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REVIEW

Real-World Effectiveness, Economic, and Humanistic Outcomes of Selected Oral Antipsychotics in Patients with Schizophrenia: A Systematic Review Evaluating Global Evidence

Keyuri Adhikari[1,*], Khalid M Kamal[1,*], Ki Jin Jeun[1], David A Nolfi[2], Mohammed Najeeb Ashraf[3], Christopher Zacker[4]

[1]Department of Pharmaceutical Systems and Policy, West Virginia University School of Pharmacy, Morgantown, WV, USA; [2]Gumberg Library, Duquesne University, Pittsburgh, PA, USA; [3]Medical Affairs, SciVoc Consulting Inc, Toronto, Ontario, Canada; [4]Global Value & Access, Cerevel Therapeutics, Cambridge, MA, USA

*These authors contributed equally to this work

Correspondence: Khalid M Kamal, Department of Pharmaceutical Systems and Policy, West Virginia University School of Pharmacy, Email kkamal@hsc.wvu.edu

Background: Schizophrenia is a complex, chronic mental health disorder that confers a substantial disease burden globally. Oral antipsychotic treatments (OATs) are the mainstay for treating early and advanced stages of schizophrenia. Our systematic review aimed to synthesize literature describing real-world effectiveness, economic, and humanistic outcomes of OATs (asenapine, brexpiprazole, cariprazine, iloperidone, lumateperone, lurasidone, olanzapine/samidorphan, paliperidone, and quetiapine) for successful management of the disease.

Methods: PubMed, American Psychological Association PsycINFO (EBSCOhost), and Cumulative Index of Nursing and Allied Health Literature were searched according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Studies reporting real-world effectiveness, costs, humanistic, behavioral (eg, interpersonal relations, suicide ideation), medication adherence, and product-switching outcomes for selected OATs published in English from January 2010 to March 2022 were identified and evaluated qualitatively.

Results: We included 48 studies with different designs providing extensive evidence on schizophrenia. All studies were conducted in countries outside of the United States. In most studies, antipsychotic medications were more effective than placebo, suggesting their value in the management of schizophrenia. Sixteen studies measured the economic outcomes of OATs. Eight studies assessed humanistic outcomes, while one reported behavioral outcomes in three second-generation antipsychotics. Medication adherence was described in two studies, while five studies evaluated product switching. Non-adherence was commonly reported for OATs. Medication non-adherence and treatment discontinuation were predominant factors contributing to the economic burden of schizophrenia.

Conclusion: Our research showcased a significant knowledge gap across OATs spanning the humanistic and behavioral outcomes and medication adherence and switching, suggesting a need for robust evidence generation to help clinicians and payers make informed decisions regarding treatment opportunities and cost-effective strategies for patients with schizophrenia.

Keywords: schizophrenia, behavioral outcomes, cost-effectiveness, humanistic outcomes, medication adherence, product switching

Introduction

Globally, schizophrenia was ranked 20th amongst the top 25 leading causes of years lived with disability across all ages and 9th amongst the 25–49-year age group.[1] Notwithstanding its prevalence of 23.6 million and age-standardized prevalence of 287.4 per 100,000 people,[1] this severe and heterogeneous mental illness with no current cure is

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a significant driver of social, economic (with both direct and indirect costs to healthcare), and societal burden for the patient, caregivers, and healthcare systems.[2–5] Patients with schizophrenia often require lifelong treatment[6] and experience a reduced life expectancy of up to 10–20 years than the general population.[7] Numerous treatment choices, including those available generically, show considerable heterogeneity across patterns of effectiveness, medication adherence, product switching, and patient treatment burden, making it essential to identify novel management strategies for cost-effective and sustained outcomes in those affected by schizophrenia.

The burden of schizophrenia becomes evident during the initial disease stages;[3] hence, treating patients during the first psychotic episode augments chances of disease improvement with optimal recovery and lowers relapse risk.[8–11] While oral antipsychotics remain the mainstay treatment for schizophrenia, with 65 oral antipsychotic formulations available globally,[12] the risk of relapses due to medication non-adherence is high.[13,14] Using long-acting injectables (LAIs) may increase medication adherence and improve patient outcomes.[13] However, considerable variation remains in clinical practice patterns, patient treatment response, and patients' perceptions and attitudes, considering the diverse efficacy outcomes of the disease and adverse effect profiles.[12] Besides, there exists variability in response to antipsychotics across countries, suggesting that different healthcare systems and cultural factors could have a global impact on medication patterns.[15] Optimizing patient outcomes for an informed decision on appropriate antipsychotic treatment and best practice guidance is essential for enhanced patient experience. Significant work is needed to bridge this impending gap in identifying and achieving optimal therapeutic opportunities for schizophrenia.

Efforts are being made to identify a balanced benefit-risk profile of currently available antipsychotics to customize treatment to patient's preferences and treatment requirements. To further understand the benefits of the therapeutic landscape, we conducted a systematic literature review to identify the real-world effectiveness, economic, and humanistic evidence that is available to decipher the value associated with ten globally available select oral antipsychotic treatments (OATs), namely asenapine, brexpiprazole, cariprazine, iloperidone, lumateperone, lurasidone, olanzapine/samidorphan, paliperidone, and quetiapine.

Methods

A systematic literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards.[16]

Literature Search Strategy

Bibliographic databases of PubMed, the EBSCOhost version of the American Psychological Association (APA) PsycINFO, and the Cumulative Index of Nursing and Allied Health Literature (CINAHL) were searched for relevant publications reporting real-world effectiveness, economic, and humanistic outcomes associated with OATs for schizophrenia from January 2010 to March 2022. Additionally, official websites and Health Technology Assessment (HTA) databases, including the National Institute for Health and Care Excellence (NICE), National Institute of Mental Health (NIMH), Database Commons, Cost Effectiveness Analysis (CEA) Registry, and the HTA Database (INAHTA) were searched for relevant studies published within the timeframe as mentioned above.

A primary search was conducted across the selected databases using controlled search terminology combining OATs (brand and generic names) for schizophrenia and terms related to "effectiveness", "economic", "humanistic", "behavioral", "adherence", and "product switching". A detailed list of keywords used is provided in Supplementary Table 1. A backward citation screening was conducted for the included studies.

Inclusion and Exclusion Criteria

All titles and abstracts obtained through literature searches were assessed against the eligibility criteria, including OATs, adults with schizophrenia, English language publications, and outcomes such as real-world effectiveness, economic outcomes, humanistic outcomes, behavioral outcomes, adherence/persistence, and product switching using a study screening hierarchy. Furthermore, the bibliographies of selected articles were reviewed to identify further articles of relevance. Studies in adults with schizophrenia analyzing real-world effectiveness, economic, or humanistic outcomes of

the following OATs approved for schizophrenia (since 2006), namely, asenapine, brexpiprazole, cariprazine, iloperidone, lumateperone, lurasidone, olanzapine, olanzapine/samidorphan, paliperidone, and quetiapine were included.

Eligible studies were full-text articles published in the English language that mentioned at least one recently approved and/or available oral antipsychotic drug, at least one outcome concerning effectiveness endpoints in real-world studies, direct and indirect costs in pharmacoeconomic studies, including work productivity in patients or their caregivers; humanistic outcomes including quality of life (QoL) activities of daily living, and patient satisfaction, among others; behavioral outcomes; adherence/persistence; description of product switching; and drug characteristics, and article types including observational, randomized controlled trials (RCTs), non-randomized experimental, cohort-based, cross-sectional, case-control, and economic evaluation, having the measure of each outcome specified for inclusion. Ineligible studies were those reporting efficacy and safety outcomes (except for HTA databases), non-pharmacological treatment, and/or treatment with different routes of administration (such as a transdermal patch) in pediatric or non-human participants conducted in the United States (US), and type of articles such as conference abstracts, reviews, dissertations, commentaries, editorials, and summary reports.

Data Extraction and Analysis

A faculty investigator (KMK) and a librarian (DAN) supervised and guided the development of the search terms. To expand the search capabilities of each database, exclusive search strings were added, including the Medical Subject Headings terminology for PubMed, APA Thesaurus Terms for APA PsycINFO, and subject headings for the CINAHL. Covidence (Veritas Health Innovation, Melbourne, Australia), a web-based collaboration platform for producing systematic and other literature reviews, was used to screen and extract articles. Searches were executed on each database, and the results were imported to Covidence to remove duplications manually and through the program function. Two reviewers (KJ and KA) checked each electronic database for prospective records under a senior team member's (KMK) supervision. The title/abstract of articles were identified and screened by two reviewers (KJ and KA) based on the disease, study population, study design, type and name of antipsychotics, and the outcome of interest. Full texts of the selected articles were then obtained, and reviewers conducted a final screening. Any discordance between the reviewers during article selection was arbitrated through discussion with a senior member (KMK).

Covidence automatically uploaded some full-text articles, and for the ones missing, the reports were manually uploaded by the two reviewers (KJ and KA), utilizing the university's library databases. An extraction log of these publications on Covidence included pertinent information such as the study design and objectives, year of publication, study medications, the country where it was conducted, and the target population. The reviewers (KJ and KA) cleaned and verified the retrieved data. This procedure ensured that included studies satisfied all requirements and that accurate data was collected.

Ethics

Our analysis included previously published evidence and did not involve studies on animals or humans; therefore, ethics approval was not required.

Results

A total of 24,190 records were identified from different databases and HTA websites. Before the initial screening, 14,005 duplicate records were removed, and 10,185 were eligible for initial screening at the title/abstract level. Of the 633 relevant studies assessed for eligibility, most were excluded based on incorrect study design (n=107), those reporting safety and efficacy outcomes (n=112), and ones conducted only in the US (n=27). The US-based study findings have been presented earlier.[17] After excluding studies that did not meet the specified criteria, 48 were selected for final review. In Figure 1, the PRISMA flow diagram summarizes the inclusion and exclusion of studies.

Study Overview

The analysis included 48 studies, including 5 RCTs,[18–22] 4 non-randomized experimental studies,[23–26] 14 cohort studies,[27–40] 10 cross-sectional studies,[41–50,] and 15 economic evaluation studies.[51–65] All 48 studies were conducted in countries outside of the United States. The characteristics of these studies are presented in Supplementary Table 2.

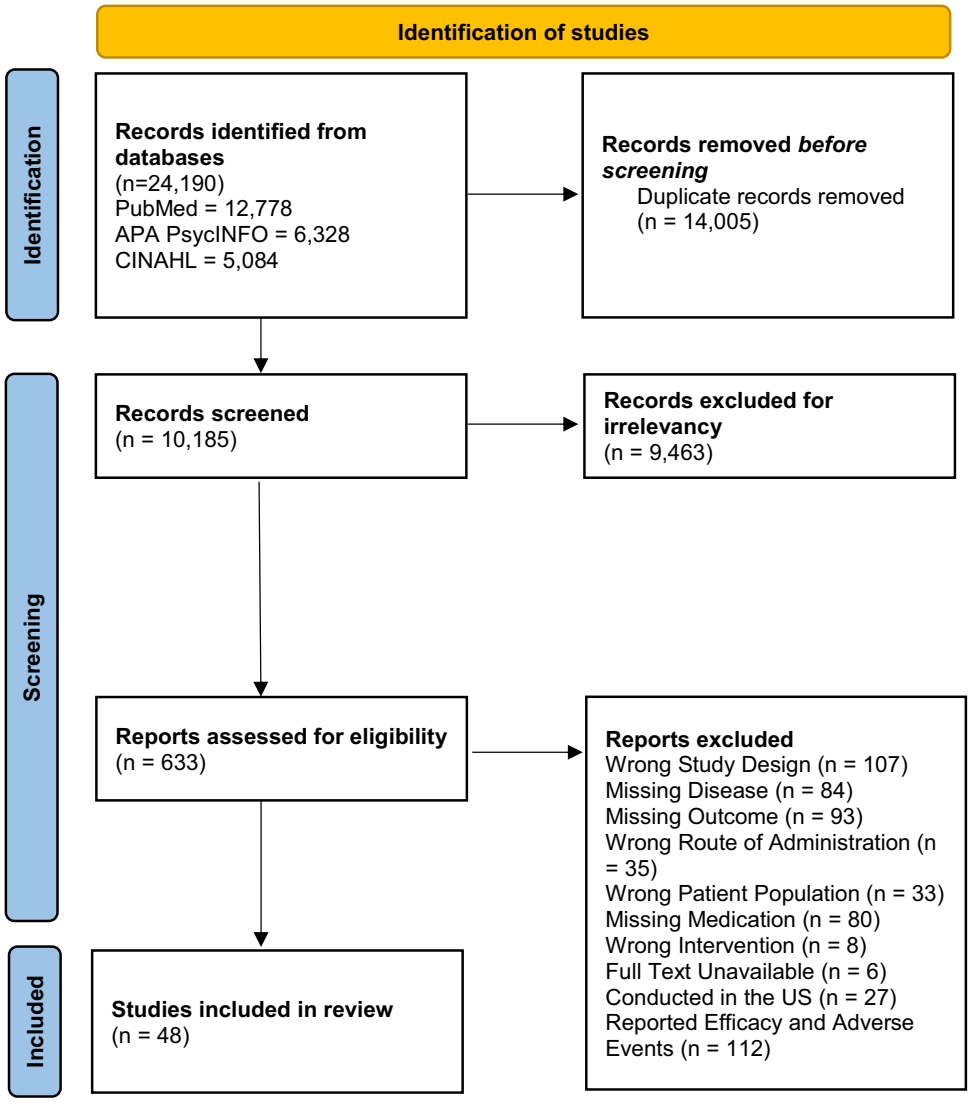

Figure 1 PRISMA flowchart for the selection of studies.
Abbreviations: APA, American Psychological Association; CINAHL, Cumulative Index to Nursing and Allied Health Literature; US, United States.

The effectiveness, economic, humanistic, and behavioral changes, medication adherence, and product switching evidence for the respective OATs are summarized in Supplementary Table 3.

Diverse Treatment Characteristics and Study Populations

This systematic literature review included all studies that analyzed treatment effects or outcomes of OATs, including asenapine (Saphris®, Sycrest®), brexpiprazole (Rexulti®, Rxulti®), cariprazine (Reagila®, Vraylar®), iloperidone (Fanapt®, Fanaptum®), lumateperone (Caplyta®), lurasidone (Latuda®), olanzapine, olanzapine samidorphan (Lybalvi®), paliperidone (Invega®), and quetiapine fumarate (Seroquel® slow release [XR]). Studies had diverse study populations and ranged from a limited number of participants (n=20) to over 200,000.[46,54] Similarly, diverse subsets of schizophrenia patients were included in the selected studies. Two studies had a population with psychosis associated with schizophrenia (one cohort study[36] and one that evaluated economic outcomes).[54] In comparison, two studies included patients with schizoaffective disorders (one non-randomized experimental study[25] and one that evaluated economic outcomes).[62]

Effectiveness of Oral Antipsychotics

Effectiveness was measured in 21 studies, including two RCTs,[21,22] three non-randomized experimental studies,[23,24,26] nine cohort studies,[27,29–31,35–37,39,40] and seven cross-sectional studies.[41,42,44,46–48,50] A real-world observational study that compared the effectiveness of different antipsychotic drugs in patients with schizophrenia and schizoaffective disorders reported that clozapine (adjusted hazard ratio [HR]: 0.36, P<0.0001) was more effective when compared to first-generation "conventional" drugs (adjusted HR: 1.22, P<0.0001) and LAI second-generation oral antipsychotics (SGAs; adjusted HR: 0.56, P<0.0001) while considering hospital discontinuations for mental disorders.[29] In a large cohort study of 64,442 patients, clozapine demonstrated worse survival rates for psychiatric admissions when compared to olanzapine (HR: 0.615).[35] Joo et al reported that patients administered LAI antipsychotics had the lowest risk for treatment discontinuation and psychiatric hospitalization compared to patients treated with typical antipsychotic drugs.[37] A cross-sectional study with 200 patients reported that risperidone was more effective in treating first-episode schizophrenia than aripiprazole and olanzapine.[50] Additional details are provided in Table 1.

Economic Outcomes of Oral Antipsychotics

Sixteen studies measured the economic outcomes of OATs, including one cross-sectional study (Table 2).[45,51–65] A Brazil-based economic evaluation study involving 174,310 schizophrenia patients showed that atypical antipsychotics (clozapine, olanzapine, quetiapine, risperidone, and ziprasidone) were accountable for most treatment costs and psychiatric hospitalization costs and contributed significantly to direct medical expenses (≈80%).[51] The mean annual costs per patient for olanzapine (US$ 2085.28+485.62) was the highest among atypical antipsychotics, while clozapine had the highest mean annual cost per patient for outpatient psychiatric care (US$ 1105.39+236.70) and psychiatric hospitalization (US$ 3509.34+854.21).[51] Olanzapine was found to be less costly than LAIs for the maintenance treatment of schizophrenia in France.[52] Another study conducted in Spain showed that paliperidone extended-release (ER) had higher quality-adjusted-life years (QALYs) gained per patient (0.7573) and was less costly than risperidone (€3194), haloperidol (€3322), olanzapine (€3893), amisulpride (€4247), and aripiprazole (€4712).[53] A United Kingdom-based economic evaluation study reported that amisulpride was the most cost-effective drug (0.39), followed by risperidone (0.30) and olanzapine (0.17), assuming a willingness to pay threshold of £20,000 (equivalent to $25,552) per QALY gained.[54] In a multi-country study, it was observed that lurasidone had the lowest lifetime cost for acute treatment compared with all other atypical antipsychotics considered.[55] Asenapine was dominant over olanzapine from a societal perspective in a Canada-based cost-effectiveness study.[57] An economic evaluation of OATs in 461 patients reported that cariprazine produced better health outcomes than risperidone, resulting in an estimated QALY gain of 0.029 per patient following one year of treatment.[60] Phanthunane et al reported that risperidone was the cheapest drug, and treating severe schizophrenic patients with clozapine was associated with an increased cost-effectiveness ratio of 320,000 Baht per disability-adjusted life years (DALYs).[61] A German-based economic evaluation study reported that the number of bed days was comparatively lower in patients treated with typical antipsychotics than those with atypical antipsychotics with a mean predicted treatment cost of €6442 (atypicals) and €4443 (typical) (P<0.0001).[64]

Humanistic and Behavioral Outcomes of Oral Antipsychotics

Nine studies measured humanistic outcomes for oral antipsychotics.[18–20,23,28,32,38,43,49] A QoL study on 1133 patients reported that patients receiving olanzapine and quetiapine showed significant improvements in the role-psychological score of the SF-36 and the goal attainment scale score compared to those receiving chlorpromazine.[23] Gründer et al reported promising improvement in QoL from SGAs compared to First Generation Antipsychotics.[32] Taipale et al reported that second-generation LAIs reduced the risk of parental psychiatric healthcare use, while OATs were associated with an increased risk of parental psychiatric healthcare use.[38] Patients treated with olanzapine and risperidone reported impaired QoL.[43] Patient adherence to medications and perceived general health were significantly higher in patients treated with paliperidone palmitate than with SGAs.[49] Additional details are presented in Table 3.

Only one study investigated the effect of three SGAs (olanzapine, aripiprazole, ziprasidone) and their association with different clusters of symptoms and insight (ability to recognize the nature of symptoms and the importance of medication

Table 1 Effectiveness Outcomes Associated with Oral Antipsychotic Treatments

Sr. No.	Author & Year, Country	Drug(s)	Study Objective	Sample Size	Measures	Main Findings
1	Rui 2014, China[21]	Paliperidone	To evaluate the long-term efficacy, safety, and tolerability of paliperidone extended-release (pali ER) in Chinese patients with schizophrenia	135	Relapse Events, PANSS score, CGI-S, Severity Sores, Side effects	• 71 (52.6%) of patients had a relapse event • Time to relapse (primary endpoint) favored pali ER (HR=5.23 [95% CI: 2.96, 9.25], P<0.0001) • Rate of relapses (55/71 [77.5%] placebo; 16/64 [25%] pali ER) • Secondary endpoints (change from baseline in PANSS and CGI-S) were significantly lower (P<0.001) in pali ER group vs placebo, in favor of pali ER
2	Sinkeviciute 2021, Norway[22]	Olanzapine; Other: Amisulpride, Aripiprazole	To compare the anti-hallucinatory effectiveness of 3 pharmacologically different antipsychotics: olanzapine, amisulpride, and aripiprazole	144	Hallucinations	A significantly less reduction of hallucinations was revealed for participants using olanzapine in weeks 12, 26, 39, and 52 when compared with amisulpride and in weeks 26 and 52 when compared with aripiprazole
3	Guo 2011, China[23]	Olanzapine; Other: Chlorpromazine, Sulpiride, Clozapine, Risperidone, Quetiapine, Aripiprazole	To evaluate the efficacy and safety of seven antipsychotic drugs for the maintenance treatment in patients with early-stage schizophrenia	1661	Treatment Discontinuation	• The percentage of patients discontinued treatment within 12 months was: ○ 41.4% for chlorpromazine ○ 39.5% for sulpiride ○ 36.7% for clozapine ○ 40.2% for risperidone ○ 39.6%for olanzapine ○ 46.9% for quetiapine ○ 40.2% for aripiprazole A nonsignificant difference (p=0.717)
4	Jariyavilas 2017, Thailand[24]	Paliperidone	To investigate the effects of paliperidone ER on hostility in Thai patients with schizophrenia	148	Hostility Aggressive Behavior	• Significant reduction in mean hostility score at 2 months (P<0.05), 3 months (P<0.05), and 6 months (P<0.01). • Significant reduction of mean PSP scores from 3 months onward, including in the disturbing and aggressive behavior subscale (P<0.001).
5	Takahashi 2015, Japan[26]	Olanzapine Other: Risperidone Aripiprazole Blonanserin Quetiapine Paliperidone Perospirone Zotepine Haloperidol Bromperidol Sulpiride Chlorpromazine Levomepromazine Fluphenazine	To compare the rates of antipsychotic response, remission, and relapse in patients with schizophrenia treated with olanzapine or other antipsychotics in usual clinical care	1089	Relapse and Remission	• No significant difference in relapse rate - olanzapine (11.7%); other antipsychotic (12.8%); other atypical antipsychotic (13.0%) • Rates of sustained remission were significantly higher among the olanzapine group (19.0%) compared with other antipsychotics (13.7%) and other atypical antipsychotics (14.0%) • An exploratory analysis found similar sustained remission rates in outpatients treated with olanzapine (22.2%) or other antipsychotic (22.8%) • Inpatients treated with olanzapine had significantly higher sustained remission rates (17.1%) than patients treated with OAN (6.6%)

6	Barbosa 2021, Brazil[27]	Olanzapine; Other: Risperidone	To evaluate the effectiveness of olanzapine and risperidone in the treatment of patients with schizophrenia in the real world and assess risk factors for their discontinuation through a national non-concurrent cohort with 16 years of follow-up.	3416	Treatment discontinuation	• Olanzapine had a longer time until discontinuation of treatment (P=0.021), and risperidone had a higher risk of discontinuation (P=0.021) • Among patients persistent for at least 24 months, there was no significant difference
7	Brodeur 2022, Canada[29]	Olanzapine; Other: Clozapine	To compare the effectiveness and safety of various SGAs, newer oral and LAI SGAs, and FGA treatments in patients with schizophrenia or schizoaffective disorder	19,615	Reduced risk of hospitalizations	• Better effectiveness of clozapine (adjusted HR: 0.36; 95% CI: 0.30 to 0.42; P<0.0001) and LAI SGAs (adjusted HR: 0.56; 95% CI: 0.51 to 0.61; P<0.0001) compared with oral olanzapine • Oral FGAs (adjusted HR: 1.36; 95% CI: 1.27 to 1.46; P<0.0001) and LAI FGAs (adjusted HR: 1.22; 95% CI: 1.12 to 1.32; P<0.0001)
8	De Yang 2017, China[30]	Paliperidone	To evaluate the changes in treatment satisfaction after switching to paliperidone ER in Chinese schizophrenia patients dissatisfied with their previous antipsychotic treatment	1693	MSQ and CGI-S	• Mean (SD) MSQ scores increased significantly from baseline to week 8 (2.48 [0.55] vs 5.47 [0.89]; P<0.0001) • The proportion of patients with MSQ score ≥4 was 95.9% at week 8, indicating that most of the patients were satisfied with their treatment • Significant improvements (P<0.0001) from baseline to week 8 were noted in CGI-S score (2.37 [1.20]) and PSP score (25.5 [15.0]).
9	Emborg 2012, Denmark[31]	Other: Quetiapine ER, Quetiapine IR	Evaluate the clinical use of two quetiapine formulations, extended-release (ER) and immediate release (IR), in outpatients with schizophrenia spectrum disorder	186	Mean daily dosage	• Use in antipsychotic dosage was seen for 89% quetiapine ER vs 63% quetiapine IR patients (mean daily dose, 400 mg/day; P<0.0001) • 75% quetiapine ER and 53% quetiapine IR patients used 600 mg/day (p= 0.0019) • Quetiapine ER was used at higher mean daily dosages than quetiapine IR (748 vs 566 mg/day; P=0.006) • 43 (23%) patients used both formulations concomitantly; 55 (30%) patients used either quetiapine ER or IR • Quetiapine IR was used as needed in 44 (23%) patients; one patient used quetiapine ER as needed
10	Jo 2021, Korea[35]	Olanzapine; Other: Clozapine	To investigate the current status of clozapine prescriptions to identify any disparity between clinical guidelines and real-world practices	64,442	Survival rate	• Clozapine showed a worse survival rate for psychiatric admissions than olanzapine (HR: 0.615) • Clinicians tended to try several antipsychotics, as recommended, before starting patients on clozapine

(*Continued*)

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Table 1 (Continued).

Sr. No.	Author & Year, Country	Drug(s)	Study Objective	Sample Size	Measures	Main Findings
11	Johnsen 2013, Norway[36]	Other: Risperidone, Olanzapine, Quetiapine, Ziprasidone	To investigate the rate and severity of hallucinations in acutely admitted psychotic patients at hospital admission and discharge or after 6 weeks at the latest, if not discharged earlier (discharge/6 weeks); and to compare the anti-hallucinatory effectiveness of risperidone, olanzapine, quetiapine, and ziprasidone with up to 2 years, follow-up	226	Reduction in hallucinations	• 68% were hallucinating at baseline, which reduced to 33% at discharge/6 weeks • Quetiapine and ziprasidone groups both had faster decreases in the mean hallucination scores than the risperidone group
12	Joo 2021, Korea[37]	Olanzapine; Paliperidone; Other: LAI Paliperidone, Clozapine, Quetiapine, Bionanserin, Risperidone, Chlorpromazine, Ziprasidone, Aripiprazole, Amisulpride, Sulpiride, Haloperidol	To investigate the treatment discontinuation and risk of psychiatric hospitalization using a nationwide population database	44,396	Treatment Discontinuation	• Among individual antipsychotics, the lowest risk of treatment discontinuation was observed in LAI paliperidone compared with olanzapine (HR: 0.45; 95% CI: 0.37 to 0.56; P<0.001) • Clozapine was found to be the most effective antipsychotic in lowering the risk of psychiatric hospitalization as monotherapy compared with no use (HR: 0.23; 95% CI: 0.18 to 0.31; P<0.001)
13	Vanasse 2016, Canada[39]	Olanzapine; Other: Clozapine, Risperidone, Quetiapine	To compare, in a real-world setting, the risk of mental and physical health events associated with different antipsychotic drugs (clozapine, olanzapine, risperidone, quetiapine, and first-generation antipsychotics) in patients with schizophrenia	18,869	Mental and physical health events	• Quetiapine and not using any antipsychotics were associated with an increased risk of mental and physical health events as compared with other drugs • The second finding is the confirmation of better performance of clozapine
14	Zhong 2021, Canada[40]	Paliperidone; Other: Haloperidol	This study aimed to evaluate the efficacy of paliperidone in improving ToM task performance in patients with schizophrenia compared with haloperidol	60	Belief task, Faux-pas task, Reading the mind in the eyes task	• Performance on the first-order false belief task – no significant differences between groups (F=0.117, P>0.05); significant differences for time effect (F=20.989, P<0.001) • Higher-order false belief task – no significant differences between groups (F=3.560, P>0.05); significant differences for the time effect (F=10.055, P<0.001) • Faux-pas task – significant differences between groups (F=6.204, mean difference=51.4, P<0.05) • Reading the mind in the eyes task – no significant differences between groups (F=3.151, P>0.05); significant differences for the time effect (F=4.479, P<0.05) • PANS – no difference between groups (F=0.006, P>0.05); significant difference in time effect (F=80.641, P<0.001)

15	Bitter 2013, Hungary[41]	Olanzapine; Other: Amisulpride, Aripiprazole, Clozapine, Quetiapine, Risperidone, Ziprasidone	To evaluate the comparative effectiveness of all marketed SGA prescribed for outpatients with a diagnosis of schizophrenia in Hungary	9567	Time to discontinuation	• Time to discontinuation for the drugs are as follows: a. depot formulation of risperidone had the longest time to discontinuation, with a median of 215 days (95% CI: 181 to 242 days) b. olanzapine (136 days; 95% CI: 121 to 153 days) c. aripiprazole (102 days; 95% CI: 81 to 126 days) d. ziprasidone (93 days; 95% CI: 82 to 119 days) e. quetiapine (89 days; 95% CI: 81 to 100 days) f. clozapine (76 days; 95% CI: 54 to 92 days) g. amisulpride (73 days; 95% CI: 62 to 85 days) h. oral risperidone (55 days; 95% CI: 41 to 63 days)
16	Buoli 2016, Italy[42]	Other: Risperidone, Olanzapine, Quetiapine, Clozapine, Aripiprazole, Haloperidol	The purpose of the study was to compare antipsychotic monotherapies in terms of time to discontinuation in a sample of schizophrenia patients followed up for 36 months	220	Discontinuation of medicine	• Patients treated with haloperidol discontinued more than the other groups: a. risperidone p<0.001 b. olanzapine p<0.001 c. quetiapine p=0.002 d. clozapine p<0.001 e. aripiprazole p=0.002
17	Hakami 2022, Saudi Arabia[44]	Olanzapine; Paliperidone; Other: Amisulpride, Aripiprazole, Clozapine, Haloperidol, Quetiapine, Risperidone, Trifluoperazine	To identify the clinical characteristics and treatment outcomes of patients with newly diagnosed schizophrenia	746	Drug retention	• The most used initial antipsychotic drugs were: a. olanzapine (48.8%) b. haloperidol (13.9%) c. aripiprazole (11.3%) • The initial drug was changed in 246 (33.0%) of patients • The median time to initial drug change was 43.9 (IQR 14.8 to 85.0) weeks • The logistic regression demonstrated that significant factors for drug change included: a. male sex (P<0.004) b. young adult age group (P<0.027) c. predominant positive symptoms (P<0.021) d. treatment with haloperidol (P<0.024) e. khat use (P<0.006)
18	Klasik 2011, Poland[46]	Olanzapine	To evaluate the effect of olanzapine treatment on selected cognitive functions in patients who have schizophrenia during an observation period of six months	20	Cognitive Function	Impairments in cognitive domains were observed at baseline as compared with published normative data, and enhancement in achieved results was observed subsequently in all stages of the treatment until the 6th month

(*Continued*)

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Table 1 (Continued).

Sr. No.	Author & Year, Country	Drug(s)	Study Objective	Sample Size	Measures	Main Findings
19	Kongsakon 2017, Thailand[47]	Paliperidone	To evaluate the effect of 6 months of treatment with paliperidone ER tablets on the sleep profile of patients with schizophrenia	984	Sleep Quality and Daytime Drowsiness	Paliperidone was associated with significantly better sleep quality (76.44 vs 65.48; P<0.001) and less daytime drowsiness (23.18 vs 34.22; P<0.001) compared with baseline
20	Matsuzaki 2021, Japan[48]	Asenapine, Olanzapine	To compare the treatment continuation rate and reason for discontinuation of asenapine or olanzapine in schizophrenia using real-world data	95	Continuation rate	Continuation rate of asenapine vs olanzapine (27.3% vs 50.8%; HR: 0.41; 95% CI: 0.21 to 0.82; P=0.0088)
21	Wang 2017, China[50]	Olanzapine; Other: Aripiprazole, Risperidone, Quetiapine, Ziprasidone	To understand whether there are any differences in efficacy, acceptability, and safety between the five atypical antipsychotics in patients with first-episode schizophrenia	200	BPRS scores	• BPRS total scores in each antipsychotic group were significantly decreased at the end of the study (P<0.01) • Only the deduction rate of BPRS total scores in the risperidone group was markedly higher than those in the groups of aripiprazole (P<0.01) and olanzapine (P<0.05) • There were significant differences between quetiapine (P=0.019), olanzapine (P=0.018), and ziprasidone regarding the proportion of maintaining on initially allocated therapy • There were significant differences between quetiapine (P=0.019), olanzapine (P=0.018), and ziprasidone regarding the proportion of maintaining on initially allocated therapy

Abbreviations: BPRS, Brief Psychiatric Rating Scale; CGI-S, Clinical Global Impression Score; ER, Extended Release; FGAs, First-Generation Antipsychotics; HR, Hazard Ratio; IQR: Inter-Quartile Range; IR, Immediate Release; LAI, Long-Acting Injectable; MSQ, Medication Satisfaction Questionnaire; PANSS; Positive And Negative Syndrome Scale; PSP, Personal Social Performance; SD, Standard Deviation; SGAs, Second-Generation Antipsychotics; ToM, Theory of Mind.

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Table 2 Economic Outcomes Associated with Oral Antipsychotic Treatments

Sr. No.	Author & Year	Study Objective	Drug Name	Main Findings
1	He 2015, China[45] (Cross-sectional study)	To evaluate the health service utilization and costs of treatment initiation with atypical antipsychotics in patients with schizophrenia in comparison with typical antipsychotics, as prescribed in the context of routine clinical practice using real-world claims data in China. (1) To explore whether initiation with atypical medications was associated with better treatment outcomes compared with typical medications, as measured by better medication adherence and reduced rates of hospitalization, and (2) to explore whether atypical initiators had lower non-medication related medical costs, and if they did, whether the reductions were enough to offset their higher medication costs	Olanzapine and Others: atypical vs typical	• Atypical medication cohort had: ○ a lower likelihood of hospitalization (45.8% vs 56.7%, P<0.001; adjusted OR: 0.58, P<0.001) ○ higher medication cost ($438 vs $187, P<0.001) ○ lower non-medication medical costs ($1223 vs $1704, P<0.001) • total direct medical costs ($1661 vs $1892, P=0.100)
2	Barbosa 2018, Brazil[51]	To use real-world data to describe the costs associated with the treatment of schizophrenia in adults receiving atypical antipsychotics in Brazil from 2000 to 2010	Olanzapine and Others: Clozapine, Quetiapine, Risperidone, Ziprasidone	• Patients who used clozapine had the highest mean annual cost per patient for outpatient psychiatric care and psychiatric hospitalization • Atypical antipsychotics accounted for 79.7% of total costs, with a mean annual cost per patient of $1578.74 ± 240.40 • Mean annual costs per patient were $2482.90 ± 302.92 for psychiatric hospitalization and $862.96 ± 160.18 for outpatient psychiatric care
3	Druais 2016, France[52]	To estimate the cost-effectiveness of paliperidone LAI (or paliperidone palmitate), a once-monthly SGA LAI, compared with the most common antipsychotic medications for the maintenance treatment of schizophrenia in France	Olanzapine and Others: Comparison with LAI	• All LAI antipsychotics had similar costs over 5 years: approximately €55,000, except for paliperidone LAI, which had a discounted price of €50,880 • Oral olanzapine was less costly than LAIs (ie €50,379 after 5 years) • Paliperidone LAI dominated aripiprazole LAI, olanzapine LAI, and haloperidol LAI in terms of costs per QALY
4	García-Ruiz 2012, Spain[53]	To assess the efficiency (efficacy + cost) of the antipsychotics used in Spain to reduce schizophrenia relapses under the National Health System perspective	Olanzapine; Paliperidone and Others: Amisulpride, Risperidone, Haloperidol (comparator)	• Paliperidone ER yielded more QALYs gained per patient (0.7573) • Paliperidone ER was the least costly strategy (€3062), followed by risperidone (€3194), haloperidol (€3322), olanzapine (€3893), amisulpride (€4247), and aripiprazole (€4712) • In the ICE analysis of the assessed antipsychotics compared with haloperidol, paliperidone ER and risperidone were the dominant options • ICER for other medications was €23,621/QALY gained, €91,584/QALY gained, and €94,558/QALY gained for olanzapine, amisulpride, and aripiprazole, respectively

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Table 2 (Continued).

Sr. No.	Author & Year	Study Objective	Drug Name	Main Findings
5	Jin 2020, UK[54]	To develop a whole-disease model for schizophrenia and use it to inform resource allocation decisions across the entire care pathway for schizophrenia in the UK; primary outcomes - lifetime costs and QALY	Olanzapine and Others: Amisulpride, Risperidone	• Assuming a WTP threshold of -£20,000 ($25,552) per QALY gained, amisulpride is most likely to be cost-effective (0.39), followed by risperidone (0.30) and olanzapine (0.17) • The probability that clozapine is the most cost-effective option compared with other medications was estimated to be 0.81 for treatment-resistant schizophrenia patients
6	Kearns 2021, Multi-country[55]	To estimate the total lifetime costs associated with the management of schizophrenia and the treatment of side effects including cardio-metabolic diseases	Brexpiprazole, Lumateperone, Lurasidone, Olanzapine, Paliperidone, and Others: Aripiprazole, Cariprazine, Quetiapine, Risperidone, Ziprasidone	• Lurasidone was associated with the lowest lifetime costs amongst patients initiating acute treatment compared with all other atypical antipsychotics considered • The second lowest costs were for ziprasidone • The main drivers of cost differences were rates of diabetes and cardiovascular diseases, which were lowest for lurasidone, followed by ziprasidone, and then lumateperone • Costs for managing weight gain were lowest for lurasidone and ziprasidone. Similar results were observed for patients initiating maintenance treatment
7	Kim 2011, Norway[56]	To develop a decision analytic model to evaluate the cost-effectiveness of antipsychotics in a Norwegian setting	Olanzapine vs Risperidone	• The model results indicated that olanzapine was a dominant alternative to risperidone ○ Cost per patient in the first year: olanzapine 68,718 vs risperidone 70,359 NOK ○ PANSS score reductions: olanzapine 112.60 vs risperidone 111.55 • Cost per patient from the second to fifth year: olanzapine 148,732 vs risperidone 154,632 NOK
8	Lachaine 2014, Canada[57]	To assess the economic impact of asenapine compared with other atypical antipsychotics in the treatment of schizophrenia in Canada	Asenapine	• In the treatment of schizophrenia, asenapine is a dominant strategy over olanzapine from both the Canadian Ministry of Health and societal perspectives • Compared with quetiapine, asenapine is also a dominant strategy • Asenapine has a favorable economic impact compared with ziprasidone and aripiprazole, as these antipsychotics are not cost-effective compared with asenapine from both the Canadian Ministry of Health and societal perspectives
9	Lubinga 2015, Uganda[58]	To examine the cost-effectiveness of antipsychotics for schizophrenia in Uganda	Olanzapine and Others: Chlorpromazine, Haloperidol, Risperidone, Quetiapine	• In the base-case analysis, mean DALYs were highest with chlorpromazine (27.608), followed by haloperidol (27.563), while olanzapine (27.552) and risperidone (27.557) had the lowest DALYs • Expected costs were highest with quetiapine ($4943) and lowest with risperidone ($4424) • Compared with chlorpromazine, haloperidol was a dominant option (ie, it was less costly and more effective), and risperidone was dominant over both haloperidol and quetiapine • The ICER comparing olanzapine to risperidone was $5868/ DALY averted

10	McIntyre 2010, Canada[59]	This study evaluates the cost-effectiveness of four second-generation antipsychotic agents used in Canada for the treatment of schizophrenia (ziprasidone, olanzapine, quetiapine, risperidone) with a focus on their long-term metabolic consequences	Olanzapine and Others: Ziprasidone, Quetiapine, Risperidone	• The total average cost of treatment with ziprasidone was $25,301 vs $28,563 with olanzapine, $26,233 with quetiapine, and $21,831 with risperidone • Ziprasidone had the lowest predicted number of type 2 diabetes cases and cardiovascular disease events and the highest QALY gains • Patients receiving quetiapine had the highest predicted number of hospitalizations • Ziprasidone was less costly and resulted in more QALYs compared with olanzapine and quetiapine • Compared with risperidone, ziprasidone was more expensive and had higher QALYs, with an incremental cost per QALY gained of $218,060
11	Németh 2017, Hungary[60]	Estimating differences in QALY gain for patients with predominantly negative symptoms of schizophrenia treated with cariprazine compared with risperidone	Cariprazine vs Risperidone	• Patients had a higher probability of reaching better health states treated with cariprazine compared with risperidone • In the model, this resulted in an estimated QALY gain of 0.029 per patient after 1 year of treatment.
12	Phanthunane 2011, Thailand[61]	To determine the optimal treatment package, including drug and non-drug interventions, for schizophrenia in Thailand	Olanzapine and Others: Risperidone, Clozapine	• Generic risperidone is more cost-effective than typical if it can be produced for less than 10 Baht per 2 mg tablet • Risperidone was the cheapest treatment, with higher drug costs offset by lower hospital costs in comparison to typicals • The most cost-effective combination of treatments was a combination of risperidone (dominant intervention) • Adding family intervention has an ICER of 1900 Baht/DALY with a 100% probability of a result less than a threshold for very cost-effective interventions of one times GDP or 110,000 Baht per DALY • Treating the most severe one-third of patients with clozapine instead of risperidone had an ICER of 320,000 Baht/DALY with just over 50% probability of a result below three times GDP per capita
13	Přibylová 2015, Czech Republic[62]	To compare the costs and effectiveness of paliperidone ER vs placebo in the treatment of schizoaffective disorder in the Czech Republic based on pooled clinical trial data	Paliperidone	• The average ICER of paliperidone compared with placebo reached €28,935/QALY • The probability of paliperidone being cost-effective compared with placebo was 99.5%
14	Rajagopalan 2016, Scotland[63]	Conduct a cost-utility analysis of lurasidone versus aripiprazole from the perspective of healthcare services	Lurasidone vs Aripiprazole	• Lurasidone yielded a cost saving of ¬£3383 and an improvement of 0.005 QALYs versus aripiprazole in Scotland • Probabilistic sensitivity analysis suggested that lurasidone had the highest expected net benefit at willingness-to-pay thresholds of £20,000 to 30,000 per QALY • According to the Welsh analysis, lurasidone was a cost-effective treatment strategy at all willingness-to-pay thresholds, with a probability of approximately 75%

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Table 2 (Continued).

Sr. No.	Author & Year	Study Objective	Drug Name	Main Findings
15	Stargardt 2012, Germany[64]	This study investigates the effectiveness and cost of typical versus atypical antipsychotics in a nationwide German cohort of patients with schizophrenia	Atypical Antipsychotics	• Risk of rehospitalization did not differ between groups but within each group severity (P=0.0003) • Males (P=0.0016) and patients <35 years (P<0.0001) had a higher risk of rehospitalization • Number of bed days was lower for treatment with typicals compared with atypicals • Bed days depended on the severity of the disease (p<0.0001) • Prescriptions of drugs against extrapyramidal symptoms, anxiety, and agitation were higher for patients treated with typicals • Mean predicted treatment cost per year was €6442 for atypicals vs €4443 for typicals (P<0.0001)
16	Zhao 2019, China[65]	This study aimed to analyze (1) the cost-effectiveness of olanzapine-ODT vs olanzapine-SOT and (2) the cost-effectiveness of olanzapine-SOT vs aripiprazole-SOT for patients with schizophrenia in China	Olanzapine vs Aripiprazole	• Total annual costs per patient: aripiprazole-SOT ($2,296.05), olanzapine-SOT ($1,940.05), and olanzapine-ODT ($2,292.81) • Average number of relapses per patient in one year: aripiprazole-SOT (0.734), olanzapine-SOT (0.325), and olanzapine-ODT (0.198) • QALYs gained per patient in one year: aripiprazole-SOT (0.714), olanzapine-SOT (0.737), and olanzapine-ODT (0.758) • The incremental ICERs of administrating olanzapine-ODT over olanzapine-SOT are $2,791.96 per relapse avoided and $16,798.39 per QALY gained • The ICERs of using olanzapine-SOT over aripiprazole-SOT are $870.39 per relapse avoided and $15,477.93 per QALY gained • All ICERs are under the willingness-to-pay threshold in China of $25,772.67 • The sensitivity analyses confirmed the robustness of the results

Note: $ refers to the United States Dollar.

Abbreviations: DALY, Disease-Adjusted Life-Years; ER, Extended Release; GDP, Gross Domestic Product; ICE, Incremental Cost-Effectiveness; ICER, Incremental Cost-Effectiveness Ratio; LAI, Long-Acting Injectable; NOK, Norwegian Krone; ODT, Orally Disintegrating Tablet; QALY, Quality-Adjusted Life-Years; SGAs, Second-Generation Antipsychotics; SOT, Standard Oral Tablet.

Table 3 Humanistic and Behavioral Outcomes Associated with Oral Antipsychotic Treatments

Sr. No.	Author Year, Country	Study Design	Drugs	Study Objective	Sample Size	Outcomes Measures	Main Findings
1	Awad 2014, Canada[18]	RCT	Olanzapine; Others: Quetiapine, Risperidone, Aripiprazole, Ziprasidone	This analysis evaluated HRQoL changes among patients with schizophrenia who switched from their current antipsychotic to lurasidone	235	PETiT scores, SF-36 scores	• Significant improvements in PETiT total scores were observed in patients switched from quetiapine, risperidone, aripiprazole, and ziprasidone (all P<0.03) but not olanzapine (P=0.893) • Improvements in the SF-12 MCS score were observed for all patients (mean change [SD]: 3.7 [11.5], P<0.001) and for those switched from quetiapine or aripiprazole (both P<0.03) • The SF-12 PCS scores remained comparable to those at baseline in all patient groups
2	Awad 2016, Canada[19]	RCT	Lurasidone; Others: Quetiapine, Risperidone, Ziprasidone, Aripiprazole	This analysis examines long-term changes in HRQoL among patients with schizophrenia who switched to lurasidone from other antipsychotics.	144	PETiT scores, SF-36 scores	• Patients who switched from quetiapine and aripiprazole showed significant improvement in PETiT total score and adherence-related attitude at extension baseline and extension endpoint • Patients who switched from quetiapine, risperidone, aripiprazole, or ziprasidone showed significant improvement in MCS scores from baseline to extension endpoint • Responders to lurasidone demonstrated greater improvement in PETiT total, psychosocial functioning, and MCS scores at extension baseline than non-responders
3	Ishigooka 2022, Japan[20]	RCT	Paliperidone; Other: Aripiprazole, Blonanserin	The Japan Useful Medication Program for Schizophrenia (JUMPs) is a large-scale, long-term naturalistic study to present pivotal 52-week data on the continuity of SGAs	251	Discontinuation rate	• The discontinuation rates were aripiprazole (68.3%), blonanserin (68.2%), and paliperidone (65.5%) • Significant improvements (all P<0.05) from baseline in PSP scores were observed at the start of monotherapy, week 26, and week 52 in the overall cohort and blonanserin group and week 26 in the aripiprazole group
4	Guo 2011, China[23]	Non-Randomized Experimental Study	Olanzapine; Other: Chlorpromazine, Sulpiride, Clozapine, Risperidone, Quetiapine, Aripiprazole	To identify the effects of antipsychotic medications on quality of life and psychosocial functioning in patients with early-stage schizophrenia: 1-year follow-up naturalistic study	1133	SF-36, GAS, and ADL scores	• At 12 months, treatment resulted in significant improvements in all 8 domain scores of SF-36, GAS, and ADL score (all P<0.001) • Olanzapine and quetiapine groups showed more significant improvement in SF-36 and GAS scores than the chlorpromazine group (all P<0.002)

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Table 3 (Continued).

Sr. No.	Author Year, Country	Study Design	Drugs	Study Objective	Sample Size	Outcomes Measures	Main Findings
5	Bianchini 2014, Italy[28]	Cohort Study	Olanzapine; Others: Aripiprazole, Ziprasidone, Haloperidol	To investigate the effect of three SGAs and haloperidol on insight and the associations among different clusters of symptoms and insight.	174,310	Insight Improvement	• Regarding the insight improvement, all SGAs were more effective than haloperidol, while no difference was detected among different SGAs • Regarding psychopathology, all SGAs showed better efficacy than haloperidol, with positive symptoms apart • All SGAs showed similar efficacy in all domains, except for negative symptoms, which resulted in less responsive to ziprasidone and haloperidol • An association between improvement of insight and psychopathology was detected
6	Gründer 2016, Germany[32]	Cohort Study	Olanzapine; Others: Haloperidol, Flupentixol, Aripiprazole, Quetiapine	To compare the quality of life in patients with schizophrenia on an FGA strategy with those on an SGA strategy	136	SF-36 scores, CGI-I scores	• The mean (SD) area under the curve values of SF-36 were significantly higher in the SGA group than in the FGA group (8.51 [1.47] vs 7.97 [1.73], P=0.0112) • Mean (SD) area under the curve values for CGI-I scores decreased in both groups but were not significantly different between the two groups (3.39 [0.89] in the FGA group vs 3.26 [0.92] in the SGA group, P=0.3423)
7	Taipale 2020, Sweden[38]	Cohort Study	Olanzapine, Paliperidone; Other: aripiprazole, clozapine, quetiapine, risperidone, ziprasidone	To identify if antipsychotic exposure in offspring is associated with psychiatric and non-psychiatric healthcare service use and work disability of their parents	18,215	Parental psychiatric healthcare service use, non-psychiatric healthcare use, and long-term sickness absence	• SGA-LAI was associated with a decreased risk (RR: 0.81–0.85) of parental psychiatric healthcare use, whereas oral antipsychotics were associated with an increased risk (RR: 1.10–1.29) • FGA-oral was associated with a decreased risk of non-psychiatric healthcare use among parents (moderate use – RR: 0.92; 95% CI: 0.87 to 0.96; P<0.01) • Use of LAI was associated with a statistically significant lower risk of long-term sickness absence of the parents, whereas use of oral medication increased such risk among the first generation (OR: 1.56)
8	Chaves 2013, Brazil[43]	Cross-Sectional Study	Olanzapine; Other: Risperidone	The study aimed to compare the effects of treatment with an atypical antipsychotic drug (olanzapine or risperidone) on QoL	115	QoL	• QoL was impaired in patients using olanzapine and in those using risperidone. Significant differences were found between groups in score items of the social domain: active friendship with lower scores for olanzapine (P<0.043) and social withdrawal (P<0.022) with lower scores for risperidone
9	Sağlam Aykut 2019, Turkey[49]	Cross-Sectional Study	Paliperidone; Other: Oral Antipsychotics	To compare paliperidone palmitate and the second-generation oral antipsychotic drugs used to treat patients with schizophrenia in terms of medication adherence, side effects, and QoL	84	Adherence, QoL	• The medication adherence and perceived general health scores of the patients treated with paliperidone palmitate were significantly higher than those of the patients treated with SGAs (P<0.001) • For QoL, the General Health Perception subscale values were statistically significantly lower in the patients taking second-generation oral antipsychotics compared with the patients taking paliperidone palmitate (P<0.001)

ADL, Activities of Daily Living; CGI-I, Clinical Global Impression-Improvement; FGA, First Generation Antipsychotic; GAS, Goal Attainment Scaling; HRQoL, Health-Related Quality of Life; LAI, Long-Acting Injectable; MCS, Mental Component Score; OR, Odds Ratio; PCS, Physical Component Score; PETiT, Personal Evaluation of Transitions in Treatment; PSP, Personal Social Performance; QoL, Quality of Life; RR, Relative Risk; SD, Standard Deviation; SGA, Second Generation Antipsychotic; SF-12, 12-Item Short Form Survey; SF-36, 36-Item Short Form Survey.

adherence).[28] Bianchini et al reported that the three SGAs were significantly more effective than haloperidol (overall P<0.001) and showed better efficacy than haloperidol in insight improvement.[28] However, no difference was reported among the different SGAs. An association between insight improvement and psychopathology was also detected (Table 3).

Adherence to Oral Antipsychotics

Two studies assessed medication adherence with SGAs for schizophrenia (Table 4).[27,49] Barbosa et al evaluated the effectiveness of olanzapine and risperidone in patients with schizophrenia; olanzapine had a significantly longer time until treatment discontinuation (P=0.021), and risperidone had a higher discontinuation rate (P=0.021).[27] Sağlam Aykut et al identified that medication adherence and general health scores of patients treated with paliperidone palmitate were significantly higher (P<0.001) than those with SGAs, and the medication adverse effects on the patient's daily performance were substantially lower.[49]

Impact of Product Switching of Oral Antipsychotics

Five studies identified the effect of product switching with OATs.[18,19,25,33,34] Awad et al reported improvements in adherence-related attitude and psychosocial functioning in patients who switched to lurasidone from quetiapine, risperidone, aripiprazole, or ziprasidone.[19] An experimental study that evaluated the efficacy, tolerability, and safety of switching from oral olanzapine to risperidone LAI reported significant changes from baseline to study end in the positive and negative syndrome scale (PANSS), the Clinical Global Impression-Severity scale, and Global Assessment of Functioning endpoint efficacy outcomes among 96 patients switching from oral olanzapine to risperidone LAI (P<0.0001).[25] Hatta et al identified that augmentation with olanzapine would be superior to switching to olanzapine among early nonresponders to risperidone, and augmentation with risperidone would be superior to switching to risperidone among early nonresponders to olanzapine.[33] Hong et al found that patients switching to olanzapine were less likely to experience relapse (HR: 3.43, 95% CI: 1.43 to 8.26) and extrapyramidal symptoms (Odds ratio [OR]: 4.02, 95% CI: 1.49 to 10.89) and amenorrhea/galactorrhea (OR: 8.99, 95% CI: 2.30 to 35.13).[34] Additional details on product switching can be found in Table 4.

Evidence from HTA Databases

Additionally, we reviewed HTA reports on the selected OATs (Supplementary Table 4). Of the 10 HTA articles identified,[66–75] seven studied adverse events,[66,68–71,74,75] six investigated efficacy,[66,68–71,74] four examined cost-effectiveness,[69,70,72,75] and one each studied effectiveness[67] and humanistic outcomes of OATs,[73] respectively.

Adverse events were measured and included treatment-emergent adverse events, side effects, metabolic effects, and extrapyramidal symptoms. The most significant side effects include asthenia/ lassitude/fatigue, somnolence/sedation, paresthesia, change in visual accommodation, increased salivation, diarrhea, and weight loss.[66,68–71,74,75] Efficacy was measured with regards to an improvement in PANSS and related scores,[66,68–71,74] while cost-effectiveness was measured in cost per QALY,[69,70,72,75] and humanistic outcomes included improvement in QoL.[73] Lurasidone significantly improved PANSS, Young Mania Rating Scale, and Montgomery-Asberg Depression Rating Scale scores[66,71] and considerably enhanced cost savings.[72] The assessments suggested that amisulpride was associated with a more significant side effect burden, including cardiac side effects.[70] Moreover, economic analyses indicated that in the shorter term, amisulpride augmentation has the potential to be cost-effective.[69,70] Overall, the findings showed that atypical antipsychotic drugs have a favorable efficacy profile, and amisulpride was more effective than other options for treating schizophrenia.[67,69,70]

Discussion

Understanding the evolving treatment landscape for schizophrenia is critical for optimal patient management. Our systematic review synthesizes this landscape by scrutinizing several important outcome measures globally, including drug effectiveness, economic considerations, humanistic and behavioral outcomes, medication adherence, and switching of OATs. Overall, the evidence from our systematic review of the ex-US OAT studies was consistent with those reported recently in the US.[17] In addition to identifying the economic impact of OATs on schizophrenia, our review also highlighted a gap in studies assessing humanistic and behavioral outcomes associated with OATs. This finding

Table 4 Adherence and Product Switching Associated with Oral Antipsychotic Treatments

Sr. No.	Author Year, Country	Study Design	Drugs	Study Objective	Sample Size	Outcomes Measures	Main Findings
1	Awad 2014, Canada[18]	RCT	Olanzapine; Others: Quetiapine, Risperidone, Aripiprazole, Ziprasidone	This analysis evaluated HRQoL changes among patients with schizophrenia who switched from their current antipsychotic to lurasidone	235	PETiT scores, SF-36 scores	• Significant improvements in PETiT total scores were observed in patients switched from quetiapine, risperidone, aripiprazole, and ziprasidone (all P<0.03) but not olanzapine (P=0.893) • Improvements in the SF-12 MCS score were observed for all patients (mean change [SD]: 3.7 [11.5], P<0.001) and for those switched from quetiapine or aripiprazole (both P<0.03) • The SF-12 PCS scores remained comparable to those at baseline in all patient groups
2	Awad 2016, Canada[19]	RCT	Lurasidone; Other: Quetiapine, Risperidone, Ziprasidone, Aripiprazole	This analysis examines long-term changes in HRQoL among patients with schizophrenia who switched to lurasidone from other antipsychotics.	144	PETiT scores, SF-36 scores	• Patients who switched from quetiapine and aripiprazole showed significant improvement in PETiT total score and adherence-related attitude at extension baseline and extension endpoint. • Patients who switched from quetiapine, risperidone, aripiprazole, or ziprasidone showed significant improvement in MCS scores from baseline to extension endpoint. • Responders to lurasidone demonstrated greater improvement in PETiT total, psychosocial functioning, and MCS scores at extension baseline than non-responders
3	Rosa 2012, Portugal*[25]	Non-Randomized Experimental Study	Olanzapine; Other: Risperidone	To evaluate the efficacy, tolerability, and safety of switching from oral olanzapine to risperidone LAI.	96	PANSS Score, Adverse Events	• Significant endpoint efficacy changes vs baseline were observed for PANSS, CGI-S, and GAF (all P<0.0001) • PANSS total score improvement was >20% for 65.6% of patients and >50% for 31.3% of patients • TEAEs were similar in the 1- and 3-week taper groups (40.0% and 46.5%, respectively). • TEAEs were generally mild (34.5%) or moderate (49.0%) in intensity

4	Barbosa 2021, Brazil[27]	Cohort Study	Olanzapine, Risperidone	To evaluate the effectiveness of olanzapine and risperidone in the treatment of patients with schizophrenia in the real world and assess risk factors for their discontinuation through a national non-concurrent cohort with 16 years of follow-up	3416	Medication Adherence	• Olanzapine had a longer time until discontinuation of treatment (P=0.021), and risperidone had a higher risk of discontinuation (P=0.021) • Among patients persistent for at least 24 months, there was no statistically significant difference
5	Hatta 2014, Japan[33]	Cohort Study	Olanzapine; Others: Risperidone	Examining whether augmentation with olanzapine would be superior to switching to olanzapine among early non-responders to risperidone and whether augmentation with risperidone would be superior to switching to risperidone among early non-responders to olanzapine	156	Treatment Discontinuation	• Time to treatment discontinuation for any cause was significantly shorter in olanzapine switched to risperidone group (56.1 days; 95% CI: 40.7 to 71.5) than in the early responders to olanzapine group (74.9 days; 95% CI: 68. To 81.3; P=0.008) • It was not significantly shorter in the olanzapine+risperidone group (64.6 days: 95% CI: 49.6 to 79.6) than in the early responders to the olanzapine group (P=0.20)
6	Hong 2012, UK[34]	Cohort Study	Olanzapine; Other: Risperidone	This study aimed to examine the impact of switching from olanzapine to risperidone and vice versa on clinical status and tolerability outcomes in outpatients with schizophrenia in a naturalistic setting	17,000	Relapse and Side Effects	• Patients switching to olanzapine were significantly less likely to experience: ○ Relapse (HR: 3.43; 95% CI: 1.43 to 8.26) ○ Extrapyramidal symptoms (OR: 4.02; 95% CI: 1.49 to 10.89) ○ Amenorrhea/galactorrhea (OR: 8.99; 95% CI: 2.30 to 35.13) • No significant difference in weight change was found between the two groups
7	Sağlam Aykut 2019, Turkey[49]	Cross-Sectional Study	Paliperidone; Other Antipsychotics	To compare paliperidone palmitate and the second-generation oral antipsychotic drugs used to treat patients with schizophrenia in terms of medication adherence, side effects, and quality of life	84	Medication Adherence	• The medication adherence and perceived general health scores of the patients treated with paliperidone palmitate were significantly higher than those of the patients treated with SGAs (P<0.001)

Note: *Patients with schizophrenia and other schizoaffective disorders.

Abbreviations: CGI-S, Clinical Global Impression-Severity; CI, Confidence Interval; GAF, Global Assessment of Functioning; HR, Hazard Ratio; HRQoL, Health-Related Quality of Life; LAI, Long-Acting Injectable; MCS, Mental Component Score; OR, Odds Ratio; PANSS, Positive and Negative Syndrome Scale; PCS, Physical Component Score; PETiT, Personal Evaluation of Transitions in Treatment; SD, Standard Deviation; SF-12, 12-Item Short Form Survey; TEAE, Treatment-Emergent Adverse Effects.

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underscores the need for assessing the humanistic burden related to schizophrenia not only on the patients but also on their family members or other caregivers. Humanistic outcomes may help explain the high prevalence of treatment discontinuation or medication non-adherence frequently observed across studies. Therefore, an opportunity exists to generate evidence-based data to assist physicians, researchers, and payers in directing appropriate treatment for schizophrenia for effective disease management.

Our review observed that the real-world effectiveness of therapeutic options for schizophrenia is a crucial parameter that determines the design of treatment regimens and choices. Any potential treatment/drug is appraised by its ability to diminish the clinical, economic, and humanistic burdens of the disease. According to the 2018 International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Special Task Force report, several value-based factors, including disease severity, insurance value, and value of hope, are being overlooked in drug value assessments, causing inaccurate resource utilization appraisals.[76] The report has listed 12 value elements to consider when reporting drug value assessments.[76] Many of these elements are directly associated with a treatment modality's economic and humanistic outcomes. Our review could identify a few reports concerning economic and humanistic results and minimal regarding behavioral outcomes. Given the burden of schizophrenia on patients and caregivers in terms of productivity loss, most of these economic studies have not explicitly provided the impact of treatments on indirect costs. Another challenge with economic evaluations is to account for switching among OATs, especially with treatment differences in adverse events, adherence, and persistence. Furthermore, only one study reported the association of three OATs with symptom clusters and insight.[28] Some patients with schizophrenia exhibit problematic behaviors such as violence or suicidal behavior, and there is a need to evaluate behavioral outcomes in these patients, which will help improve intervention strategies and reduce recurrence. Exploring these outcome measures in value assessments open a window of opportunity to demonstrate greater incremental value for OATs and/or any new drug.

It is well known that in patients with schizophrenia, inadequate medication adherence is a significant barrier to optimal symptom control despite adequate drug efficacy.[77] An interruption of therapy by the patient can also trigger relapses and subsequent hospitalizations.[78–80] Our review identified seven observational studies reporting treatment adherence (n=2) and product switching (n=5). Olanzapine was reported to have higher treatment adherence with a higher continuation rate (50.8% vs 27.3% for asenapine)[48] and longer time until treatment discontinuation (p=0.021 vs risperidone),[39] while risperidone exhibited an increased risk of discontinuation (p=0.021 vs olanzapine).[39] In another study, asenapine was reported to have high discontinuation due to bitter taste and dosing method burden.[48] Other behavioral and/or humanistic outcomes could contribute to low adherence and high discontinuation of OAT; however, these measures remain primarily unexplored for various OATs, forming an evidence gap in this landscape. Treatment adherence has been associated with reduced relapse event rate, healthcare utilization, and costs, leading to significant savings for commercial payers.[81] A meta-analysis reported that LAIs significantly lower hospitalization rates than OATs (risk/reward ratio: 0.85, 95% CI: 0.78 to 0.93, P<0.001).[82] Although there is evidence of poor adherence to oral antipsychotics, many clinicians decline the use of LAI antipsychotics in the early stages of schizophrenia, assuming patients would favor oral antipsychotics,[83] and that LAIs are generally administered to very sick and difficult-to-handle patients.[81] Our study however, did not explore the underlying parameters leading to OAT medication adherence/non-adherence; this should be a potential area of research for clinicians in the future.

Limitations

Our systematic review should be interpreted relative to certain limitations. First, the studies included in this systematic review were considerably varied regarding study medications, patient populations, and study outcomes. Hence, the degree of coverage of individual themes and measures and extrapolation of one finding to another should be interpreted cautiously. Second, considering this heterogeneity of available evidence for OATs, a formal quality assessment utilizing a standardized tool like the Cochrane Collaboration's tool[84] for assessing bias risk could not be performed, but only a qualitative appraisal was conducted. Third, grey literature was not considered for our review. Even though grey literature does not fall into the inclusion criteria to maintain quality standards, first-person descriptions regarding humanistic, caregiver, and familial burdens of schizophrenia are being overlooked. This can increase the risk of reporting bias in the study. Fourth, reports specifying drug-related mortality, lifelong disability, and severe adverse events were not

considered in our review. These determinants could influence the economic burden of the disease. Fifth, the effect of OATs on schizophrenia was not studied on the elderly or geriatric population, and this forms a significant gap in the present-day research (indicated by the bibliometric analysis), especially in a scenario where current evidence points out the fact that there is a high prevalence of schizophrenia at the age of 60 years.[85]

Conclusions

Our analysis identified that a single antipsychotic medication or dosage is not best for all patients. Therefore, making decisions about changing a patient's treatment, including the choice of antipsychotic medication and dose, requires careful consideration and ongoing, shared, collaborative decision-making by the clinician-patient dyad. With scarce evidence on humanistic and behavioral outcomes, developing relevant research questions and implementing well-designed studies that address such impending gaps is the hour's need. Developing economic and budget models congruent with the ISPOR value flower elements could lead to better global resource allocations and strategies for effective disease management but requires greater evidence, including humanistic outcomes. A comprehensive approach to current treatment options utilizing outcome measures encompassing clinical, economic, behavioral, and humanistic factors is needed to fill the much-needed gap of disease awareness, impact on patient QoL, and comparative treatment value.

Abbreviations

APA, American Psychological Association; CI, confidence interval; CINAHL, Cumulative Index of Nursing and Allied Health Literature; DALY, disability-adjusted life years; ER, extended-release; HR, hazard ratio; HTA, Health Technology Assessment; INAHTA, HTA Database; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; LAI, long-acting injectables; NICE, National Institute for Health and Care Excellence; NIMH, National Institute of Mental Health; OAT, oral antipsychotic treatment; OR, odds ratio; PANSS, positive and negative syndrome scale; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QALY, quality-adjusted life years; QoL, quality of life; RCT, randomized controlled trial; SGA, second-generation oral antipsychotic; US, United States.

Data Sharing Statement

Full access to study data is with the corresponding author.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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