist is included in Supplementary Table S1. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors; thus, review by an institutional review board was not applicable for this study.

Literature searches were conducted in Medline (via PubMed) and Embase using a combination of medical subject heading and free-text terms to identify English-language articles published from January 1, 2008, to June 1, 2018 (for full search details, see Supplementary Tables S2–S5). Database searches were supplemented by a review of abstracts from relevant scientific conferences (2016–2018), including the International Society for Pharmacoeconomics and Outcomes Research, American Psychiatric Association Annual Meeting, US Psychiatric Congress, and the Academy of Managed Care Pharmacy. A manual check of references in the bibliographies of previously published systematic reviews (2015–2018) was performed to ensure comprehensive identification of relevant articles.

Study Eligibility and Data Extraction

Eligibility for inclusion was determined using prespecified populations, interventions, comparisons, outcomes, and study design (PICOS) inclusion/exclusion criteria [14] (Supplementary Table S6). Observational, real-world studies reporting on patterns of treatment and/or associated costs for adult patients with schizophrenia treated with oral antipsychotics in the USA were included. Treatment patterns of long-acting injectable (LAI) antipsychotics were not the subject of this review.

Abstracts and full-text publications were screened by one reviewer (KS or AC), with

independent review and confirmation of 20% of excluded abstracts and 100% of excluded full-text articles by a second reviewer (AM or RH). Data points from included studies were extracted by a single reviewer (KS, AC, or RH), with accuracy and presence of each data point confirmed by a second reviewer (AM or RH). Discrepancies were resolved through discussion with a third reviewer (AM or RH). Data were summarized for oral antipsychotic treatment patterns, including real-world use, adherence, medication discontinuation, switching, and augmentation (e.g., combination treatment with more than one antipsychotic) using qualitative, thematic, and narrative synthesis. Costs associated with treatment patterns were summarized where data were available. Because this systematic review was limited to observational, real-world studies, a risk-of-bias assessment was not conducted, as that assessment is focused mainly on randomized controlled trials that would be included in a meta-analysis.

Schizophrenia Terminology and Treatment Pattern Definitions

Results reported for treatment patterns and associated costs followed the definitions and terminologies that were used by study authors. Definitions of schizophrenia-related clinical terms, such as discontinuation, augmentation, switch, and treatment resistance, often varied among the studies. Table 1 summarizes the definitions of various treatment pattern-related terms included in this systematic review. Adherence was defined using one of two pharmacy-based proxy approaches: proportion of days covered (PDC) or medication possession ratio (MPR) [15]. Consistent with expert consensus, rates of 80% or higher were considered adherent [8].

Additionally, results from the initial Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study [16], published in late 2005, suggested that, while olanzapine was the most effective antipsychotic on the basis of time to all-cause discontinuation, it was also associated with the greatest amount of weight gain and the emergence of metabolic disturbances over time.

Therefore, prescribing trends for oral SGAs were compared between observational studies that reported data derived before 2006 and those that reported data derived after 2006.

Cost Definitions and Costing Approach

Cost definitions were presented as reported by authors of included publications. Costs included in this review are direct medical costs. Cost data were converted to 2018 US dollars (USD) using an inflation factor calculated by the US Department of Labor Statistics Consumer Price Index. The inflation factor corresponding to average medical care in US cities for all urban consumers was applied [17] and costs were determined on the basis of the year(s) reported in source articles. If cost year was not reported, the publication year was used as a proxy.

RESULTS

Study Identification

A total of 6605 unique records were identified. Of these, 603 abstracts were considered potentially eligible for inclusion, and full-text articles of their associated publications were reviewed. A total of 71 studies met inclusion criteria; 10 additional studies were identified from conference proceedings, resulting in a total of 81 included studies (Fig. 1).

Study Characteristics

Of the 81 included studies, most were retrospective in design (90%), and the remaining were prospective cohort (5%), cross-sectional (4%), or case control (1%) studies. A table of study characteristics is included in Supplementary Table S7. Medication adherence and information on treatment changes were the most commonly reported outcomes; both were reported in 41% of studies. Direct costs of drugs, treatment patterns, or outcomes of treatment were reported in 42% of studies, with some studies presenting costs stratified by medication type (50%), treatment change versus no

Table 1 Schizophrenia treatment pattern terminology, as defined by study authors

Term	Study count	Definition
Discontinuation	21 [18, 21, 24, 25, 29, 30, 38, 42, 45–47, 49, 50, 54–61]	Any change in treatment, including medication substitution or stoppage
		First gap in therapy exceeding a predefined threshold (3, 7, or 37 days)
		Discontinuation of clozapine for any reason
		A switch between olanzapine and risperidone or self-discontinuation
		Adherence falling below 25%
		14-day gap in refill
		Gap in therapy of ≥ 30 days (4 studies)
		Gap in therapy of ≥ 45 days (2 studies) of ≥ 46 days (1 study)
		Gap in therapy of ≥ 60 days (2 studies); ≥ 60 day gap or switch (1 study)
		Gap in therapy of 90 days
Adherent	18 [29, 34, 38, 42, 44–47, 49–54, 56, 76–78]	PDC or MPR ≥ 80%
	1 [79]	Physician perception of adherence was assessed over the last 12 months and responses ranged from a low of "0–10% of the time" to a high of "91–100% of the time"
		Claims-based adherence was defined according to the MPR. MPR categories were low (0–30%), moderate (31–70%), or high (71–100%) adherence
	1 [80]	Self-reported scores ranging from 1 to 5; lower scores indicate better adherence
	1 [81]	MEMS cap; proportion of medication vial cap openings relative to the prescribed doses for that month
Augmentation	1 [22, 63]	When a patient changed therapies without a break in therapy and continued to purchase one or more of their previous medications beyond 60 days
	1 [66]	The addition of another antipsychotic drug within 60 days of continuous use of the index drug
	3 [27, 77, 82]	Initiation/addition of a second antipsychotic without discontinuing the index antipsychotic

Table 1 continued

Term	Study count	Definition
Switch	3 [24, 30, 59]	A new prescription to an alternative drug
	3 [22, 27, 53, 63]	Medication change while still on active therapy and discontinued use of all previous medications within 60 days or fewer than 2 refills after starting new therapy
	2 [25, 38]	Medication initiation or claim of a different antipsychotic agent within 90 days of discontinuing a prior antipsychotic
	2 [56, 64]	NR
	2 [22, 63]	Switching episode: an episode in which a patient changed medication while still on active therapy or within 15 days of terminating a previous therapy, and discontinued use of all previous medications within 60 days
	1 [65]	When an individual initially fills a prescription for one drug product, then at a later point in the same quarter fills a prescription for a product in the same class and never refills the first product within the quarter
Treatment resistant	1 [83]	Prescription fills for 2 or more different standard antipsychotic agents with a combined MPR for antipsychotics of > 0.75 in addition to 1 or more psychiatric hospitalizations in the 180 days preceding the index date
	1 [84]	NR
Combination treatment (Antipsychotic polypharmacy)	1 [24]	Use of ≥ 2 antipsychotics within a 45-day period
	1 [51]	Overlapping coverage of ≥ 2 unique antipsychotic agents for ≥ 60 consecutive days with no more than a 7-day gap
	1 [66]	Use of additional concurrent antipsychotic drugs for ≥ 60 days of continuous supply over the first 90-day period, without discontinuation of the index drug
	1 [69]	≥ 2 overlapping SGA claims, defined on the basis of fill date plus days' supply
	1 [38]	≥ 2 OAT prescriptions or administrations with an overlap of 60 days
Combination treatment (Psychiatric polypharmacy)	1 [51]	Overlapping coverage of ≥ 1 antipsychotic and ≥ 1 anxiolytic, antidepressant, or mood stabilizer for ≥ 60 consecutive days, with no more than a 7-day gap

ICD-9-CM International Classification of Diseases, Ninth Revision, Clinical Modification, *MEMS* Medication Event Monitoring System, *MPR* medication possession ratio, *NR* not reported, *OAT* oral antipsychotic treatment, *PDC* proportion of days covered, *SGA* second-generation antipsychotic
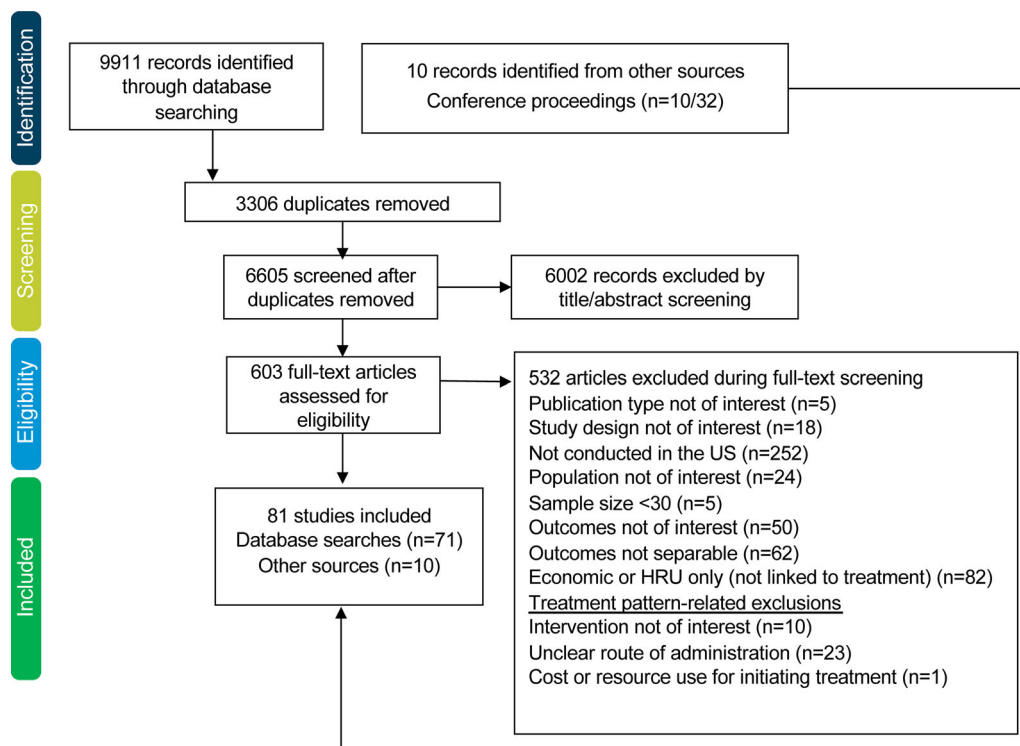
Fig. 1 PRISMA flow diagram. *HRU* health care resource use, *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-analyses

treatment change (15%), treatment adherence versus suboptimal adherence (6%), and polypharmacy versus monotherapy (6%).

Direct Costs Associated with Oral Antipsychotic Treatment

Patterns of Use
Among the included studies, the most frequently reported oral SGAs were olanzapine, quetiapine, risperidone, and aripiprazole (Fig. 2). In these studies, 9.4–50.9% of patients in the study population took olanzapine [18–33], 11.5–30.7% took quetiapine [18–33], 2.0–40.0% took risperidone [18–21, 23, 24, 26–34], 4.0–21.5% took aripiprazole [18–21, 23, 24, 26–32, 35], and 0–7% took clozapine [20, 24–26, 31, 36]. In real-world studies published prior to 2006, olanzapine was the administered treatment for an estimated 16.0–50.9% [18, 21, 25, 27, 30, 32, 33] of patients making up the study population;

however, this range dropped to below 20% after 2006 (9.4–17.4%) [20, 23, 24, 26, 28, 29, 31]. Conversely, prescribing trends for quetiapine and risperidone have remained relatively constant over time. Aripiprazole was approved by the US Food and Drug Administration in 2002, a time after data collection began for five studies included in this review. Excluding those studies, the reported proportion of patients treated with aripiprazole between 2008 and 2018 ranged from 8.7% to 21.5% [19, 20, 23, 24, 26, 28, 29, 31, 35].

Direct Costs of Oral Antipsychotic Medications
Mean total annual direct costs by type of oral antipsychotic are summarized in Fig. 3 [28, 31, 32, 37–42]. Total annual direct costs ranged from $8465 for patients taking lurasidone to $28,101 for those taking quetiapine. In the subset of studies that did not provide cost estimates by a specific oral antipsychotic agent,
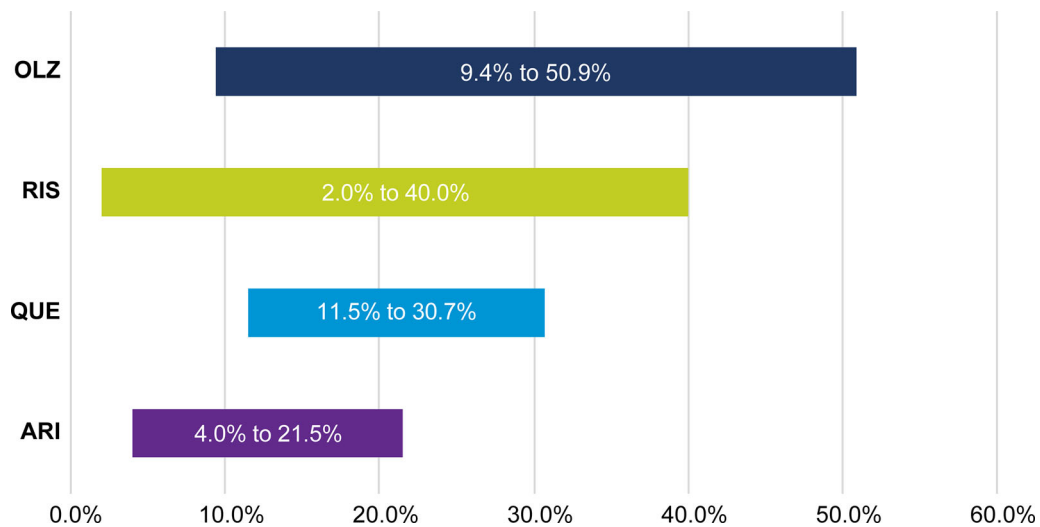
Fig. 2 Proportion of patients with schizophrenia prescribed oral SGAs in real-world evidence observational studies [18, 20, 21, 23–33, 63]. All studies reflected in this figure report on use of oral SGAs after 2006. The years in which generic drug versions became available are as follows: ARI, 2015; OLZ, 2011; QUE, 2016; RIS, 2008. *ARI* aripiprazole, *OLZ* olanzapine, *QUE* quetiapine, *RIS* risperidone, *SGA* second-generation antipsychotic
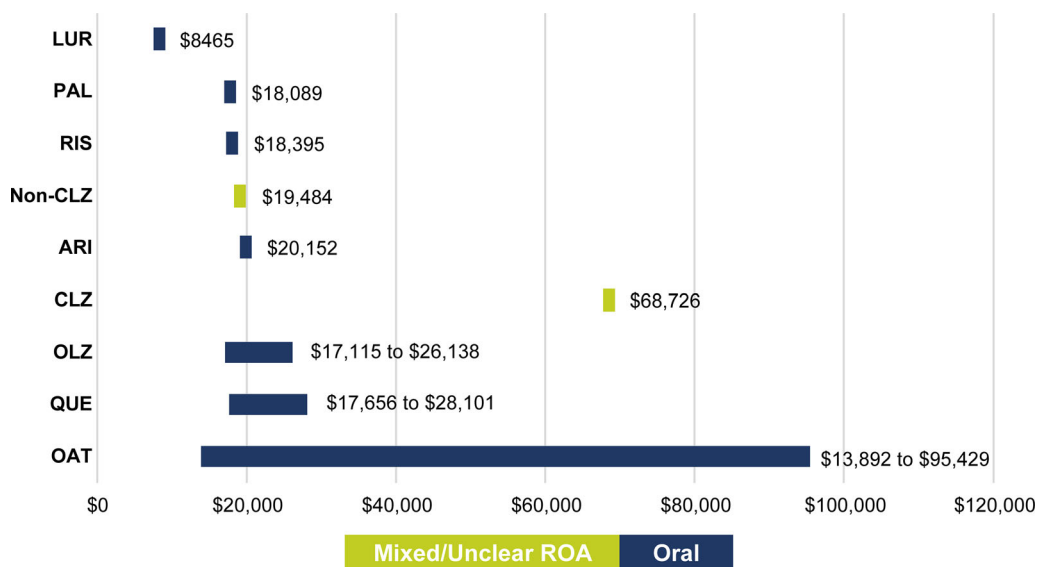

Fig. 3 Total annual direct costs by oral antipsychotic type in 2018 USD [28, 31, 32, 37–42]. *ARI* aripiprazole, *CLZ* clozapine, *LUR* lurasidone, *OAT* oral antipsychotic treatment (drugs not specified), *OLZ* olanzapine, *PAL* paliperidone, *QUE* quetiapine, *RIS* risperidone, *ROA* route of administration, *USD* US dollars

total annual direct cost estimates ranged from $13,892 to $95,429.

Annual medication costs are presented in Fig. 4 [28, 32, 33, 37, 38, 40, 41]. The largest estimated range came from studies that pooled results from all treatments ($936 to $9290). Those treated with olanzapine or quetiapine had similar ranges of annual medication costs. Estimates of annual medication cost of
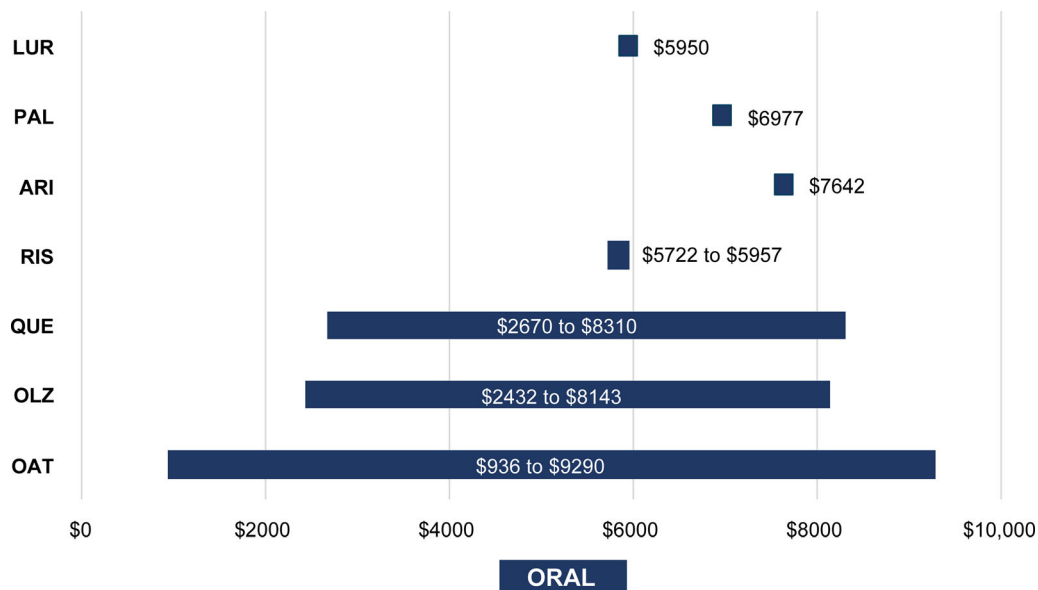
Fig. 4 Annual medication costs by oral medication type in 2018 USD [28, 32, 33, 37, 38, 40, 41]. *ARI* aripiprazole, *LUR* lurasidone, *OAT* oral antipsychotic treatment, *OLZ* olanzapine, *PAL* paliperidone, *QUE* quetiapine, *RIS* risperidone, *USD* US dollars
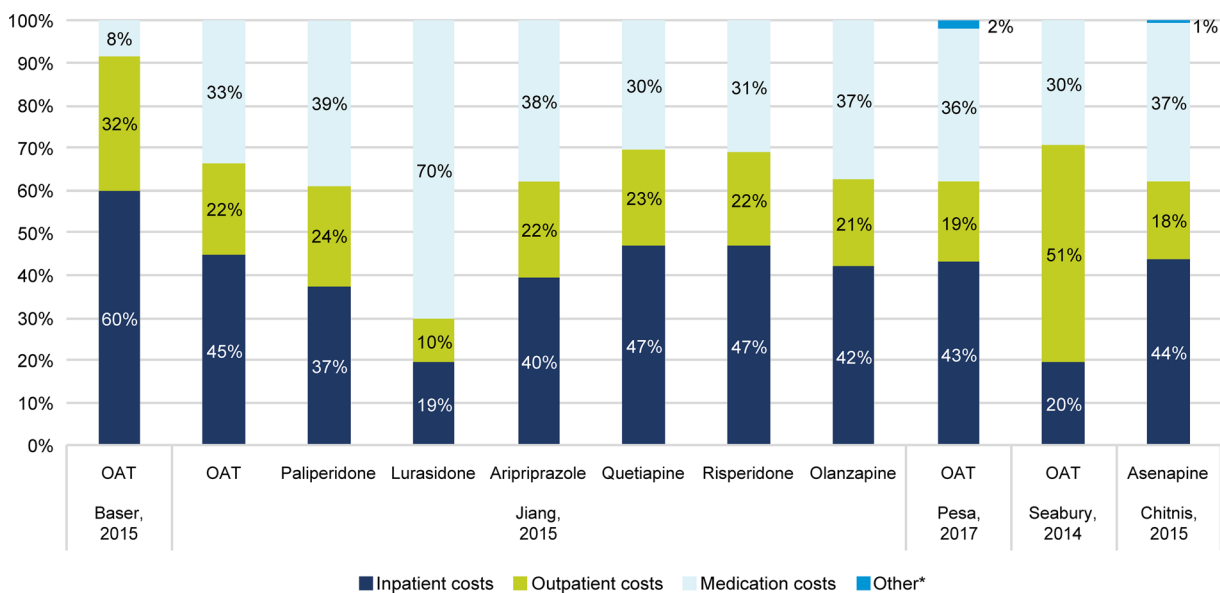

Fig. 5 Components of total direct costs associated with schizophrenia in the USA by medication type [28, 32, 38, 41, 43]. *Other costs included emergency department service costs. *OAT* oral antipsychotic treatment

lurasidone, paliperidone, and aripiprazole originated from only one study [28].

Direct cost components associated with schizophrenia by agent are provided in Fig. 5

[28, 32, 38, 41, 43]. The proportions of medication costs contributing to annual total direct costs ranged from 30% for quetiapine to 70% for lurasidone. The proportion of inpatient

Table 2 Overview of 6-month and 12-month adherence in patients with schizophrenia using oral antipsychotics in the USA

Adherence[a] (PDC or MPR ≥ 80%)	Number of studies	Range of proportions	Key drivers or populations
Overall[b]	17 [25, 29, 34, 42, 44–54, 78][b,c]	6 months: 22.0–67.7% 12 months: 9.0–71.0%	PDC as the measure of adherence at 6 months generated higher adherence rates than MPR (67.7% vs 22–43.8%). The opposite was true at 12 months (9–33.2% vs 25–71%) High adherence at 12 months driven by a population of Medicaid patients in Florida
Olanzapine	1 [29]	6 months: 28.3–31.0%	Slightly better adherence among commercially insured patients compared with Medicaid patients
Risperidone	1 [29]	6 months: 24.3–38.3%	Slightly better adherence among commercially insured patients compared with Medicaid patients
Quetiapine	1 [29]	6 months: 19.7–25.2%	Significantly worse adherence compared with lurasidone ($P < 0.05$)
Aripiprazole	2 [29, 46]	6 months: 22.0–30.6% 12 months: 61.6%	Higher adherence at 12 months driven by a small population of Medicaid patients in Missouri

MPR medication possession ratio, *PDC* proportion of days covered

[a]Studies in which adherence was not clearly defined or other definitions of adherence were used were excluded [20, 27, 35, 55, 79, 85]

[b]PDC ≥ 80% was calculated from provided data on percentage of patients with a PDC < 80% [50]

[c]Studies were excluded for using measures of adherence other than PDC or MPR [19, 80, 81]; for reporting an 18-month time point or only baseline adherence [38, 56, 77]; for not reporting a time period [76]; and for reporting mean PDC or MPR values only [32, 37, 65, 66]

costs attributable to individual antipsychotics was similar among medications, ranging from 37% to 47%, except for lurasidone. A similar finding was noted for outpatient costs, with ranges between 21% and 24%, except for lurasidone. Although associated with lower inpatient and outpatient costs relative to paliperidone, aripiprazole, risperidone, quetiapine, and olanzapine, medication costs for lurasidone were the highest observed, making up 70% of the total direct costs associated with it.

Direct Costs Associated with Oral Antipsychotic Treatment Adherence

Adherence and Discontinuation Patterns

Thirty-three studies assessed patient adherence to oral antipsychotic medications. When a PDC of 80% or higher was used, adherence was reported to be below 50% (range 9.0–33.2%) in 11 of 12 studies with 6–12 months of follow-up [34, 42, 44–52] (Table 2). These findings were consistent with adherence rates assessed by MPRs of 80% or higher (Table 2), with oral antipsychotic adherence of less than 50% in 5 of 7 studies over 6–12 months of follow-up [29, 45, 53, 54], and by MPRs of 70% or higher

Table 3 Overview of treatment discontinuation in patients with schizophrenia using oral antipsychotics in the USA

Treatment discontinuation[a]	Number of studies	Range of proportions	Mean time to outcome	Key drivers
Overall	21 [18, 21, 24, 25, 29, 30, 38, 42, 45–47, 49, 50, 54–61]	6 months (n = 2): 39.4–72.7% 12 months (n = 12): 27.4–92.6% 24 months (n = 2): 70.0–76.0%	(n = 9): 15–282 days	Discontinuation rates varied widely, with trends toward higher rates over longer follow-up (highest among 2 studies using Veterans Health Association data, and a third among commercially insured quetiapine users). Shorter average time to discontinuation was driven by a study with only 6 months of follow-up
Olanzapine	3 [29, 30, 59]	6 months (n = 1): 62.0–62.3% 24 months (n = 1): 70.0%	(n = 3): 51–150 days	Rates of olanzapine discontinuation are high, regardless of follow-up period. Shorter average time to discontinuation was driven by a study with only 6 months of follow-up
Risperidone	2 [29, 59]	6 months (n = 1): 54.1–66.2% 24 months (n = 1): 76.0%	(n = 2): 45–90 days	Rates of risperidone discontinuation are high, regardless of follow-up period. Shorter average time to discontinuation was driven by a study with only 6 months of follow-up
Quetiapine	2 [29, 30]	6 months (n = 1): 63.3–72.7%	(n = 2): 46–87 days	Rates of quetiapine discontinuation are high. Shorter average time to discontinuation was driven by a study with only 6 months of follow-up
Aripiprazole	2 [29, 30]	6 months (n = 1): 63.1–64.2%	(n = 2): 56–93 days	Rates of aripiprazole discontinuation are high. Shorter average time to discontinuation was driven by a study with only 6 months of follow-up

[a]Studies were excluded for reporting binary data without a time period [25, 56, 57]; median values [18, 46, 57, 59, 86]; data in person years [21]; or a 15-year time period [55]

Table 4 Range of costs across adherence studies in 2018 USD

Direct cost of adherence[a]	All-cause		Schizophrenia or mental health related		Key drivers or populations
	Number of studies	Range of costs (USD)	Number of studies	Range of costs (USD)	
Total direct	1 [62]	$6067–9340			Total direct costs were typically higher for adherent patients except for during the acute phase
Inpatient care	2 [20, 62]	$2378–10,316	1	$944–2812	Inpatient costs were consistently higher for patients with low adherence or who were nonadherent to medication
Outpatient care	1 [62]	$1643–3359			Outpatient costs were higher for adherent patients and increased from the acute phase to the maintenance phase
Medication/ pharmacy	2 [20, 62]	$559–8867	1	$1236–3550	Medication costs were higher for adherent patients, with the proportion attributable to schizophrenia-related costs higher compared to patients with low adherence or nonadherence

USD US dollars

[a]Only studies reporting on annual costs are included. Those reporting monthly, 6-month, or 2-year costs were excluded. If all-cause or schizophrenia-related was not reported in the text, it was assumed to be all-cause. If both baseline and follow-up costs were reported, follow-up costs were included in the ranges

[20], with adherence ranges of 22.0–45.1%. Patient adherence rates for individual oral antipsychotics were not extensively characterized in the literature reviewed.

Twenty-one studies reported outcomes related to treatment discontinuation (Table 3) [18, 21, 24, 25, 29, 30, 38, 42, 45–47, 49, 50, 54–61]. The overall frequency of treatment discontinuation varied widely, due in part to different definitions used for discontinuation and different durations of follow-up (ranging from 6 months to 15 years). Among the 15 studies assessing discontinuation rates, 12 reported a discontinuation rate of greater than 50% over follow-up periods of 6 months to 15 years; overall discontinuation rates for oral antipsychotics were greater than 70% in four studies with follow-up periods of 6 months to 4.5 years [29, 47, 57, 59]. Among the oral SGAs, discontinuation rates were generally comparable.

Cost of Suboptimal Adherence

The distribution of major cost components in the treatment of schizophrenia differed according to adherence status (Table 4). Overall, cost differences for adherent patients relative to those with suboptimal adherence were driven by medication and inpatient costs. Patients with suboptimal adherence had higher annual all-cause inpatient costs ($10,316 vs $5723) and schizophrenia-related inpatient costs ($2812 vs $944) relative to those who were considered adherent [20]. This trend was confirmed by data on quarterly inpatient costs, which ranged from $2378 to $4347 in adherent patients compared with $3444 to $5342 in patients with suboptimal adherence [62]. Adherent patients had nearly three times the annual antipsychotic medication costs of those with suboptimal adherence ($1806 vs $559 in a Medicaid population study [62]; $3550 vs $1236 in a Medicare population study [20]), whereas patients with suboptimal adherence had annual inpatient costs, on average, that were approximately 50%

Table 5 Overview of treatment changes in patients with schizophrenia using oral antipsychotics in the USA

Treatment pattern/change	Number of studies	Range of proportions	Mean time to outcome	Key drivers
Treatment switch[a]				
Overall	11 [22, 24, 25, 27, 38, 53, 56, 59, 63, 64, 66]	6 months (*n* = 1): 26.0% 10–12 months (*n* = 6): 10.6–41.5% 24 months (*n* = 1): 20.0–30.0%	(*n* = 3): 47–282.9 days	Rates of treatment switching across all oral antipsychotics did not drastically change over time; time to switch varied widely
Olanzapine	5 [22, 24, 59, 63, 66]	12 months (*n* = 4): 11.0–38.1% 24 months (*n* = 1): 20.0%	(*n* = 2): 65–177.2 days	Patients are more likely to switch off olanzapine over longer periods of follow-up; however, time to switch was variable
Risperidone	4 [22, 24, 59, 63]	12 months (*n* = 3): 12.8–39.2% 24 months (*n* = 1): 30.0%	(*n* = 2): 64–154.9 days	Patients are more likely to switch off risperidone over longer periods of follow-up; however, time to switch was variable
Quetiapine	4 [22, 24, 63, 66]	12 months (*n* = 4): 10.6–39.2%	(*n* = 2): 68–140.3 days	Switching rates were higher, with shorter time to switching over 6 months of follow-up in 1 study, which was limited to Medicaid patients in California
Aripiprazole	1 [24]	12 months (*n* = 1): 8.8%	(*n* = 1): 222.8 days	NA
Treatment augmentation[b]				
Overall	3 [22, 63, 66]	6 months (*n* = 1): 12.9–16.7% 12 months (*n* = 2): 9.4–41.6%	(*n* = 1): 84–106 days	Treatment augmentation occurred more frequently during the first year than over 6 months of follow-up; however, time to augmentation was roughly 90 days

Table 5 continued

Treatment pattern/ change	Number of studies	Range of proportions	Mean time to outcome	Key drivers
Olanzapine	3 [22, 37, 63]	6 months (n = 1): 12.9% 12 months (n = 2): 9.4–39.8%	(n = 1): 106 days	Rates of augmenting olanzapine therapy were similar among 2 studies of Medicaid patients limited to California or Pennsylvania
Risperidone	2 [22, 63]	12 months (n = 3): 11.6–41.2%	(n = 1): 105 days	NA
Quetiapine	3 [22, 63, 66]	12 months (n = 3): 16.7–41.6%	(n = 1): 102 days	Patients initiating quetiapine were significantly more likely to add another antipsychotic compared with olanzapine
Aripiprazole	0	NA	NA	NA

NA not applicable

[a]Studies were excluded for reporting person years [65] or binary data without a time period [25, 30, 64]

[b]Studies were excluded for reporting combined treatment switch or augmentation outcomes [77, 82]; reporting person years [21]; or binary data without a time period [27, 64]

higher than those of patients who were adherent.

Direct Costs Associated with Oral Antipsychotic Treatment Changes

Patterns of Treatment Restarting or Switching

Treatment changes for which data were available included restarting or switching treatment and antipsychotic combination therapy (Table 5). Twelve studies provided data on antipsychotic treatment restarts or switches [22, 24, 25, 27, 30, 37, 38, 53, 56, 59, 63, 64]. Of these studies, two reported the proportion of patients who restarted treatment, defined as a medication gap of at least 15 days followed by continuing the previously taken oral antipsychotic medication [22, 63]. Restarting rates were highest for olanzapine (61.5%) and risperidone (57.6%) and lower for quetiapine (38.3%) and FGAs (43.8%). Although treatment restarts were defined as a gap of at least 15 days, the mean

times to restart for individual oral antipsychotic medications were 73 days for olanzapine, 72 for risperidone, 56 for quetiapine, and 99 for FGAs [63].

Treatment switches (defined variably across studies in terms of length of gap between prescriptions) occurred in 2.7% to 50% of patients over time periods ranging from 6 to 24 months [22, 24, 25, 27, 38, 53, 56, 59, 63–66]. The average time to switch across all oral antipsychotics ranged from 47 to 282.9 days [24, 56, 63]. Treatment switching rates over follow-up periods from 6 months to 2 years ranged from 11.0% to 20.0% with olanzapine, 12.8% to 30.0% with risperidone, 10.6% to 19.4% with quetiapine, and 8.8% with aripiprazole [22, 24, 59, 63, 66]. Time to medication switch was shorter for patients receiving FGAs (47 days) compared with those receiving olanzapine, risperidone, or quetiapine (64–68 days) [63]. Among patients treated with olanzapine or risperidone, those on risperidone were more

Table 6 Costs of treatment patterns by drug in 2018 USD

Cost type	Clozapine[a]	Olanzapine	Risperidone[a]	Quetiapine[a]
Restart				
Total costs	$21,438	$17,278–18,763	$18,750	$22,199
Acute hospital	$362	$354–555	$600	$685
Psychiatric hospital	$735	$1470–1771	$1201	$1762
Ambulatory care	$1714	$1815–1824	$1773	$2349
Medication costs	$6622	$5838–7482	$6108	$8670
Switch				
Total costs	$24,460	$23,346–28,232	$27,905	$27,885
Acute hospital	$497	$529–743	$949	$726
Psychiatric hospital	$1314	$1951–2511	$2114	$23,835
Ambulatory care	$2451	$2405–2498	$2345	$2520
Medication costs	$8446	$7370–9635	$8404	$9615
Delayed switch				
Total costs	$25,131	$21,922–23,054	$23,362	$24,265
Acute hospital	$356	$637–682	$739	$749
Psychiatric hospital	$2495	$2154–2331	$1922	$2119
Ambulatory care	$2149	$1995–2338	$2169	$2320
Medication costs	$7267	$6149–8283	$7526	$9012
Augmentation				
Total costs	$27,006	$24,045–28,356	$29,344	$29,020
Acute hospital	$599	$560–649	$574	$706
Psychiatric hospital	$1465	$1372–1523	$1460	$1425
Ambulatory care	$2610	$2301–2322	$2276	$2173
Medication costs	$10,089	$8615–11,555	$11,673	$12,523

Data from Thomas et al. and Chen et al. [22, 67], unless stated otherwise

USD US dollars

[a]Data on risperidone and quetiapine were estimated from reference [63]; data on clozapine were estimated from reference [67]

likely to switch medications within 2 years (30.0% vs 20.0%) [59]. For olanzapine, risperidone, and quetiapine, when switches occurred, they more commonly occurred after a break in treatment versus an acute switch within days of discontinuation, regardless of the index SGA taken [63].

Cost of Treatment Restarting or Switching

In patients with an antipsychotic treatment gap of at least 15 days who then restarted their previous oral antipsychotic medication, mean annual total costs ranged from $17,278 in patients taking olanzapine to $22,199 in patients taking quetiapine [22, 67] (Table 6). For

those switching from one oral medication to another, defined as a change while still on active treatment or within 15 days of terminating the previous treatment and with discontinuation of the previous antipsychotic medication within 60 days, mean total costs ranged from \$23,346 to \$28,232 [22, 67]. Patients with a delayed switch (i.e., no antipsychotic medication for at least 15 days followed by initiation of a different antipsychotic medication) had mean total direct costs similar to those of patients who switched without a gap in treatment, ranging from \$21,922 to \$24,265 [22, 67].

Patterns of Combination Treatment

Rates of combination treatment with an additional oral antipsychotic (Table 5) ranged from 9.4% to 29.2% over 6 to 12 months of follow-up [51, 63, 66, 68]. Data regarding specific combinations of antipsychotic medications taken by patients were limited. One study reported that, among 968 patients receiving antipsychotic combination treatment, quetiapine and risperidone were the most frequently used combination (9.9%), followed by quetiapine and aripiprazole (9.7%) [24]. Compared with patients treated with quetiapine, those treated with olanzapine had lower rates of combination treatment with any additional antipsychotic or specifically with an additional SGA [66]. Rates of combination treatment with non-antipsychotic psychotropic medications were substantially higher than rates of combination treatment with an additional oral antipsychotic, ranging from 52.0% to 67.7% over 12 months of follow-up [34, 51].

Cost of Combination Treatment

Total annual costs associated with augmentation of treatment with an additional antipsychotic medication ranged from a mean of \$24,045 in those treated with olanzapine to \$29,344 in those treated with risperidone (Table 6). The difference in costs associated with augmentation is likely attributable to increased medication costs [22, 67]. Clozapine monotherapy was associated with an average estimated total cost reduction of \$23,025 per

year versus antipsychotic combination treatment. These cost reductions were attributed to lower use of mental disorder-related and schizophrenia-related emergency department services. There were no differences for clozapine monotherapy versus combination antipsychotic treatment in terms of the likelihood of hospitalization or all-cause emergency department visits [69]. Additionally, cost related to adding the nonindexed antipsychotic medication(s) was lower for olanzapine than for quetiapine (33.7% and up to 64.6% of the total annual medication costs, respectively). The main cost driver was the type of co-prescription added (FGA vs SGA) [33].

Costs of Any Antipsychotic Treatment Change

Overall, medication costs were a driver of annual total direct costs in patients experiencing a treatment change, accounting for 28% to 44% of this overall expenditure [22, 67, 70], with the higher end of the range represented by patients who augmented their treatment owing to inadequate symptom control (Table 7) [22, 67]. Mean inpatient costs associated with a treatment change were generally a small portion (5–14%) of total annual costs associated with caring for patients with schizophrenia, the majority of which were psychiatric hospital care costs. Acute hospital costs ranged from a mean of \$354 to \$949 annually, while psychiatric hospital costs averaged between \$735 and \$2551 annually. However, it should be noted that this figure excluded one study as an outlier that reported on patients switching from quetiapine [22]; when this study was included, the range of psychiatric hospital costs was \$735 to \$23,835 per annum. Ambulatory care costs accounted for approximately 7% to 11% of total annual costs.

DISCUSSION

This systematic review identified and synthesized available evidence associated with real-world treatment patterns in schizophrenia to provide critical information regarding the extent of disease burden and economic implications associated with these treatment

Table 7 Range of costs across treatment change studies in 2018 USD

Direct cost of treatment changes[a]	All-cause		Schizophrenia or mental health related		Key drivers or populations
	Number of studies	Range of costs (USD)	Number of studies	Range of costs (USD)	
Treatment changes					
Total direct	2 [63, 67]	$17,278–29,344			Total costs were lowest for patients restarting treatment and highest for those augmenting treatment
Inpatient care	2 [63, 67]	Acute: $354–949	2	Psychiatric: $1314–23,835	Psychiatric hospital costs were higher than acute hospital costs
Ambulatory care[b]	2 [63, 67]	$1714–2715			Ambulatory care costs were fairly consistent across treatment patterns
Medication/ pharmacy	2 [63, 67]	$3868–12,523			Medication costs were highest for those augmenting

USD US dollars

[a]Only studies reporting on annual costs are included. Those reporting monthly, 6-month, or 2-year costs were excluded. If all-cause or schizophrenia-related was not reported in the text, it was assumed to be all-cause. If both baseline and follow-up costs were reported, follow-up costs were included in the ranges

[b]Changed from outpatient care to ambulatory care to allow for synthesis across studies. Psychotropic medication costs were included in the all-cause pharmacy costs, as it was not clear if such costs were schizophrenia specific

patterns. Annual medication-related treatment costs were highly variable, even when stratified by drug, because of differences in study populations, severity of disease (e.g., relapsed vs stable), setting (e.g., outpatient vs hospitalized patients), or phase of treatment (e.g., switching vs restarting). Despite the wide range across studies, medication costs for oral antipsychotics contributed 28% to 44% of annual mean total direct costs and represent a significant proportion of the economic burden of schizophrenia [22, 67, 70].

Although continuous long-term pharmacologic treatment is a goal in the management of schizophrenia, real-world studies indicated that adherence to oral antipsychotics was commonly below 50% and treatment discontinuations were high (greater than 50%) [29, 34, 42, 44–54].

Suboptimal medication adherence has been linked to relapse and rehospitalization [71–73], with one study reporting that 68% of rehospitalization costs were attributed to loss of efficacy and 32% were attributed to lack of adherence [71]. In this review, patients with suboptimal adherence to their oral antipsychotic medication had higher medical costs that were driven by increased inpatient care costs [20, 62].

Furthermore, up to half of patients switched from their index antipsychotic medication to a different agent, while approximately 30% augmented with an additional antipsychotic (i.e., combination antipsychotic therapy), highlighting the need for residual symptom control and/ or the treatment of other psychiatric comorbidities in this population. Although these strategies may improve treatment response, both options were associated with higher costs of care. For patients who switched oral

antipsychotic medications, total direct costs were as high as \$24,265 per patient, while the cost of augmenting was as high as \$29,344. Regardless of the pattern of switch that occurs, switching is costly. These issues highlight the importance of first-line antipsychotic treatments that are both highly effective and well tolerated to avoid unnecessary medication discontinuations, switches, or treatment augmentation and their associated increased treatment costs.

LIMITATIONS

As is the case with all systematic reviews, this review is limited by potential reporting and publication biases, restricting the scope of patient characteristics, outcome definitions, and time periods reported. In addition, definitions of schizophrenia-related clinical terms often varied between studies. Some outcomes (e.g., switching or discontinuation rates) were not standardized into person-months of exposure but are presented as aggregates with variable follow-up times. While discontinuation from medication was commonly reported, the reason for stopping medication or the subsequent next step in patients' treatment journeys were rarely available, reflecting that many included studies utilized administrative claims databases to elucidate costs, and reasons for discontinuation are generally not coded as part of the claim. Additionally, there is not enough information on differences between settings of care to allow for comparisons between these outcomes.

Because only a subset of studies contributed to cost estimates of antipsychotic treatment patterns, the range of estimates should be interpreted with caution. As reported in this review, treatment costs are highly variable across patients. Patients with schizophrenia who have suboptimal adherence or who discontinue their medication have higher inpatient costs due to episodes of relapse and hospitalization [7]. Furthermore, given the uncontrolled nature of the studies examined, confounding by indication cannot be ruled out.

Another limitation is that only direct costs related to oral antipsychotic medications were considered. Disease-related indirect costs comprise most of the excess economic burden of schizophrenia [3, 5], and the loss of productivity by patients and caregivers and premature patient mortality are substantial contributors to the societal costs of schizophrenia [3, 74]. Also, this review did not include LAI antipsychotics in estimates of medication costs, although some studies have found that these agents may be associated with lower inpatient but higher pharmacy costs [75]. As the review was restricted to the US health care system, the economic burden of schizophrenia in other countries was not evaluated.

Furthermore, none of the articles included in this review reported on prescribing patterns or cost differences after a branded product became available as a generic product. This review builds on previous research by focusing on data specific to treatment patterns for schizophrenia in the USA, but without a limitation to population, as was the case with a recent systematic review that restricted inclusion to studies in privately insured patients [12]. By including additional evidence published after previous reviews, we aimed to provide a broader understanding of treatment patterns and costs associated with the treatment of schizophrenia.

CONCLUSIONS

This systematic review of oral antipsychotic treatment patterns and associated costs among patients with schizophrenia in the USA found that antipsychotic medication adherence is low and discontinuation rates are high in this population. Therefore, many patients living with schizophrenia have symptoms that may not be optimally managed, leading to higher treatment costs when subsequent efforts aimed at reducing those symptoms include switches in treatment and/or augmentation with additional agents. Suboptimal adherence in these patients contributes to greater economic burden relative to those who are adherent to medications. Despite the number of available oral antipsychotics for schizophrenia, there remains an

unmet need for new, highly efficacious treatments that may improve adherence. Such treatments may decrease health care resource utilization and the overall cost burden associated with schizophrenia over time.

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