

PRELIMINARY DRAFT

**Leveraging Analytics to
Overcome Barriers in Evidence-
Based Mental Health Care:
Clozapine**

Draft compendium

Preliminary and non-exhaustive

Content

- I. Approach and emerging insights**
- II. Compilation of analytic outputs
- II. Current insights from patient journey analytics

Emerging insights: Leveraging Analytics to Overcome Barriers to Evidence-Based Mental Health Care: Clozapine

Clozapine is the most effective antipsychotic medication for treatment-resistant schizophrenia, but it has been historically underutilized in the US

- Despite having a robust evidence-base of effectiveness, Clozapine is prescribed for a fraction of US patients who may benefit
- Underutilization of Clozapine has persisted since first reported in Medicaid populations between 2001 and 2005
- By using a novel data source and sharing the data in an open-access way, we hope to bring new, actionable insights to help increase scale of this evidence-based treatment and improve patient outcomes

While average number of patients with Clozapine Rx across the U.S. has remained flat between 2015 and 2019, there is some notable variation across states

- Proportion of Clozapine in both prescribers and patients of antipsychotics is growing in 16 US states, but this is offset by decline in the remaining 35
- Clozapine prescription varied up to 10x across states in 2019, and the relative level of prescription was similar between 2005 and 2019
- Previous research has linked Clozapine underutilization with various barriers in prescribing, accessing and maintaining Clozapine (e.g. limited prescriber exposure to Clozapine, burden of blood monitoring, lack of resources & infrastructure to manage Clozapine, etc)
- Some states with highest Clozapine prescription (e.g. MA, MD) have conducted programs that help with prescriber education and patient experience

Among various tested factors investigated in the literature, proportion of prescribers writing Clozapine Rx is one of the most impactful in increasing Clozapine adoption

- State racial makeup, urbanization, proportion of prescribers writing Clozapine Rx, and Medicaid spending per capita are shown to be correlated with proportion of patients with Clozapine Rx, with proportion of prescribers writing Clozapine Rx showing the strongest and most actionable link
- Growth in proportion of prescribers writing Clozapine Rx has the highest impact on growth in proportion of patients with Clozapine Rx, compared to other antipsychotic medications

By visualizing the journeys of patients with schizophrenia receiving antipsychotic medications, we aim to highlight what prescribers and patients could expect when they begin a clozapine treatment regimen and help reduce anxiety about this less frequently prescribed antipsychotic medication

- For individuals with commercial insurance, those receiving Clozapine have fewer behavioral health (BH) comorbidities, stay on medication longer, and have fewer BH hospitalizations per year of medication than those on other antipsychotics
- In addition, combination therapies of Clozapine with other antipsychotic medications (e.g. Aripiprazole, Haloperidol, and Risperidone) have higher medication possession ratio, longer time until discontinuation and fewer behavioral health hospitalizations per year of medication, compared to Clozapine monotherapy

Content

I. Approach and emerging insights

II. Compilation of analytic outputs

II. Current insights from patient journey analytics

Methodology & definitions

For analyses on Clozapine's geographic variation and trend¹

Methodology	Ctr for Societal Benefit team analysis	Reference in literature	Limitations
Database	<ul style="list-style-type: none"> Outpatient prescription drug claims from Compile (<i>for more details on this data source, see Appendix</i>) 	<ul style="list-style-type: none"> Bachmann et al 2017: Outpatient prescription dispensing from UnitedHealth (Commercial) and Medicaid Analytics Extract Torrey et al 2016: Claims from Medicaid Analytics Extract; pharmacy claims from IMS Health Stroup et al 2014: Claims from Medicaid Analytics Extract 	<ul style="list-style-type: none"> N/a
Timeframe	<ul style="list-style-type: none"> 2015 – 2019 	<ul style="list-style-type: none"> Bachmann et al 2017: 2010 (Medicaid); 2014 (Commercial) Torrey et al 2016: 2006 – 2009 (Medicaid); 2009-2011 (IMS) Stroup et al 2014: 2001 – 2005 	<ul style="list-style-type: none"> N/a
Data sampling	<ul style="list-style-type: none"> Convenience sample from pharmacies across the US, inclusive of all insurance types (Commercial, Medicare, Medicaid) 	<ul style="list-style-type: none"> Bachmann et al 2017: Complete data from UnitedHealth; complete data for selected states from Medicaid Torrey et al 2016: Complete data for 45 states from Medicaid; convenience sample from IMS Health Stroup et al 2014: Complete data for 45 states from Medicaid 	<ul style="list-style-type: none"> Convenience sampling is prone to selection bias (e.g. oversampling in some states and vice versa) Insurance status is not controlled and may have different distributions across states Data may not capture 100% of prescription drug activity for patients and providers
Patients with antipsychotic Rx in 10K population with any Rx <i>Used on pg 11-13, 17</i>	<ul style="list-style-type: none"> Numerator: Individuals with at least two prescription claims for any antipsychotics (including Clozapine) Denominator: All individuals in dataset (individuals on at least one prescription drug) 	<ul style="list-style-type: none"> Bachmann et al 2017: <ul style="list-style-type: none"> Numerator: Individuals with at least one prescription of Clozapine Denominator: All individuals in dataset 	<ul style="list-style-type: none"> Cohort in dataset are individuals on at least one prescription drug, thus may have higher health needs than a general population
Clozapine – proportion of patients with antipsychotic Rx <i>Used on pg 14, 17-20</i>	<ul style="list-style-type: none"> Numerator: Individuals with at least two prescription claims for Clozapine Denominator: Individuals with at least two prescription claims for any antipsychotic medication in dataset 	<ul style="list-style-type: none"> Torrey et al 2016 & Stroup et al 2014: <ul style="list-style-type: none"> Numerator: Individuals with schizophrenia and a Clozapine prescription Denominator: Individuals with schizophrenia in dataset 	<ul style="list-style-type: none"> Cohort with any antipsychotic medication is used as a proxy for cohort with schizophrenia due to lack of diagnosis data Cohort with antipsychotic medication may include less severe mental health conditions (e.g. depression)
Clozapine – proportion of prescribers writing antipsychotic Rx <i>Used on pg 14, 17-20</i>	<ul style="list-style-type: none"> Numerator: Prescribers writing at least two Rx for Clozapine Denominator: Prescribers writing at least two Rx for any antipsychotic medication in dataset 	<ul style="list-style-type: none"> Tang et al 2017: <ul style="list-style-type: none"> Numerator: Prescribers writing at least one prescription of Clozapine Denominator: Prescribers prescribing antipsychotics to ten or more patients with schizophrenia 	<ul style="list-style-type: none"> Prescribers with any antipsychotic medication is used as a proxy for those that treat schizophrenia Prescribers writing antipsychotic Rx may not treat any patients with schizophrenia

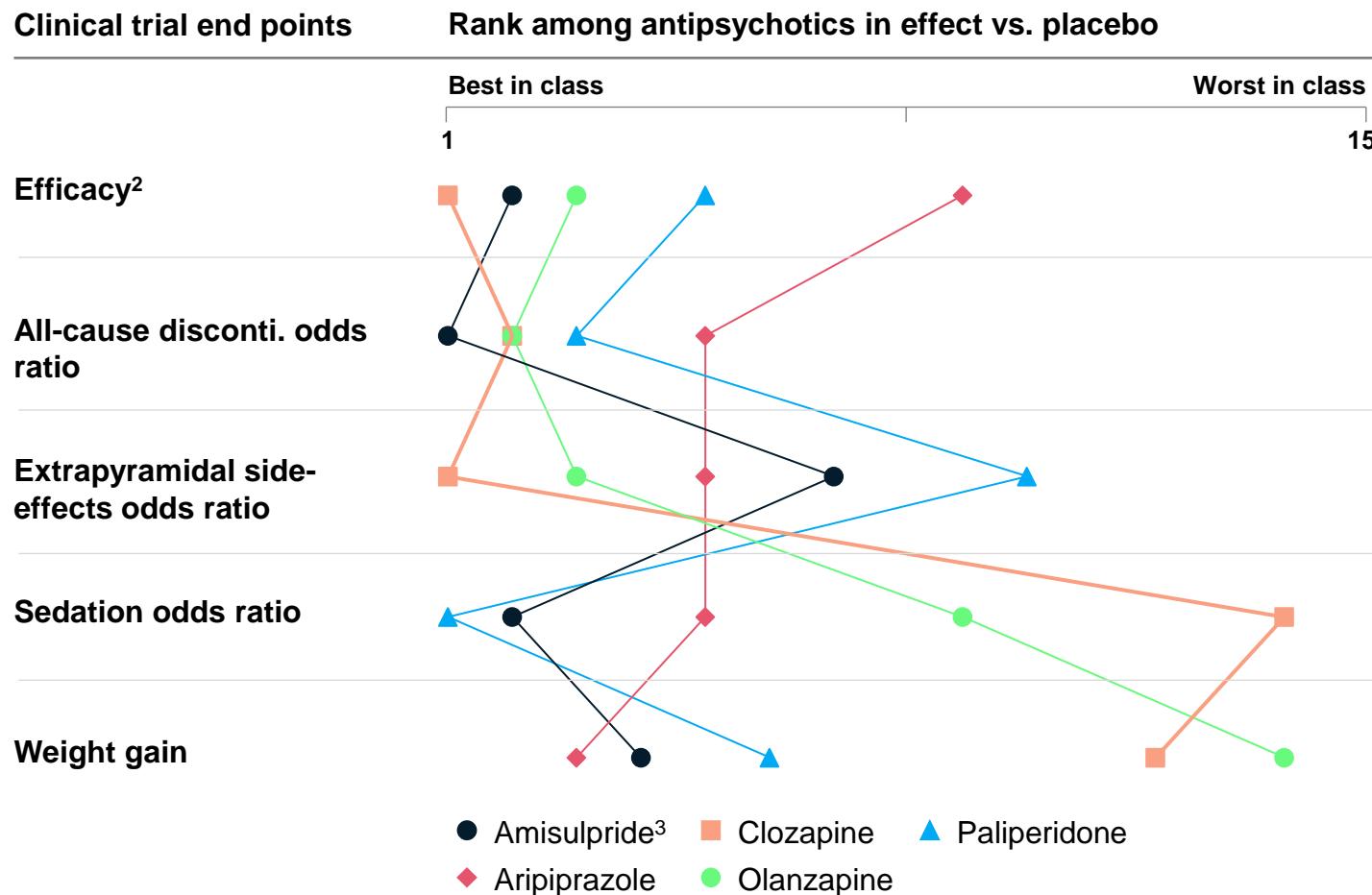
1. Methodology for analyses on patient journeys will be included separately when output is available

Insight index of supporting analytic outputs

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Clozapine is the most effective antipsychotic medication for schizophrenia, but does have side effects that may hinder uptake

Top 5 antipsychotics (out of 15) by average rank of clinical trial end points¹



1. Does not include serious adverse effects (e.g. neutropenia)

2. Change in "Positive and Negative Syndrome Scale" or "Brief Psychiatric Rating Scale"

3. In the US, Amisulpride is currently only indicated for prevention of postoperative nausea and vomiting

Takeaway

Data is from a meta-analysis of 212 studies on antipsychotic medications for schizophrenia-related disorders between 1955 and 2012

Clozapine is the most efficacious antipsychotic medication for schizophrenia; however, it is also ranked among the worst in causing sedation and weight gain – significantly affecting patients' quality of life

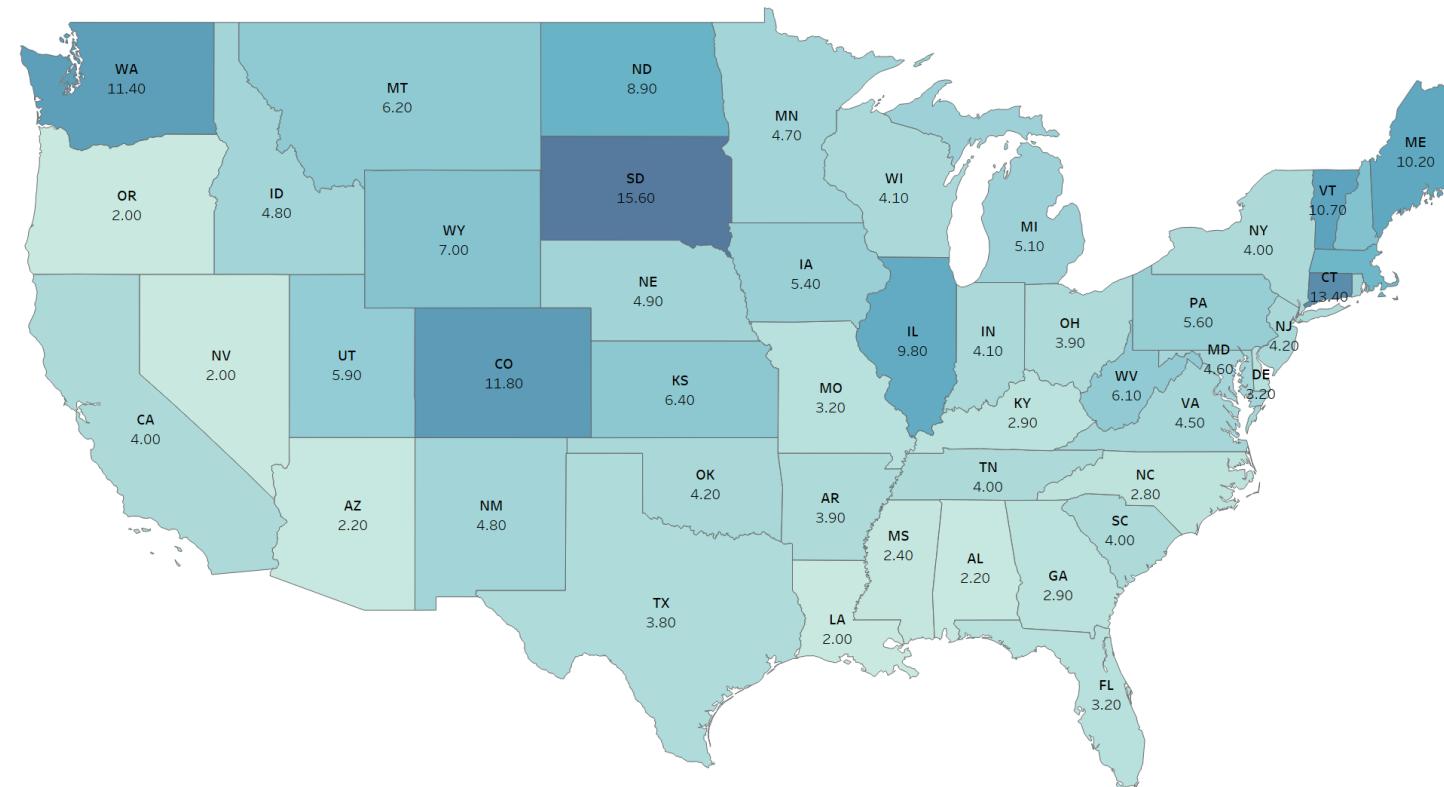
Aripiprazole (ie. Abilify) - the current best-selling antipsychotic medication, has an average clinical trial profile. It only ranks as best in class for one end point in weight gain

According to Leucht et al, Clozapine is 2x more efficacious than Aripiprazole

A 2015 study of Medicaid patients with schizophrenia found a 7-fold variation in Clozapine uptake across states

Clozapine uptake in Medicaid patients across US states, 2006-2009

% Medicaid patients with schizophrenia prescribed Clozapine



Source: Based on Torrey et al 2015, "Clozapine for Treating Schizophrenia: A Comparison of States"

Takeaway

Clozapine uptake in South Dakota (15.6%) is 7 times greater than that in Louisiana (2%)

Only six states have Clozapine uptake rate greater than 10%. Clozapine is the recommended drug for treatment-resistant schizophrenia, accounting for up to 30% of patients with schizophrenia

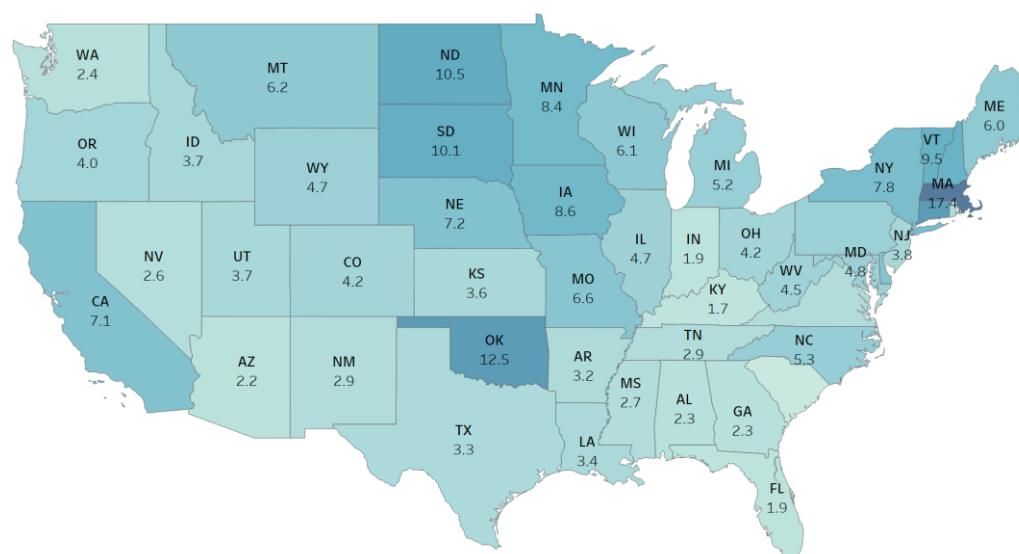
This analysis uses 2006-2009 data to build upon the original analysis of 2001-2005 data conducted by Stroup et al 2014, "Geographic and Clinical Variation in Clozapine Use in the United States"

Number of patients with Clozapine Rx per 10K population with Rx varied up to 10x across states in 2019, and the relative level of prescription is similar between 2005 and 2019

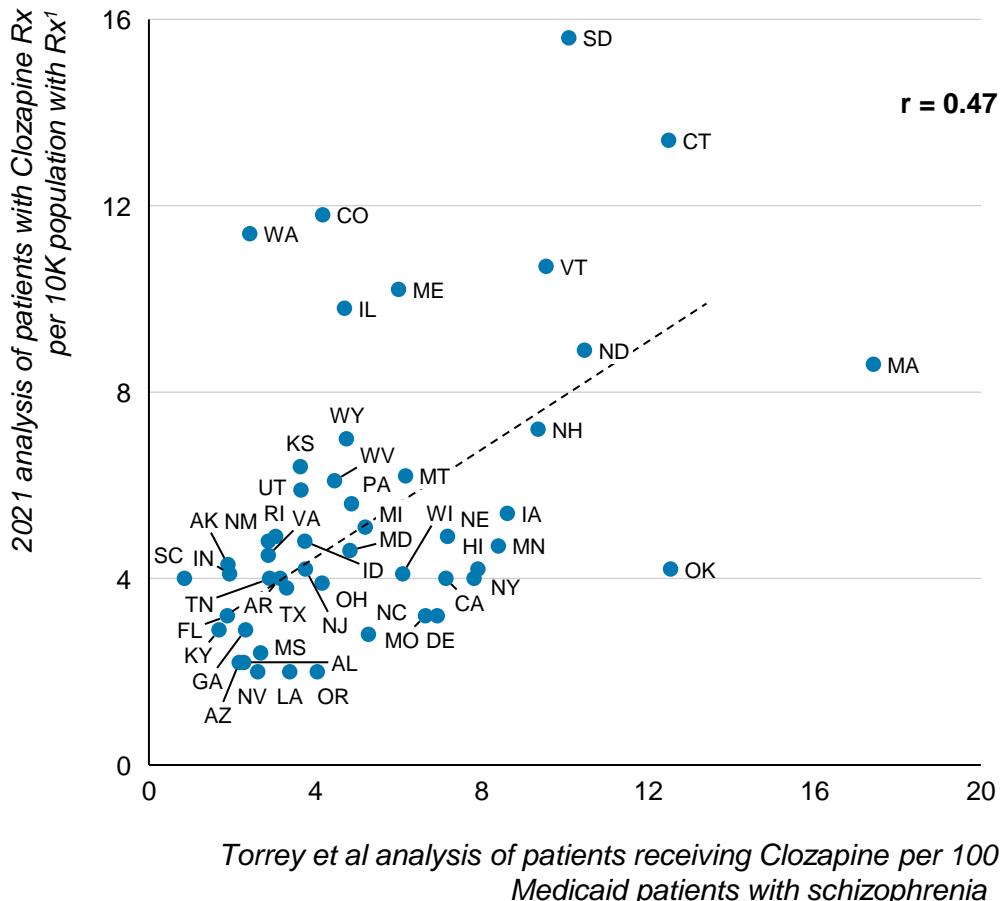
Preliminary

Clozapine prescription across US states, 2019¹

Patients with Clozapine Rx per 10K population with Rx³



Analysis of 2019 claims vs Torrey et al^{1 2}

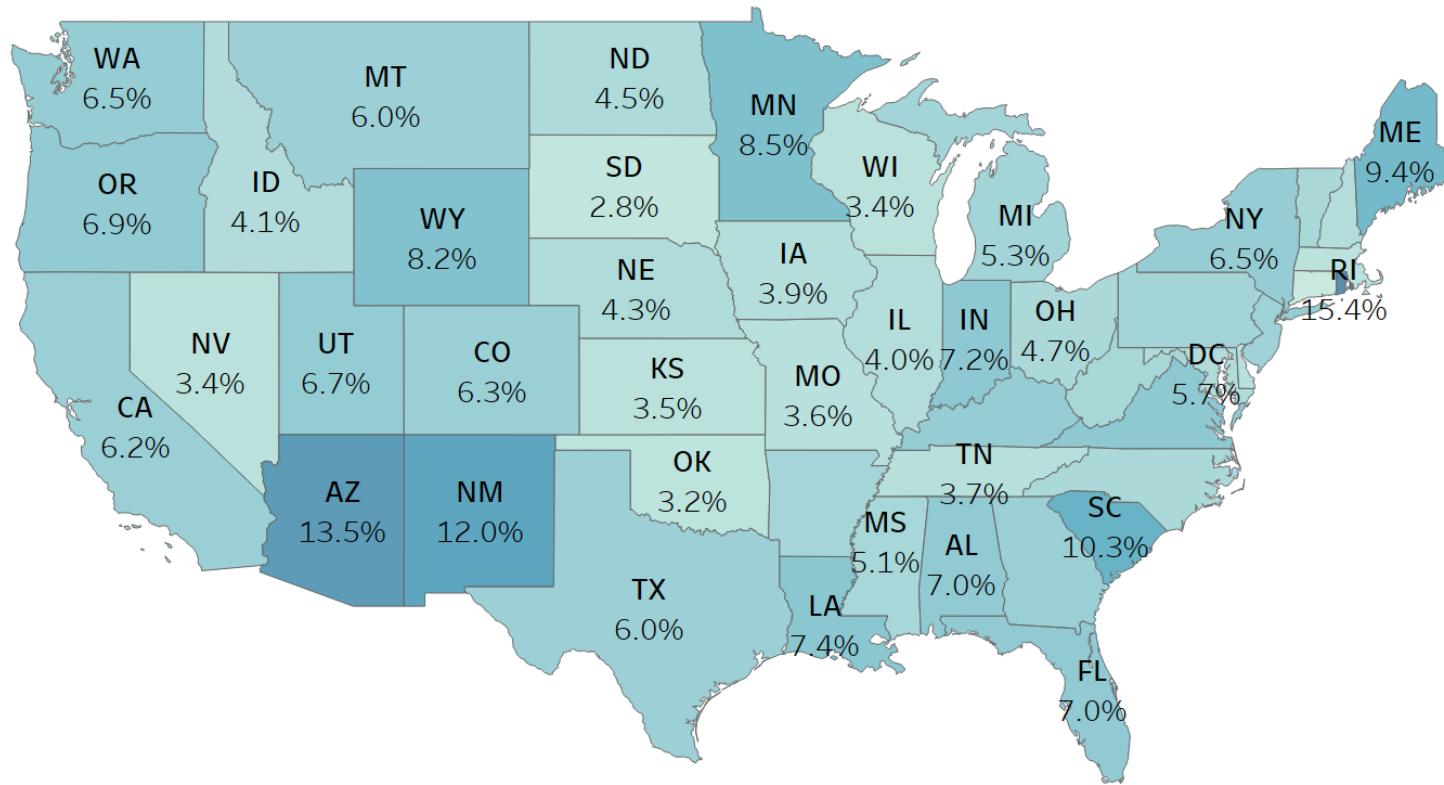


1. Claims analysis on Compile 2019 pharmacy claims data
2. Torrey et al., 2015 analysis on Medicaid 2006 - 2009 data
3. Calculated as number of individuals with at least two prescription claims for Clozapine, divided by number of individuals in the data with at least two prescription claims of any drugs

States vary up to 7x in proportion of patients with Clozapine Rx filling one claim for Clozapine per year

Patients with one Clozapine claim per year across US states

% individuals with Clozapine Rx, having 1 Clozapine Rx claim in 2019



Takeaway

Rhode Island has the highest proportion of patients with Clozapine Rx filling one claim for Clozapine per year at 15%, while Connecticut has the lowest at 2%

More than 1 in 10 individuals with Clozapine Rx in Arizona, New Mexico, and Rhode Island have only one Clozapine prescription in 2019

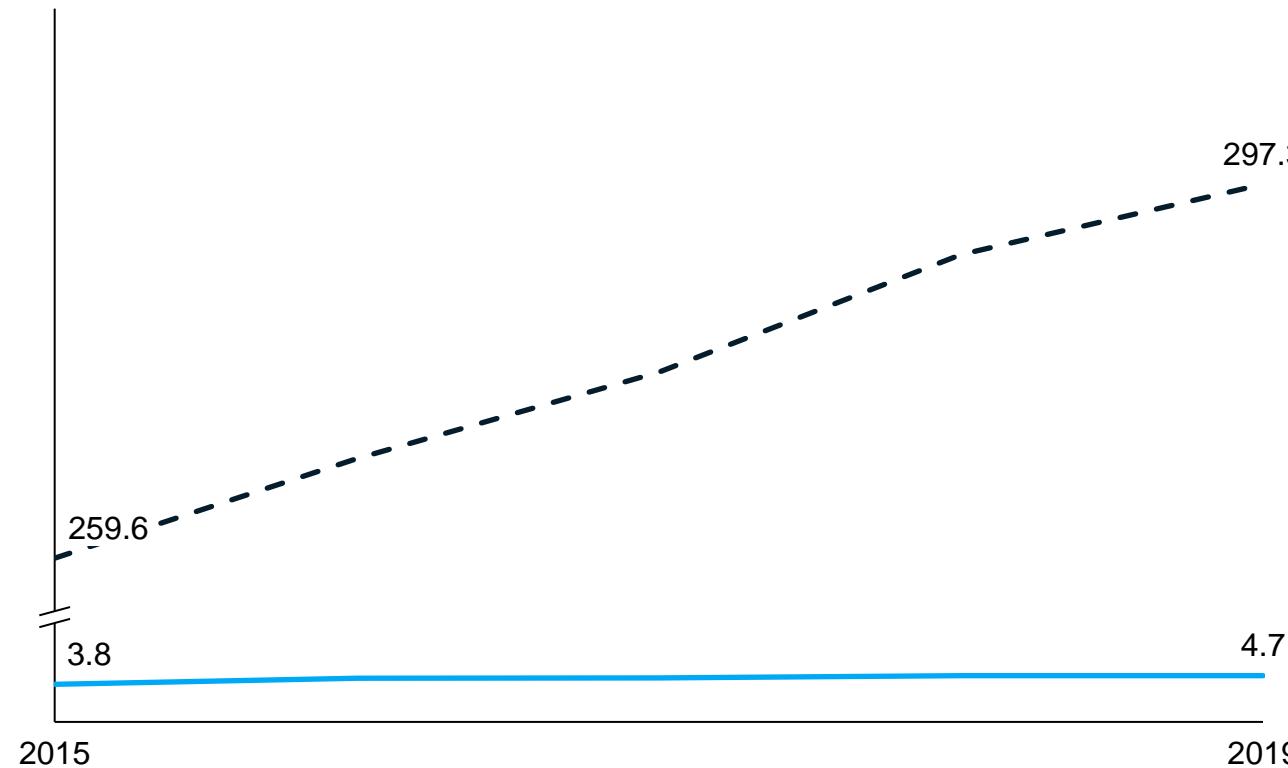
States with high Clozapine prescription (ie. ND, SD, MA, OK) also have low proportion of patients with Clozapine Rx having only one Clozapine claim per year

While change in patients with Clozapine Rx was significantly lower than that in patients with antipsychotic Rx between 2015 and 2019...

Preliminary

Clozapine trend in the US (2015-2019)

Patients with antipsychotic Rx per 10K population with Rx¹



1. Calculated as number of individuals with at least two prescription claims for any antipsychotic medication/Clozapine, divided by number of individuals in the data with at least two prescription claims of any drugs

How to interpret this data

- Data is collected from pharmacies, thus will represent outpatient prescription mostly
- Convenience sampling was used and must be considered when drastic trends are observed
- Value might be higher than seen in other studies
 - Patients with Clozapine Rx per 10K population: 4 vs 1.4 reported by Bachmann
 - Cohort included in this analysis include patients with prescription drugs, thus more likely to have higher needs (both PH and BH) than average population

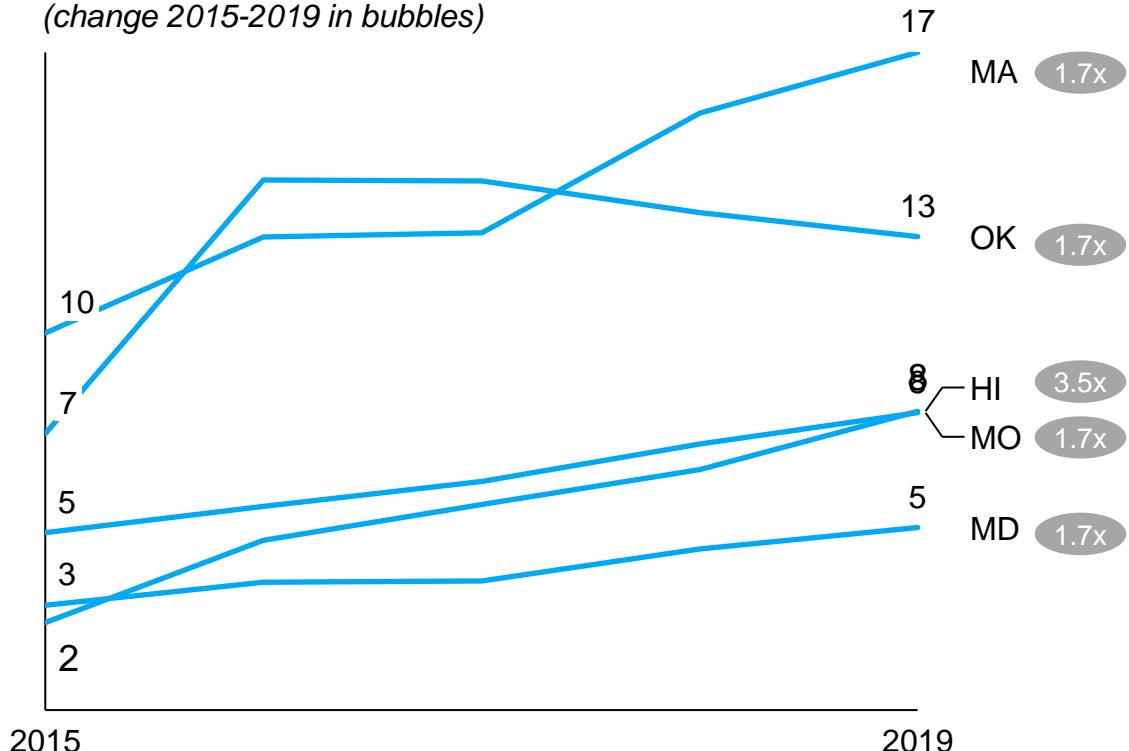
... there is some variation across states that yields insights

Preliminary

5 states in highest Clozapine growth

Patients with Clozapine Rx per 10K population with Rx¹

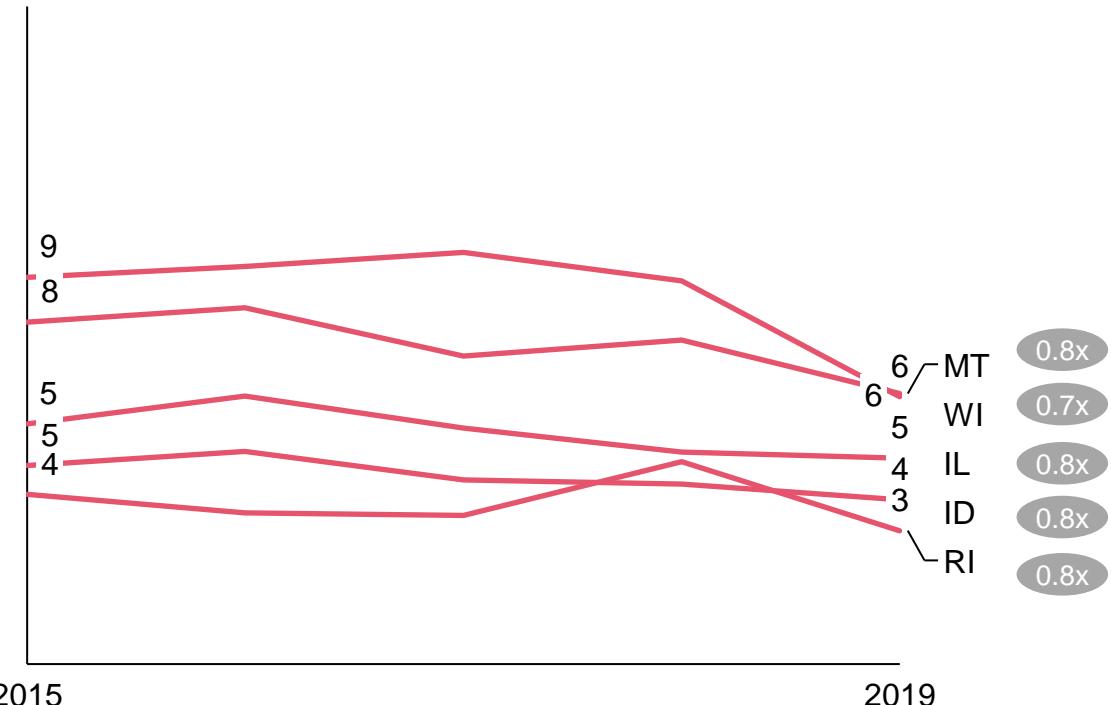
(change 2015-2019 in bubbles)



5 states in lowest Clozapine growth

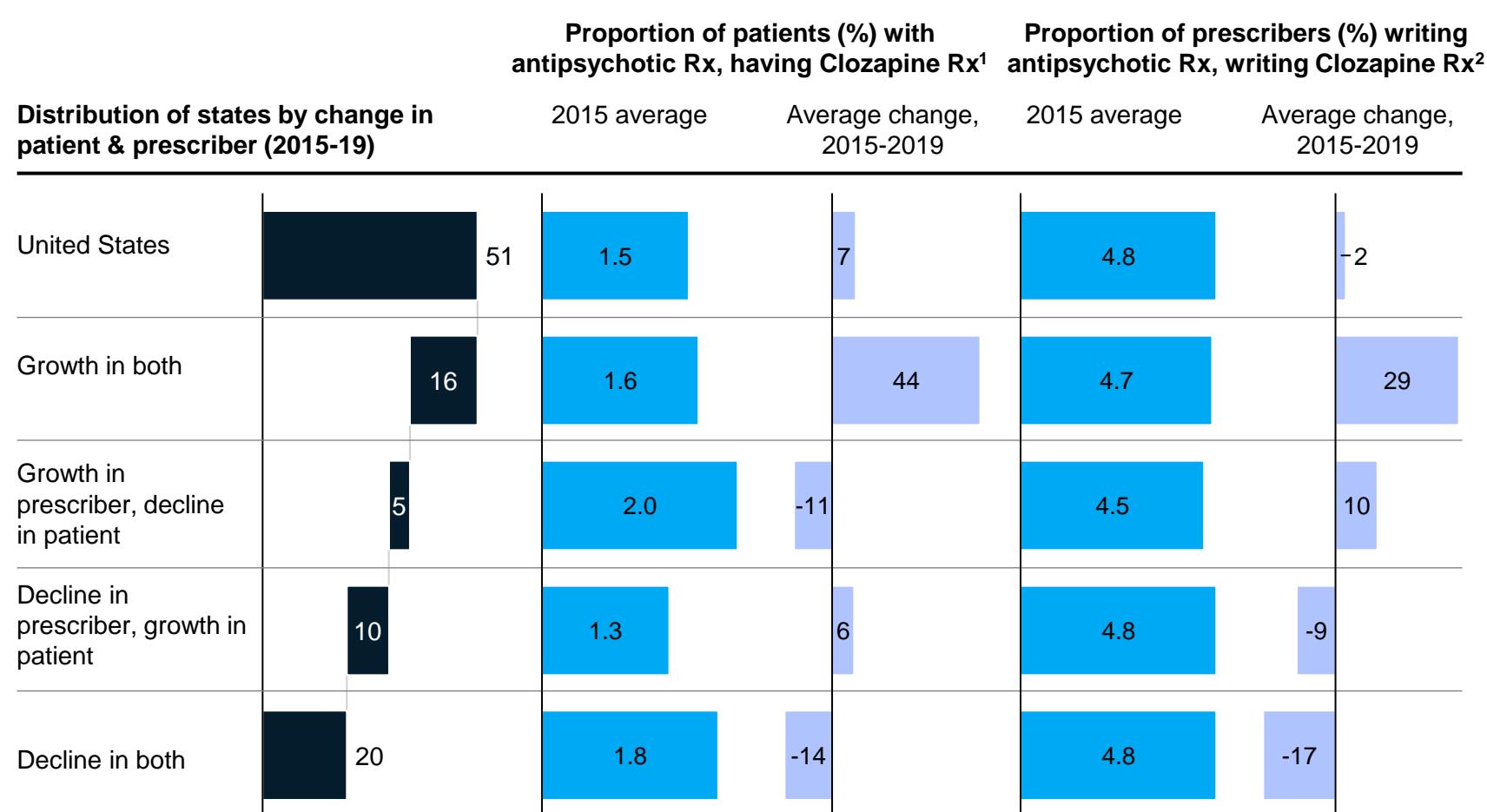
Patients with Clozapine Rx per 10K population with Rx

(change 2015-2019 in bubbles)



1. Calculated as number of individuals with at least two prescription claims for any antipsychotic medication/Clozapine, divided by number of individuals in the data with at least two prescription claims of any drugs

Clozapine as a proportion of antipsychotic prescription is growing in 16 US states, but this is offset by declines in the remaining 35



1. Calculated as number of individuals with at least two prescription claims for Clozapine, divided by number of individuals in the data with at least two prescription claims of any antipsychotics
2. Calculated as number of prescribers writing at least two prescription claims for Clozapine, divided by number of prescribers writing at least two prescription claims of any antipsychotics

Takeaway

30% of US states is growing in both proportion of prescribers and patients of antipsychotic Rx, while 40% of US states is declining in both

States with growth in both patient and prescriber have x2-3 times larger magnitude of change compared to the rest of US

States with different Clozapine trajectories did not seem to have major difference in initial baseline in 2015

Previous research has linked Clozapine underutilization to various barriers in prescribing, accessing and maintaining Clozapine

Barriers to Clozapine utilization in patients with schizophrenia

Barriers to prescription



Prescribers' attitude towards clozapine management & complications

Prescriber's lack of education & experience with clozapine

Prescribers' concern for patient adherence

Patients' need for/refusal of blood monitoring

REMS administrative burden for prescribers

Outpatient medication initiation

Psychiatrist availability

Barriers to access



Formulary status of clozapine

Lacking ready clozapine stock

Lacking staffing, protocols & procedures to manage clozapine

Historical African American exclusion due to benign ethnic neutropenia

Barriers to maintenance

Burden of blood monitoring

Patients' burden of side effects (e.g. sedation, weight gain)

Patients' serious adverse reactions to Clozapine (ie. neutropenia, constipation, etc)

Some states with highest Clozapine prescription had conducted programs that help with prescriber education and patient experience

Illustrative

Non-exhaustive

In the Massachusetts General Hospital-McLean Adult Residency Program, psychiatry residents rotate for six weeks in a clozapine clinic and are taught an accompanying curriculum about the clinical use of clozapine, which has been shown to increase their knowledge about the therapy

Massachusetts

2015 – 2019 change in proportion of patients with Clozapine Rx 153%

The Maryland Behavioral Health Administration partnered with the University of Maryland School of Pharmacy, to implement Clozapine Authorization and Monitoring Program. Through the program, more than 15% of patients with schizophrenia in MBHA inpatient facilities receiving clozapine

Maryland

2015 – 2019 change in proportion of patients with Clozapine Rx 124%

Fairview Health Services partnered with the University of Minnesota to streamline the clozapine monitoring program in 2013. The program innovated by deploying at-home blood tests and ensuring transparency and continuity of care. The program since then was expanded to serve patients from multiple health systems

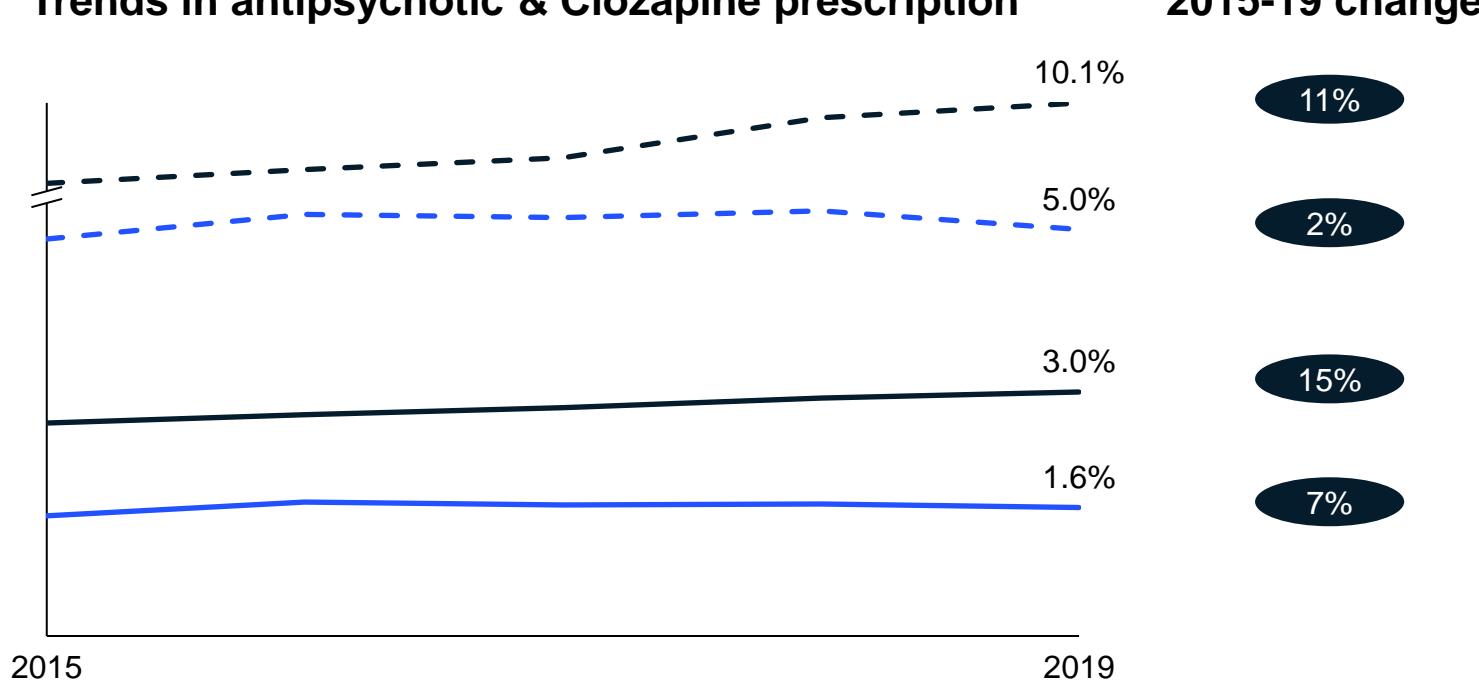
Minnesota

2015 – 2019 change in proportion of patients with Clozapine Rx 147%

Change in patients and prescribers of Clozapine has remained less than half that of overall antipsychotic medications

Preliminary

Trends in antipsychotic & Clozapine prescription



2015

2019

- Proportion of patients with any Rx, having antipsychotic Rx¹
- Proportion of patients with antipsychotic Rx, having Clozapine Rx³
- - Proportion of prescribers writing any Rx, writing antipsychotic Rx²
- - Proportion of prescribers writing antipsychotic Rx, Writing Clozapine Rx⁴

1. Calculated as count of individuals having at least two antipsychotic Rx divided by count of all individuals in the dataset

2. Calculated as count of prescribers writing at least two antipsychotic Rx divided by count of all prescribers in the dataset

3. Calculated as count of individuals having at least two Clozapine Rx divided by count of individuals having at least two antipsychotic Rx

4. Calculated as count of prescribers writing at least two Clozapine Rx divided by count of prescribers writing at least two antipsychotic Rx

Takeaway

Clozapine prescribers as a proportion of antipsychotic prescribers grew 80% slower than overall antipsychotic prescribers

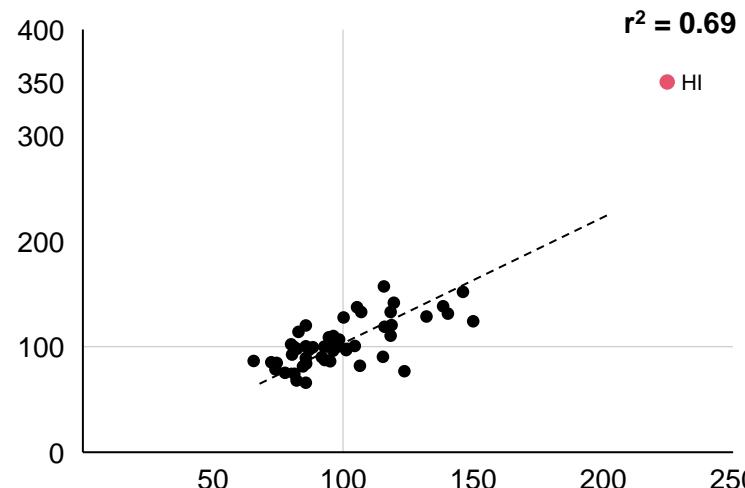
Slower growth in prescribers writing Clozapine Rx correlates with slower growth in patients with Clozapine Rx

Change in proportion of prescribers prescribing Clozapine has the strongest correlation with proportion of patients with Clozapine Rx among various tested factors investigated in the literature (1/2)

Correlations between proportion of patients with Clozapine Rx & various factors¹

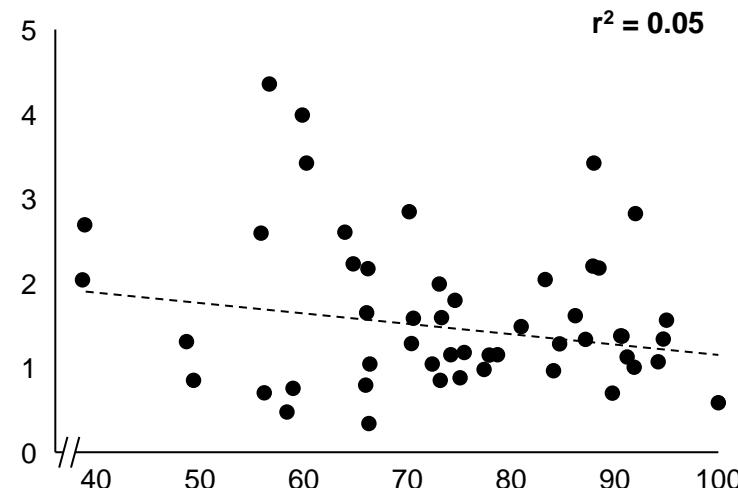
Preliminary

2015-19 change in proportion of patients with antipsychotic Rx, Proportion of patients with antipsychotic Rx, having Clozapine Rx (2015)



2015-19 change in % of prescribers writing antipsychotic Rx prescribing Clozapine

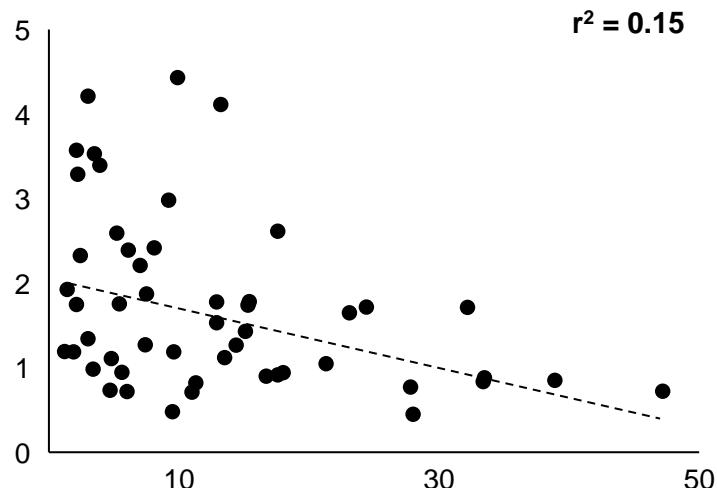
- Change in patients with Clozapine Rx is strongly correlated with change in prescribers writing Clozapine Rx
- Hawaii is an outlier in its expansion of Clozapine patient base (300%) and prescriber base (200%)



% of state population, living in urban areas (2010)

- No correlation detected for change in % of patients prescribed Clozapine
- Proportion of patients with Clozapine Rx is negatively correlated with state urbanization, measured by percent of state population living in urban areas²

Proportion of patients with antipsychotic Rx, having Clozapine Rx (2019)



% of state population, African American (2019)

- No correlation detected for change in % of patients prescribed Clozapine
- Proportion of patients with Clozapine Rx is negatively correlated with percent of population being African American – consistent with previous reports

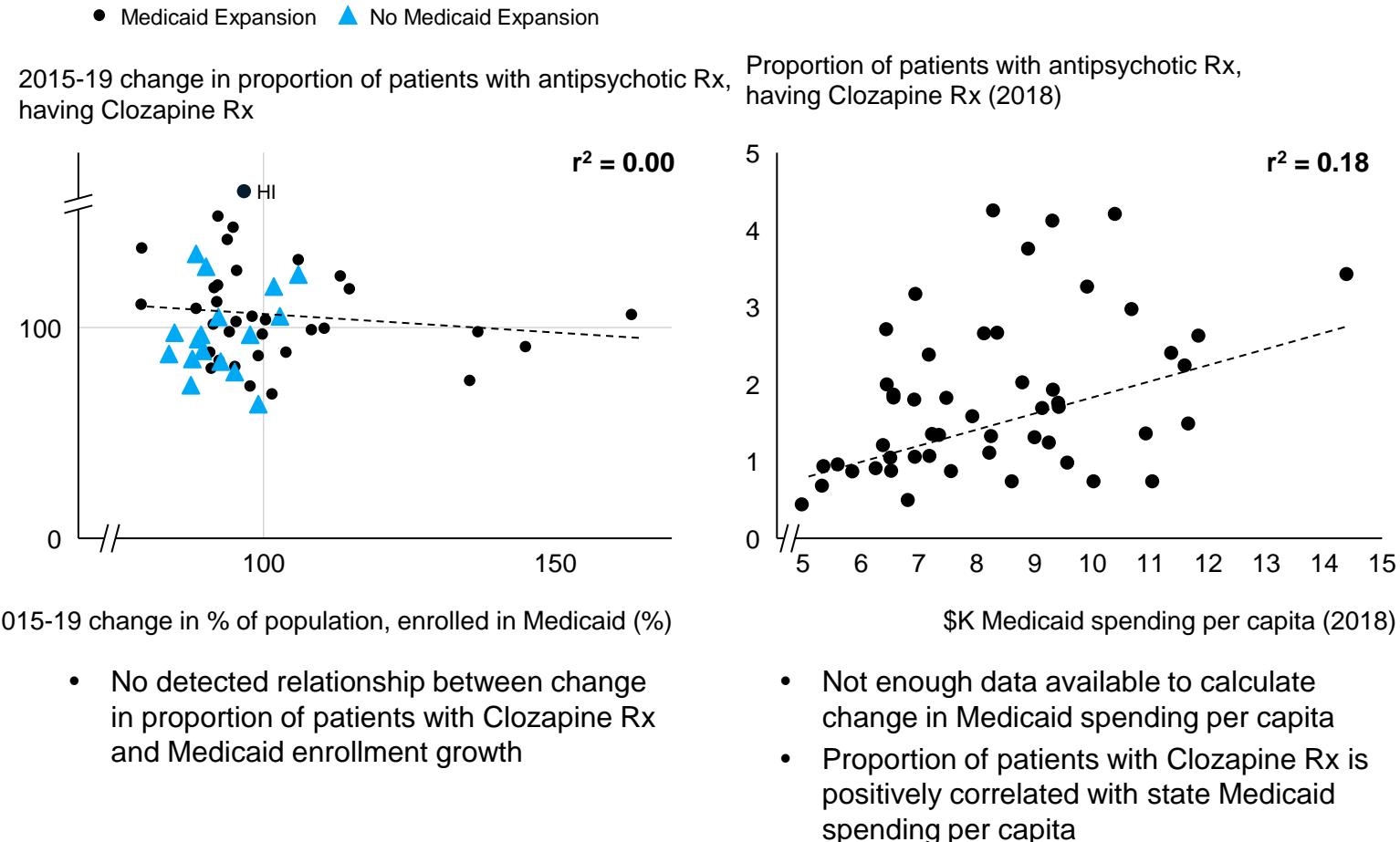
1. Correlation uses the latest and most relevant data year as available, if data is insufficient to calculate rate of change

2. Correlation is observed using data from different time frames

Change in proportion of prescribers prescribing Clozapine has the strongest correlation with proportion of patients with Clozapine Rx among various tested factors investigated in the literature (2/2)

Correlations between proportion of patients with Clozapine Rx & various factors¹

Preliminary



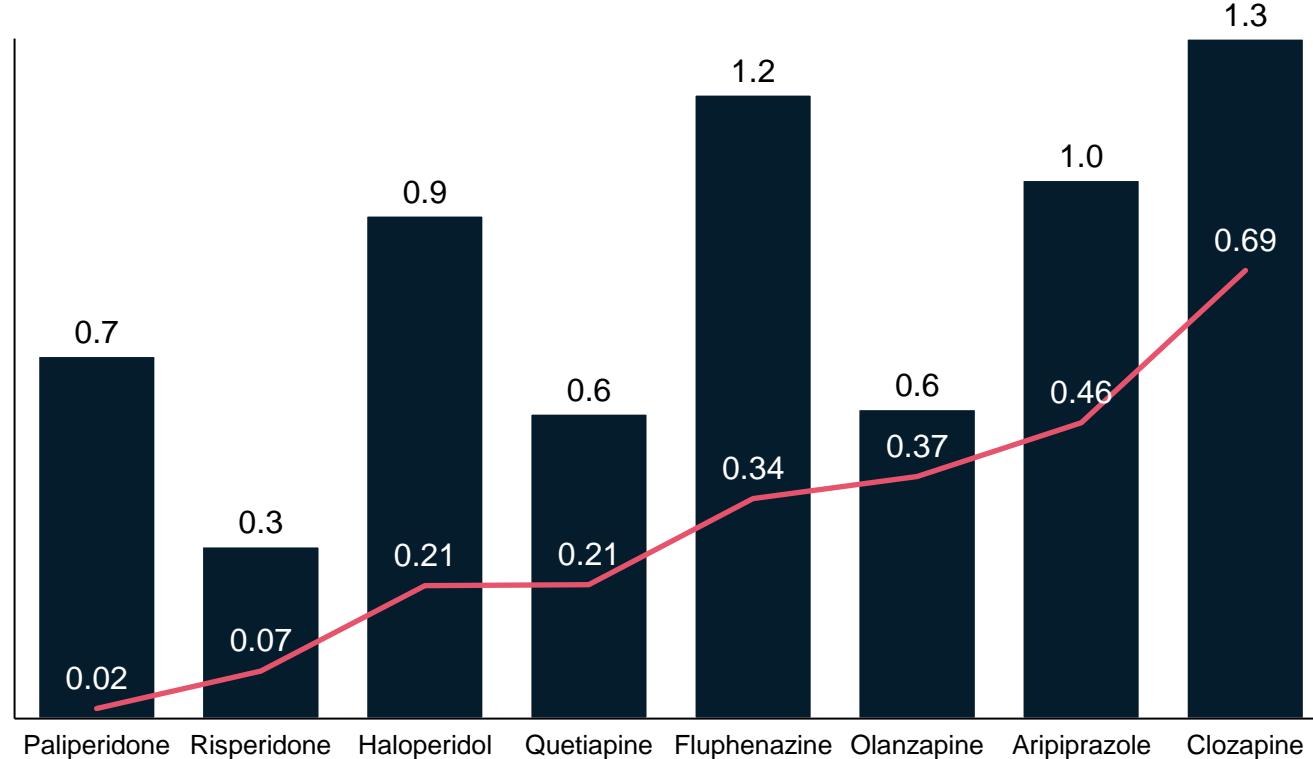
1. Correlation uses the latest and most relevant data year as available, if data is insufficient to calculate rate of change

Growth in proportion of prescribers prescribing Clozapine has a higher impact on growth in proportion of patients with Clozapine Rx than for other antipsychotic medications

Preliminary

— r-squared ■ Regression line slope

Correlations between change in proportions of patients¹ with antipsychotic Rx and prescribers² of antipsychotic Rx (2015-19)



- Calculated as number of individuals with at least two prescription claims for each respective antipsychotic medication, divided by number of individuals in the data with at least two prescription claims of any antipsychotics
- Calculated as number of prescribers writing at least two prescription claims for each respective antipsychotic medication, divided by number of prescribers writing at least two prescription claims of any antipsychotics

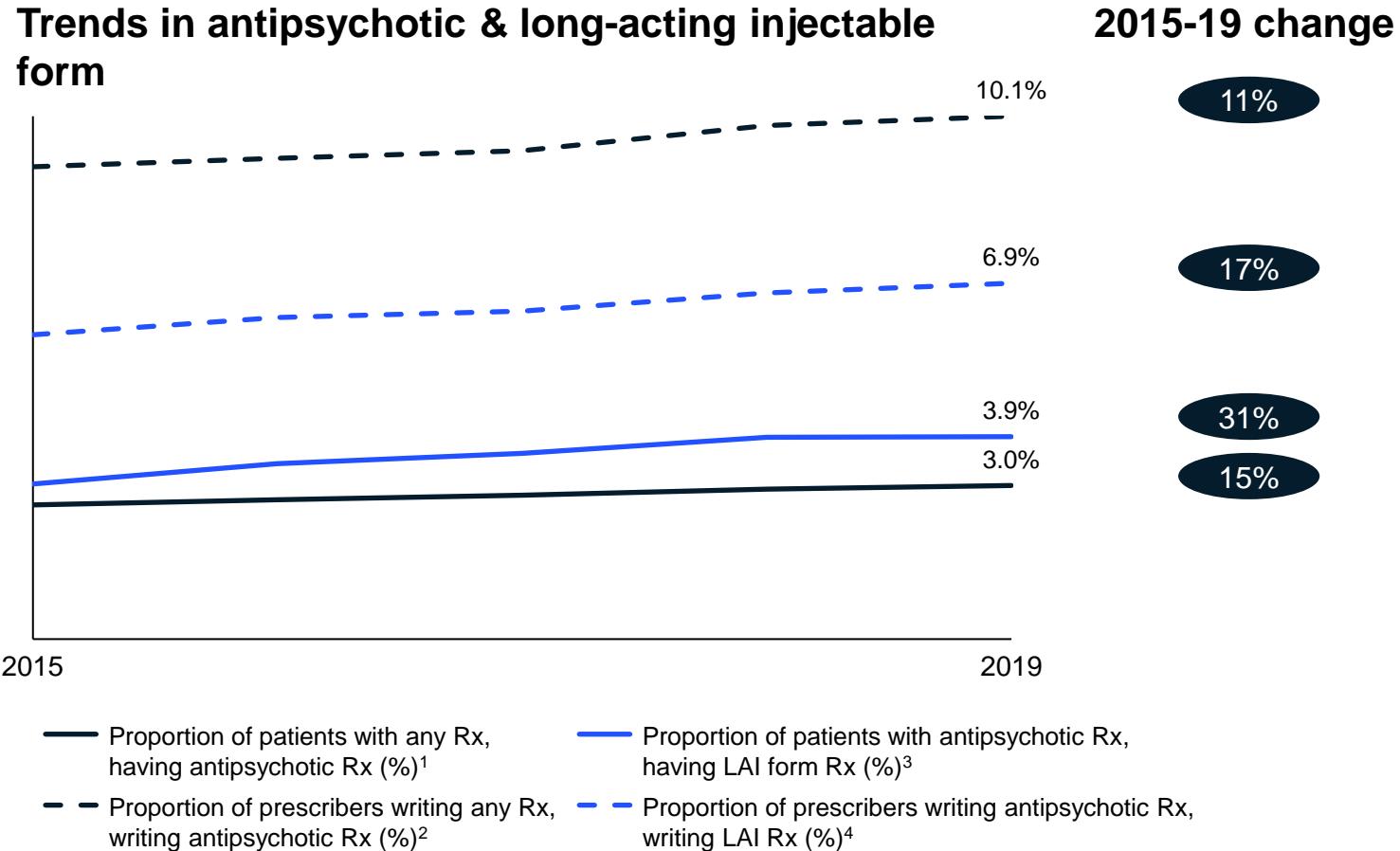
Takeaway

Among antipsychotic medications, Clozapine has the strongest correlation between patient growth and prescriber growth, with r-squared of 0.69

For each percent change in prescribers, Clozapine has the highest impact on the change in patients, at 1.3x

Growth in patients and prescribers of long-acting injectable antipsychotic Rx was faster than overall antipsychotic medications

Preliminary



1. Calculated as count of individuals having at least two antipsychotic Rx divided by count of all individuals in the dataset
2. Calculated as count of prescribers writing at least two antipsychotic Rx divided by count of all prescribers in the dataset
3. Calculated as count of individuals having at least two LAI Rx divided by count of individuals having at least two antipsychotic Rx
4. Calculated as count of prescribers writing at least two LAI Rx divided by count of prescribers writing at least two antipsychotic Rx

Note: Supplemental preliminary insight not included in draft 'emerging insights' executive summary

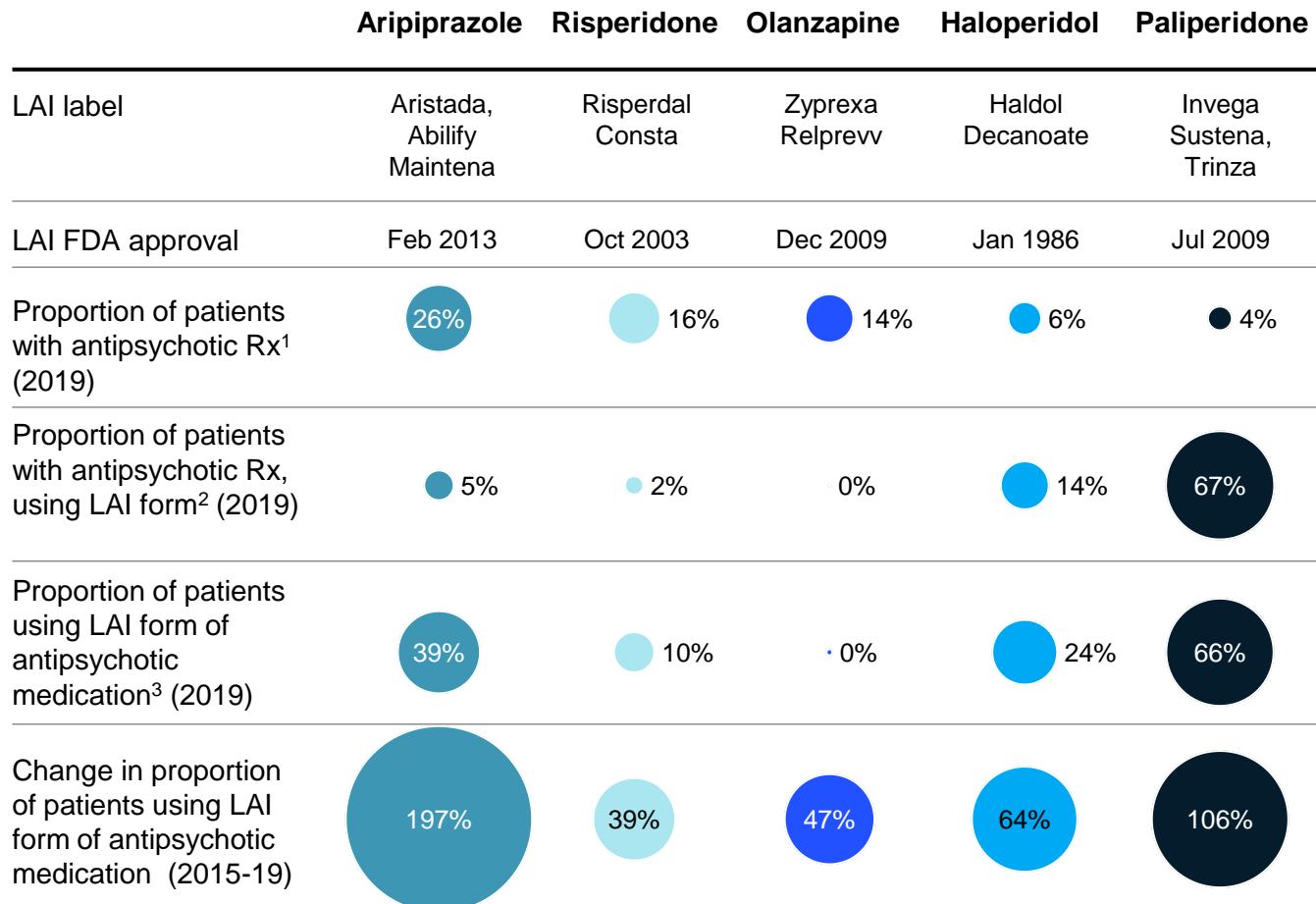
Takeaway

Proportion of prescribers writing long-acting injectable (LAI) Rx grew 2x faster than overall antipsychotic prescription

Growth in proportion of prescribers writing LAI Rx correlates with growth in proportion of patients with Rx, 1.5x faster than overall antipsychotic medication

Aripiprazole LAI prescription grows, while older alternatives decline

Trends in uptake of LAI antipsychotic formulations



- Calculated as count of individuals having at least two Rx of the antipsychotic on column header divided by count of individuals having at least two antipsychotic Rx
- Calculated as count of individuals having at least two Rx of the LAI form of the antipsychotic on column header divided by count of individuals having at least two Rx of any LAI form antipsychotic (regardless of substance)
- Calculated as count of individuals having at least two Rx of the LAI form of the antipsychotic on column header divided by count of individuals having at least two Rx of that antipsychotic (regardless of form)

Note: Supplemental preliminary insight not included in draft 'emerging insights' executive summary

Takeaway

Paliperidone, Aripiprazole, and Haloperidol are the most commonly used LAIs

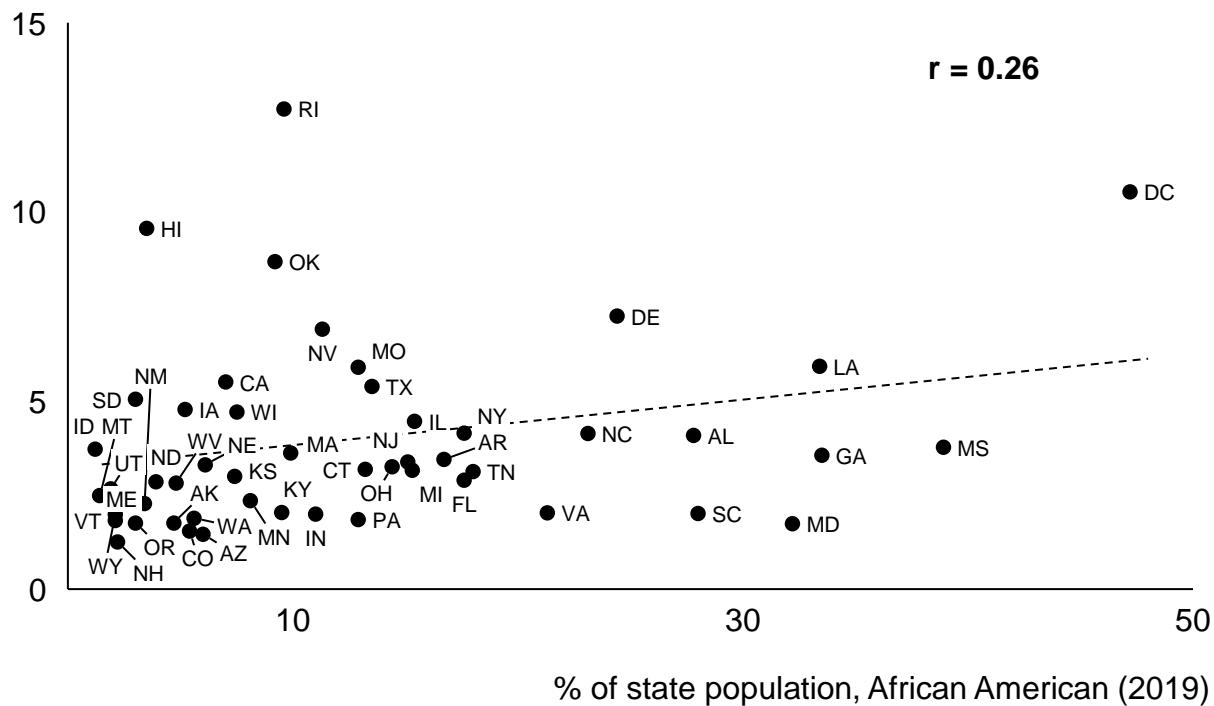
Utilization of the LAI form of Aripiprazole's grew significantly, from 19.7% of LAI antipsychotic patients in 2015 to 39% in 2019

Proportion of patients with LAI Rx has a weak positive correlation with size of the state's African American population

Preliminary

Correlation between proportion of patients with LAI Rx¹ and state racial makeup

% of patients with antipsychotic Rx, using LAI form (2019)



1. Calculated as count of individuals having at least two LAI Rx divided by count of individuals having at least two antipsychotic Rx

Note: Supplemental preliminary insight not included in draft 'emerging insights' executive summary

Takeaway

Proportion of patients with LAI Rx is positively correlated with percent of population being African American

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Methodology & definitions

PRELIMINARY WORK-IN-PROGRESS

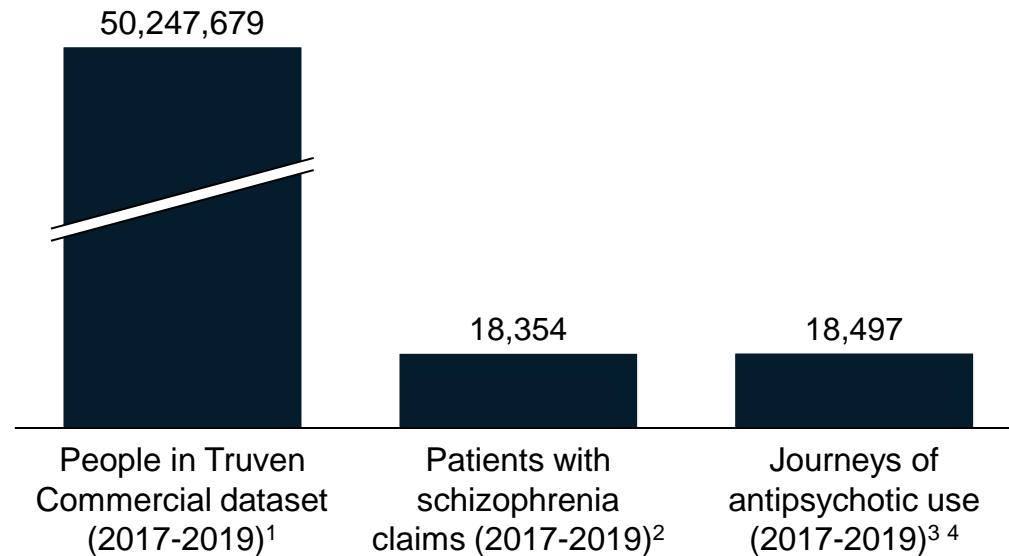
For analyses on antipsychotic patient journeys

Methodology/definition	Description
Truven Commercial dataset	<ul style="list-style-type: none">Truven Commercial dataset includes medical and outpatient pharmacy claims from employer sponsored plans in the U.S. for ~50 million members per year. Weights are available each members and each year to extrapolate to the U.S. Commercial population of ~150 million lives
Journey of antipsychotic medication	<ul style="list-style-type: none">An journey of antipsychotic medication starts at the first antipsychotic prescription in available patient claim historyA journey continues for as long as the patient continues filling antipsychotic prescriptions. If there are no antipsychotic prescription 3 months after the last medication possession period ends, end the journeyAfter a journey ends for a patient, a subsequent antipsychotic prescription will be identified as the start of a new journeyAntipsychotic medications are identified through First Data Bank's Enhanced Therapeutic Classification of "Antipsychotic"
Patients with schizophrenia	<ul style="list-style-type: none">If the patient had a schizophrenia diagnosis as primary diagnosis on any claim in their available claim data, they are flagged as having schizophreniaICD-10 schizophrenia diagnosis codes: "F20", "F200", "F201", "F202", "F203", "F205", "F208", "F2089", or "F209"
Chronic condition comorbidities	<ul style="list-style-type: none">Chronic condition comorbidities (including both physical and mental) are identified using the CMS Chronic Conditions Data Warehouse code sets
CMS Hierarchical Condition Category (CMS-HCC) risk score	<ul style="list-style-type: none">CMS-HCC risk score gives an assessment of a patient's relative risk for Medicare's reimbursement purposeCMS-HCC risk score is calculated using CMS HCC Exchange modelIn Truven Commercial dataset, the median CMS HCC risk score is 0.16 and inter-quartile range is 0.06 – 0.25
Time to all-cause prescription discontinuation	<ul style="list-style-type: none">Defined as the length between the first prescription date and the date after the last prescription medication supply runs out
Polypharmacy	<ul style="list-style-type: none">A journey is flagged as polypharmacy if during treatment period: there are more than 60 consecutive days when the patient has active prescriptions of more than one unique antipsychotic (e.g. aripiprazole, olanzapine)
Long-acting injectable antipsychotic	<ul style="list-style-type: none">Abilify Maintena, Aripiprazole Lauroxil, Aristada, Fluphenazine Decanoate, Prolixin Decanoate, Haloperidol Decanoate, Haldol Decanoate, Olanzapine Pamoate, Zyprexa Relprevv, Paliperidone Palmitate, Invega Sustenna, Invega Trinza, Risperdal Consta
Care category	<ul style="list-style-type: none">Care category is created using a McKinsey proprietary algorithm that evaluates standard codes (e.g. billing type, service place, procedure, diagnosis) to assign each claim to a single type of healthcare service
Medication possession ratio	<ul style="list-style-type: none">Medication possession ratio is calculated as the number of days with at least one active antipsychotic prescription divided by the time until discontinuation of the journey
Behavioral health (BH) hospitalization	<ul style="list-style-type: none">BH hospitalization is identified as an emergency room or hospital inpatient visit with any mental/behavioral health primary diagnosis
Average BH hospitalizations per day of treatment	<ul style="list-style-type: none">Average BH hospitalizations per day of treatment is calculated as the number of BH hospitalizations during treatment period divided by the time until discontinuation of the journey
Time to first BH hospitalization on treatment	<ul style="list-style-type: none">Time to first BH hospitalization on treatment is the length between the first prescription date and the first BH hospitalization date after the treatment starts

Cohort selection and demographic characteristics

PRELIMINARY WORK-IN-PROGRESS

Selection of antipsychotic use journeys from Truven Commercial



Demographic characteristics of Truven Commercial & selected cohort

Age, count (%)	Truven Commercial data	Patients with schizophrenia
18 and below	11.8M (23.6)	1,277 (6.9)
19 - 34	14.2M (28.3)	9,567 (51.7)
35 - 49	11.8M (23.5)	3,526 (19.1)
50 - 64	11.2M (22.3)	3,965 (21.4)
65 and above	1.1M (2.3)	162 (0.9)
Mean (SD)	33.3 (18.1)	34.6 (14.7)
Male, count (%)	24.4 (48.6)	11,535 (62.4%)
Count of behavioral health conditions, mean (SD)	0.5 (1.5)	4.5 (2.6)
CMS-HCC risk score, mean (SD)	0.6 (2.3)	3.5 (5.2)

1. Truven Commercial dataset includes medical and outpatient pharmacy claims from employer sponsored plans in the U.S. for ~50 million members per year. Weights are available each members and each year to extrapolate to the U.S. Commercial population of ~150 million lives.

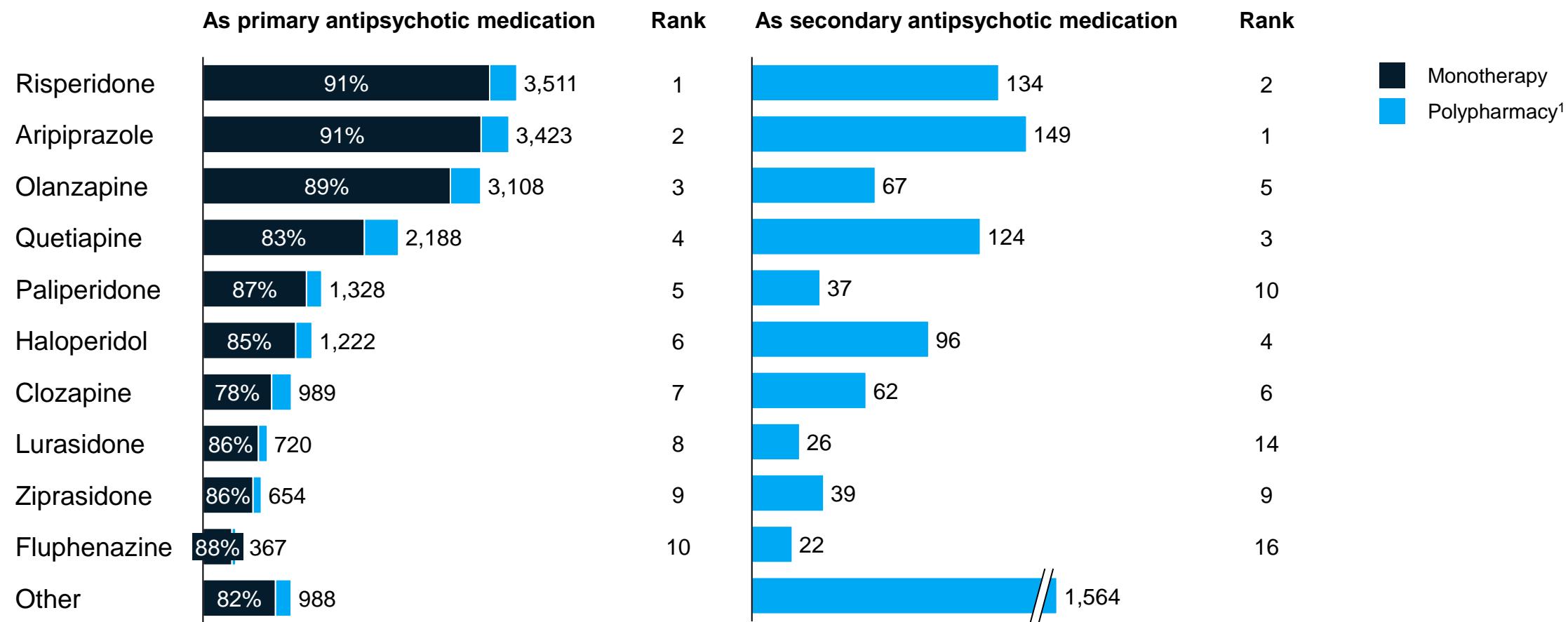
2. Schizophrenia claim is identified as a claim with a primary ICD-10 diagnosis code of "F20", "F200", "F201", "F202", "F203", "F205", "F208", "F2089", or "F209"

3. Journey of antipsychotic use starts when there is a prescription of antipsychotic - identified by First Data Bank's grouper of "Antipsychotic". The journey ends if there is no antipsychotic prescription for ≥ 3 months

4. A patient with schizophrenia can have multiple journeys of antipsychotic use

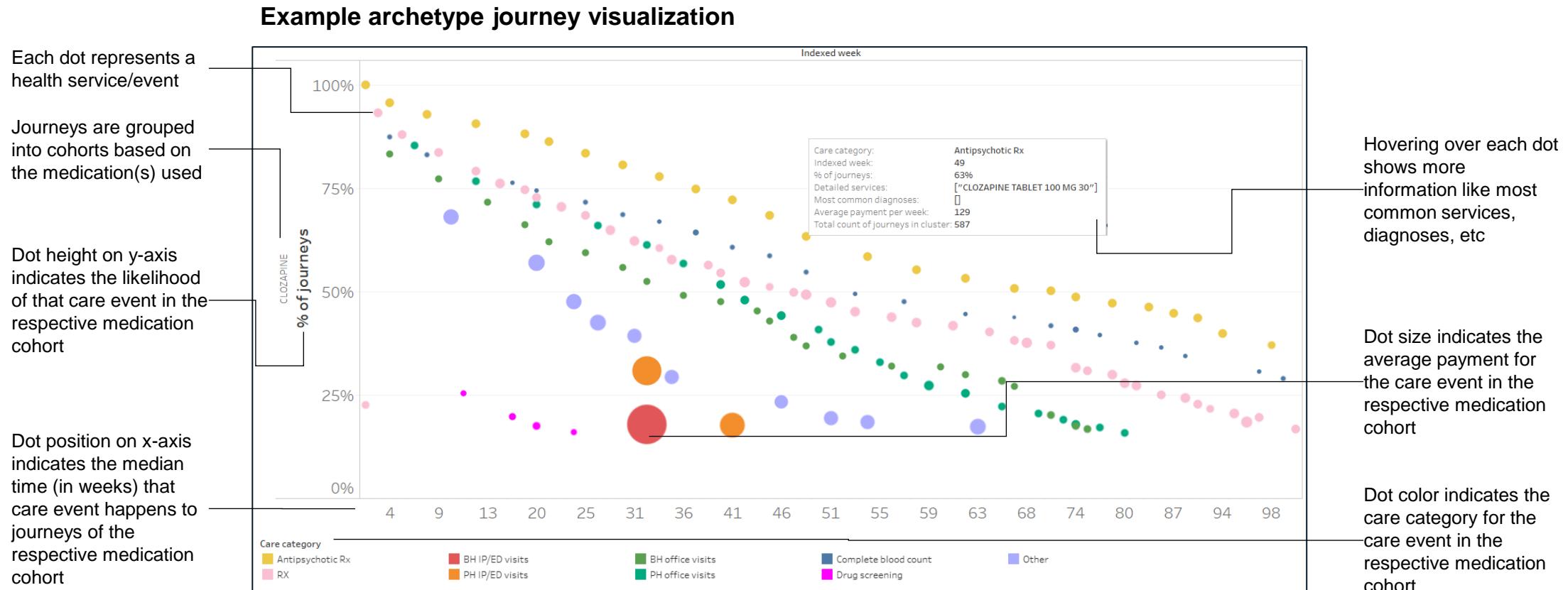
Clozapine is outside of top 5 most common antipsychotic medications, both as the primary and secondary medication in therapies

Distribution of antipsychotic journeys in patients with schizophrenia, by most common antipsychotic medications



1. In a polypharmacy journey, the antipsychotic medication with the higher days' supply is considered as primary. The rest of antipsychotic medications in that journey are considered secondary and polypharmacy companions.

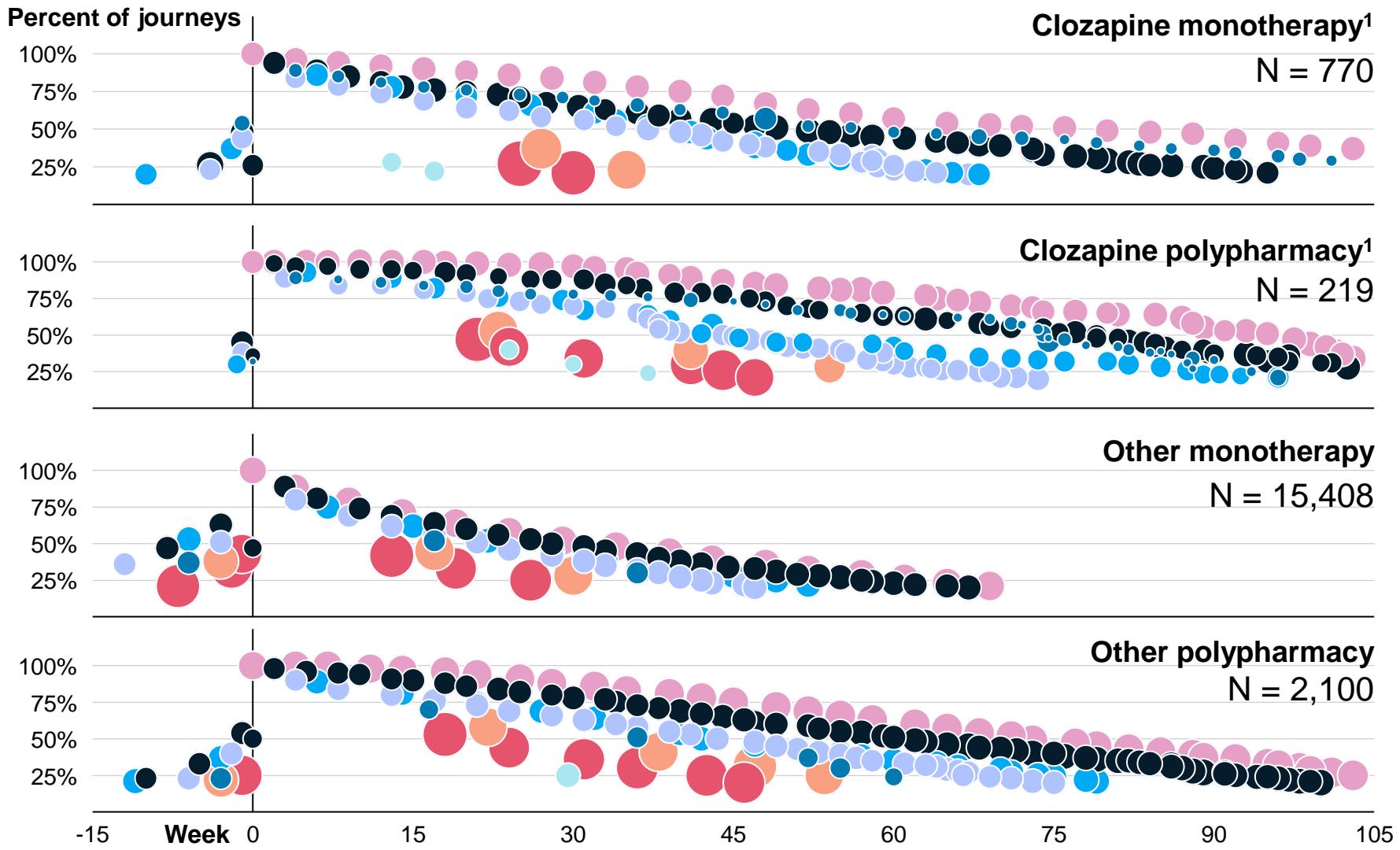
How to interpret archetype journey¹ visualization



1. Archetype journey is a methodology to average all journeys that belong to one group to create a probabilistic journey that represent shared features of the group

Patients with Clozapine journeys have fewer BH comorbidities, stay on medication longer and have fewer BH hospitalizations per year of medication

Archetype journey visualization of Clozapine vs other antipsychotic medications



Source: Truven Commercial Claims 2017-2019

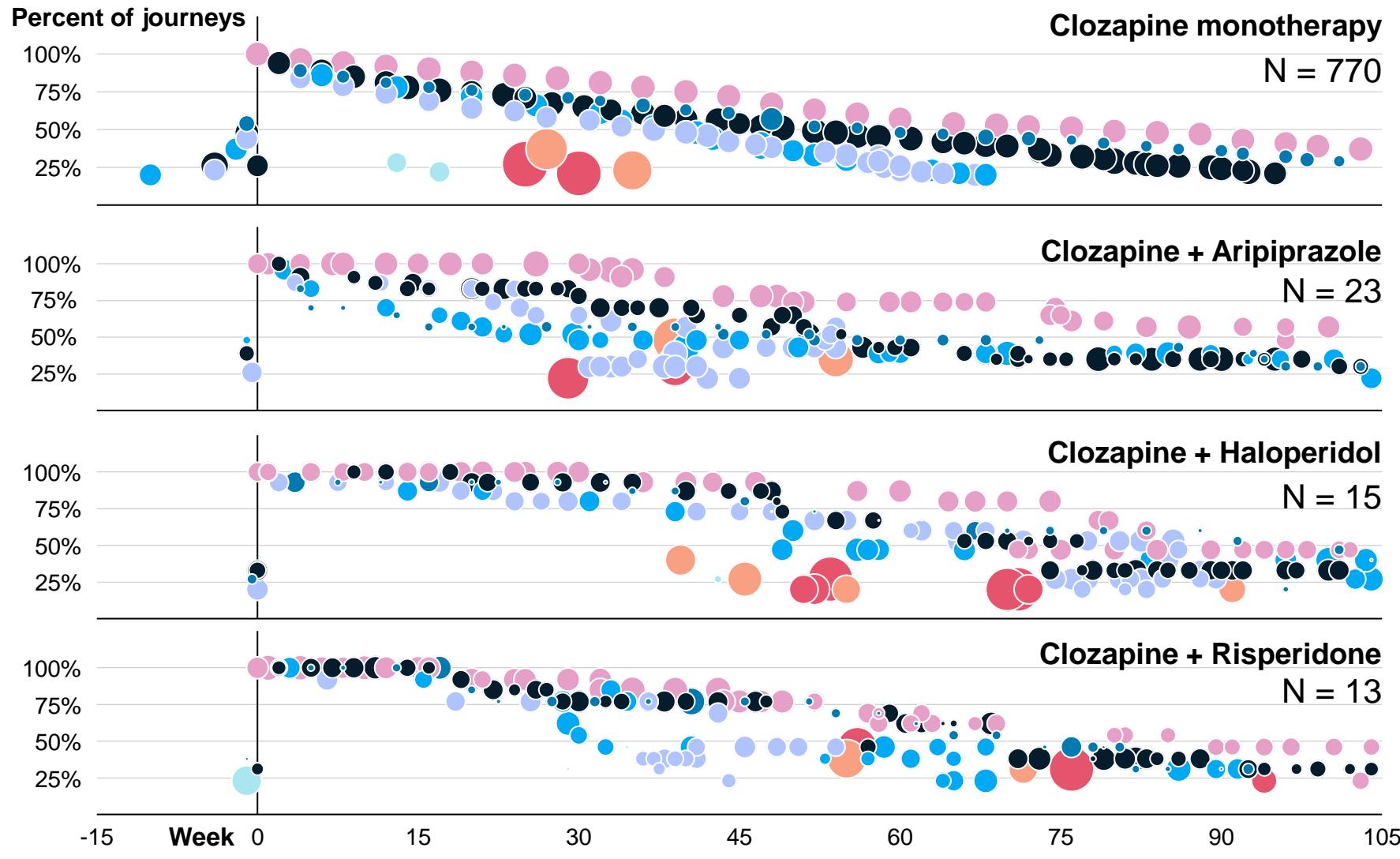
1. In this analysis, most of the Clozapine journeys starts in outpatient setting. This is most likely because the patients are already on Clozapine medication when their data becomes available

- Antipsychotic Rx
- Drug screening
- BH IP/ED visits
- PH IP/ED visits
- BH office visits
- PH office visits
- Complete blood count
- Rx

- Avg. 36.7 years old, 33% female
- Avg. 3.6 BH conditions
- Avg. 543 days until Rx discontinuation, 89% MPR
- Avg 1.4 BH hospitalizations per year of medication
- Avg 211 days to first BH hospitalization
- Avg \$27,468 TCOC per year of medication
-
- Avg. 33.8 years old, 32% female
- Avg. 4.4 BH conditions
- Avg. 745 days until Rx discontinuation, 95% MPR
- Avg 1.2 BH hospitalizations per year of medication
- Avg 235 days to first BH hospitalization
- Avg \$34,224 TCOC per year of medication
-
- Avg. 34.3 years old, 38% female
- Avg. 4.5 BH conditions
- Avg. 299 days until Rx discontinuation, 88% MPR
- Avg 3.6 BH hospitalizations per year of medication
- Avg 114 days to first BH hospitalization
- Avg \$49,885 TCOC per year of medication
-
- Avg. 36.3 years old, 39% female
- Avg. 4.8 BH conditions
- Avg. 645 days until Rx discontinuation, 93% MPR
- Avg 1.9 BH hospitalizations per year of medication
- Avg 209 days to first BH hospitalization
- Avg \$95,992 TCOC per year of medication

Among Clozapine journeys, patients on polypharmacy stay longer on medication and have fewer BH hospitalizations than those on monotherapy

Archetype journey visualization of most common Clozapine polypharmacy journeys



- Antipsychotic Rx
- Drug screening
- BH IP/ED visits
- PH IP/ED visits
- BH office visits
- PH office visits
- Complete blood count
- Rx

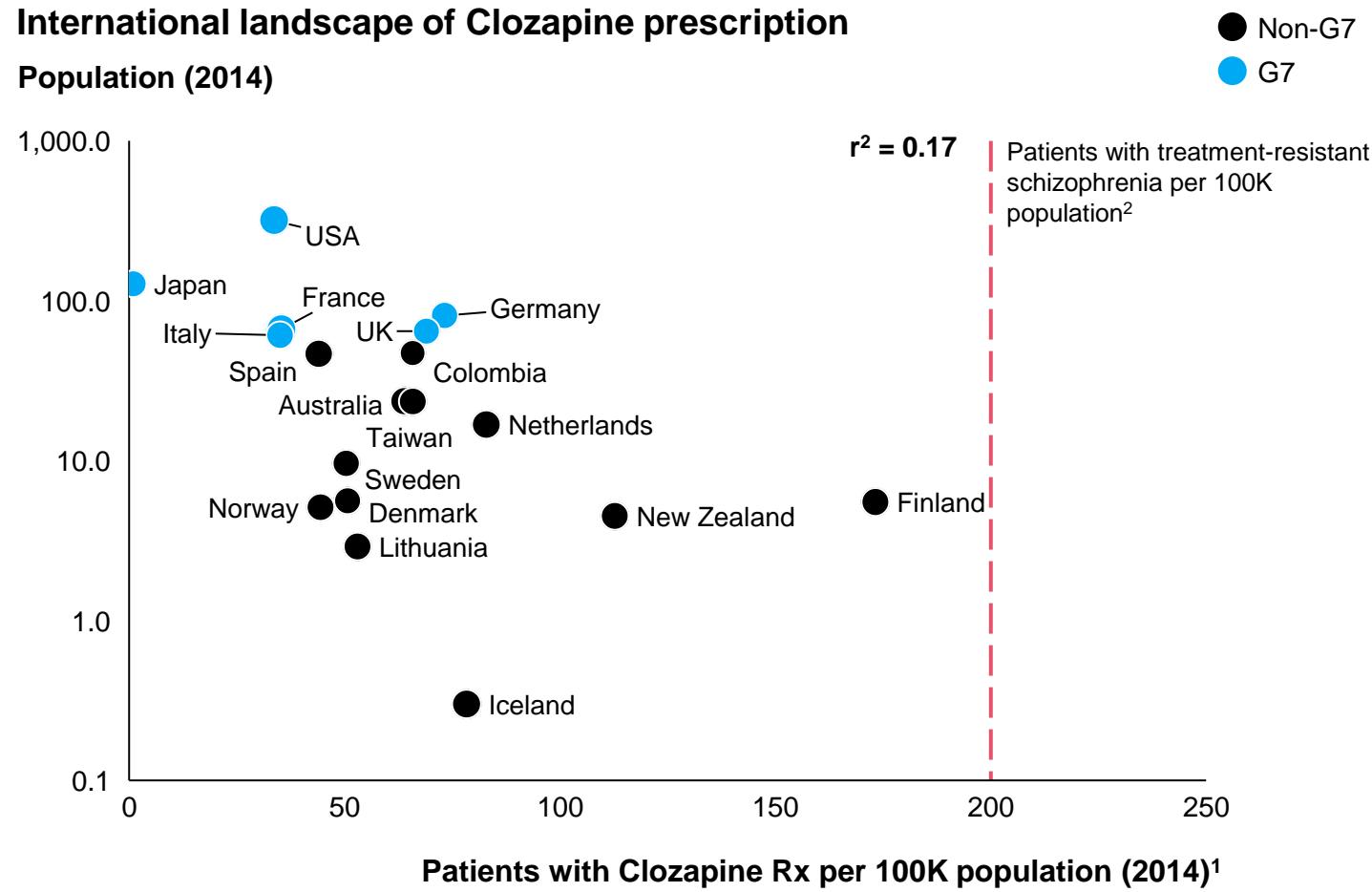
- Avg. 36.7 years old, 33% female
- Avg. 3.6 BH conditions
- Avg. 543 days until Rx discontinuation, 89% MPR
- Avg 1.4 BH hospitalizations per year of medication
- Avg 211 days to first BH hospitalization
- Avg \$27,648 TCOC per year of medication
- Avg. 36.2 years old, 17% female
- Avg. 3.0 BH conditions
- Avg. 743 days until Rx discontinuation, 96% MPR
- Avg 0.5 BH hospitalizations per year of medication
- Avg 465 days to first BH hospitalization
- Avg \$14,736 TCOC per year of medication
- Avg. 35.2 years old, 27% female
- Avg. 4.1 BH conditions
- Avg. 711 days until Rx discontinuation, 96% MPR
- Avg 0.5 BH hospitalizations per year of medication
- Avg 488 days to first BH hospitalization
- Avg \$10,298 TCOC per year of medication
- Avg. 36.2 years old, 46% female
- Avg. 3.3 BH conditions
- Avg. 678 days until Rx discontinuation, 96% MPR
- Avg 0.3 BH hospitalizations per year of medication
- Avg 389 days to first BH hospitalization
- Avg \$31,423 TCOC per year of medication

Appendix

Clozapine prescription varies across countries, and countries with larger population have fewer patients with Clozapine Rx

International landscape of Clozapine prescription

Population (2014)



1. Adapted from Bachmann et al 2017, except for the UK. UK data is 2019 from Whiskey et al 2021

2. Estimated by Bachmann et al 2017, calculated from schizophrenia prevalence of 0.5% and treatment resistance rate of 33%

Takeaway

Among 18 countries analyzed, all have fewer patients prescribed Clozapine than estimated number of patients with treatment-resistant schizophrenia

Countries in this analysis with larger population have fewer patients with Clozapine Rx

The US is in the bottom five of the countries analyzed, along with three other G7 countries (Japan, France, Italy)

Compile's claims and affiliations datasets provide broad coverage of all players in the US healthcare market

Data Sources



Broad coverage of the US market including open claims and provider affiliations

COMPILE
LICENSED RWD

CMS + .GOV

CLINICAL TRIALS
+ PUBMED

OPEN PAYMENTS

IRS + SEC

PROVIDER
WEBSITES

NEWS + DEEP
WEB CONTENT

SOCIAL MEDIA

Proprietary data

Public databases

Unstructured data

220M+

ANNUAL UNIQUE PATIENTS

30B+

MEDICAL AND RX CLAIMS

2M+

PRACTITIONERS

6.7M

AFFILIATIONS

217K

PHYS GROUPS

67,500

PHARMACIES

7,100

HOSPITALS

+++

MANY MORE

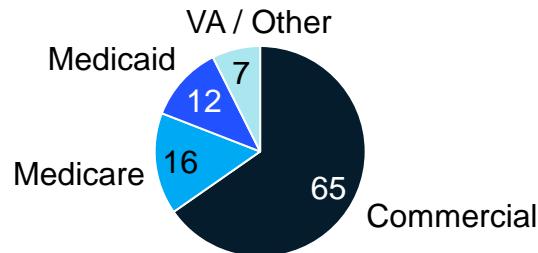
Has historical and recent data

Claims data goes back **5+ years** with similar coverage of US market (2015-on)

Limited time lag, with data available as of **April 2020**; data refreshed every 2 weeks (timed to minimize time lag)¹

Includes patients in all channels

% of Patients by Insurance (med claims)



Represents a large portion of US market

Claims type	Claims per year	% of US claims
Pharmacy	1.7B+	45-50%
Medical	1.5B+	60-65%
In-patient	300M+	TBD

Enables a number of common use cases

Important fields

Identified prescribers (NPI)

Identified payers

HCP affiliations by affinity score

Relationships of practices, IDNs, GPOs, etc.



Common use cases

Physicians prescribing behaviors

Market sizing and share by HCP / Payer

Patient affordability analytics

HCP referrals and influence maps

Account profiling

1. Data lag also due to submission of claims by providers / pharmacies; >85% of medical claims are submitted within 60 days and most Rx claims are adjudicated same day.

Potential collaboration deliverables

 Outline discussed next page

Potential deliverables	Complexity →				
	Clozapine uptake data on open-access dashboard	Microinsights ¹	Infographic	Patient journey visualization	Academic journal article
Timeline	~ May/June	~May/June	~May/June	TBD	TBD
Objective	<ul style="list-style-type: none"> To provide dashboard users access to a novel data cut on recent Clozapine uptake To enable combination with Vulnerable Population Dashboard data for additional insights To enable open-access download 	<ul style="list-style-type: none"> To highlight key findings in standalone short form and reach a broader audience To showcase potential use of Clozapine data on Vulnerable Population Dashboards 	<ul style="list-style-type: none"> To synthesize key findings in an up-to-date perspective on persistent Clozapine underutilization, employing a highly-visual format To provide a data-backed overview and improve understanding of different patient experience archetypes on Clozapine 	<ul style="list-style-type: none"> To provide an education & exploration tool that helps dimensionalize Clozapine patient experience 	<ul style="list-style-type: none"> To Proportion methodology and validate findings To connect with the research community and enhance the knowledge base To articulate gaps in the literature and identify next steps
Audience	<ul style="list-style-type: none"> Clinical, pharmacy & health system researchers Practitioners & prescribers 	<ul style="list-style-type: none"> People with schizophrenia and their families Public sector leaders 		<ul style="list-style-type: none"> Health systems/payers 	

1. Micro-insight is a short-form publication, consisting of one chart, one insight, and notable statistics

Running list of other topics discussed

- **Patient experience:** Elucidating the patient experience on Clozapine may present a key data point to improve understanding, awareness and usage of Clozapine
 - Extensive evidence has proven financial benefits of Clozapine, as shown by Commercial payers' willingness to pay for Clozapine
 - Besides financial outcomes, patient experience should also be evaluated qualitatively in treatment delay, multi antipsychotic trials, parent/guardian experience
 - Historically, prescribers are not able to observe their patients' medication adherence and healthcare. Thus, a tool showing them whether the patients fill Rx and receive appropriate care will be a game changer
 - **State variation:** While not conclusive of states' attitude to Clozapine, these following states have elements that show dedication to improve Clozapine usage
 - New York implemented a multi-faceted program between 2009 and 2013, increasing Clozapine initiation in patients with schizophrenia by 40%
 - Minnesota had state-wide initiatives to increase diversity of Clozapine prescribers
 - Additional states have focused on Clozapine programs given the professional experience of the state mental health directions, such as Missouri and Massachusetts
-

Questions for future exploration

Clozapine underutilization

- How do guidelines and usage of Clozapine vary internationally?
- What does success look like for uptake of evidenced-based medication in chronic diseases (e.g. diabetes medication)?
- How does the gap between antipsychotic and Clozapine growth look if antipsychotics indicated for less severe mental conditions (e.g. Abilify) were excluded?

Blood-testing

- For stable long-term patients on Clozapine, how does the frequency of blood draws relate to serious adverse events?
- What is the impact of point-of-care blood testing during Clozapine initiation?

Treatment plan

- For patients on Clozapine, what is the effect of polypharmacy, especially in bridging acute exacerbation? What drug combination has the most positive effect?
- What is the impact of Clozapine dosage and administration form on a patient's care journey?
- Nationally, is there a preference to initiate Clozapine treatment in a setting that can provide close monitoring (e.g. inpatient, outpatient group homes)

COVID-19

- For patient on Clozapine, how were prescription refills, blood counts, intake of new patients, and behavioral health office visits during COVID?