Efficacy and Safety of Lumateperone versus Atypical Antipsychotics as Adjunctive Therapy in Major Depressive Disorder: A Pooled-Dose Network Meta-Analysis

Andrew J. Cutler[1], Anaïs Lemyre[2], Qiaoyi Zhang[3], Carol Mao[3], Todor I. Totev[4], Marjolaine Gauthier-Loiselle[2], Yujie Wu[4], Jingyi Liu[2], Mahmoud Hashim[5], Madhav Namjoshi[1], John J. Sheehan[3], Dominic Pilon[2], Patrick Lefebvre[2], Antoine El Khoury[6], Leslie Citrome[7]

[1]SUNY Upstate Medical University, Syracuse, NY, USA [2]Analysis Group ULC, Montreal, Québec, Canada [3]Johnson & Johnson, Raritan, NJ, USA [4]Analysis Group, Inc., Boston, Massachusetts, USA [5]Johnson & Johnson, Leiden, South Holland, Netherlands [6]At the time of study Johnson & Johnson, Raritan, NJ, USA [7]New York Medical College, Valhalla, NY, USA

Introduction

- A substantial proportion of adults with MDD continue to experience clinically meaningful symptoms despite ADT, prompting consideration of adjunctive treatment strategies.
- In the United States, five atypical antipsychotics are indicated for adjunctive use in adults with MDD: aripiprazole, brexpiprazole, cariprazine, lumateperone, and quetiapine XR.
- Lumateperone was approved by the FDA in 2025 as an adjunctive treatment for MDD. Evidence comparing its efficacy and safety with other approved options remains limited.
- A network meta-analysis provides a framework to evaluate relative efficacy and safety in the absence of head-to-head clinical trials.

Objective

To assess the comparative efficacy and safety of lumateperone and other FDA-approved atypical antipsychotics as adjunctive therapy in adults with MDD.

Methods

Study design and data sources

- Trials of interest were identified from Section 14 of the United States product labeling for each therapy and included 10 short-term, randomized, double-blind, placebo-controlled registrational trials evaluating aripiprazole[1,2], brexpiprazole[3,4], cariprazine[5,6], lumateperone[7,8], and quetiapine XR[9,10], representing a total of 11 treatment doses (**Table 1**).
- To reflect clinical decision-making at the treatment level, doses were pooled within treatments in this analysis, resulting in a star-shaped network comprising 5 treatment nodes anchored on placebo+ADT (**Figure 1**).
- Trial design, eligibility criteria, and baseline patient characteristics (e.g., age, sex, race, BMI, and MDD severity) were broadly similar across trials supporting the validity of the indirect comparisons (**Table 1**).

Figure 1. NMA network

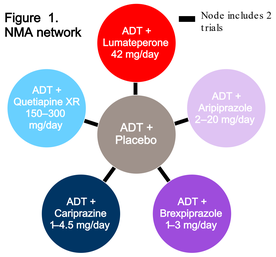


Table 1. Key characteristics of included registrational trials

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 NCT04469377	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 NCT00359190	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.
- Week 6 data were used for all comparisons, except cariprazine (NCT04469377), where Week 8 data were used for MADRS remission, CGI-S, and safety outcomes. When SE values were unavailable, missing values were imputed using the mean SE from the other trials, where 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. Continuous outcomes were modeled using normal likelihoods, and binary outcomes were modeled using binomial likelihoods, with non-informative priors.
- In this analysis, results were estimated for pooled doses for treatment + ADT versus placebo + ADT. Pairwise treatment comparisons and pairwise probabilities of superiority were also reported. Probabilities above 85% or below 15% were interpreted as indicating a treatment was favored or unfavored relative to the comparator, while values between these thresholds (15%–85%) were considered comparable.

Results

Efficacy

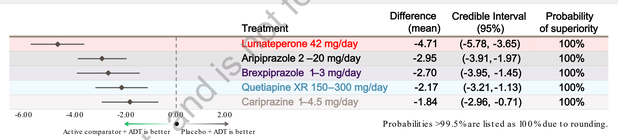
- All treatment nodes were favored versus placebo + ADT for MADRS change from baseline (**Figure 2**), MADRS response, and CGI-S change from baseline, while 4/5 treatment nodes were favored for MADRS remission, with the remainder comparable.
- Compared with placebo + ADT, lumateperone had the largest effect among all pooled treatments for all studied efficacy endpoints, that is MADRS change from baseline (MD -4.71; 95% CrI -5.78, -3.63), MADRS response (OR 2.33; 95% CrI 1.77, 3.05), MADRS remission (OR 2.22; 95% CrI 1.57, 3.07), and CGI-S change from baseline (MD -0.60; 95% CrI -0.74, -0.46).
- In pairwise treatment comparisons anchored to lumateperone, lumateperone was favored against all comparators for MADRS and CGI-S change from baseline, and versus all but 1 comparator for MADRS response and MADRS remission (**Table 2**).

Safety

- Safety profiles varied across treatments.
- Lumateperone was the only treatment node favored versus placebo + ADT for ≥7% weight increase (OR 0.41; 95% CrI 0.04, 1.42; **Figure 3**), a clinically meaningful threshold for metabolic change, with a 94% probability of lower risk. For weight change from baseline, lumateperone showed essentially no mean weight increase versus placebo + ADT (MD -0.08; 95% CrI -0.30, 0.13; probability of superiority: 77%).
- The risk of akathisia was unfavorable versus placebo + ADT for 4/5 treatment nodes while lumateperone was comparable to placebo + ADT (OR: 3.78; 95% CrI 0.40, 17.17; **Figure 4**)
- The risk of somnolence was unfavorable versus placebo + ADT for all treatment nodes (**Figure 5**)
- In pairwise treatment comparisons anchored to lumateperone, lumateperone was favored versus all comparators for both weight-related endpoints. For akathisia, lumateperone was favored versus two treatments and comparable versus the remaining. For somnolence, lumateperone was comparable versus two treatments and unfavorable versus the remaining **Table 2**).

Figure 2. MADRS change from baseline with atypical antipsychotics + ADT vs placebo + ADT

Negative values favor active comparator (greater improvement in MADRS change from baseline total score)

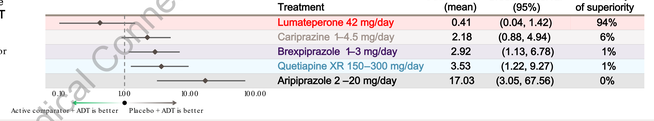


Treatment	Difference (mean)	Credible Interval (95%)	Probability of superiority
Lumateperone 42 mg/day	-4.71	(-5.78, -3.65)	100%
Aripiprazole 2 –20 mg/day	-2.95	(-3.91, -1.97)	100%
Brexpiprazole 1–3 mg/day	-2.70	(-3.95, -1.45)	100%
Quetiapine XR 150–300 mg/day	-2.17	(-3.21, -1.13)	100%
Cariprazine 1–4.5 mg/day	-1.84	(-2.96, -0.71)	100%

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

Figure 3. ⩾7% weight increase with atypical antipsychotics + ADT vs placebo + ADT

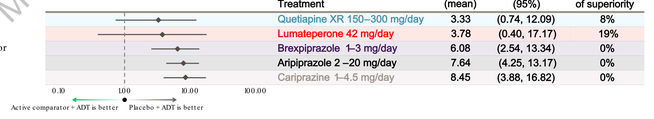
Odds ratio < 1 favors active comparator (lower odds of ≥7% weight increase)



Treatment	Odds Ratio (mean)	Credible Interval (95%)	Probability of superiority
Lumateperone 42 mg/day	0.41	(0.04, 1.42)	94%
Cariprazine 1–4.5 mg/day	2.18	(0.88, 4.94)	6%
Brexpiprazole 1–3 mg/day	2.92	(1.13, 6.78)	1%
Quetiapine XR 150–300 mg/day	3.53	(1.22, 9.27)	1%
Aripiprazole 2 –20 mg/day	17.03	(3.05, 67.56)	0%

Figure 4. Akathisia with atypical antipsychotics + ADT vs placebo + ADT

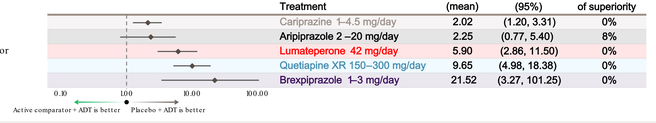
Odds ratio < 1 favors active comparator (lower odds of akathisia)



Treatment	Odds Ratio (mean)	Credible Interval (95%)	Probability of superiority
Quetiapine XR 150–300 mg/day	3.33	(0.74, 12.09)	8%
Lumateperone 42 mg/day	3.78	(0.40, 17.17)	19%
Brexpiprazole 1–3 mg/day	6.08	(2.54, 13.34)	0%
Aripiprazole 2 –20 mg/day	7.64	(4.25, 13.17)	0%
Cariprazine 1–4.5 mg/day	8.45	(3.88, 16.82)	0%

Figure 5. Somnolence with atypical antipsychotics + ADT vs placebo + ADT

Odds ratio < 1 favors active comparator (lower odds of somnolence)



Treatment	Odds Ratio (mean)	Credible Interval (95%)	Probability of superiority
Cariprazine 1–4.5 mg/day	2.02	(1.20, 3.31)	0%
Aripiprazole 2 –20 mg/day	2.25	(0.77, 5.40)	8%
Lumateperone 42 mg/day	5.90	(2.86, 11.50)	0%
Quetiapine XR 150–300 mg/day	9.65	(4.98, 18.38)	0%
Brexpiprazole 1–3 mg/day	21.52	(3.27, 101.25)	0%

Table 2. Pairwise treatment comparisons and pairwise probabilities anchored to lumateperone across efficacy and safety outcomes

Lumateperone was favored versus the treatment comparator in the column (>85% probability of superiority)

Lumateperone was unfavored versus the treatment comparator in the column (<15% probability of superiority)

Lumateperone 42 mg/day versus:	Aripiprazole 2–20 mg/day	Brexpiprazole 1–3 mg/day	Cariprazine 1–4.5 mg/day	Quetiapine XR 150–300 mg/day
Efficacy Outcomes				
MADRS change from baseline, MD (95% CrI)	-1.77 (-3.20, -0.32) Probability of superiority: 99%	-2.54 (-4.02, -1.04) Probability of superiority: 100%	-2.87 (-4.44, -1.29) Probability of superiority: 100%	-2.01 (-3.66, -0.36) Probability of superiority: 99%
MADRS response, OR (95% CrI)	1.20 (0.78, 1.87) Probability of superiority: 80%	1.32 (0.84, 2.09) Probability of superiority: 89%	1.60 (1.13, 2.29) Probability of superiority: 100%	1.55 (1.05, 2.30) Probability of superiority: 99%
MADRS remission, OR (95% CrI)	1.15 (0.70, 1.90) Probability of superiority: 72%	1.43 (0.83, 2.42) Probability of superiority: 91%	2.20 (1.45, 3.31) Probability of superiority: 91%	1.30 (0.84, 2.02) Probability of superiority: 88%
CGI-S change from baseline, MD (95% CrI)	-0.16 (-0.36, 0.05) Probability of superiority: 93%	-0.37 (-0.55, -0.19) Probability of superiority: 100%	-0.40 (-0.62, -0.18) Probability of superiority: 100%	-0.25 (-0.45, -0.06) Probability of superiority: 99%
Safety Outcomes				
Weight change from baseline, MD (95% CrI)	-1.42 (-1.82, -1.03) Probability of superiority: 100%	-1.34 (-1.70, -0.98) Probability of superiority: 100%	-0.86 (-1.17, -0.54) Probability of superiority: 100%	-1.01 (-1.40, -0.61) Probability of superiority: 100%
≥7% weight increase from baseline, OR (95% CrI)	0.03 (0.00, 0.21) Probability of superiority: 100%	0.11 (0.01, 0.69) Probability of superiority: 99%	0.15 (0.02, 0.91) Probability of superiority: 98%	0.10 (0.01, 0.61) Probability of superiority: 99%
Akathisia, OR (95% CrI)	0.30 (0.05, 2.54) Probability of superiority: 88%	0.40 (0.06, 3.52) Probability of superiority: 81%	0.28 (0.04, 2.52) Probability of superiority: 88%	0.91 (0.09, 10.07) Probability of superiority: 53%
Somnolence, OR (95% CrI)	2.78 (0.84, 9.22) Probability of superiority: 5%	0.45 (0.05, 2.04) Probability of superiority: 83%	2.83 (1.21, 6.87) Probability of superiority: 1%	0.61 (0.23, 1.58) Probability of superiority: 85%

Abbreviations: ADT: antidepressant therapy; BMI: body mass index; CGI-S: Clinical Global Impressions Severity; CrI: credible interval; FDA: Food and Drug Administration; MADRS: Montgomery-Asberg Depression Rating Scale; MD: mean difference; MDD: major depressive disorder; NCT: national clinical trial; NMA: network meta-analysis; OR: odds ratio; SE: standard error; XR: extended release.

Conclusions

- Clinical guidelines emphasize adjusting treatment strategies until remission is achieved in patients with MDD, and therapy changes are often required due to insufficient symptom control or tolerability concerns .
- In this pooled-dose NMA, adjunctive lumateperone demonstrated a favorable efficacy profile relative to other approved adjunctive antipsychotics. While safety profiles varied across approved atypical antipsychotics, lumateperone showed consistent favorability for risk of weight gain, was favorable for akathisia, and was less favorable for somnolence risk.
- To optimize patient care, selection of adjunctive atypical antipsychotic therapy for MDD should carefully balance efficacy and safety.

Limitations

- Findings are based on indirect comparisons in the absence of head-to-head randomized trials and should therefore be interpreted in the context of the inherent limitations of indirect evidence and the assumptions underlying the NMA framework, including transitivity.
- Pooling across doses assumes comparable effects across dose levels; if a dose-response relationship exists, the resulting estimates may be less interpretable and may not reflect the effects of individual doses. Nevertheless, findings from the pooled-dose NMA were consistent with those from the analysis conducted at the treatment-dose level.
- Although trials and patient populations were generally comparable, some degree of between-study heterogeneity may remain.
- As the analysis was limited to registrational trials, results may not fully reflect outcomes observed in broader real-world clinical practice.

Key contributors

Conceptualization: QZ, CM, TT, MGL, MH, MN, JJS, DP, PL, AEK; methodology: all authors; formal analysis and visualization: AL, TT, MGL, YW, JL, DP, PL; writing and revision: all authors.

Funding

This study was funded by Johnson & Johnson Innovative Medicine.

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, ImmuneBio, 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/indico, 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)

Presented at: 2026 NEI Spring Congress, May 1–3, 2026 | Kissimmee, Florida | USA

References:
1. Berman RM, et al. J Clin Psychiatry 2007; 68(6): 843–53.
2. Marcus RN, et al. J Clin Psychopharmacol 2008; 28(2): 156–65.
3. Thase ME, et al. J Clin Psychiatry 2015; 76(9): 1224-31.
4. Thase ME, et al. J Clin Psychiatry 2015; 76(9): 1232-40.
5. Durgam S, et al. J Clin Psychiatry 2016; 77(3): 3748.
6. Sachs GS, et al. Am J Psychiatry 2023; 180(3): 241-51.
7. Durgam S, et al. J Clin Psychiatry 2025; 86(4): 25m15848.
8. Durgam S, et al. Am J Psychiatry 2025; 182(12): 1072-82.
9. Bauer M, et al. J Clin Psychiatry 2009; 70(4): 540 –9.
10. El-Khalili N, et al. Int J Neuropsychopharmacol 2010; 13: 917-32.