Retrospective Analysis of Real-World Transition Strategies for Xanomeline and Trospium Chloride in Adult Patients With Schizophrenia

Psych Congress 72

Christen Kutz,[1] James Appio,[2] Vanessa Hobbs,[2*] Jenna Hoogerheyde,[2] Cristi Bundukamara[3]

[1]Rocky Mountain Research and Consulting, Colorado Springs, CO, USA; [2]Bristol Myers Squibb, Princeton, NJ, USA; [3]Mentally Strong, Colorado Springs, CO, USA

*At the time the analysis was conducted

Background

- All antipsychotic drugs currently approved for the treatment of schizophrenia have D_2 dopamine receptor affinities that are believed to mediate antipsychotic activity[1]
- Some first- and second-generation antipsychotics are associated with high rates of extrapyramidal symptoms (eg, akathisia, tardive dyskinesia)[2,3] and metabolic disturbances (eg, weight gain,[4] hyperlipidemia,[4] increased risk for type 2 diabetes mellitus,[5] and metabolic syndrome[6]), respectively
- The dual M_1/M_4 preferring muscarinic receptor agonist xanomeline in combination with the peripherally restricted pan muscarinic antagonist trospium chloride (X/T) is the first treatment approved by the U.S. Food and Drug Administration for schizophrenia in adults with no direct D_2 dopamine receptor binding activity[7]
- X/T's novel mechanism of action (MOA) necessitates a comprehensive understanding of its distinct clinical profile for appropriate integration into clinical treatment paradigms
- This study aims to collect and analyze retrospective data from psychiatric healthcare providers (HCPs) to determine their methodology for initiating X/T in adults with schizophrenia, inclusive of switching from a first- or second-generation antipsychotic

Objectives

- Primary: to assess the methodology and rationale for initiating X/T or transitioning from current antipsychotic treatments in adults with schizophrenia
- Secondary
  - To identify the demographics of real-world patients with schizophrenia in the United States treated with X/T and the reasons for switching from a previous antipsychotic
  - To collect data on real-world practices for titrating X/T, including cross-titrating from a previous antipsychotic, and strategies to mitigate side effects such as nausea and vomiting

Methods

Retrospective analysis and chart review

- Psychiatric HCPs (psychiatrists, nurse practitioners, or physician assistants) throughout the United States with experience treating with X/T were asked to contribute deidentified retrospective data from their patients' electronic medical records; there was no direct contact with patients
- Records from adults aged ≥18 years with a confirmed DSM-5 diagnosis of schizophrenia and who had been treated with a therapeutic dose of X/T as defined in the US prescribing information for ≥1 month after having switched from an antipsychotic were eligible
- Data were collected from July 22, 2025, to August 29, 2025

Results

Provider and patient demographics/characteristics

- A total of 90 surveys were collected, each representing a unique patient undergoing a switch from a first- or second-generation antipsychotic to X/T
  - Nearly all HCPs were psychiatric/mental health nurse practitioners (97%) in an outpatient psychiatry setting (96%)
- Most patients were male (58.9%) and White, not Hispanic (69%) (**Table 1**)
  - The most common previous antipsychotics were olanzapine (24.4%) and risperidone (18.9%); 5.6% were antipsychotic naïve prior to X/T

Table 1. Patient demographics and characteristics

Characteristic	Adults With Schizophrenia (N=90)
Age, years, mean±SD	39.2±12.6
Sex, %	
Male	58.9
Female	41.1
Ethnicity/race, %	
White, not Hispanic	69
Hispanic or Latino	13
Asian	1
Black or African American	12
Native American or Alaska native	1
Multiracial	3
Time since diagnosis, %	
<1 year	8
1-10 years	50
>10 years	42
Prior antipsychotic, %	
Oral[a]	94.4
Olanzapine	24.4
Risperidone	18.9
Aripiprazole	12.2
Haloperidol	12.2
Lumateperone	12.2
Clozapine	11.1
Other	46.7
Injectable	34.4
Paliperidone	21.1
Other	16.7

[a]Individuals may have been prescribed >1 antipsychotic.
SD, standard deviation.

Drivers for switching treatment

- Inadequate symptom control (46.7% each for positive or negative symptoms) and weight gain/metabolic changes (34.4%) were the most common reasons for discontinuation of patients' previous antipsychotic (**Table 2**)

Table 2. Most common reasons for discontinuation of previous antipsychotic (≥10% of patients)

Reason,[a] %	Adults With Schizophrenia (N=90)
Lack of adequate control of positive symptoms (hallucinations, delusions)	46.7
Worsened or lack of improvement of negative symptoms (apathy, anhedonia, social withdrawal)	46.7
Weight gain and metabolic changes (obesity, diabetes, dyslipidemia)	34.4
Cognitive dulling or emotional blunting	34.4
Sedation or fatigue that interferes with daily functioning	23.3
Emotional flattening	23.3
EPS (tremor, rigidity, akathisia, dystonia)	13.3
Limits motivation or creativity	11.1
Interferes with work, school, or social life	10.0

[a]Respondents were directed to select all that apply.
EPS, extrapyramidal symptoms.

- Novel MOA (74.4%) was the most common reason for HCPs selecting X/T (**Table 3**)
- Most patients were on X/T for ≤3 months (57.8%); 28.9% were on for >6 months

Table 3. Most common reasons for selecting X/T (≥50% of HCPs)

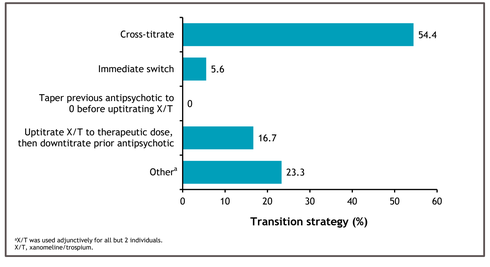
Reason,[a] %	Adults With Schizophrenia (N=90)
Novel MOA	74.4
Improvement in cognitive impairment	70.0
Failure of multiple prior D_2 dopamine receptor blocking antipsychotics	64.4
Improvement in mood symptoms and negative symptoms	64.4
Lack of weight gain or metabolic side effects	61.1
Reduced EPS or tardive dyskinesia	58.9
Efficacy across domains of symptoms of schizophrenia	57.8

[a]Respondents were directed to select all that apply.
EPS, extrapyramidal symptoms; HCP, healthcare provider; MOA, mechanism of action; X/T, xanomeline/trospium.

Transition strategies

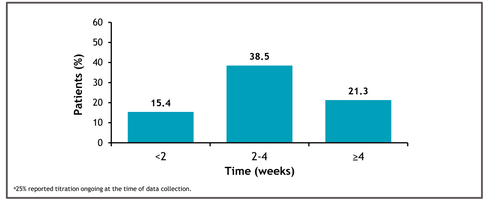
- A majority of HCPs employed a cross-titration approach (54.4%) (**Figure 1**)
  - The most common duration of cross-titration was 2-4 weeks (38.5%) (**Figure 2**)
  - Among those who tapered the previous antipsychotic
    - 32.8% reduced by 50% per step
    - 36.2% reduced by 25% per step
    - 12.1% reduced by smaller increments (eg, 10% per step)
    - 19.0% responded "other"
- When switching from a "-pine" compound, the majority of HCPs adjusted their tapering strategy to minimize anticholinergic burden
- Uptitration of X/T proceeded more slowly than in the EMERGENT clinical trials
  - 60% and 32% of patients remained on xanomeline/trospium chloride 50 mg/20 mg for 3-14 days and >14 days, respectively (**Figure 3**)
  - 28% and 35% of patients remained on xanomeline/trospium chloride 100 mg/20 mg for 6-14 days and >14 days, respectively
  - <20% of patients were titrated to the maximum xanomeline/trospium chloride 125 mg/30 mg dose (**Figure 4**)

Figure 1. Transition strategies



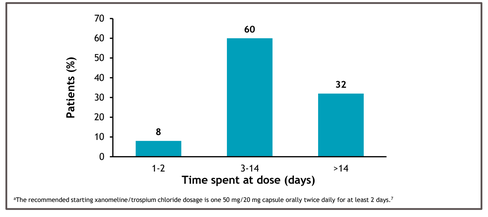
[a]X/T was used adjunctively for all but 2 individuals.
X/T, xanomeline/trospium.

Figure 2. Length of time for cross-titration[a]



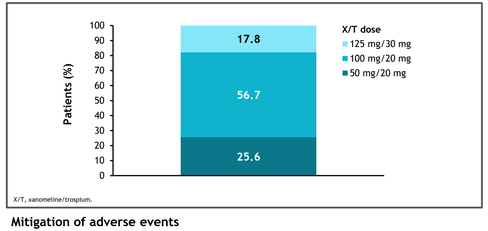
[a]25% reported titration ongoing at the time of data collection.

Figure 3. Length of time on xanomeline/trospium chloride 50 mg/20 mg[a]



[a]The recommended starting xanomeline/trospium chloride dosage is one 50 mg/20 mg capsule orally twice daily for at least 2 days.[7]

Figure 4. Maximum dose of X/T administered

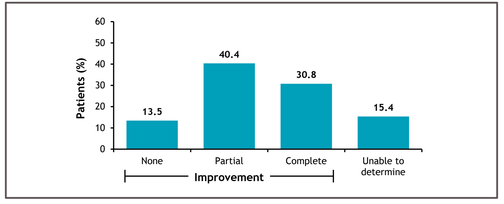


X/T, xanomeline/trospium.

Mitigation of adverse events

- A total of 64.4% and 36.7% of patients experienced nausea and vomiting, respectively
  - Among patients who experienced nausea or vomiting
    - 55% received pharmacologic intervention
    - 21% had their dose of X/T reduced
    - 24% required no intervention
  - The most common pharmacologic interventions were ondansetron and additional trospium
- An antiemetic was used prophylactically or as needed in 21.1% and 44.4% of patients, respectively. When used as needed, antiemetic treatment led to partial or complete improvement in 40.4% and 30.8% of patients, respectively (**Figure 5**)

Figure 5. Effect of pharmacologic treatment on nausea and vomiting



Conclusions

- X/T is being used across disease durations, from <1 year to >10 years since diagnosis
- This cohort of individuals was predominantly switched from atypical antipsychotics due to lack of efficacy and weight gain/metabolic issues
- X/T was most often chosen due to its novel MOA and favorable weight/metabolic profile
- The most common strategy for switching was cross-titration over 2-4 weeks
- Nausea and vomiting were still reported despite slower titration than that used in the pivotal trials
  - Nausea and vomiting were primarily and effectively treated with antiemetics
- **A new MOA requires a new way of thinking:** Although dose reductions are conventionally implemented for adverse event mitigation, the higher ratio of trospium in the xanomeline/trospium chloride 125 mg/30 mg dose may provide benefit in patients experience nausea or vomiting at the 100 mg/20 mg dose

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Acknowledgments

- The authors thank the participants and families who made the study possible and the clinical study team that participated
- This study was supported by Karuna Therapeutics, a Bristol Myers Squibb company
- All authors contributed to and approved the poster; writing and editorial assistance were provided by Gerard D'Angelo, PhD, and Paula Stuckart of Apollo Medical Communications, part of Helios Global Group, which was funded by Bristol Myers Squibb

Declaration of interests

CK is a consultant for Alexion, Amgen, Biogen, Bristol Myers Squibb, EMD Serono, Genzyme, and Teva. **JA** and **JH** are employees of Bristol Myers Squibb. **VH** was an employee of Bristol Myers Squibb at the time the analysis was conducted. **CB** is a speaker for Bristol Myers Squibb.

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Presented at the Psych Congress 2025, September 17-21, 2025, San Diego, CA, USA

Email: James.Appio@BMS.com