Comparative Efficacy and Safety of Lumateperone and Other Atypical Antipsychotics Approved as Adjunctive Therapy for Major Depressive Disorder: A Network Meta-Analysis

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Background

- Many adults with MDD do not achieve adequate symptom control with ADT alone and may require adjunctive treatment.
- Five atypical antipsychotics are approved in the United States as adjunctive therapy for adults with MDD: aripiprazole, brexpiprazole, cariprazine, lumateperone, and quetiapine XR.
- Lumateperone was approved in 2025, and comparative evidence versus other approved adjunctive atypical antipsychotics is limited.
- In the absence of head-to-head clinical trials, a network meta-analysis can help clarify the relative efficacy and safety within current psychopharmacology practice.

Objective

To compare the efficacy and safety of lumateperone with other atypical antipsychotics approved as adjunctive therapy for adults with MDD and inadequate response to ADT.

Methods

Study design and data sources

- Registrational trials were identified from Section 14 of the respective United States product labeling and included 10 short-term, randomized, double-blind, placebo-controlled trials of adjunctive aripiprazole[1,2], brexpiprazole[3,4], cariprazine[5,6], lumateperone[7,8], and quetiapine XR[9,10] (**Table 1**). Together, these studies formed a placebo-anchored, star-shaped network with 11 treatment-dose nodes (**Figure 1**).
- Eligibility criteria, study design, and baseline patient characteristics (e.g., age, sex, race, BMI, and MDD severity) were broadly aligned across trials, supporting indirect comparison; all studies were assessed as low risk of bias (**Table 1**).

Figure 1. NMA network

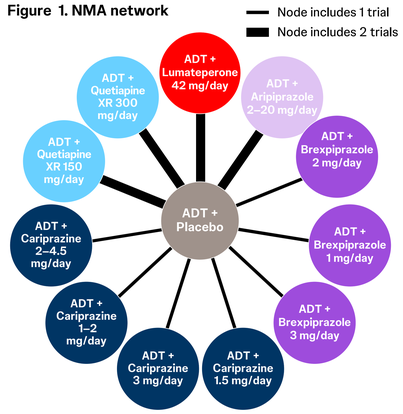

Table 1. Key characteristics of included registrational trials

Trials	Study Phase	Dosage type	Dosage	Trial design	Geographic distribution
Lumateperone NCT04985942	3	Fixed dose	42 mg/day	Screening; **6-week double blind treatment phase**	United States, Bulgaria, Czech Republic, Hungary, India, Slovakia, South Korea
Lumateperone NCT05061706	3	Fixed dose	42 mg/day	Screening; **6-week double blind treatment phase**	United States, Argentina, Bulgaria, Germany, Poland, Sweden
Aripiprazole NCT00095823	3	Flexible dose	2–20 mg/day	Screening; 8-week single blind prospective antidepressant therapy treatment phase; **6-week double blind treatment phase**	United States
Aripiprazole NCT00095758	3	Flexible dose	2–20 mg/day	Screening; 8-week single blind prospective antidepressant therapy treatment phase; **6-week double blind treatment phase**	United States
Brexpiprazole NCT01360645	3	Fixed dose	2 mg/day	Screening; 8-week single blind prospective antidepressant therapy treatment phase; **6-week double blind treatment phase**	United States, Poland, France, Canada, Slovakia
Brexpiprazole NCT01360632	3	Fixed dose	1 mg/day 3 mg/day	Screening; 8-week single blind prospective antidepressant therapy treatment phase; **6-week double blind treatment phase**	United States, Germany, Ukraine, Russia, Hungary, Canada, Romania
Cariprazine NCT03738215	3	Fixed dose	1.5 mg/day 3 mg/day	Screening; **6-week double blind treatment phase**	United States, Bulgaria, Estonia, Germany, Hungary, Ukraine, and the United Kingdom
Cariprazine NCT01469377	2	Flexible dose	1–2 mg/day 2–4.5 mg/day	Screening; **8-week double blind treatment phase**	United States, Estonia, Finland, Slovakia, Sweden, Ukraine
Quetiapine XR NCT00326105	3	Fixed dose	150 mg/day 300 mg/day	Screening; **6-week double blind treatment phase**	United States
Quetiapine XR NCT00351910	3	Fixed dose	150 mg/day 300 mg/day	Screening; **6-week double blind treatment phase**	Australia, Canada, Europe, and South Africa

Note: For three trials, the dosages evaluated differed slightly from the FDA-approved recommended dose ranges for aripiprazole (2–15 mg/day) and cariprazine (1.5–3 mg/day).

Outcomes and analyses

- Outcomes included efficacy endpoints and adverse events consistently reported and available for ≥9 of 10 trials.
- Outcomes at Week 6 were used for all comparisons, except for cariprazine (NCT01469377), for which Week 8 data were used for MADRS remission, CGI-S, and all safety outcomes. Missing SE were imputed using the mean SE from other trials, as applicable.
- Bayesian fixed-effect NMAs were conducted using 3 Markov Chain Monte Carlo simulations with 30,000 iterations each, including 20,000 burn-in iterations. Normal likelihoods were used for continuous outcomes and binomial likelihoods for binary outcomes with non-informative priors.
- Treatment effects were reported for all active treatment-dose + ADT versus placebo + ADT. In addition, pairwise comparisons along with probabilities of superiority were reported; a probability of superiority >85% (<15%) indicated that a treatment was favored (unfavored) versus the comparator. Network-wide treatment rankings were summarized using SUCRA.

Results

Efficacy

- All active treatment-dose nodes but cariprazine 3 mg/day were favored versus placebo + ADT for MADRS response (**Figure 2**). Similar patterns were observed for other efficacy endpoints, with most or all active treatment-nodes favored versus placebo + ADT: 6/11 were favored for MADRS remission, 11/11 nodes for MADRS change from baseline, and 10/11 for CGI-S change from baseline.
- Compared with placebo + ADT, lumateperone 42 mg/day had the largest effect among all active treatment-nodes for all studied efficacy endpoints, that is MADRS response (OR 2.33; 95% CrI 1.75, 3.07), MADRS remission (OR 2.21; 95% CrI 1.56, 3.04), MADRS change from baseline (MD -4.70; 95% CrI -5.77, -3.63), and CGI-S change from baseline (MD -0.60; 95% CrI -0.74, -0.46).
- In pairwise comparisons, lumateperone 42 mg/day was favored versus most active treatment-nodes for MADRS response and remission and versus all regimens for MADRS change from baseline and CGI-S change from baseline.
- Lumateperone 42 mg/day had the highest likelihood of ranking first across all efficacy outcomes (SUCRA: MADRS response 91.9%; MADRS remission 90.4%; MADRS change from baseline 97.4%; CGI-S 98.9%) (**Table 2**).

Safety

- Safety profiles varied across treatments.
- Lumateperone 42 mg/day was the only regimen favored versus placebo + ADT for ≥7% weight increase (**Figure 3**) and ranked first on both weight-related endpoints based on SUCRA values.
- Relative to placebo + ADT, lumateperone showed essentially no mean weight increase (MD -0.08; 95% CrI -0.30, 0.14) and a 94% probability of lower risk of ≥7% weight increase (OR 0.40; 95% CrI 0.04, 1.38).
- Akathisia was unfavorable versus placebo + ADT for 9/11 treatment-dose nodes; for lumateperone, the OR was 3.95 (95% CrI, 0.40 to 17.61). Based on SUCRA values, lumateperone ranked third best after placebo + ADT.
- Somnolence was unfavorable versus placebo + ADT for 10/11 treatment-dose nodes; for lumateperone, the OR was 6.02 (95% CrI 2.86, 12.13). Based on SUCRA values, lumateperone ranked sixth best after placebo + ADT.

Figure 2. MADRS response with atypical antipsychotics + ADT vs placebo + ADT

Odds ratio > 1 favors active comparator (greater odds of MADRS response)

Treatment	Odds ratio (mean)	Credible interval (95%)	Probability of superiority
Lumateperone 42 mg/day	2.33	(1.75, 3.07)	100%
Aripiprazole 2–20 mg/day	1.94	(1.38, 2.68)	100%
Brexpiprazole 1 mg/day	1.90	(1.11, 3.06)	99%
Brexpiprazole 3 mg/day	1.88	(1.09, 3.03)	99%
Brexpiprazole 2 mg/day	1.72	(0.97, 2.83)	97%
Quetiapine XR 300 mg/day	1.64	(1.18, 2.23)	100%
Cariprazine 1–2 mg/day	1.62	(1.11, 2.27)	99%
Cariprazine 2–4.5 mg/day	1.54	(1.07, 2.16)	99%
Cariprazine 1.5 mg/day	1.49	(1.02, 2.10)	98%
Quetiapine XR 150 mg/day	1.37	(0.98, 1.85)	97%
Cariprazine 3 mg/day	1.22	(0.84, 1.72)	83%

Note: MADRS response was defined as a ≥50% or >50% reduction in MADRS score from baseline, depending on trials.

Probabilities >99.5% are listed as 100% due to rounding.

Figure 3. MADRS remission with atypical antipsychotics + ADT vs placebo + ADT

Odds ratio > 1 favors active comparator (greater odds of MADRS remission)

Treatment	Odds ratio (mean)	Credible interval (95%)	Probability of superiority
Lumateperone 42 mg/day	2.21	(1.56, 3.04)	100%
Aripiprazole 2–20 mg/day	1.93	(1.32, 2.77)	100%
Quetiapine XR 300 mg/day	1.85	(1.32, 2.54)	100%
Brexpiprazole 2 mg/day	1.89	(0.92, 3.51)	96%
Quetiapine XR 150 mg/day	1.55	(1.10, 2.13)	99%
Brexpiprazole 1 mg/day	1.49	(0.79, 2.60)	88%
Brexpiprazole 3 mg/day	1.42	(0.74, 2.48)	84%
Cariprazine 1.5 mg/day	1.13	(0.74, 1.66)	69%
Cariprazine 2–4.5mg/day	1.13	(0.77, 1.61)	71%
Cariprazine 1–2 mg/day	1.12	(0.76, 1.59)	69%
Cariprazine 3 mg/day	0.67	(0.42, 1.02)	3%

Note: MADRS remission was defined as a score ≤10 in the cariprazine, lumateperone, and quetiapine XR trials, and as a score ≤10 with a ≥50% reduction from baseline in the aripiprazole and brexpiprazole trials.

Probabilities >99.5% are listed as 100% due to rounding.

Figure 4. ≥7% weight increase with atypical antipsychotics + ADT vs placebo + ADT

Odds ratio < 1 favors active comparator (lower odds of ≥7% weight increase)

Treatment	Odds ratio (mean)	Credible interval (95%)	Probability of superiority
Lumateperone 42 mg/day	0.40	(0.04, 1.38)	94%
Cariprazine 1–2 mg/day	0.95	(0.18, 2.91)	66%
Cariprazine 3 mg/day	2.90	(0.23, 13.09)	31%
Cariprazine 2–4.5 mg/day	2.18	(0.60, 6.03)	15%
Quetiapine XR 150 mg/day	2.27	(0.63, 6.38)	14%
Brexpiprazole 2 mg/day	2.39	(0.65, 6.88)	12%
Brexpiprazole 3 mg/day	3.83	(0.39, 16.57)	19%
Quetiapine XR 300 mg/day	4.73	(1.52, 12.57)	0%
Cariprazine 1.5 mg/day	9.96	(1.39, 42.52)	1%
Brexpiprazole 1 mg/day	11.04	(1.68, 44.68)	0%
Aripiprazole 2–20 mg/day	18.74	(3.11, 76.85)	0%

Note: A weight increase of ≥7% or more is a clinically meaningful threshold that is commonly used to identify potentially important treatment-related weight gain.

Table 2. SUCRA values for efficacy and safety outcomes

	Lumateperone 42 mg/day	Brexpiprazole 2 mg/day	Aripiprazole 2–20 mg/day	Quetiapine XR 300 mg/day	Cariprazine 1.5 mg/day	Quetiapine XR 150 mg/day	Cariprazine 2–4.5 mg/day	Brexpiprazole 3 mg/day	Cariprazine 3 mg/day	Brexpiprazole 1 mg/day	Cariprazine 1–2 mg/day	Placebo + ADT
Efficacy Outcomes												
MADRS response	91.9%	55.6%	73.7%	55.4%	41.9%	30.9%	45.1%	65.5%	18.9%	67.2%	51.8%	2.5%
MADRS remission	90.4%	71.9%	79.8%	78.2%	32.2%	60.3%	31.7%	49.6%	1.5%	54.6%	30.7%	20.1%
MADRS change from baseline	97.4%	73.5%	69.1%	66.3%	60.0%	56.7%	49.3%	42.6%	33.5%	25.5%	21.9%	1.9%
CGI-S change from baseline	98.9%	63.7%	81.9%	64.2%	57.0%	67.5%	38.7%	36.6%	37.6%	26.6%	21.4%	4.1%
Safety Outcomes												
≥7% weight increase	95.6%	52.4%	8.3%	28.7%	20.3%	55.0%	54.9%	50.1%	59.4%	17.1%	81.7%	77.6%
Weight change from baseline	97.8%	18.2%	13.2%	29.6%	74.5%	64.4%	50.1%	14.3%	66.8%	28.9%	49.5%	93.0%
Akathisia	69.6%	28.3%	33.5%	62.0%	32.6%	78.5%	13.7%	34.0%	15.7%	75.8%	62.1%	93.9%
Somnolence	37.8%	23.2%	71.1%	19.8%	71.0%	28.0%	66.6%	11.2%	78.4%	21.7%	73.5%	96.7%

Abbreviations: ADT: antidepressant therapy; BMI: body mass index; CGI-S: Clinical Global Impression-Severity; CrI: credible interval; MADRS: Montgomery-Asberg Depression Rating Scale; MD: mean difference; MDD: major depressive disorder; NMA: network meta-analysis; OR: odds ratio; SUCRA: surface under the cumulative ranking curve; XR: extended release.

Conclusions

- In this NMA, lumateperone demonstrated a favorable efficacy profile versus other approved adjunctive antipsychotics, with no weight change.
- Balancing efficacy and safety is crucial when selecting adjunctive antipsychotic treatment for MDD to optimize patient care. These findings may inform treatment selection, health economic evaluations, and reimbursement discussions in adults with MDD requiring adjunctive therapy.

Limitations

- Findings are based exclusively on indirect comparisons, as no head-to-head randomized controlled trials of atypical antipsychotics as adjunctive therapy in MDD are available; consequently, findings rely on the validity of key NMA assumptions, including transitivity.
- Cross-trial differences may remain despite overall similarity in design and patient characteristics.
- Because the evidence base was limited to registrational trials, findings may not fully reflect broader routine-care populations.

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Disclosures

- QZ, CM, MH, MN, and JJS are employees of Johnson & Johnson Innovative Medicine; AEK was an employee at the time of study.
- AL, TIT, MGL, YW, JL, DP, and PL are employees of Analysis Group ULC and Analysis Group Inc., which received consulting fees from Johnson & Johnson Innovative Medicine for this study.
- AJC served as a consultant to AbbVie, Alkermes, Axsome, Bristol Myers Squibb, Johnson & Johnson, Neurocrine, Otsuka, Supernus, Teva, Vanda, Luye, and 4M Therapeutics; has participated in speakers bureau activities for AbbVie, Alkermes, Axsome, Bristol Myers Squibb, Johnson & Johnson, Neurocrine, Otsuka, Supernus, Teva, Vanda, and Luye; and holds stock/equity in 4M Therapeutics (privately held company).
- LC has served as a consultant to AbbVie/Allergan, Acadia, Adamas, Adheretech, Alkermes, Alumis, Angelini, Astellas, Autobahn, Avanir, Axsome, Biogen, BioXcel, Bristol-Myers Squibb, Boehringer Ingelheim, Cadent Therapeutics, Cerevel, Clinilabs, COMPASS, Delpor, Draig Therapeutics, Eisai, Enteris BioPharma, HLS Therapeutics, Idorsia, INmune Bio, Impel, Intra-Cellular Therapies, Janssen, Karuna, Lundbeck, Luye, Lyndra, MapLight, Marvin, Medavante-ProPhase, Merck, Mitsubishi-Tanabe Pharma, Neumora, Neurocrine, Neurelis, Noema, Novartis, Noven, Otsuka, Ovid, Praxis, Recordati, Relmada, Reviva, Sage, Sumitomo/Sunovion, Supernus, Teva, University of Arizona, Vanda, Wells Fargo, and one-off ad hoc consulting for individuals/entities conducting marketing, commercial, or scientific scoping research; speaker for AbbVie/Allergan, Acadia, Alkermes, Angelini, Axsome, BioXcel, Bristol-Myers Squibb, Eisai, Idorsia, Intra-Cellular Therapies, Janssen, Lundbeck, Neurocrine, Neopharm, Noven, Otsuka, Recordati, Sage, Sunovion, Takeda, Teva, Vanda, and CME activities organized by medical education companies such as Medscape, NACCME, NEI, Vindico, and Universities and Professional Organizations/Societies; owns stocks (small number of shares of common stock) in Bristol-Myers Squibb, Eli Lilly, J & J, Merck, Pfizer purchased >10 years ago, and stock options in Reviva; and has received royalties/publishing income from Taylor & Francis (Editor-in-Chief, Current Medical Research and Opinion, 2022-date), Wiley (Editor-in-Chief, International Journal of Clinical Practice, through end 2019), UpToDate (reviewer), Springer Healthcare (book), Elsevier (Topic Editor, Psychiatry, Clinical Therapeutics, through Spring 2025)

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