Efficacy and Safety of Adjunctive Lumateperone in Major Depressive Disorder: Pooled Analysis of Demographic and Clinical Subgroups from Phase 3 Trials

Willie R. Earley, MD[1]; Suresh Durgam, MD[2]; Changzheng Chen, PhD[1]; Raffaele Migliore, MA[1]; Jesper Riise, PhD[3]; Susan G. Kornstein, MD[4]; Roger S. McIntyre, MD[5,6]; Maurizio Fava, MD[7]

[1]Intra-Cellular Therapies, a Johnson & Johnson Company, Bedminster, NJ, USA; [2]Former employee of Intra-Cellular Therapies, a Johnson & Johnson Company, Bedminster, NJ, USA; [3]Johnson & Johnson, Copenhagen, Denmark; [4]Department of Psychiatry, Virginia Commonwealth University School of Medicine, Richmond, VA, USA; [5]Department of Psychiatry, University of Toronto, Toronto, ON, Canada; [6]Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada; [7]Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

This material is distributed by Johnson & Johnson Medical Affairs for scientific purposes only. Promotional use is not for promotional use.

Background

- Major depressive disorder (MDD) is a common mental illness associated with functional impairment, comorbidities, reduced quality of life, and impaired work productivity[1,2]
- Despite available treatments, many patients with MDD experience inadequate response to antidepressant therapy (ADT)[3]
- The clinical heterogeneity of MDD may influence treatment response, highlighting the need to establish consistency of treatment effect across patient subgroups according to demographic and clinical characteristics[4,5]
- Lumateperone is an atypical antipsychotic indicated for: treatment of schizophrenia in adults; treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate; and treatment of MDD in adults as adjunct to ADT[6]
  - Evidence supports that lumateperone is a modulator of serotonin, dopamine, and glutamate neurotransmission[7]
  - Specifically, lumateperone is a potent serotonin 5-HT_{2A} receptor antagonist, a serotonin reuptake inhibitor, a dopamine D_2 receptor presynaptic partial agonist and postsynaptic antagonist, and a D_1 receptor-dependent indirect modulator of glutamatergic AMPA and NMDA currents[7]
  - This novel mechanism of action with multimodal effects may confer robust efficacy with improved tolerability compared with current treatment options
- The efficacy and safety of lumateperone 42 mg adjunctive to ADT were demonstrated in 2 Phase 3, double-blind, placebo-controlled studies (Study 501 [NCT04985942]; Study 502 [NCT05061706]) in patients with MDD with inadequate ADT response[8,9]
  - The primary and key secondary efficacy endpoints were met in both studies, with lumateperone 42 mg + ADT significantly improving Montgomery-Åsberg Depression Rating Scale (MADRS) Total score and Clinical Global Impression–Severity (CGI-S) score from baseline to Day 43 compared with placebo + ADT, and was generally well tolerated[8,9]
- This pooled analysis of Studies 501 and 502 evaluated lumateperone 42 mg adjunctive to ADT across demographic and clinical subgroups of patients with MDD with inadequate response to ADT

Methods

- Data were pooled from Studies 501 and 502, which enrolled eligible adults (aged 18–65 years) who met DSM-5 criteria for MDD with inadequate response to 1-2 courses of ADT in the current depressive episode (MADRS Total score ≥24 and CGI-S score ≥4) and had Quick Inventory of Depressive Symptomatology-Self Report-16 (QIDS-SR-16) item score ≥14 at screening and baseline[8,9]
  - Inadequate response to ADT was defined as <50% improvement with ≥6 weeks ADT monotherapy, as confirmed by the Antidepressant Treatment Response Questionnaire
- Patients were randomized 1:1 to 6-week oral lumateperone 42 mg/day + ADT or placebo + ADT
- The primary and key secondary endpoints were the changes from baseline to Day 43 in MADRS Total score and CGI-S score, respectively
  - Change from baseline to Day 43 in patient-rated scales for depression (QIDS-SR-16 Total score, range from 0 to 27; higher scores indicate more severe depression[10]) was also assessed
- Efficacy was evaluated in the overall population and across patient subgroups defined by demographic and baseline disease characteristics using a mixed-effects model for repeated measures (MMRM) or analysis of covariance (**Table 1**)
- Safety assessments included adverse events (AEs), physical examinations, vital signs, and changes in laboratory parameters

Table 1. Demographic and Baseline Disease Characteristic Subgroups

Demographic subgroups	Baseline disease characteristic subgroups
• Age: ≤40 or >40 years • Sex: male or female • Race: White or non-White • Ethnicity: Hispanic/Latino or not Hispanic/Latino • Region: US or non-US	• Disease severity • Type of ADT • Number of ADT failures in the current episode • Presence/absence of DSM-5–defined anxious distress

ADT, antidepressant therapy; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

Results

Patient Population

- The pooled modified intent-to-treat (mITT) population comprised 950 patients (lumateperone + ADT, n=471; placebo + ADT, n=479) from Studies 501 and 502
- Demographics and baseline characteristics were similar between treatment groups
  - The mean age of patients was 45.2 years for the lumateperone + ADT group and 45.8 years for the placebo + ADT group
  - Most patients were White (86.0%) and female (67.7%)

Efficacy

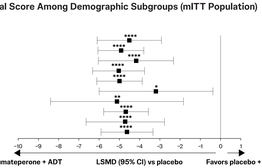
- Lumateperone + ADT met the primary endpoint, showing significantly greater MADRS Total score improvement from baseline to Day 43 vs placebo + ADT in the mITT population (least squares mean difference vs placebo [LSMD]=−4.7; effect size [ES]=−0.59; *P*<.0001)
- Significant improvement in the CGI-S score from baseline to Day 43 was observed with lumateperone + ADT vs placebo + ADT in the mITT population (LSMD=−0.6; ES=−0.59; *P*<.0001)
- Lumateperone + ADT demonstrated significantly greater improvement in QIDS-SR-16 Total score at Day 43 compared with placebo in the ITT population (LSMD=−2.2; ES=−0.4; *P*<.0001)

Subgroup Analysis

- Significant improvement in MADRS Total score at Day 43 with lumateperone + ADT vs placebo + ADT was observed across all demographic subgroups (age, sex, race, ethnicity, and region) (**Figure 1A**)
- Lumateperone + ADT significantly improved MADRS Total score from baseline to Day 43 across all baseline disease characteristics, including disease severity, type of ADT, number of ADT failures in the current episode, and presence/absenceof anxious distress (**Figure 1B**)

Figure 1A. Change From Baseline to Day 43 in MADRS Total Score Among Demographic Subgroups (mITT Population)

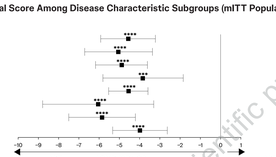
	Luma 42 mg + ADT n/N1	Placebo + ADT n/N1	LSMD (95% CI)	Effect Size
≤40 years	142/167	152/164	−4.51 (−6.09, −2.92)	−0.65
>40 years	277/304	298/315	−4.92 (−6.06, −3.79)	−0.71
Male	136/153	142/154	−4.17 (−6.03, −2.32)	−0.52
Female	283/318	308/325	−5.03 (−6.31, −3.76)	−0.63
White	359/404	388/413	−4.99 (−6.11, −3.86)	−0.62
Non-White	60/67	62/66	−3.19 (−5.98, −0.38)	−0.40
Hispanic/Latino	43/50	45/49	−5.11 (−8.4, −1.83)	−0.64
Not Hispanic/Latino	376/420	405/430	−4.68 (−5.78, −3.57)	−0.58
US	121/150	134/149	−4.71 (−6.64, −2.78)	−0.58
Non-US	298/321	316/330	−4.62 (−5.9, −3.34)	−0.56



*P<.05 **P<.01 ***P<.001 ****P<.0001. MMRM in the mITT population. N1=Number of mITT patients in each group at baseline, n=Number of patients with Day 43 assessment.
ADT, antidepressant therapy; CI, confidence interval; LSMD, least squares mean difference; Luma, lumateperone; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures.

Figure 1B. Change From Baseline to Day 43 in MADRS Total Score Among Disease Characteristic Subgroups (mITT Population)

	Luma 42 mg + ADT n/N1	Placebo + ADT n/N1	LSMD (95% CI)	Effect Size
Baseline MADRS Total score <32	254/285	275/288	−4.56 (−5.91, −3.21)	−0.57
Baseline MADRS Total score ≥32	165/186	175/191	−5.04 (−6.71, −3.36)	−0.63
SSRI	285/320	292/310	−4.89 (−6.17, −3.61)	−0.62
SNRI	112/122	130/138	−3.83 (−5.82, −1.84)	−0.48
1 ADT failure	376/424	392/418	−4.55 (−5.53, −3.58)	−0.65
2 ADT failure	43/47	58/61	−6.06 (−8.8, −3.31)	−0.87
Anxious distress at baseline	179/197	174/189	−5.86 (−7.51, −4.21)	−0.73
No anxious distress at baseline	240/274	276/290	−3.98 (−5.34, −2.62)	−0.50

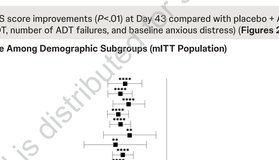


***P<.001 ****P<.0001. MMRM in the mITT population. N1=Number of mITT patients in each group at baseline, n=Number of patients with Day 43 assessment.
ADT, antidepressant therapy; CI, confidence interval; LSMD, least squares mean difference; Luma, lumateperone; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

- Treatment with lumateperone + ADT led to significant CGI-S score improvements (*P*<.01) at Day 43 compared with placebo + ADT in all subgroups (age, sex, race, ethnicity, region, baseline disease severity, type of ADT, number of ADT failures, and baseline anxious distress) (**Figures 2A and 2B**)

Figure 2A. Change From Baseline to Day 43 in CGI-S Score Among Demographic Subgroups (mITT Population)

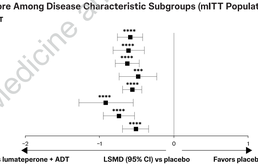
	Luma 42 mg + ADT n/N1	Placebo + ADT n/N1	LSMD (95% CI)	Effect Size
≤40 years	142/167	152/164	−0.56 (−0.79, −0.33)	−0.56
>40 years	277/304	298/315	−0.62 (−0.79, −0.46)	−0.61
Male	136/153	142/154	−0.51 (−0.72, −0.29)	−0.55
Female	283/318	308/325	−0.65 (−0.8, −0.51)	−0.71
White	359/404	388/413	−0.62 (−0.76, −0.48)	−0.61
Non-White	60/67	62/66	−0.5 (−0.85, −0.14)	−0.49
Hispanic/Latino	43/50	45/49	−0.69 (−1.11, −0.27)	−0.68
Not Hispanic/Latino	376/420	405/430	−0.59 (−0.73, −0.45)	−0.58
US	121/150	134/149	−0.65 (−0.9, −0.4)	−0.62
Non-US	298/321	316/330	−0.57 (−0.73, −0.4)	−0.54



**P<.01 ****P<.0001. MMRM in the mITT population. N1=Number of mITT patients in each group at baseline, n=Number of patients with Day 43 assessment.
ADT, antidepressant therapy; CI, confidence interval; CGI-S, Clinical Global Impression–Severity; LSMD, least squares mean difference; Luma, lumateperone; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures.

Figure 2B. Change From Baseline to Day 43 in CGI-S Score Among Disease Characteristic Subgroups (mITT Population)

	Luma 42 mg + ADT n/N1	Placebo + ADT n/N1	LSMD (95% CI)	Effect Size
Baseline MADRS Total score <32	254/285	275/288	−0.59 (−0.76, −0.42)	−0.59
Baseline MADRS Total score ≥32	165/186	175/191	−0.61 (−0.82, −0.4)	−0.60
SSRI	285/320	292/310	−0.63 (−0.79, −0.47)	−0.62
SNRI	112/122	130/138	−0.48 (−0.74, −0.23)	−0.48
1 ADT failure	376/424	392/418	−0.56 (−0.69, −0.43)	−0.61
2 ADT failure	43/47	58/61	−0.92 (−1.28, −0.55)	−1.0
Anxious distress at baseline	179/197	174/189	−0.74 (−0.95, −0.53)	−0.73
No anxious distress at baseline	240/274	276/290	−0.51 (−0.69, −0.34)	−0.51

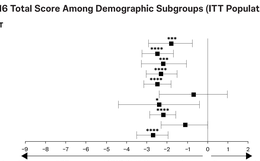


***P<.001 ****P<.0001. MMRM in the mITT population. N1=Number of mITT patients in each group at baseline, n=Number of patients with Day 43 assessment.
ADT, antidepressant therapy; CI, confidence interval; CGI-S, Clinical Global Impression–Severity; LSMD, least squares mean difference; Luma, lumateperone; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

- Significant improvements in QIDS-SR-16 Total score (*P*<.05) at Day 43 were observed with lumateperone + ADT vs placebo + ADT in all patient subgroups, except for race (White; *P*<.0001; non-White, *P*=.4062) and region (non-US, *P*<.0001; US, *P*=.0522) (**Figures 3A and 3B**)

Figure 3A. Change From Baseline to Day 43 in QIDS-SR-16 Total Score Among Demographic Subgroups (ITT Population)

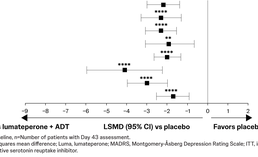
	Luma 42 mg + ADT n/N1	Placebo + ADT n/N1	LSMD (95% CI)	Effect Size
≤40 years	162/171	160/165	−1.8 (−2.93, −0.76)	−0.38
>40 years	308/312	310/316	−2.5 (−3.23, −1.68)	−0.51
Male	152/156	152/156	−2.2 (−3.28, −1.06)	−0.45
Female	318/327	318/325	−2.3 (−3.04, −1.52)	−0.47
White	404/415	405/414	−2.5 (−3.15, −1.82)	−0.52
Non-White	66/68	65/67	−0.7 (−2.4, 0.97)	−0.15
Hispanic/Latino	49/51	48/49	−2.4 (−4.4, −0.41)	−0.5
Not Hispanic/Latino	420/431	422/432	−2.2 (−2.87, −1.56)	−0.46
US	146/153	145/151	−1.1 (−2.3, −0.01)	−0.23
Non-US	324/330	325/330	−2.7 (−3.51, −1.96)	−0.55



*P<.05 ***P<.001 ****P<.0001. ANCOVA in the ITT population. N1=Number of ITT patients in each group at baseline, n=Number of patients with Day 43 assessment.
ADT, antidepressant therapy; ANCOVA, analysis of covariance; CI, confidence interval; LSMD, least squares mean difference; Luma, lumateperone; ITT, intent-to-treat; QIDS-SR-16, Quick Inventory of Depressive Symptomatology-Self Report-16 item.

Figure 3B. Change From Baseline to Day 43 in QIDS-SR-16 Total Score Among Disease Characteristic Subgroups (ITT Population)

	Luma 42 mg + ADT n/N1	Placebo + ADT n/N1	LSMD (95% CI)	Effect Size
Baseline MADRS Total score <32	285/292	283/289	−2.2 (−2.98, −1.37)	−0.45
Baseline MADRS Total score ≥32	185/191	187/192	−2.3 (−3.29, −1.29)	−0.48
SSRI	317/328	303/312	−2.3 (−3.07, −1.53)	−0.48
SNRI	125/126	136/138	−1.9 (−3.07, −0.66)	−0.39
1 ADT failure	421/434	409/420	−2.0 (−2.63, −1.32)	−0.41
2 ADT failure	49/49	61/61	−4.1 (−5.96, −2.23)	−0.86
Anxious distress at baseline	198/202	185/190	−3.0 (−3.96, −1.98)	−0.62
No anxious distress at baseline	272/281	285/291	−1.7 (−2.53, −0.91)	−0.36



**P<.01 ****P<.0001. ANCOVA in the ITT population. N1=Number of ITT patients in each group at baseline, n=Number of patients with Day 43 assessment.
ADT, antidepressant therapy; ANCOVA, analysis of covariance; CI, confidence interval; LSMD, least squares mean difference; Luma, lumateperone; MADRS, Montgomery-Åsberg Depression Rating Scale; ITT, intent-to-treat; QIDS-SR16, Quick Inventory of Depressive Symptomatology-Self Report-16 item; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Safety

- Treatment-emergent AEs (TEAEs) occurred in 68.1% of patients in the lumateperone + ADT group, compared with 45.1% in the placebo + ADT group
- In the lumateperone + ADT group, dizziness, dry mouth, somnolence, nausea, fatigue, and diarrhea were reported in ≥5% of patients and at more than twice the rate in the placebo + ADT group
- Weight, body mass index, and waist circumference remained stable in both groups (mean [SD] change from baseline to the end of treatment: lumateperone + ADT, −0.1 [1.7], −0.0 [0.6], and −0.2 [4.0]; placebo + ADT, 0.0 [1.7], 0.0 [0.6], and −0.3 [4.4], respectively)
- Mean changes from baseline to the end of treatment in cardiometabolic parameters (cholesterol, glucose, and insulin levels) were comparable between lumateperone + ADT and placebo + ADT groups, with no clinically relevant prolactin increases at end of treatment
- There were no notable changes in extrapyramidal symptoms (EPS) scales (Barnes Akathisia Rating Scale, Abnormal Involuntary Movement Scale, and Simpson-Angus Scale) and low rates of EPS-related TEAEs with lumateperone + ADT treatment

Conclusions

- In this pooled analysis, lumateperone 42 mg adjunctive to ADT demonstrated consistent and clinically meaningful improvements compared with placebo adjunctive to ADT across demographic and baseline disease subgroups of patients with MDD enrolled in Studies 501 and 502
- Lumateperone + ADT was generally well tolerated, supporting its use as an adjunctive treatment option for patients with MDD with inadequate response to ADT

Acknowledgements

This study was funded by Intra-Cellular Therapies, a Johnson & Johnson company. The authors thank all study investigators, research staff, and patients for their participation. Medical writing support was provided by Keri Ramessar, PhD, of Nucleus Global, an Inizio company, funded by Intra-Cellular Therapies, a Johnson & Johnson company. Layout design and formatting for this encore presentation were provided by Amit Kavle of SIRO Medical Writing Pvt. Ltd., India (funded by Johnson & Johnson).

Disclosures

WR Earley, **C Chen**, and **R Migliore** are full-time employees of Intra-Cellular Therapies, a Johnson & Johnson company. **S Durgam** is a former employee of Intra-Cellular Therapies, a Johnson & Johnson company. **J Riise** is an employee of Johnson & Johnson. **SG Kornstein** receives research support from the National Institutes of Health and the National Science Foundation. She has served as a consultant for AbbVie, Arrivo BioVentures, Gerbera, Eli Lilly, Relmada, Reunion Neuroscience, and Sage Therapeutics. **RS McIntyre** has received research grant support from CIHR/GACD/National Natural Science Foundation of China (NSFC) and the Milken Institute; and speaker/consultation fees from AbbVie, Alkermes, Atai Life Sciences, Axsome, Bausch Health, Biogen, Boehringer Ingelheim, Eisai, Intra-Cellular Therapies, Johnson & Johnson, Kris Pharma, Lundbeck, Mitsubishi Tanabe Pharma, Neumora Therapeutics, NeuraWell, Neurocrine, NewBridge Pharmaceuticals, Novo Nordisk, Otsuka, Pfizer, Purdue, Sage, Sanofi, Sunovion, Takeda, and Viatris. **M Fava** reports the following disclosures related to the last 3 years: Research Support: AbbVie; Acadia Pharmaceuticals; Aditum Bio; Management Company, LLC; Allergan; Alkermes, Inc.; Altimate Health Corporation; Alto Neuroscience, Inc.; Ancora Bio, Inc.; Angelini S.p.A; Aptinyx; Arbor Pharmaceuticals LLC; Avanir Pharmaceuticals Inc.; Axsome; Benckiser Pharmaceuticals, Inc.; BioClinica, Inc.; Biogen; BioHaven; BioShin Limited; Cambridge Science Corporation; Cerecor; Centrexion Therapeutics Corporation; Cybin IRL Limited; Damona Pharmaceuticals; Eliem Therapeutics LTD; EmbarkNeuro; Gate Neurosciences, Inc.; GenOmind, LLC; Gentelon, LLC; Gerbera Therapeutics, Inc.; Happify; Johnson & Johnson; Lundbeck Inc.; Marinus Pharmaceuticals; Medpace, Inc.; Methylation Sciences, Inc.; Millennium Pharmaceutics, Inc.; Minerva Neurosciences; National Institute of Drug Abuse (NIDA); National Institute of Mental Health (NIMH); National Institutes of Health (NIH); Neuralstem; Neurocrine Biosciences, Inc.; NeuroRX Inc.; Novaremed; Novartis; Otsuka; PCORI; Pfizer; Premiere Research International; Praxis Precision Medicines Protagenic Therapeutics, Inc.; Reckitt; Relmada Therapeutics Inc.; Shenox Pharmaceuticals; Stanley Medical Research Institute (SMRI); Taisho; Takeda; University of Michigan; Vistagen; WinSanTor, Inc.; Xenon Pharmaceuticals, Inc. M Fava has not done any personal consulting. Any consulting he has done has been on behalf of Massachusetts General Hospital, except for Revival Therapeutics and Sensorium Therapeutics. Speaking/Publishing: Lecture given at Global Medical Education, Inc. Mood Disorders Summit, November 2020. Stock/Other Financial Options: Equity Holdings: Compellis; Neuromity; Psy Therapeutics; Revival Therapeutics; Sensorium Therapeutics. Royalty/patent, other income: Patents for Sequential Parallel Comparison Design (SPCD), licensed by MGH to Pharmaceutical Product Development, LLC (PPD) (US,7840419, US,7647235, US,7983936, US,8145504, US,8145505); and patent application for a combination of Ketamine plus Scopolamine in Major Depressive Disorder (MDD), licensed by MGH to Biohaven. Patents for pharmacogenomics of Depression Treatment with Folate (US,9546401, US,9540691). Copyright for the MGH Cognitive & Physical Functioning Questionnaire (CPFQ), Sexual Functioning Inventory (SFI), Antidepressant Treatment Response Questionnaire (ATRQ), Discontinuation-Emergent Signs & Symptoms (DESS), Symptoms of Depression Questionnaire (SDQ), and SAFER; Belvoir; Lippincott, Williams & Wilkins; Wolters Kluwer; World Scientific Publishing Co. Pte. Ltd.

PREVIOUSLY PRESENTED AT: The 34th European Congress of Psychiatry (EPA), March 28–31, 2026; Prague, Czech Republic.

Neuropsychiatry

Scan the QR code

The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

https://www.congresshub.com/Neuroscience/NEI2026/Lumateperone/Earley-Efficacy

Email questions to Willie R. Earley at wearley@its.jnj.com

Presented at Neuroscience Education Institute (NEI) Fall Congress, November 5–8, 2026; Colorado Springs, CO, USA

References:
1. Marx W, et al. *Nat Rev Dis Primers.* 2023;9:44; **2.** Proudman D, et al. *PharmacoEconomics.* 2021;39:619–625; **3.** Alva G. *CNS Spectr.* 2023;28:521–525; **4.** Iniesta R, et al. *Sci Rep.* 2018;8:5530; **5.** Perna G, et al. *Psychiatry Investig.* 2020;17:193–206; **6.** CAPLYTA® (lumateperone). Prescribing information. Intra-Cellular Therapies, Inc.; 2025; **7.** Snyder G, et al. *Psychopharmacology (Berl).* 2015;232:605–621; **8.** Durgam S, et al. *J Clin Psychiatry.* 2025;86:25m15848; **9.** Durgam S, et al. *Am J Psychiatry.* 2025;182:1072–1082; **10.** Rush J, et al. *Biol Psychiatry.* 2003;54:573–583.