Comparative Efficacy, Safety, and Tolerability of Xanomeline and Trospium Chloride versus Eight Atypical Antipsychotics for the Acute Treatment of Adults with Schizophrenia - A Network Meta Analysis

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Objective

- To expand prior network meta-analyses (NMAs) investigating the relative efficacy, safety, and tolerability of xanomeline and trospium for the acute treatment of schizophrenia[1], to facilitate indirect comparison of xanomeline/trospium with aripiprazole, cariprazine, olanzapine, risperidone, brexpiprazole, quetiapine, clozapine, and lumateperone

Conclusions

- Xanomeline/trospium treatment significantly improved odds of clinical response versus aripiprazole, brexpiprazole, and cariprazine, and reduced odds of clinically significant weight gain versus aripiprazole, brexpiprazole, cariprazine, lumateperone, olanzapine, quetiapine, and risperidone
- Further favorable results for xanomeline/trospium included improvements in: change from baseline (CFB) Clinical Global Impression – Severity (CGI-S) scale versus aripiprazole, brexpiprazole, cariprazine, and olanzapine; CFB Positive and Negative Syndrome Scale (PANSS) positive symptoms score versus brexpiprazole; and CFB weight versus brexpiprazole, clozapine, olanzapine, quetiapine, and risperidone
- Base case and scenario analyses also suggested that acute treatment with xanomeline/trospium had a higher relative odds of all-cause discontinuation than all comparators except cariprazine. However, the unadjusted absolute all-cause discontinuation rates from EMERGENT 1, 2, and 3 were generally lower than those from comparator studies (for both intervention and placebo arms). A smaller absolute difference in rates relative to placebo can result in a greater odds ratio (OR) when the baseline placebo rate is lower
- In this NMA, xanomeline/trospium compares favorably to comparator atypical antipsychotics. These findings support the compound as the first in a new class of medications to treat schizophrenia based on muscarinic receptor agonism, without any direct dopamine D_2 receptor-blocking activity

Limitations

- Substantial heterogeneity was present in NMAs (base case and scenario analyses) for ≥ 30% improvement in PANSS total score, CFB PANSS scores (total, positive symptoms, negative symptoms), CFB CGI-S score, CFB weight, and somnolence endpoints. In each case, I^2 values > 50% were observed between studies contributing direct evidence for at least one treatment pair within the network. Potential reasons for this include:
  - Inclusion of evidence for any treatment dose within the Food and Drug Administration (FDA) label ranges without consideration of potential dose–efficacy relationships
  - Population differences with respect to race (the EMERGENT studies were outliers that enrolled majority black populations)
  - Variability of placebo effect size between included studies
- Lack of reported data precluded inclusion of clozapine in NMAs for several endpoints

Introduction

- Current antipsychotics – most of which have direct D_2 dopamine receptor-blocking activity – are associated with well-established efficacy and tolerability limitations.[2,3] There is a high level of unmet need for more effective, better-tolerated treatment options with a different mechanism of action for people with schizophrenia
- Xanomeline/trospium is a new FDA-approved treatment for people with schizophrenia, with a novel mechanism of action based on muscarinic receptor agonism
- The efficacy and safety of xanomeline/trospium has been studied in three 5-week, randomized, double-blind, placebo-controlled clinical trials: EMERGENT-1 (NCT03697252)[4], EMERGENT-2 (NCT04659161)[5], and EMERGENT-3 (NCT04738123)[6]

Methods

Evidence base:

- An updated systematic literature review (SLR) was conducted, building on an existing 2019 SLR[7], to identify randomized controlled trials (RCTs) of eight comparator oral antipsychotics for the acute treatment of adults with schizophrenia
- The updated search, covering the period from January 1, 2019, to March 20, 2024, also re-evaluated previously identified records against newly established inclusion criteria. The SLR assessed key databases, including MEDLINE®, Embase®, MEDLINE In-Process, PsycInfo®, CENTRAL, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), and ClinicalTrials.gov. Publications retrieved through these searches were evaluated against pre-defined population, intervention, comparators, outcomes, study design (PICOS) criteria, as outlined in **Table 1**

Table 1. Inclusion criteria for the acute treatment SLR update

Category	Inclusion criteria
Population	Adult (≥ 18 years) hospitalized patients with schizophrenia
Interventions/ comparators	Oral formulations for the acute treatment of schizophrenia, specifically: aripiprazole, cariprazine, olanzapine, risperidone, brexpiprazole, quetiapine, clozapine, lumateperone
Outcomes	• Changes in PANSS scores (total, positive sub-score, negative sub-score) from baseline • Percentage of patients with a ≥ 30% improvement in PANSS total score • Discontinuation rates due to all causes and AEs • Percentage with > 7% increase from baseline and change from baseline weight • Changes from baseline CGI-S and response rates (CGI-S of 1 or 2) • Percentage that experienced somnolence/sedation
Study design	• Blinded RCTs • Systematic reviews[b]

Key: AE, adverse event; CGI-S, Clinical Global Impressions - Severity; PANSS, Positive and Negative Syndrome Scale; RCT, randomized controlled trial; SLR, systematic literature review.
Notes: [a] Studies assessing mixed populations (any schizoaffective disorder) with > 80% of the population of interest or reporting separate subgroup data for the population of interest were included and extracted. [b] Relevant SLRs and meta-analyses were included during the title/abstract review stage to identify any additional studies not found in the database searches. Reference lists were hand-searched; however, studies were excluded during the full-text review unless they reported primary, original research.

- A feasibility assessment excluded 53 studies identified by the SLR from the network meta-analysis (NMA). This was due to substantial differences in trial design, patient population, and treatment regimen; and/or the inability to form network connections

Statistical analysis:

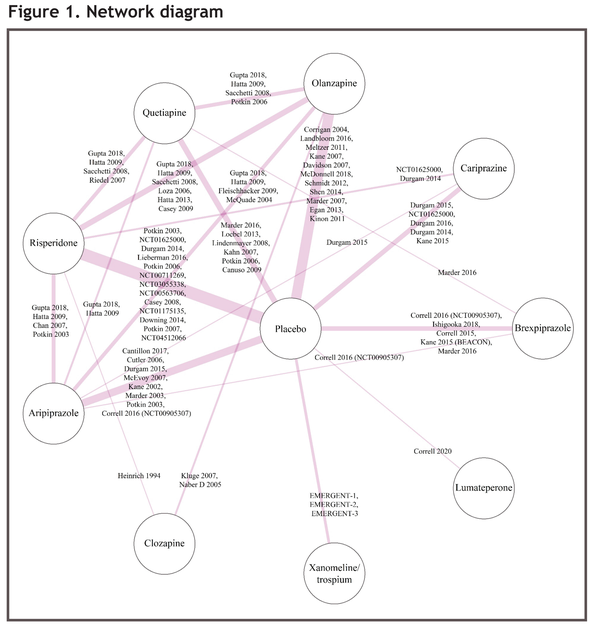
- Bayesian random-effects NMAs were conducted for eleven outcomes following guidance from the National Institute for Health and Care Excellence (NICE)[8]: ≥ 30% improvement in Positive and Negative Syndrome Scale (PANSS) total score, all-cause discontinuation, discontinuation due to adverse events (AEs), sedation, somnolence, clinically meaningful weight gain (≥ 7% increase), change from baseline (CFB) PANSS scores (total, positive symptoms, and negative symptoms), CFB Clinical Global Impressions – Severity (CGI-S) score, and CFB weight
- Endpoint data were reported across comparator studies following 4–6 weeks of acute treatment, based on the duration of the trials and the timing of assessments
- Within studies, endpoint data were pooled for treatment arms that shared the same investigated treatment but with different dosing regimens within FDA label dose ranges. Study arms that investigated doses outside the Food and Drug Administration (FDA) label range were excluded from NMA
- I^2 statistics – derived from direct head-to-head meta-analysis of those treatment comparisons in each network that are reported by more than one study – were used to assess statistical heterogeneity, while node-splitting analyses were conducted to assess consistency[9,10]
- Sensitivity analyses investigated the impact of excluding studies that enrolled exclusively or predominantly Asian populations and studies with outlier placebo effect size
- All analyses were conducted in R using the gemtc package[11,12]

Results

Evidence network:

- The SLR identified 3,664 unique references. Following deduplication, 2,232 records proceeded to title and abstract screening, where 1,836 records were excluded. Full-text evaluation of the remaining 396 references resulted in the exclusion of 368 records. An additional 114 records, identified from other sources, brought the total to 142 records from 111 unique studies.
- A connected network of 58 eligible RCTs was formed (**Figure 1**). NMAs for each endpoint investigated included only a subset of these studies that had relevant published endpoint data, since data were not available from all 58 studies for all eleven endpoints analyzed. The endpoint-specific base case networks included between 17 and 45 studies
- Clozapine endpoint data were only available for discontinuation due to all causes, discontinuation due to AEs, and CFB weight. Clozapine is only included in NMAs for these three endpoints

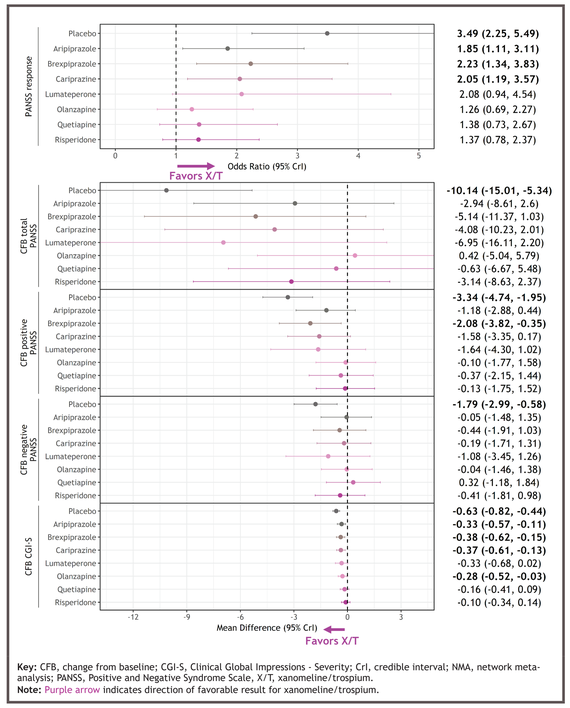
Figure 1. Network diagram



Efficacy endpoints:

- Xanomeline/trospium treatment significantly improved odds of achieving ≥ 30% improvement in PANSS total score versus aripiprazole (odds ratio [OR]: 1.85; 95% credible interval [CrI]: 1.11, 3.11), brexpiprazole (OR: 2.23; 95% CrI: 1.34, 3.83), and cariprazine (OR: 2.05; 95% CrI: 1.19, 3.57). OR point estimates versus lumateperone, olanzapine, quetiapine, and risperidone were also numerically favorable for xanomeline/trospium but were not statistically significant
- For the CFB PANSS scores (total, positive symptoms, negative symptoms), the NMAs yielded results between xanomeline/trospium and active comparator treatments that numerically favored xanomeline/trospium but were not statistically significant. However, there were several noteworthy exceptions:
  - Xanomeline/trospium versus brexpiprazole results significantly favored xanomeline/trospium for PANSS positive symptoms score (mean difference [MD]: -2.08; 95% CrI: -3.82, -0.35)
  - Olanzapine had a numerical advantage over xanomeline/trospium for CFB total PANSS score
  - Quetiapine had a numerical advantage over xanomeline/trospium for CFB PANSS negative symptoms score
- Xanomeline/trospium also demonstrated statistically significant improvement in CFB CGI-S score compared with aripiprazole (MD: -0.33; 95% CrI: -0.57, -0.11), brexpiprazole (MD: -0.38; 95% CrI: -0.62, -0.15), cariprazine (MD: -0.37; 95% CrI: -0.62, -0.13), and olanzapine (MD: -0.28; 95% CrI: -0.52, -0.03), and numerically favorable results versus lumateperone, quetiapine, and olanzapine
- The base case CFB PANSS total score analysis produced statistically significant evidence of inconsistency (inconsistency factor [IF] ≠ 0). As such, the scenario analysis excluding studies with predominantly Asian patient populations (which did not show similar evidence of inconsistency) was preferred, though the results (presented in **Figure 2**) were consistent with the base case

Figure 2. NMA results of efficacy endpoints

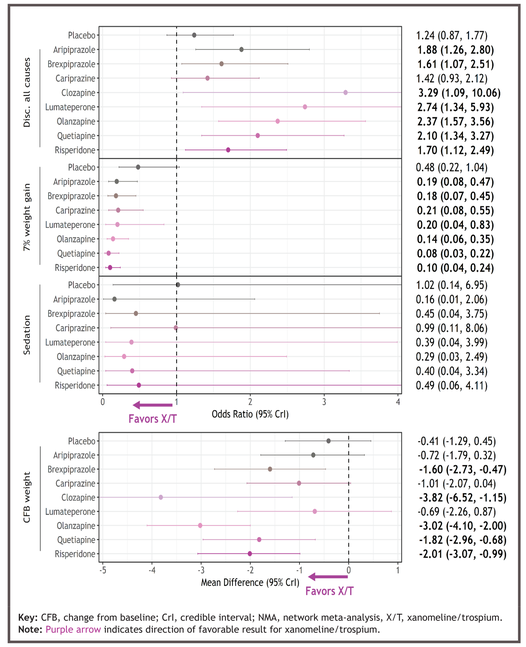


Key: CFB, change from baseline; CGI-S, Clinical Global Impressions - Severity; CrI, credible interval; NMA, network meta-analysis; PANSS, Positive and Negative Syndrome Scale, X/T, xanomeline/trospium.
Note: Purple arrow indicates direction of favorable result for xanomeline/trospium.

Safety and tolerability endpoints:

- Xanomeline/trospium had a statistically significantly lower odds of clinically meaningful weight gain versus all active treatments (except clozapine, for which there were no data available for this endpoint). ORs ranged from 0.08 (95% CrI: 0.03, 0.22) versus quetiapine to 0.21 (95% CrI: 0.08, 0.55) versus cariprazine
- NMA results for the continuous CFB weight endpoint were largely consistent with statistically significant favorable results for xanomeline/trospium compared with brexpiprazole, clozapine, olanzapine, quetiapine, and risperidone. CFB weight results versus aripiprazole, cariprazine, and lumateperone were numerically favorable for xanomeline/trospium but did not achieve statistical significance. Due to inconsistency in the base case analysis, the scenario analysis that excluded studies with outlier placebo effect size was preferred for this endpoint (results presented in **Figure 3**), though the base case had largely consistent findings (the only difference being an additional favorable statistically significant result for xanomeline/trospium versus cariprazine)
- The results for discontinuation due to all causes were unfavorable for xanomeline/trospium, with statistically significantly higher odds for xanomeline/trospium than all active comparators except cariprazine (for which the result was numerically unfavorable)
- No statistically significant differences in odds of sedation were found between xanomeline/trospium and active comparators, though point estimates generally favored xanomeline/trospium
- NMAs were also performed for discontinuation due to AEs and somnolence. However, statistically significant inconsistency (IF ≠ 1) was present in base case analyses and all scenario analyses investigated. As such, we do not present results for these endpoints in **Figure 3**. No statistically significant results were found by the NMAs of these endpoints

Figure 3. NMA results of tolerability and safety endpoints



Key: CFB, change from baseline; CrI, credible interval; NMA, network meta-analysis, X/T, xanomeline/trospium.
Note: Purple arrow indicates direction of favorable result for xanomeline/trospium.

References

1. Hickey, C., et al. (2024). "CO135 Comparative Efficacy, Safety, and Tolerability of xanomeline/trospium Versus Aripiprazole and Cariprazine for the Acute Treatment of Adults With Schizophrenia: A Network Meta-Analysis." Value in Health 27(6): S42. | 2. Leucht S et al. Am J Psychiatry. 2017; 174(10):927-42 | 3. McCutcheon RA et al. JAMA Psychiatry. 2020; 77(2):201-10 | 4. Brannan SK et al. N Engl J Med. 2021; 384(8):717-26 | 5. Corell CU et al. Poster presentation at ECNP. Oct 15-18, 2022; Vienna. P.0193 | 6. Tamminga C et al. Oral presentation at SIRS. May 11-15, 2023; Toronto | 7. Huhn M NA et al. Focus. 2020; 18(4):443-55 | 8. Dias S et al. NICE DSU Technical Support Document 2. 2011. https://www.ncbi.nlm.nih.gov/books/NBK310366/pdf/Bookshelf_NBK310366.pdf. Accessed: April 9, 2024 | 9. Higgins JP et al. Stat Med. 2002; 21(11):1539-58 | 10. Van Valkenhoef G et al. Res Synth Methods. 2016; 7(1):80-93 | 11. R core team. 2021. https://www.R-project.org/. Accessed: April 9, 2024 | 12. Van Valkenhoef G et al. 2016. https://CRAN.R-project.org/package=gemtc. Accessed: April 9, 2024.

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Declaration of interests

KK, KK, and MFS are employees of Bristol Myers Squibb. CH, AG, JYAC, and VT are employees of Lumanity, which was a paid consultant to Bristol Myers Squibb. They did not receive direct payment as a results of this work outside of their normal salary payments. AJC is an employee and board member of the Neuroscience Education Institute and has received advising, consulting, and/or speaking fees in the prior 24 months from AbbVie, Acadia, Akili Interactive, Alfasigma, Alkermes, Axsome, Biogen, BioXcel, Boehringer Ingelheim, Bristol Myers Squibb, Cerevel, Idorsia, Intra-Cellular Therapies, Janssen, Lundbeck, Luye, Neumora, Neurocrine, Noven, Otsuka, Pear Therapeutics, Relmada, Sage Therapeutics, Sunovion, Supernus, Teva, and VistaGen.

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