 AMCP

Learning Objectives

1. Identify the regional variances in prevalence, disease burden, health care utilization, and unmet needs for schizophrenia.
2. Distinguish the new and emerging therapies for schizophrenia, including clinical efficacy, safety, and adherence considerations.
3. Discuss managed care opportunities to support patients with schizophrenia to improve access, adherence, and health outcomes.

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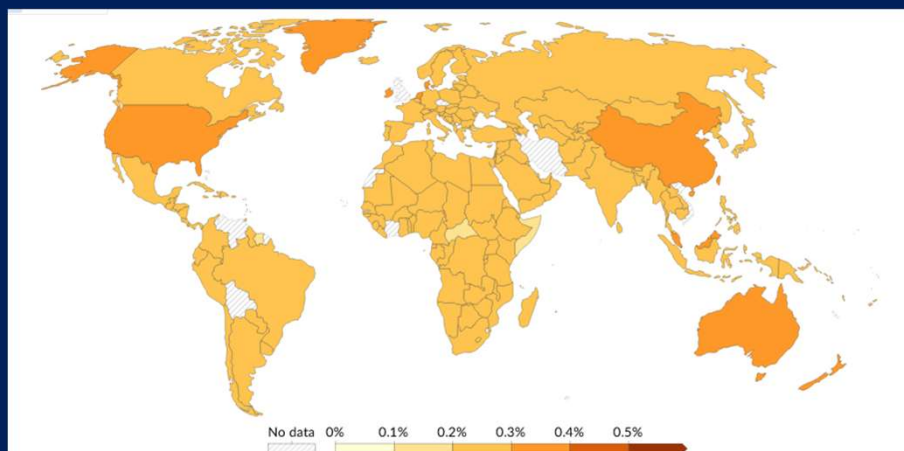


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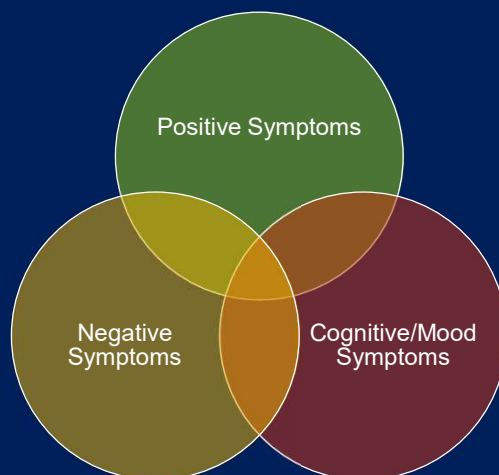
Schizophrenia

Schizophrenia Prevalence-2021



IHME, Global Burden of Disease (2024) – with major processing by Our World in Data; Creative Common License

Schizophrenia



Grube BS, et al. Schizophre Res 1998;31:113-20.
Shafer A, et al. J Psychiatr Res 2019;115:113-20.

Schizophrenia

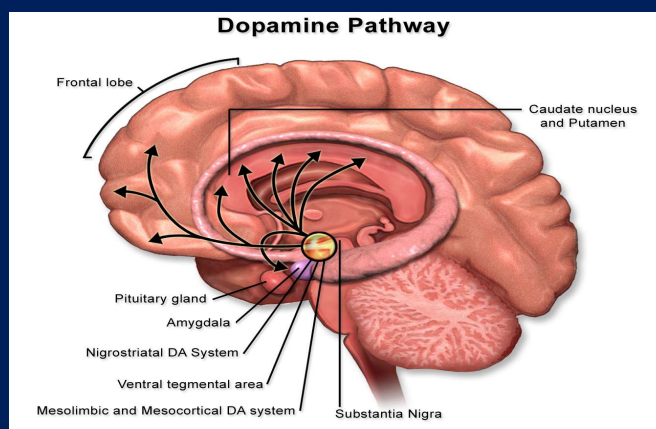
- Life-changing consequences
 - Social isolation
 - Stigma
 - Reduced prospects of finding a partner
- Reduced life expectancy (13-15 years)
 - Poor dietary habits
 - Weight gain
 - Smoking
 - Comorbid substance use

Jauhar S, et al. Lancet 2022;399:473-86.
Huorthøj C, et al. Lancet Psychiatry 2017;4:295-301.

Patient Testimonial Video



Dopamine Pathways and Beyond...



BruceBlaus, CC BY-SA 4.0 <<https://creativecommons.org/licenses/by-sa/4.0/>>, via Wikimedia Commons.

Pharmacotherapy of Schizophrenia

APA Schizophrenia Treatment Guidelines

- Pharmacotherapy:
 - Patients with schizophrenia should be treated with an antipsychotic medication; monitored for effectiveness and side effects
 - Evidence-based ranking of FGAs and SGAs- not possible
 - Patient-centered care, past responses, adverse effects, co-morbidities, drug-drug interactions, available formulations, pharmacokinetic considerations, cost

Keepers GA, Fochtman LJ, Anzia JM, et al.
The American Psychiatric Association Practice Guideline
For the Treatment of Patients with Schizophrenia; Am J Psych;2020;177:868-872.

Antipsychotics

- First Generation
 - Chlorpromazine
 - Fluphenazine
 - Haloperidol
 - Loxapine
 - Perphenazine
 - Pimozide
 - Thioridazine
 - Thiothixene
 - Trifluoperazine
- Second Generation
 - Clozapine
 - Olanzapine
 - Risperidone
 - Paliperidone
 - Quetiapine
 - Aripiprazole
 - Ziprasidone
 - Iloperidone
 - Asenapine
 - Lurasidone
 - Brexpiprazole
 - Cariprazine
 - Pimavanserin*
 - Lumateperone

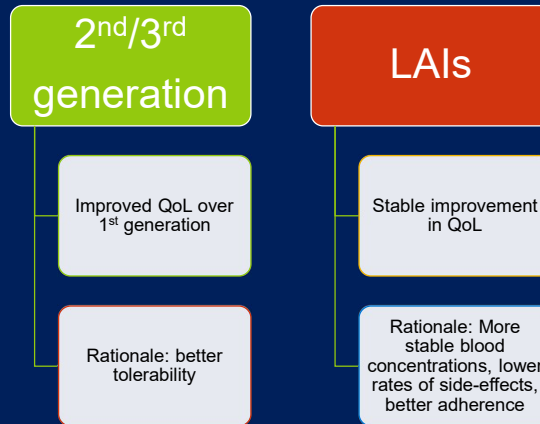
*not currently FDA-indicated for Schizophrenia

Long-Acting Injectable Antipsychotics

- Haloperidol Decanoate
- Fluphenazine Decanoate
- Risperidone Microspheres
- Olanzapine Pamoate
- Paliperidone Palmitate
- Aripiprazole Monohydrate
- Aripiprazole Lauroxil

Quality of Life: Antipsychotic treatment

Evidence base: QoL often a secondary outcome in studies



Sampogna G, et al. Brain Sci. 2023 Nov 10;13(11):1577.

New and Emerging Treatments

Likelihood Likert Scale



My healthcare organization utilizes Long-Acting Injectable Antipsychotic Medications as first-line treatment options for patients with schizophrenia.

- a) Most Likely
- b) Fairly Likely
- c) Likely
- d) Slightly Likely
- e) Not Likely



New/Pipeline LAI Antipsychotics



| | Risperidone Extended-Release (Uzedy®) | Risperidone Extended-Release (Risvan®) | Risperidone Extended-Release (Rykindo®) | Paliperidone Palmitate Extended-Release (Erzofri®) | TV-44749 |
|----------------------|---------------------------------------|--|---|--|---------------|
| Route | Subcutaneous | Intramuscular | Intramuscular | Intramuscular | Subcutaneous |
| Frequency | Once monthly or every other month | Once monthly | Every two weeks | Once monthly injection | Once monthly |
| Oral Dose Equivalent | 2-5/6 mg of oral risperidone | 3 or 4 mg of oral risperidone | 2-5/6 mg of oral risperidone | | |
| Notes | | | | One 351 mg dose on day one, then maintenance dose | Lack of PDSS? |

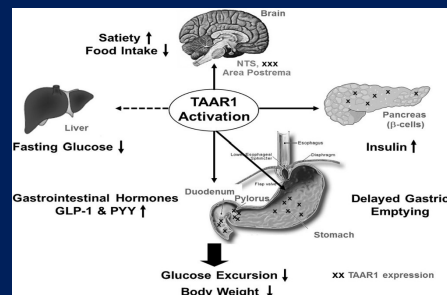
Uzedy [package insert]; Teva Neuroscience, Inc. 2024; Risvan [package insert]; Rovi Pharma Industrial Services. 2024. Rykindo [package insert]; Luye Pharmaceutical Co. 2023.; Erzofri [package insert]; Luye Pharmaceutical Co. 2024. Franzenburg KR. SOLARIS Protocol. Psych Congress 2023.

New/Pipeline Agents

| Drug/Chemical Entity | Mechanism of Action | Clinical Trial Status |
|---------------------------------|---|---|
| Ulotaront | Trace amine-associated receptor (TAAR) 1 agonist | Failed phase 3 trials |
| Ralmitaront | TAAR1 partial agonist | Failed phase 2 trials |
| Pimvanserin | 5-HT _{2A} receptor inverse agonist; 5-HT _{2C} receptor antagonist | Currently approved: Treatment of hallucinations and delusions associated with Parkinson's disease psychosis |
| Roluperidone | Antagonist at 5-HT _{2A} and sigma ₂ receptors | Complete Response Letter received: 2/27/24 |
| Iclepertin | Potent and selective glycine transporter type 1 inhibitor | Phase 3 trials |
| Luvadaxistat | Selective inhibitor with a high binding affinity to d-amino acid oxidase | Phase 2 trials |
| Xanomeline and Trospium (KarXT) | Muscarinic acetylcholine receptor agonist at M ₁ & M ₄ receptors | PDUFA date: 9/26/24 |
| TerXT; oral and LAI | Prodrugs of xanomeline and trospium | FDA 505(b)(2) |
| Emraclidine | Positive allosteric modulator that selectively acts on the M ₄ muscarinic receptor | Completing phase 2 trials |
| NBI-117568 | M ₄ selective agonist | Entering phase 2 trials |

Ulotaront

- Trace amine-associated receptor (TAAR) agonist: selectively activate trace amine receptors
- Partial agonist at 5-HT_{1a} receptors (antidepressant and antianxiety effects)
- Potentially addressing cognitive impairments (i.e., attention and memory deficits)



https://commons.wikimedia.org/wiki/File:TAAR1_organ-specific_expression_and_function.jpg
 Accessed: 8/2/24. Dedic N, et al. J Pharmacol Exp Ther 2019;371:1-14.

Other TAAR1 Partial Agonists Under Development

- RO06889450/ralmitaront
- TAAR1 full agonists: attenuate dopaminergic signaling
- Partial agonists: potentially normalize or increase dopaminergic signaling

RO6889450; Roche, Basel, Switzerland; NCT0366940; NCT04512066

Serotonin Receptor Antagonism/Inverse Agonism

- Pimvanserin
 - Potent 5-HT_{2A} receptor inverse agonist (functional antagonist) & 5-HT_{2C} receptor antagonist
 - Current research: adjunctive pimvanserin in stable outpatients with schizophrenia and predominant negative symptoms
- MIN-101/Roluperidone
 - Antagonist at 5-HT_{2A} and sigma₂ receptors
 - Phase 3 failed to meet prespecified primary outcome but did show a trend-level significance favoring roluperidone monotherapy on the primary endpoint

Pimvanserin [package insert]. Acadia Pharmaceuticals Inc; 2020.
Davidson M, et al. Am J Psychiatry 2017;174:1195-1202.

Glutamatergic Modulation

- BI 425809/Iclepertin
 - Potent and selective glycine transporter type I inhibitor
 - Demonstrated significant ($d=0.34$) improvements in cognition over 12 weeks of treatment in patients with schizophrenia (phase 2)
 - Phase 2: iclepertin added to current antipsychotic therapy and computer-based training for cognitive symptoms of schizophrenia
 - Phase 3: Add-on therapy with iclepertin are underway
- Sodium Benzoate
 - Phase 2/3 trials underway
 - TAK-831/luvadaxistat- not effective for negative symptoms but showed signal for improving cognitive symptoms

Fleischhacker WW, et al. *Lancet Psychiatry* 2021;8:191-201.
Huang CC, et al. *Neurochem Res* 2023;48:2066-76.

KarXT: Xanomeline and Trospium

Xanomeline

- Crosses BBB
- M1 receptor agonist
- M4 receptor agonist

Trospium

- Doesn't cross BBB
- M1-M5 receptor
- Antimuscarinic

- Increasing dopamine release in hippocampus and prefrontal cortex
- Decreasing dopamine release in substantia nigra, nucleus accumbens, and ventral striatum

Azargoonjahromi A. *Clin Drug Investig* 2024;44:471-93.

Other Muscarinic Agents Under Development

- CVL-231/Emraclidine
 - Positive allosteric modulator that selectively acts on the M4 muscarinic receptor
 - EMPOWER-1 and EMPOWER-2: Patients who are experiencing an acute episode of psychosis
 - EMPOWER-3: Patients who have stable symptoms

- NBI-1117568
 - M4 selective agonist
 - Successful completion of a long-term preclinical toxicity program- support safe, chronic dosing

Cerevel Therapeutics Press Release. <https://investors.cerevel.com/news-releases/news-release-details/cerevel-therapeutics-announces-positive-topline-results-cvl-231/>. Accessed: 8/2/24
 Neurocrine Biosciences, San Diego, CA, USA, NCT05545111

Xanomeline-trospium – ICER’s evidence ratings

- xanomeline-trospium versus....

| | |
|------------------|------------------------------|
| aripiprazole | • Insufficient |
| olanzapine | • Promising but inconclusive |
| risperidone | • Promising but inconclusive |
| no antipsychotic | • Promising but inconclusive |

Xanomeline-trospium – ICER’s Health Benefit Price Benchmarks

- Model assumptions (selected)
 - Population: adults with schizophrenia (not treatment-resistant)
- Xanomeline-trospium assumptions (selected)
 - Same risk of metabolic syndrome as the general population not taking antipsychotics
 - Same risk of tardive dyskinesia as second-generation antipsychotics

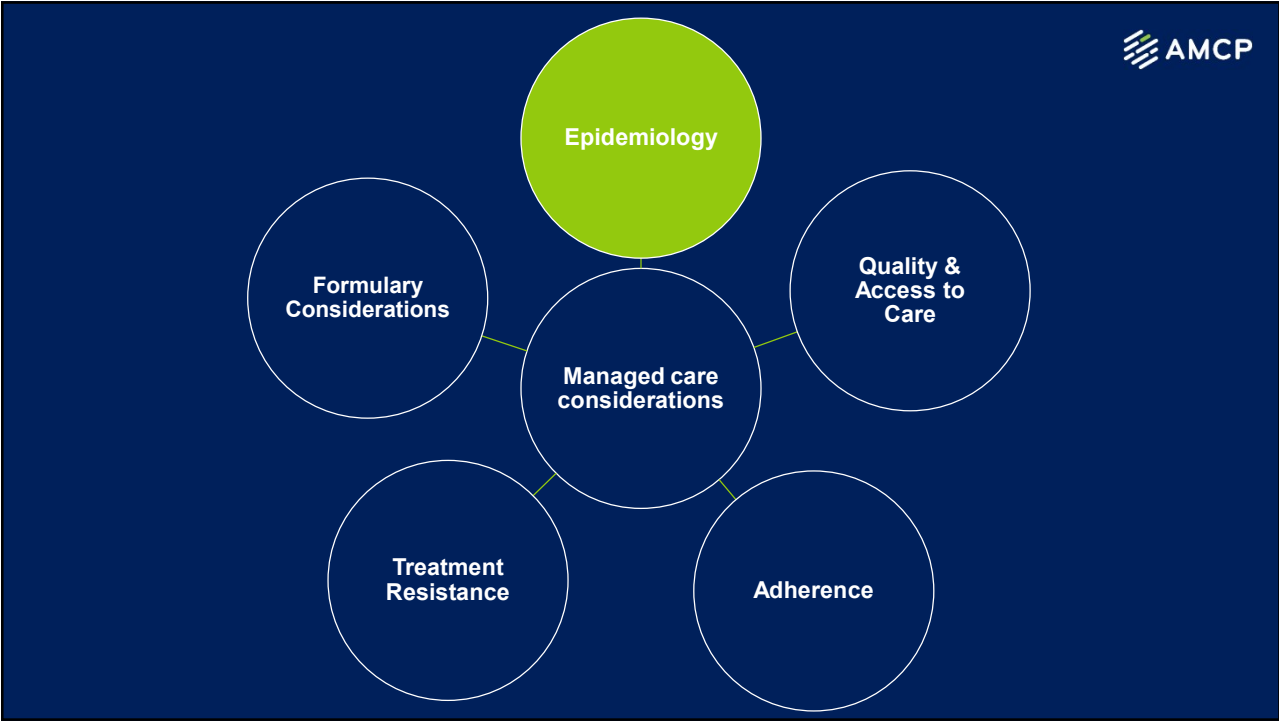
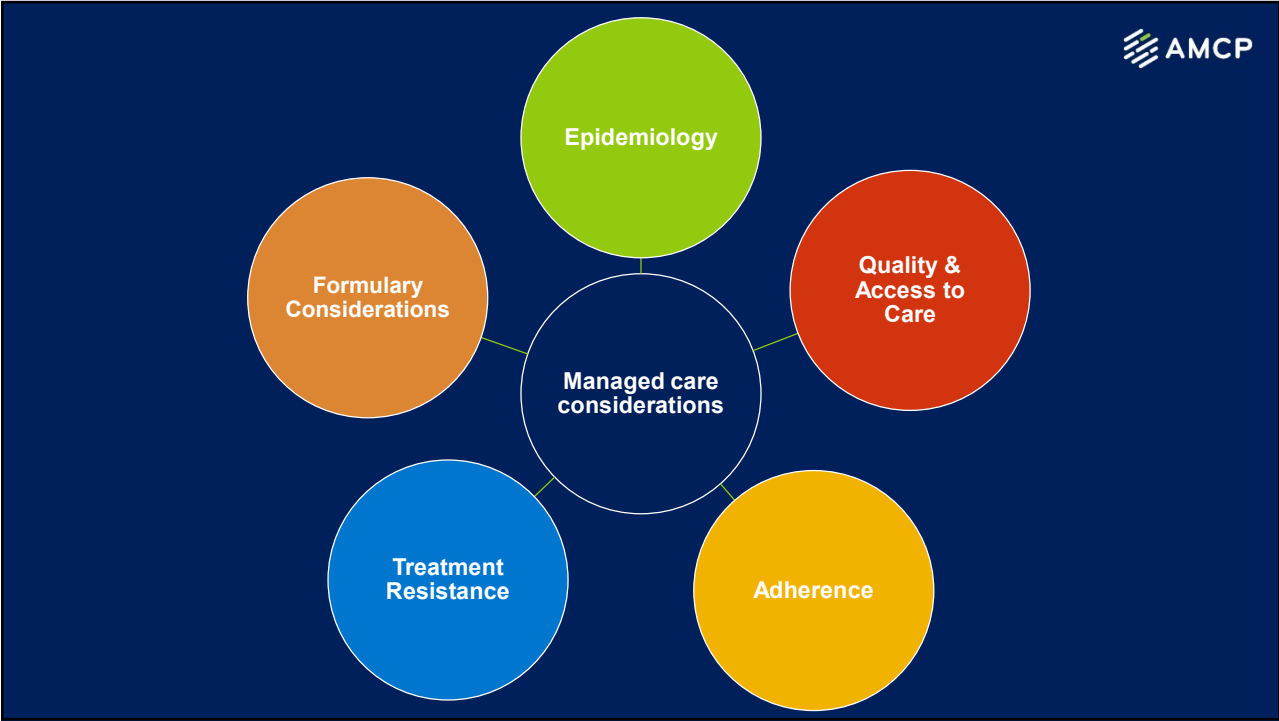
| | Annual price at \$100,000 threshold | Annual price at \$150,000 threshold |
|--------------------|-------------------------------------|-------------------------------------|
| QALy gained | \$16,000 | \$19,000 |
| evLY gained | \$16,000 | \$20,000 |

QALy: quality-adjusted life year; evLY: equal value life year

Tice JA, Whittington MD, McKenna A, Wright A, Richardson M, Pearson SD, Rind DM. KarXT for Schizophrenia: Effectiveness and Value: Evidence Report. Institute for Clinical and Economic Review, January 25, 2024. <https://icer.org/assessment/schizophrenia2024#overview>.

Managed Care Considerations





Epidemiology

Lines of Business

- Prevalence of schizophrenia higher among Medicaid recipients compared to those with commercial health plans
- Medicaid deep dive – Patel et al.; Journal of Medical Economics, 2022
 - Study design: Cross-sectional retrospective study
 - Data source: Medicaid data (2018) for adults with schizophrenia in 45 U.S. states

| Patel et al. (2022) | | | | | | | | |
|---------------------|--------------|----------|--------|-------|-------|----------|----------------|-------------------|
| | Demographics | | | Race | | | Coverage Type | |
| | N | Mean age | Female | White | Black | Hispanic | Dual coverage* | Managed care plan |
| Total U.S. | 688,437 | 48.2 | 43% | 42% | 27% | 12% | 44% | 67% |
| California | 110,528 | 46.7 | 39% | 37% | 20% | 24% | 36% | 91% |

*Includes patients with dual Medicaid and Medicare eligibility

Finnerty et al. *Schizophrenia (Heidelb)*. 2024;10(1):68.; Patel et al. *J Med Econ*. 2022;51(1):792-807.

Epidemiology

Annual Healthcare Utilization & Spend

| Patel et al. (2022) | | | | | | |
|---------------------|------------------------|-------------|---------------------|-----------------------------|--------------|---------------|
| | Healthcare Utilization | | | Mean Healthcare Cost (PPPY) | | |
| | ≥1 inpatient admission | ≥1 ED visit | ≥1 outpatient visit | Total healthcare cost | Medical cost | Pharmacy cost |
| Total U.S. | 34% | 45% | 86% | \$32,920 | \$25,908 | \$7,012 |
| California | 32% | 37% | 84% | \$36,187 | \$19,587 | \$16,599 |

ED = emergency department, PPPY = per person per year

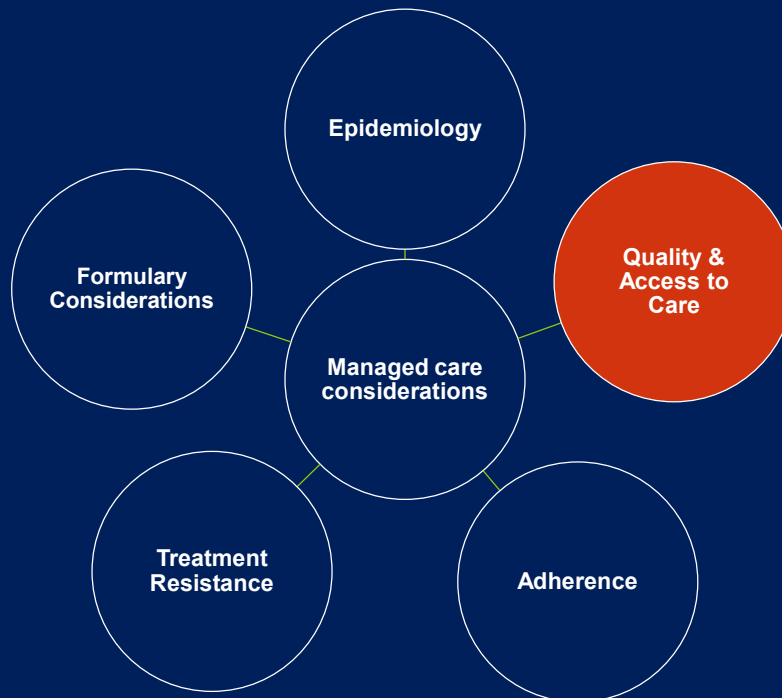
Patel et al. *J Med Econ*. 2022;51(1):792-807.

Epidemiology

Additional Economic Impact of Schizophrenia

- Direct non-healthcare costs
 - Law enforcement
 - Social Security Disability Income (SSDI) & Supplemental Security Income (SSI)
 - Homeless shelters
 - Research & training
- Indirect costs
 - Caregiving
 - Premature mortality
 - Unemployment
 - Productivity loss

Kadakia A, et al. *J Clin Psychiatry*. 2022;83(6):22m14458.



Quality

Readmission rates & follow-up care

| Patel et al. (2022) | | | | |
|---------------------|--------------------------------------|---------------------------------------|---|----------------------------------|
| Quality Measures | Readmission | | Follow-up care | |
| | Inpatient readmission within 7 days* | Inpatient readmission within 10 days* | Antipsychotic dispensed within 30 days* | Outpatient visit within 30 days* |
| Total U.S. | 8% | 12% | 14% | 22% |
| California | 9% | 12% | 15% | 17% |

*Data reported for patients with ≥ 1 all-cause inpatient admission

Patel et al. *J Med Econ.* 2022;51(1):792-807.

Access to care

Challenges

Geographical location

- Mean number of pharmacies per county in the U.S.
 - Metropolitan areas: 78.21
 - Rural areas: 1.72
- California: 43.1% of counties had ≤ 1.38 pharmacies per 10,000 residents

Healthcare literacy

- ~15% of California residents aged ≥ 25 years estimated to have never achieved high-school diploma level of education

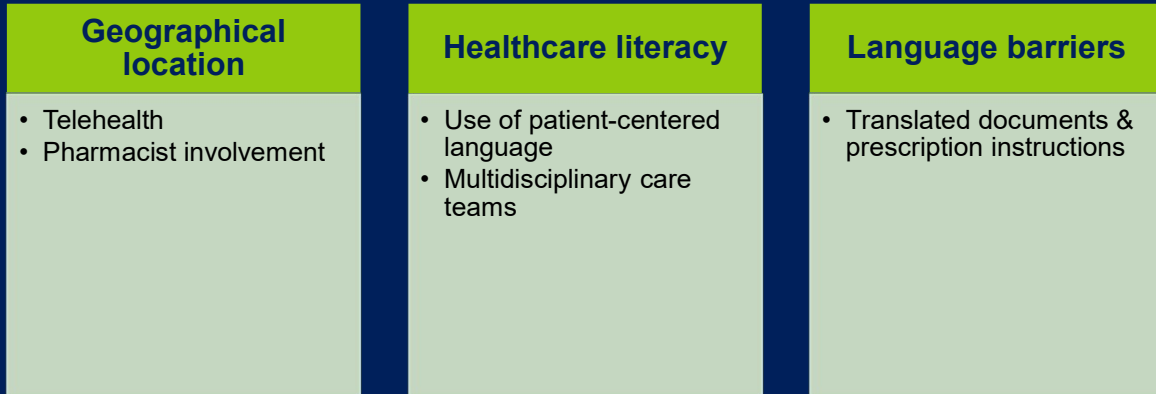
Language barriers

- ~44% of California residents aged ≥ 5 years estimated to speak a language other than English at home

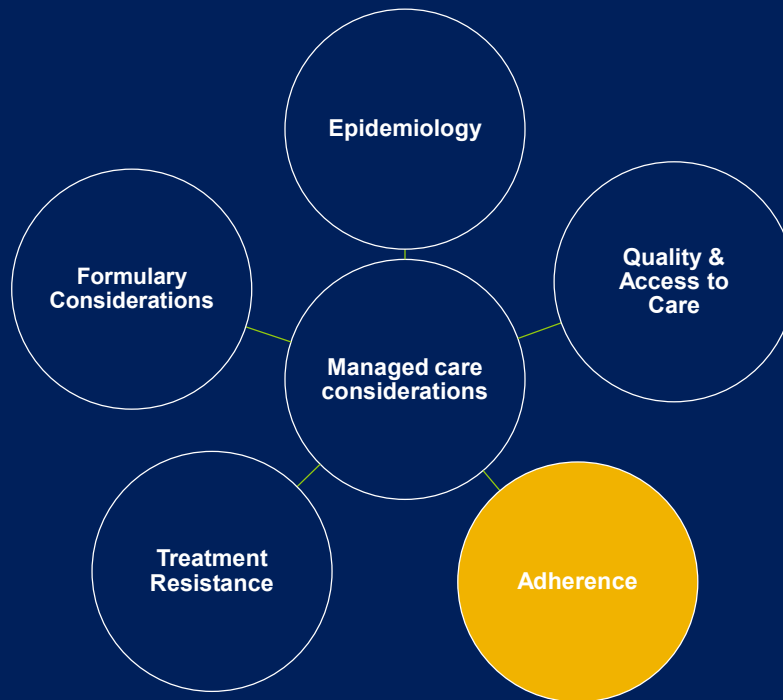
United States Census Bureau; Berenbrok et al. *J Am Pharm Assoc* (2003). 2022;62(6):1816-1822.e2.

Access to care

Opportunities



Roach et al. *J Manage Care Spec Pharm.* 2021;27(10-a Suppl):S2-S13.



Adherence

Overview

Prevalence varies, but some literature suggests >70% of patients with schizophrenia experience non-adherence

Risk factors for non-adherence

- Poor insight into disease
- Lack of social support
- Drug ineffectiveness
- Drug-related adverse events

Healthcare impact of non-adherence

- Higher healthcare utilization (e.g., ED visits, inpatient admission)
- Increase in healthcare spend by ~\$20,700 per person per year

Desai et al. *J Manag Care Spec Pharm.* 2019;25(1):37-46.; Acosta et al. *World J Psychiatry.* 2012;2(5):74-82.; Pilon et al. *J Manag Care Spec Pharm.* 2021;27(7):904-914.

Adherence

Adherence rates among U.S. Medicaid population

| Patel et al. (2022) | | | | |
|---------------------|-----------------------|------------------------|--|-----------------|
| | Any antipsychotic use | Oral antipsychotic use | Long-acting injectable antipsychotic use | Adherence rate* |
| Total U.S. | 51% | 39% | 13% | 56% |
| California | 58% | 46% | 12% | 58% |

*Adherence defined as proportion of days covered \geq 80%

Patel et al. *J Med Econ.* 2022;51(1):792-807.

Adherence

Strategies for improvement

- Shared decision making
- “Whole Person” approach
- Gradual dose titrations
- Comorbidity management
- Multidisciplinary care
- Long-acting injectable antipsychotics (LAI)

Wander. *Am J Manag Care.* 2020;26(3 Suppl):S62-S68.

Adherence

Strategies for improvement

- Shared decision making
- “Whole Person” approach
- Gradual dose titrations
- Comorbidity management
- Multidisciplinary care
- Long-acting injectable antipsychotics (LAI)

Wander. *Am J Manag Care.* 2020;26(3 Suppl):S62-S68.

Adherence

Long-acting injectable antipsychotics (LAIs)

- American Psychiatric Association suggests LAI use in patients who prefer this modality or in patients with history of nonadherence (level 2B)
- LAI deep dive – Lin et al.; CNS Drugs, 2021.
 - Study design: Systematic review and meta-analysis of 25 studies
 - Study inclusion criteria (selected): adults with schizophrenia
 - Patients initiated on a LAI were 89% more likely to be adherent to their medication compared to those initiated on an oral antipsychotic (Odds ratio [OR]: 1.89, 95% confidence interval [95% CI]: 1.52 to 2.35)
 - LAIs were associated with higher pharmacy costs that were mostly offset by lower medical costs (driven by decreased hospitalizations)

Keepers et al. *Am J Psychiatry*. 2020;177(9):868-872.; Lin et al. *CNS Drugs*. 2021;35(5):469-481.

Adherence

Long-acting injectable antipsychotics (LAIs)

Opportunities

- May lead to improved adherence
- Associated with lower medical costs
- Real-world data supports effectiveness and safety

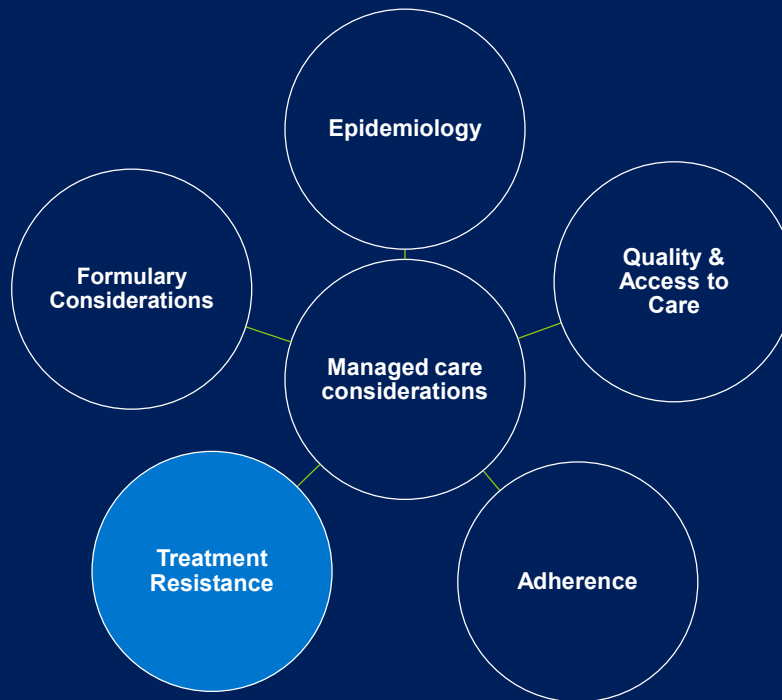
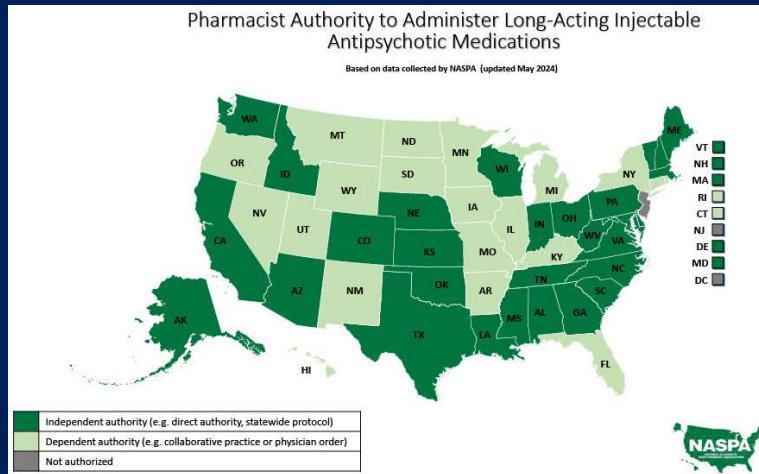
Challenges

- Associated with higher pharmacy costs
- May lead to less points of contact with patient
- Potential for waste
- Accessibility

Keepers et al. *Am J Psychiatry*. 2020;177(9):868-872.

Adherence

Long-acting injectable antipsychotics (LAIs)



Treatment resistance

Overview

Prevalence of treatment resistance

- Estimated to affect up to 30% of patients with schizophrenia

Predictors of treatment resistance

- Young age of onset
- Presence of negative symptoms
- Rural upbringing

Impact of treatment resistance

- Reduced quality of life
- Increased rates of non-adherence
- Increased risk of suicidal behavior

Wander. *Am J Manag Care.* 2020;26(3 Suppl):S62-S68.; Smart et al. *Psychol Med.* 2021;51(1):44-53.

Treatment resistance

Role of & barriers associated with clozapine

- American Psychiatric Association recommends that patients with treatment-resistant schizophrenia be treated with clozapine (level 1B)
- Barriers associated with clozapine utilization:

Frequency of monitoring

Side effect profile

Clinician unfamiliarity

Adherence

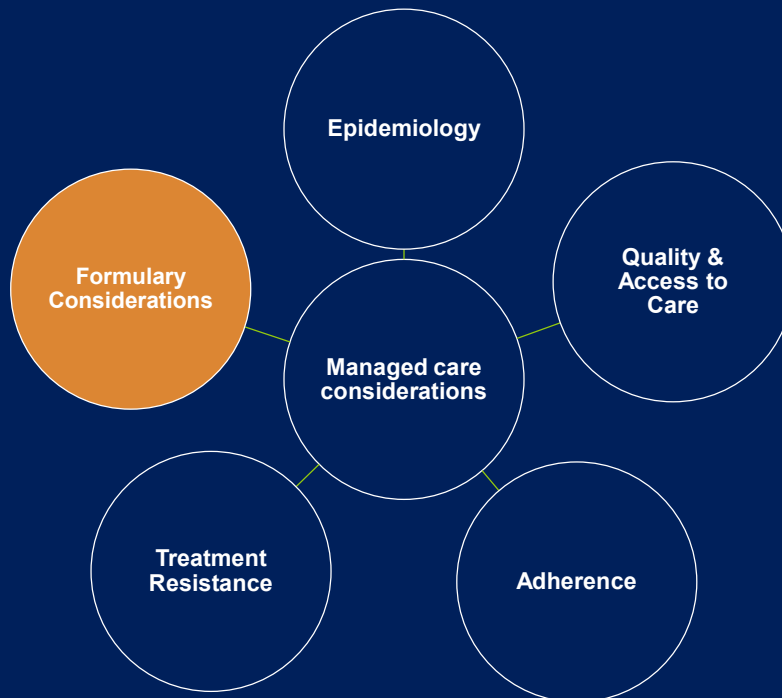
Healthcare resources

Keepers et al. *Am J Psychiatry.* 2020;177(9):868-872.; Farooq et al. *BJPsych Bull.* 2019;43(1):8-16.

Treatment resistance

Strategies for addressing barriers to clozapine

- Increased provider and patient education
- Point of care laboratory testing
- Multidisciplinary care
- REMS re-evaluation (pending November 2024)



Formulary Considerations

Professional Guidance

- No algorithm-like approach to therapy
 - Differs from other disease states (e.g., heart failure, diabetes)
 - Few exceptions with clear place in therapy (e.g., clozapine)
- Limitations with comparative effectiveness data
 - Often based on indirect comparisons
 - Patient-specific evaluation needed to select medication

Formulary Considerations

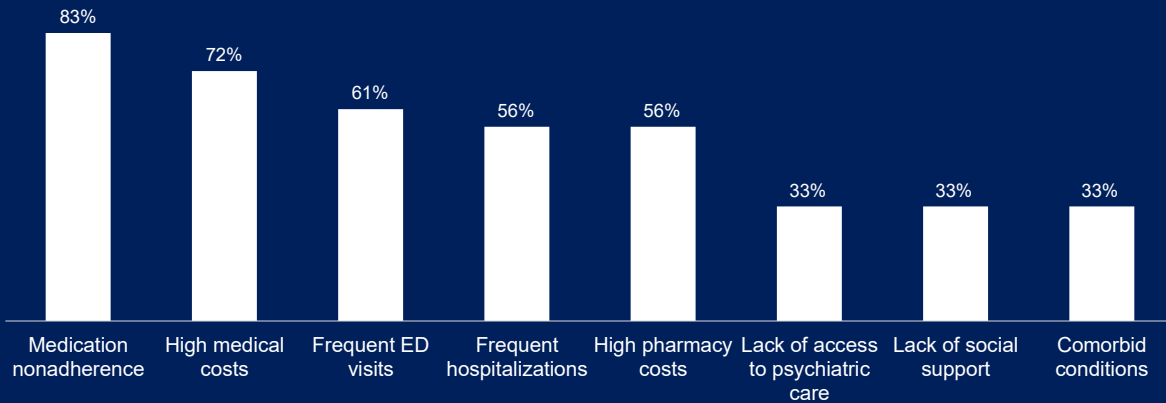
Perspectives from formulary decision makers

- Perspectives from formulary decision makers deep dive – Roach et al., *Journal of Managed Care Pharmacy*, 2021.
 - Study design: Observational study using interviews and web-based surveys
 - Study objective: elicit challenges and best practices in schizophrenia population health management
 - Data source: 18 physicians and pharmacists representing >104 million covered lives

Formulary Considerations

Perspectives from formulary decision makers

Top Challenges Identified in Schizophrenia Population Health Management

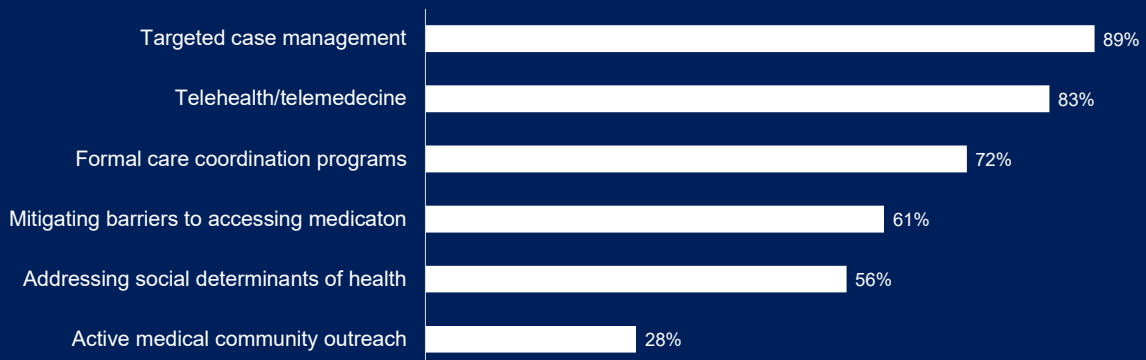


Roach M, et al. *J Manag Care Spec Pharm.* 2021;27(10-a):S2-S13

Formulary Considerations

Perspectives from formulary decision makers

Perceived Effectiveness of Strategies to Improve Outcomes in Patients With Schizophrenia



Roach M, et al. *J Manag Care Spec Pharm.* 2021;27(10-a):S2-S13

Formulary Considerations

Recommendations from formulary decision makers

Reduce hospitalizations and ED visits

Increase care coordination efforts

Implement multidisciplinary care teams

Encourage provider collaboration

Improve medication adherence

Remove barriers to treatment options (e.g., prior authorizations)

Decrease out-of-pocket costs

Make all treatment options available on formularies

Address social determinants of health

Increase patient outreach and follow-up

Implement community-based care

Employ peer specialists

Roach M, et al. *J Manag Care Spec Pharm.* 2021;27(10-a):S2-S13

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Kaiser Permanente**

Madeleine Ciobanu, PharmD, BCPS is a Pharmacist Evidence Analyst & Strategist at Kaiser Permanente. Her responsibilities include producing drug monographs for national formulary decision-making, contributing to the pharmaceutical pipeline report and forecast, and performing evidence analyses to support physician groups and other committees.

Dr. Ciobanu is a Board Certified Pharmacotherapy Specialist. Dr. Ciobanu received her Bachelor of Science degree in Biochemistry and Cellular Biology from the University of California, San Diego and Doctor of Pharmacy degree from the University of New England College of Pharmacy in Portland, Maine. Subsequently, she completed a PGY1 Pharmacy Practice Residency with the Massachusetts State Office for Pharmacy Services/CompleteRx and a PGY2 National Medication Use Safety & Policy Residency with Kaiser Permanente in Downey, California.

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