Budget impact analysis of xanomeline and trospium chloride for the treatment of adults with schizophrenia in the US

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Background

- Schizophrenia is a severe mental health condition characterized by disruptions in thought processes, perceptions, emotional responsiveness, and social interactions
- The estimated US prevalence of schizophrenia varies greatly from 0.3%-1.2% of the population[1-4], translating to ~1-3.8 million impacted individuals
- Commonly prescribed pharmacological treatment consists of first- and second-generation antipsychotics (SGAs). Choice of treatment is based on patient preferences, prior treatment responses, and other factors such as comorbidities, adherence history, and medication side effects[5]
- SGAs are often associated with chronic adverse events (AEs), including extrapyramidal symptoms, weight gain, diabetes, and other cardiometabolic conditions. These contribute to low treatment adherence and symptom relapses, thereby increasing inpatient and outpatient visits and direct healthcare costs[6-9]
- Xanomeline and trospium chloride (X/T), a muscarinic agonist, was approved by the Food and Drug Administration (FDA) for the treatment of adults with schizophrenia in September 2024. X/T's distinct mechanism of action may result in a differentiated efficacy, safety and tolerability profile.[10-14]

Objectives

- To estimate the budget impact of X/T as a second line (2L) therapy for adults with schizophrenia

Methods

- A budget impact model was developed in Microsoft Excel® to assess the financial implications of introducing X/T to a hypothetical 1-million member US health plan weighted across Medicare, Medicaid, and commercial plan types
- The model tracked a cohort of eligible patients, defined by payer-specific epidemiology estimates, across 2L and subsequent therapy over a 3-year time horizon
- Patients were assigned to either X/T, an oral generic or branded SGA, or a long-acting injectable (LAI), which is representative of the entire LAI treatment class; distribution between treatment options were based on market share estimates
- The model captured costs associated with drug acquisition, drug administration, and AE management
- While the oral SGAs are assumed to incur no administration costs, LAIs are injected and incur a $14.31 (2024 USD) cost per administration
- Select "chronic" AEs identified by the Institute of Clinical and Economic Review (ICER) as key cost drivers in schizophrenia were modeled: tardive dyskinesia (TD) and metabolic syndrome and its associated sequelae (diabetes and cardiovascular disease [CVD])
  - Patients that acquired these AEs continued to accrue management costs for the remainder of the time horizon
- To capture the distinct AE profile of X/T, the analysis also considered costs associated with the acute, "common" AEs reported in X/T's FDA prescribing information at a ≥ 5% incidence cut-off; common AE costs were also applied to comparators reporting the same AEs as X/T in their FDA prescribing information using the same cut-off
  - These AEs are those recorded during the acute phase (the first 4-8 weeks) of each treatments' pivotal trials
  - Common AE management costs capture the cost of a doctor visit and/or the assumed pharmaceutical treatment, depending on the AE

Table 1. Adverse event management costs

Cost Description	Annual Cost (2024 USD)
Chronic Adverse Event Management Costs	
Metabolic Syndrome	$1,798.91[15]
Diabetes[a]	$12,237.85[16]
Cardiovascular Disease[a]	$20,382.34[15, 17]
Tardive Dyskinesia	$32,116.96[18,b]
Acute, Common Adverse Event Management Costs[c]	
Outpatient Doctor Visit	$220.36[19]
Ondansetron (per 30-day Supply)[d]	$7.34[20]
Metoprolol (per 100 Count)[e]	$6.00[20]

Key: AE, adverse event; CVD, cardiovascular disease; TD, tardive dyskinesia; VMAT2, Vesicular Monoamine Transporter 2 (inhibitor); X/T, xanomeline and trospium chloride.
Notes: a). Diabetes and CVD are assumed to be consequences of metabolic syndrome and not direct AEs of treatment. b). TD costs capture direct healthcare costs, including inpatient and emergency room visits, but do not consider the cost of VMAT2 inhibitors (Ingrezza® and Austedo®). c). With the exception of hypertension, all common AEs are assumed to be transient; associated costs are accrued over 5-weeks (the duration of X/T's acute clinical trials). Costs are applied as one-off upon treatment initiation and occur during the initial 5-week period. Common AEs are assumed not to incur a prescription cost as these AEs are managed with over-the-counter medications. Common AEs are assumed to be managed by one outpatient doctor visit. d). Nausea/vomiting are assumed to be managed by a 30-day supply of ondansetron. e). Hypertension is assumed to require two outpatient visits. In the EMERGENT-4 trial, five of eight patients with hypertension required long-term medication. Therefore, a proportion (5/8 = 62.5%) of those with hypertension are assumed to accrue costs associated with metoprolol for the remainder of the 3-year time horizon.

BASE CASE RESULTS

Figure 2: Total budget impact per year

X/T results in an estimated budget impact ranging from ~$208,000 in Year 1 to ~$1.2M in Year 3

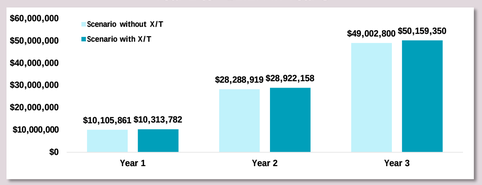


Figure 3: PTMPM budget impact over 3 years

X/T results in an estimated per treated member per month (PTMPM) budget impact ranging from $8 in Year 1 to ~$15 in Year 3

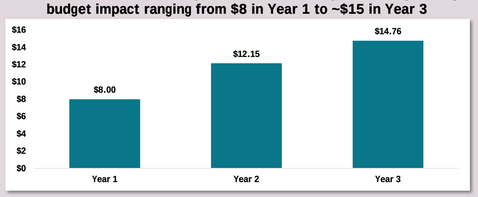


Figure 4: PMPM budget impact over 3 years

X/T results in an estimated PMPM budget impact ranging from $0.017 in Year 1 to $0.095 in Year 3

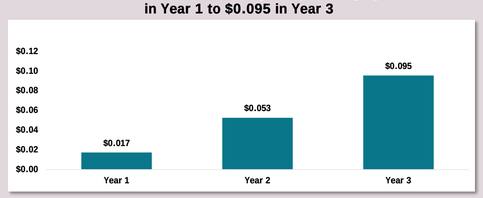
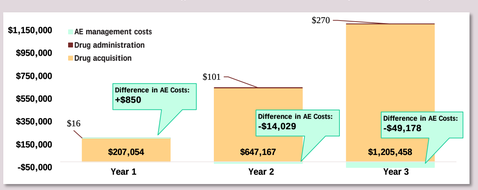


Figure 5: Total budget impact by cost category

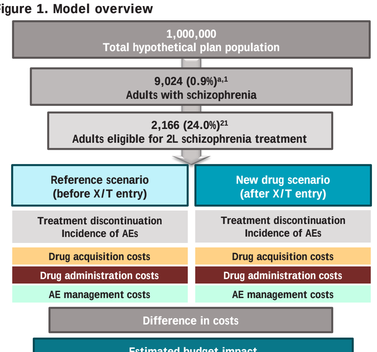
X/T results in an AE management cost offset of $62,357 over 3 years



Key: AE, adverse event; PMPM, per member per month; PTMPM, per treated member per month; X/T, xanomeline and trospium chloride.

- Base case comparators included the 10 treatments with the largest 2L market share (split between five granular treatments and five additional treatments captured under a 2L treatment basket)

Figure 1. Model overview



Key: 2L, second line; AE, adverse event; X/T, xanomeline and trospium chloride.
Notes: a). Prevalence of schizophrenia is weighted across Medicaid (47.9%), Medicare (41.7%), and commercial (10.4%) health plan types.

Table 2. Treatment-specific parameters

Treatment[a]	Market Share in Year 1[22,23]	30-Day Cost (USD 2024)[20]	Annual Discontinuation	Annual Incidence of TD	Annual Incidence of Metabolic Syndrome	Annual Risk of Type 2 Diabetes[47,h]	Annual Risk of CVD[47,h]
0. X/T	1.0%[b]	$1,850	57.1%[13,14]	0.0%[33]	2.9%[38,g]	0.1%	0.1%
1. Olanzapine (10 mg)	19.2%	$7.15	35.1%[24]	2.9%[34]	32.9%[39]	0.7%	0.5%
2. Risperidone (8 mg)	17.6%	$10.17	27.9%[24]	2.4%[34]	20.6%[39]	0.5%	0.3%
3. Aripiprazole (15 mg)	13.9%	$4.50	51.0%[24]	1.7%[34]	14.1%[40]	0.3%	0.2%
4. Quetiapine (400 mg)	11.5%	$9.01	70.7%[25]	2.5%[34]	16.7%[41]	0.4%	0.3%
5. LAIs[c]	14.4%	$3,478.70	58.5%[26]	0.5%[35]	43.1%[42]	1.0%	0.7%
6. 2L treatment basket[d]	*22.3%*						
6.a Lurasidone (120 mg)	34.0%	$40.65	51.3%[27]	4.8%[34]	34.8%[43]	0.8%	0.5%
6.b Ziprasidone (80mg)	21.4%	$35.00	54.3%[28]	3.5%[34]	2.9%[38,41,g]	0.1%	0.0%
6.c Paliperidone (9 mg)	16.7%	$95.00	71.4%[24]	0.5%[35e]	41.6%[44]	0.9%	0.6%
6.d Clozapine (200 mg)	11.9%	$182.90	25.8%[29]	4.2%[34]	37.8%[41]	0.8%	0.6%
6.e Vraylar® (cariprazine) (6 mg)	15.9%	$1,446.55	52.9%[30]	0.6%[36]	17.3%[45]	0.4%	0.3%
Caplyta® (lumateperone) (42 mg)[e]	-	$1,661.75	52.4%[f]	0.0%[37]	2.9%[38,46,g]	0.1%	0.0%
Rexulti® (brexpiprazole)[e]	-	$1,471.54	51.5%[31]	0.1%[31]	18.7%[31]	0.4%	0.3%
Lybalvi® (olanzapine/samidorphan)[e]	-	$1,599.20	37.1%[32]	2.3%[32]	21.6%[32]	0.5%	0.3%

Key: 2L, second line; 3L, third line; AE, adverse event; CVD, cardiovascular disease; FDA, Food and Drug Administration; LAI, long-acting injectable; SGAs, second-generation antipsychotics; TD, tardive dyskinesia; WAC, wholesale acquisition cost; X/T, xanomeline and trospium chloride.
Notes: a). Maximum recommended dose is selected for all treatments based on their FDA-approved labels. If a dose could not be given as one administration (e.g. maximum dose is not manufactured so multiple tablets would be required), the highest strength formulation is assumed. b). Analysis assumes that X/T market share increases by 1.0% annually and displaces all oral comparators equally. c). LAIs are included as a treatment class and represent a mix of individual LAIs. For cost and clinical inputs associated with LAIs, Invega Sustenna® (paliperidone palmitate) is used to represent all LAIs as it comprises the LAI largest market share. d). The 2L treatment basket comprises five additional treatments with smaller market share compared with the five granular 2L treatments. e). Caplyta®, Rexulti®, and Lybalvi® are not included in the base case set of 10 comparators because their market share is small compared with other treatments included in the base case. However, as these three treatments are among the newest to market, they are included in the analysis for a branded comparison to X/T. As market shares between 2L and 3L are similar, the same treatments are used in the initial line of therapy and the subsequent line of therapy. f). Due to a lack of long-term data, Caplyta® discontinuation is assumed equal to a market share-weighted average of the other branded agents (Vraylar®, Rexulti®, Lybalvi®). g). Long-term open label studies found no statistically significant rates of metabolic syndrome (or clinically significant weight gain as a proxy for metabolic syndrome, defined as ≥ 7.0% change from baseline) for X/T, Caplyta® and ziprasidone. To ensure consistency across treatments, the rate of metabolic syndrome for these treatments is assumed to be equal to rates of metabolic syndrome in the general population (as reported in Li et al. 2023). h). Diabetes and CVD estimates are calculated as consequences of metabolic syndrome and not direct AEs of treatment.

SCENARIO ANALYSIS

Table 3. Scenario analyses summary results

Summary Budget Impact Results	Year 1 (USD)	Year 2 (USD)	Year 3 (USD)
A. Budget impact results, without AEs			
Reference scenario	$9,532,655	$25,211,300	$41,316,934
New drug scenario	$9,739,725	$25,858,568	$42,522,662
Total budget impact, per year	$207,070	$647,268	$1,205,728
PMPM budget impact	$0.0173	$0.0537	$0.0995
B. Budget impact results versus branded agents			
Reference scenario	$19,404,977	$49,427,235	$76,138,788
New drug scenario	$19,450,710	$49,552,708	$76,351,984
Total budget impact, per year	$45,734	$125,472	$213,196
PMPM budget impact	$0.0038	$0.0104	$0.0176
C. Budget impact results, no discontinuation from 2L treatment			
Reference scenario	$10,231,527	$28,820,044	$49,754,105
New drug scenario	$10,487,746	$29,774,977	$51,830,671
Total budget impact, per year	$256,219	$954,933	$2,076,566
PMPM budget impact	$0.0214	$0.0792	$0.1713

Key: 2L, second line; AE, adverse event; PMPM, per member per month.

Key assumptions

- Market share estimates, without X/T, are assumed to be static across the 3-year time horizon
- Following X/T's introduction, market share is assumed to be 1.0% in Year 1, 2.0% in Year 2, and 3.0% in Year 3. X/T is assumed to pull market share equally from the oral SGAs
- The analysis uses wholesale acquisitions costs to estimate drug acquisition costs (no rebates or discounts are applied). This may overestimate annual drug costs, particularly for branded agents
- With the exception of hypertension, which is associated with long-term metoprolol use in the model, all other common AEs are assumed to occur only once upon treatment initiation, and are transient by nature
- Select AEs are assumed to be chronic and not resolved within the 3-year time horizon. Once patients experience a select AE, they accrue associated costs for the remainder of the time horizon
- Patients who initiate X/T are assumed to be adherent to therapy until they discontinue and will not reinitiate X/T following discontinuation. The model does not account for patients in the real world who may reinitiate therapy and experience the common transient AEs again
- As X/T did not demonstrate clinically meaningful weight gain (used as a proxy for metabolic syndrome) in the EMERGENT-4 and EMERGENT-5 trials, the rate of metabolic syndrome associated with X/T is assumed to be equivalent to the rate of metabolic syndrome for the general population, in line with the assumption made for Caplyta® and ziprasidone
- There is significant variability, and a lack of data associated with the duration of each line of therapy and its relationship to AE rates. Thus, discontinuation rates and treatment-specific AE rates are assumed to be equivalent across all lines of therapy
- Only the costs of select chronic AEs and the most common AEs for X/T were costed in this analysis. This may underestimate the total cost of AE management
- The analysis does not account for the approval and use of vesicular monoamine transporter 2 inhibitors for the treatment of TD, which may underestimate associated AE management costs

Results

- In a hypothetical 1,000,000-member health plan with commercial, Medicare, and Medicaid patients, approximately 2,166 individuals are eligible for treatment with X/T in Year 1, rising to 2,187 by Year 3
- Introducing X/T as a 2L treatment for schizophrenia to this hypothetical plan results in an estimated additional cost of $207,921 in Year 1 up to $1,156,550 in Year 3
- X/T results in a per member per month (PMPM) budget impact ranging from $0.017 in Year 1 up to $0.095 in Year 3
- Estimated PMPM was lower with a comparator basket limited to branded treatments but higher in a scenario with no discontinuation from 2L therapy onto subsequent treatment
- Sensitivity analysis indicated results were sensitive to schizophrenia epidemiology inputs and X/T acquisition costs

Conclusions

The introduction of X/T as a 2L therapy for adults with schizophrenia in a hypothetical 1,000,000-member health plan is projected to incur a modest PMPM budget impact and a potential reduction in AE costs when compared with other commonly utilized schizophrenia treatments

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