Ketamine for Treatment Resistant Depression: From Research to Clinical Practice

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Disclosure:

- Research Contracts: Janssen Pharmaceuticals, Inc., NeoSync, Inc.
- Treatment-Resistant Depression (TRD) Speaker Bureau, Janssen Pharmaceuticals, Inc.

Objectives:

- Unmet needs of Treatment Resistant Depression (TRD)
- Discuss efficacy data of ketamine for TRD
- Review of efficacy and safety data of Spravato (esketamine) for TRD and its use in clinical practice
- ketamine suggested mechanism of action

MDD is a Serious Disease with Far-Reaching Impact

- Global health problem, >300 million worldwide,[1] >17 million in US[2]
  - Almost 50% of patients suffer from treatment resistant depression (TRD) defined as: *inadequate response to at least 2 antidepressants of adequate dose and duration*[4]
  - 65% report a significant inability to function in life[2]
  - Major cause of disability in US[2] and worldwide[5]
- MDD increases the risk for other physical and psychiatric illnesses[6]
  - MDD worsens the outcomes of other general medical and mental conditions
  - 10-year reduction in life-expectancy[7]

1. WHO News Release 30 Mar 2017; 2. NIMH Mental Health Website release November 2017; 3. Rush AJ et al. Am J Psychiatry . 2006;163(11):1905-1917; 4. Agency for Healthcare Research and Quality. https://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id105TA.pdf; 5. Global Burden of Disease 2010; 6. Taksler GB et al. Am J Public Health. 2017;107(10):1653–1659; 7. Walker ER, McGee RE, Druss BG. JAMA Psychiatry. 2015;72:334-341.

Consequences of TRD as Compared to MDD

More comorbidities

(e.g., hypertension, diabetes, hear failure)[1]

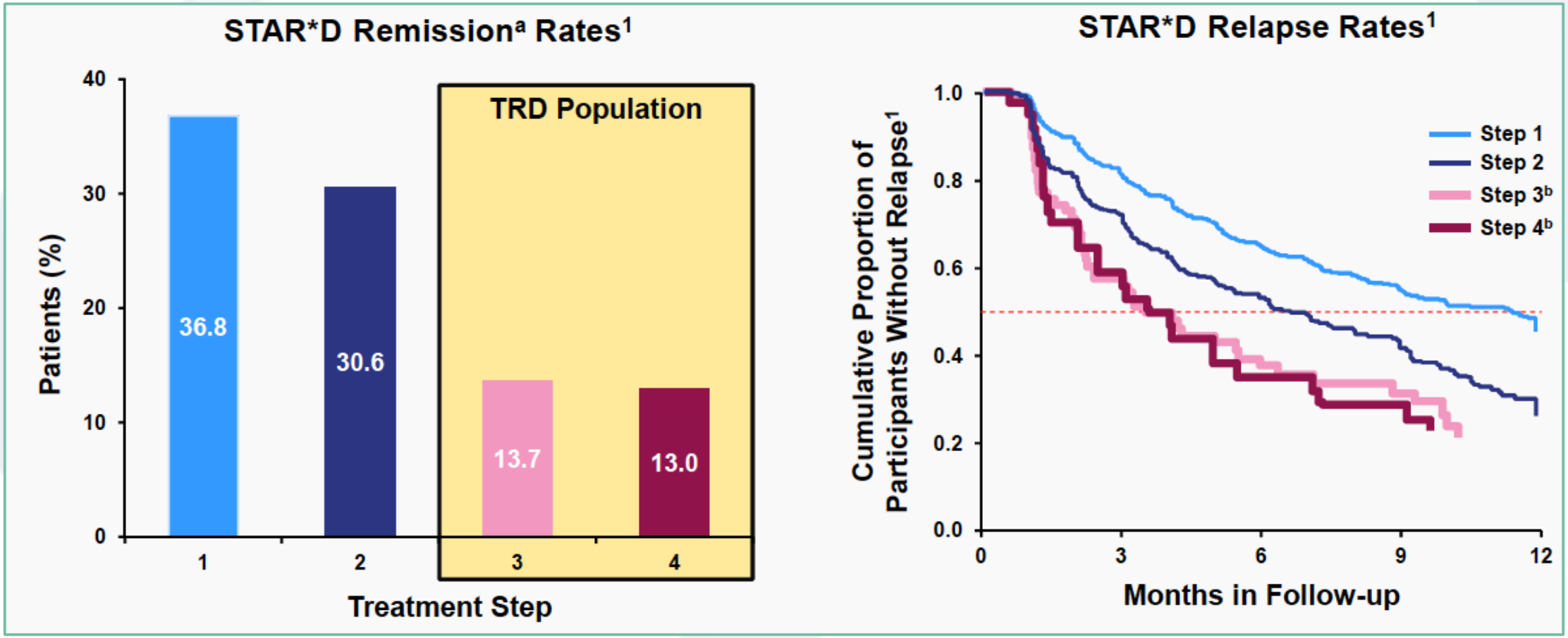
2x Hospitalization rate[2]

36% longer mean hospital length of stay[2]

7-fold Increase in suicide rate[3]

1. Amos T, Witt, EA, Alphs L, et al. Poster Presented at: 29th Annual US Psychiatric & Mental Health Congress, October 21-24, 2016; San Antonio, Texas;
2. Amos TB, Tandon N, Lefebvre P, et al. (2018). J Clin Psychiatry;
3. Feldman RL, Dunner DL, Muller JS, Stone DA (2012). J Med Econ.

Challenges with TRD:



Time to remission: 5-7 weeks

Rush AJ et al. Am J Psychiatry . 2006;163(11):1905-1917.

Current Treatments Fail to Address Patient Needs

- Current antidepressant offer[1]:
  - slow onset of action
  - suboptimal remission rates
  - substandard relapse rates
- All current pharmacotherapies target the same mechanism of action
  - MDD/TRD likely a heterogeneous disease that goes beyond monoamines
- Only 1 pharmacotherapy (olanzapine/fluoxetine combination) approved for TRD[2]
  - Significant weight gain, movement disorder side effects[3]
- Only 1 somatic therapy (Transcranial Magnetic Stimulation) approved for TRD
  - Limited data on efficacy[4] and long-term benefit [5]
- Other treatments do not meet patient needs (e.g., Electroconvulsive therapy)
  - Anesthesia required, potential for severe side effects like memory loss

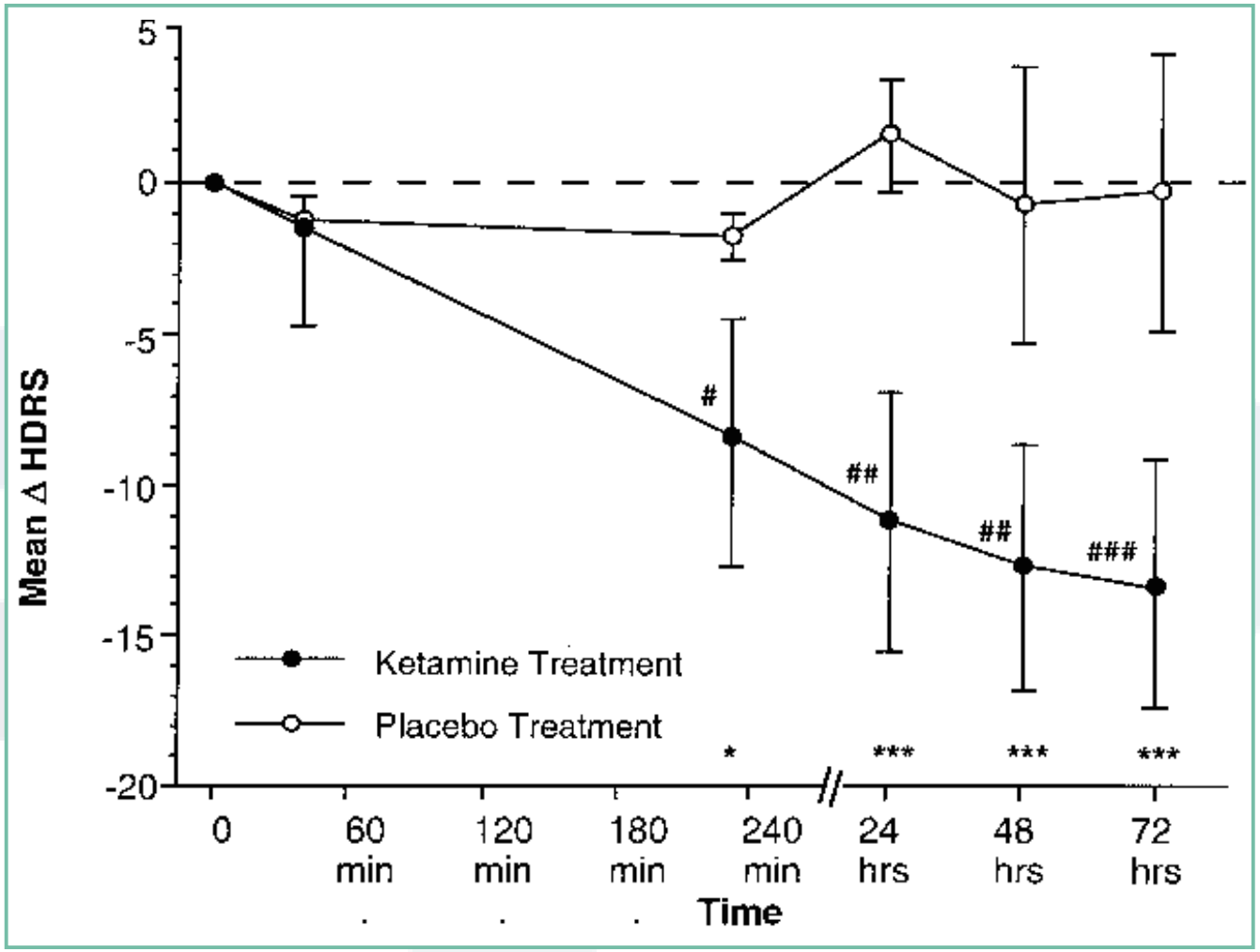
1. Moser G, Pink Sheet: Major Depressive Disorder Patients Emphasize Long-Term Nature of Disease In Feedback Meeting, 2018; 2. Sanacora G, et al. Neuropharmacology. 2012; 62(1):63-77; 3. Philip NS, et al. Expert Opin Pharmacother. 2010 Apr; 11(5): 709–722; 4. Work Group on Major Depressive Disorder, Gelenberg, AJ, Freeman, MP, et al. Practice Guideline for the Treatment of Patients With Major Depressive Disorder. 3rd. Washington, DC: American Psychiatric Association; 2010; 5. Ont Health Technol Assess Ser. 2016; 16(5): 1–66.

2-(2-chlorophenyl)-2-(methylamino)cyclohexan-1-one

Single Ketamine Treatment and Depression

Author	Design	Dose	Control	Sample Size	Endpoint
Breman et al. (2000)	CO	0.5mg/kg X1 IV x 40mn	Placebo	8	72 hours

Mean Changes from Baseline in the HDRS



Breman et al. *Biological Psychiatry.* 2000; 47(4):351-354

Single Ketamine Treatment and Depression

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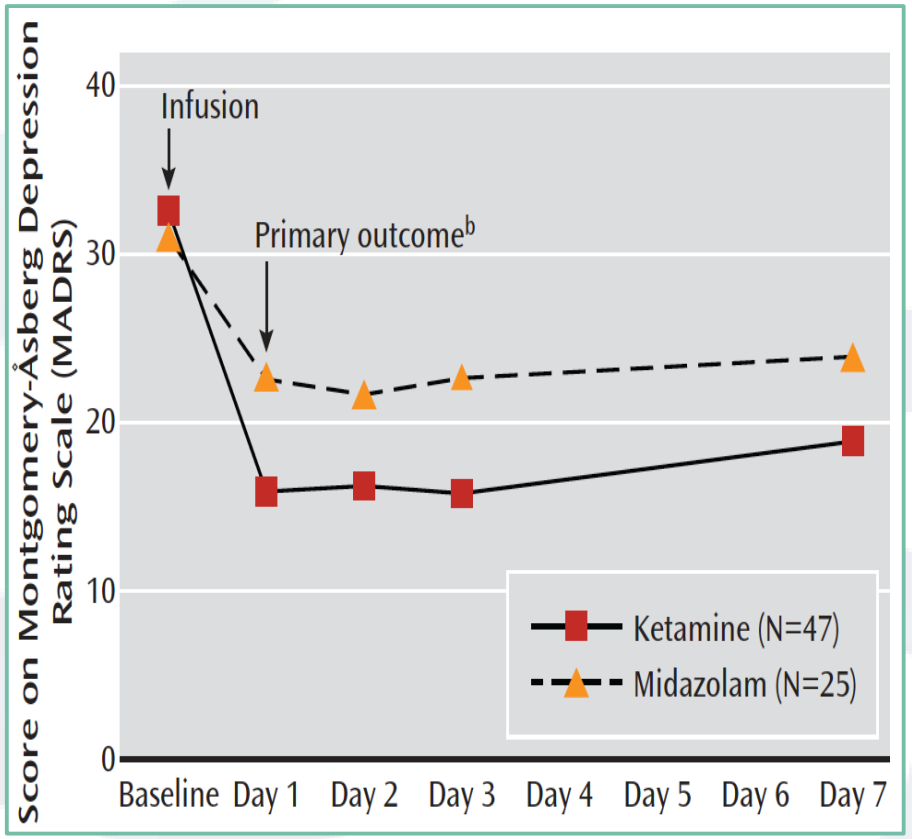
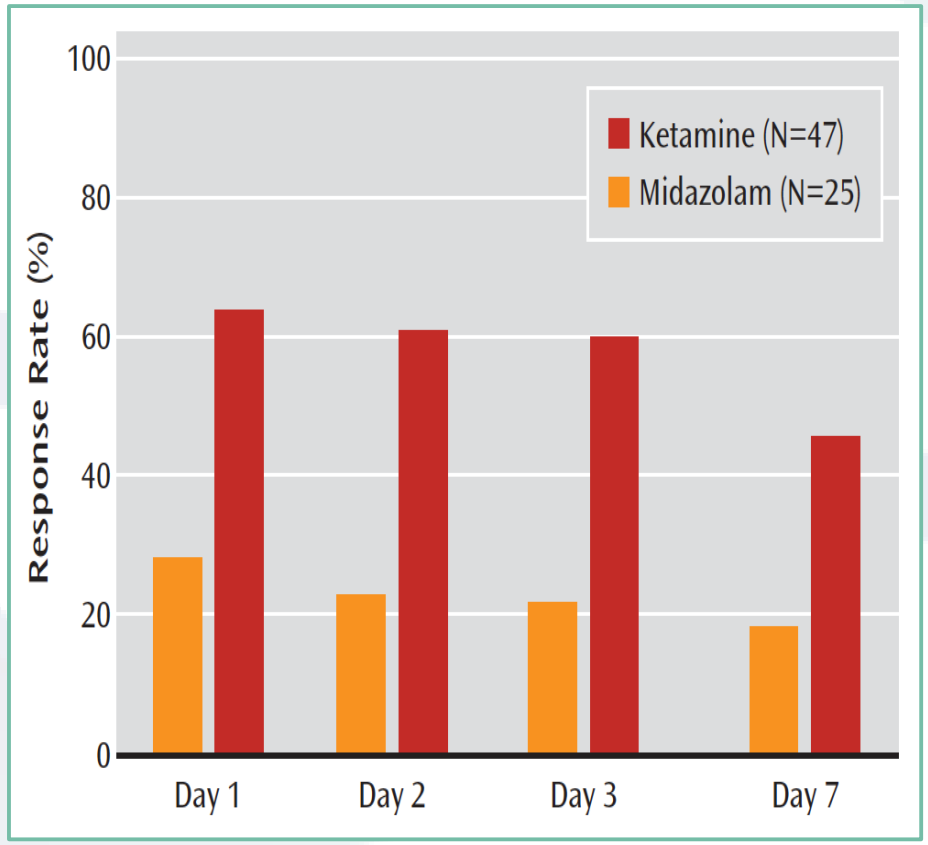
Breman et al. (2000)	CO	0.5mg/kg X1 IV x 40mn	Placebo	8	72 hours
Zarate et al. (2006)	CO	0.5mg/kg X1 IV x 40mn	Placebo	17	24 hours
Sos et al. (2013)	CO	0.5mg/kg X1 IV x 30mn	Placebo	27	24 hours
Lapidus et al. (2014)	CO	50mg IN X1	Placebo	18	24 hours

Single Ketamine Infusion is Superior to Psychoactive Control in TRD: Baylor/Mt Sinai Study (N = 72)





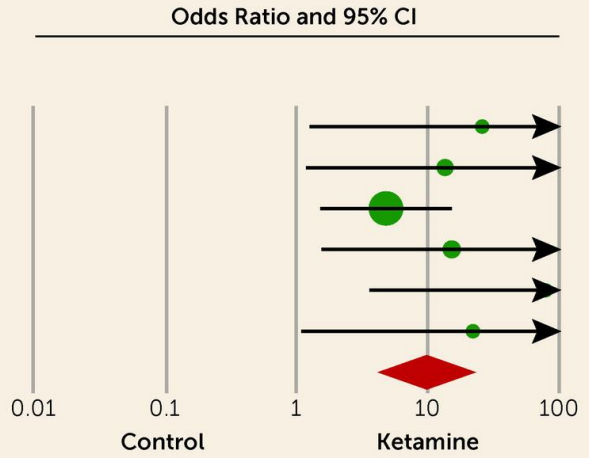
Reduction in MADRS score 24 hours after infusion was the primary outcome measure and was significantly greater for the ketamine group than for the midazolam group ($P \leq .002$).

Murrough JW, et al. *Am J Psychiatry*. 2013;170(10):1134-1142.

Single Infusion of Ketamine: Meta-analysis

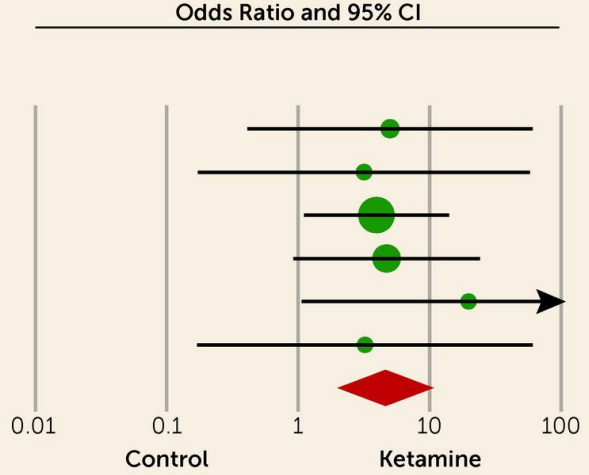
A

Study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Diazgranados et al. (85)	26.053	1.359	499.339	2.164	0.030
Lapidus et al. (84)	13.600	1.238	149.455	2.134	0.033
Murrough et al. (87)	4.833	1.578	14.803	2.759	0.006
Sos et al. (91)	15.294	1.610	145.305	2.374	0.018
Zarate et al. (88)	79.545	3.762	1681.833	2.811	0.005
Zarate et al. (86)	22.176	1.133	434.158	2.042	0.041
	9.865	4.366	22.293	5.503	0.000



B

Study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Diazgranados et al. (85)	5.000	0.426	58.636	1.281	0.200
Lapidus et al. (84)	3.171	0.179	56.222	0.787	0.431
Murrough et al. (87)	3.937	1.149	13.492	2.181	0.029
Sos et al. (91)	4.706	0.950	23.302	1.898	0.058
Zarate et al. (88)	19.783	1.060	369.109	1.999	0.046
Zarate et al. (86)	3.222	0.176	58.849	0.789	0.430
	4.610	2.076	10.236	3.754	0.000



Newport DJ, et al. *Am J Psychiatry*. 2015;172(10):950-966.

Single Ketamine Treatment and Depression

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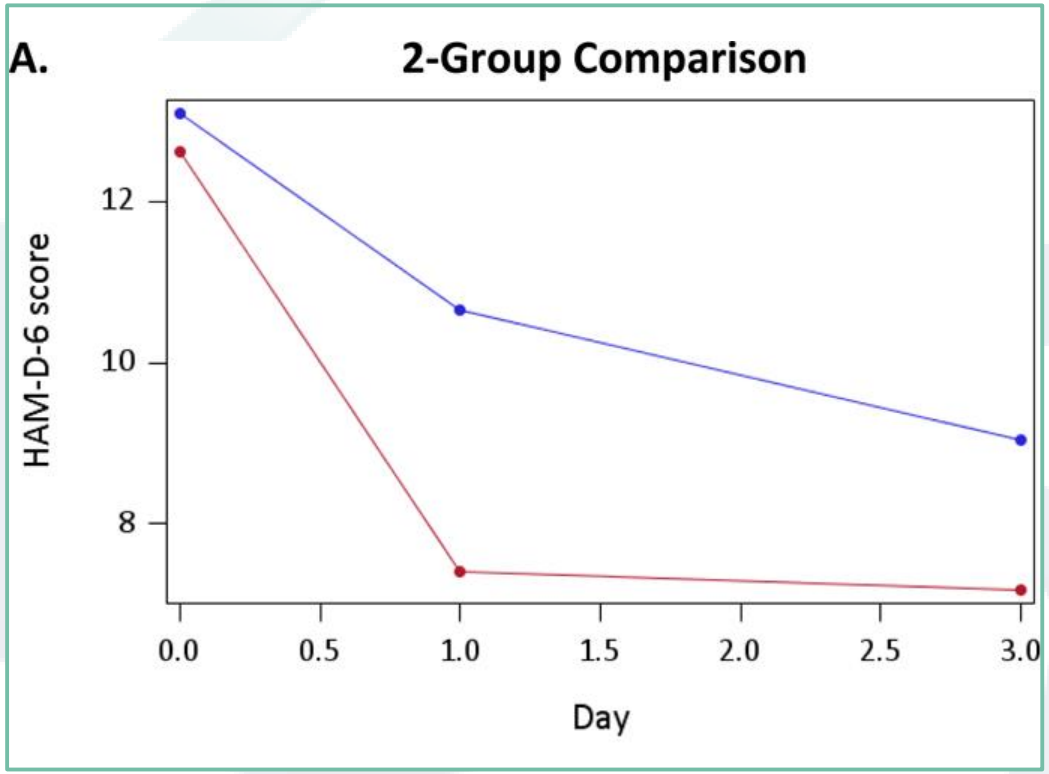
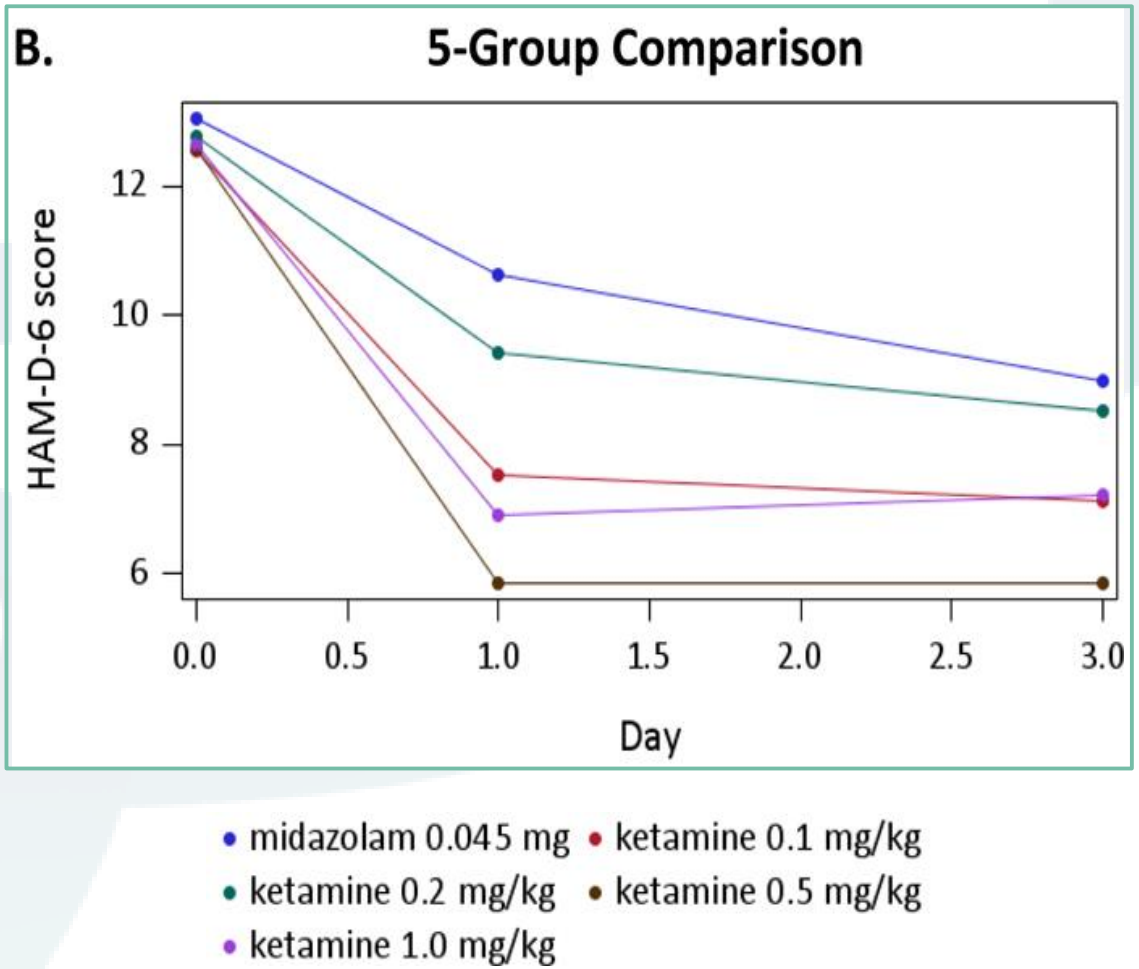
Zarate et al. (2006)	CO	0.5mg/kg X1 IV x 40mn	Placebo	17	24 hours
Murrough et al. (2013)	Parallel	0.5mg/kg X1 x 40mn	Midazolam	73	24 hours
Sos et al. (2013)	CO	0.54mg/kg X1 IV x 30mn	Placebo	27	24 hours
Hu et al. (2014)	Parallel	0.5mg/kg X1 IV X 40mn	Placebo	30	Time to response
Lapidus et al. (2014)	CO	50mg IN X1	Placebo	18	24 hours
Su et al. (2017)	Parallel	0.2 or 0.5 mg/kg X1 IV x 40mn	Placebo	71	24 hours

HAM-D-6 Scores Over First 72 Hours of Different Dosed Treatments





Fava M et al. *Mol Psychiatry*. 2019

Multiple Ketamine Treatments and Depression

Author	Sample Size	Frequency	Mean Time to Relapse	Response Rate	Remission Rate
Murrough JW, et al. (2013)	24	3x per week	18 days	70.8%	Not reported
Shiroma PR, et al. (2014)	14	3x per week	16 days	92%	67%
Vande Voort JL et al. (2016)	12	3x per week	Not reported	58.3%	41.7%
Singh JB, et al. (2016)	67	2x per week & 3x per week	Not reported	2x/week: 69% 3x/week: 54%	2x/week: 38% 3x/week: 23%

Esketamine (Spravato)

SPRAVATO™ [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.

Esketamine Phase 3 Clinical Development Program in Treatment-Resistant Depression (TRD)

Study	Design	n	Duration (wk)	Main endpoints
Acute, fixed dose study (3001, TRANFORM-1)[1]	Double-blind, active controlled	346	4-week induction	**MADRS change at 4 weeks**

1. Fedgchin M, et al. *Poster presented at: the 9th Biennial Conference of the International Society for Affective Disorders (ISAD); September 20-22, 2018; Houston, TX.* 2. Popova V, et al. Poster presented at the *2018 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP);* May 29-June 1, 2018; Miami FL. 3. Daly EJ, et al. Poster presented at *the European College of Neuropsychopharmacology (ECNP) Congress*; October 7, 2018; Barcelona, Spain. 4. Wajs E, et al. Poster presented at *the European College of Neuropsychopharmacology (ECNP) Congress*; October 7, 2018; Barcelona, Spain. 5. Ochs-Ross R, et al. Poster presented at the *2018 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP);* May 29-June 1, 2018; Miami FL.

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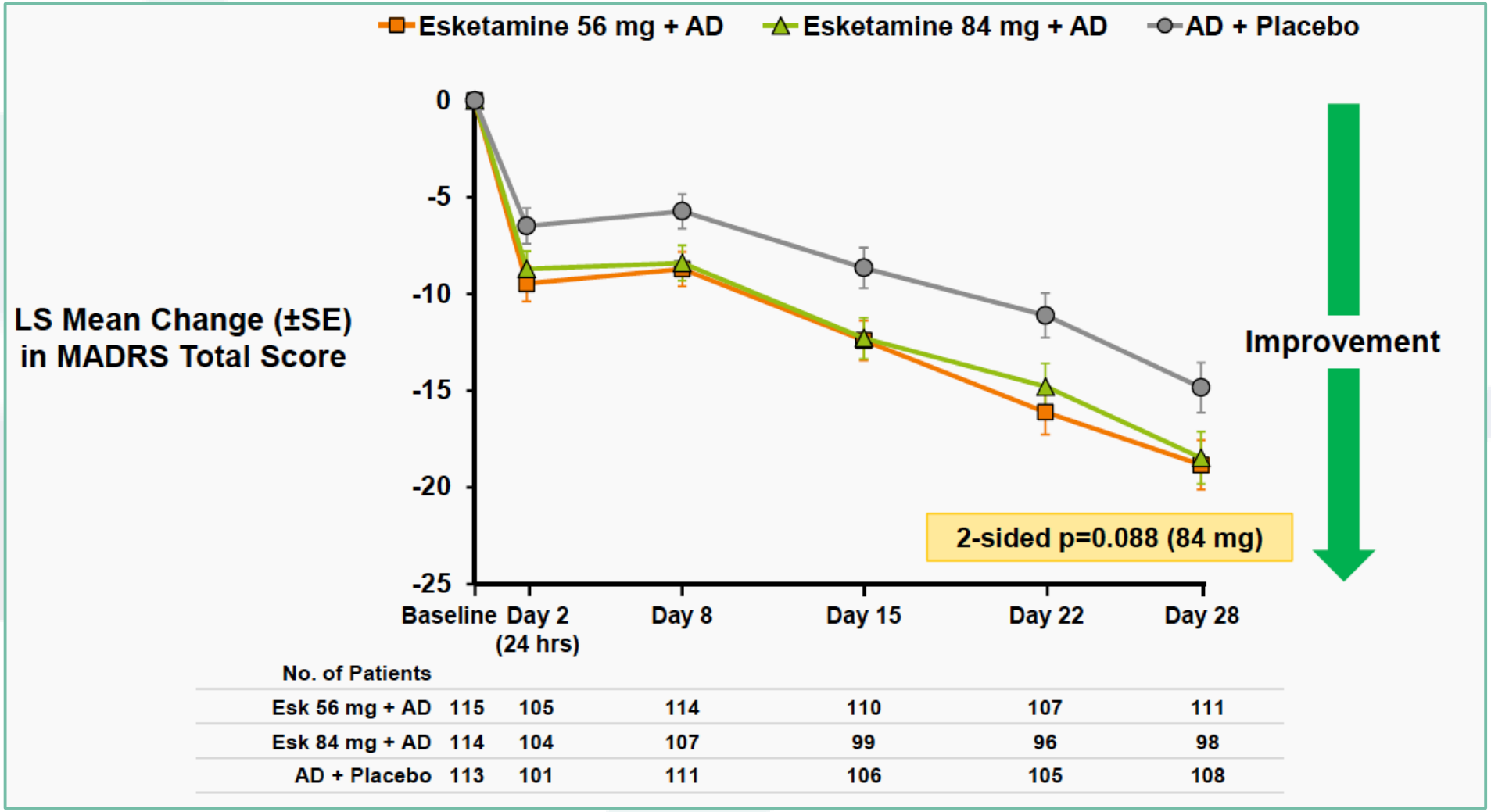

No. of Patients						
Esk 56 mg + AD	115	105	114	110	107	111
Esk 84 mg + AD	114	104	107	99	96	98
AD + Placebo	113	101	111	106	105	108

Fedgchin M, et al. Poster presented at: *the 9th Biennial Conference of the International Society for Affective Disorders (ISAD);* September 20-22, 2018; Houston, TX

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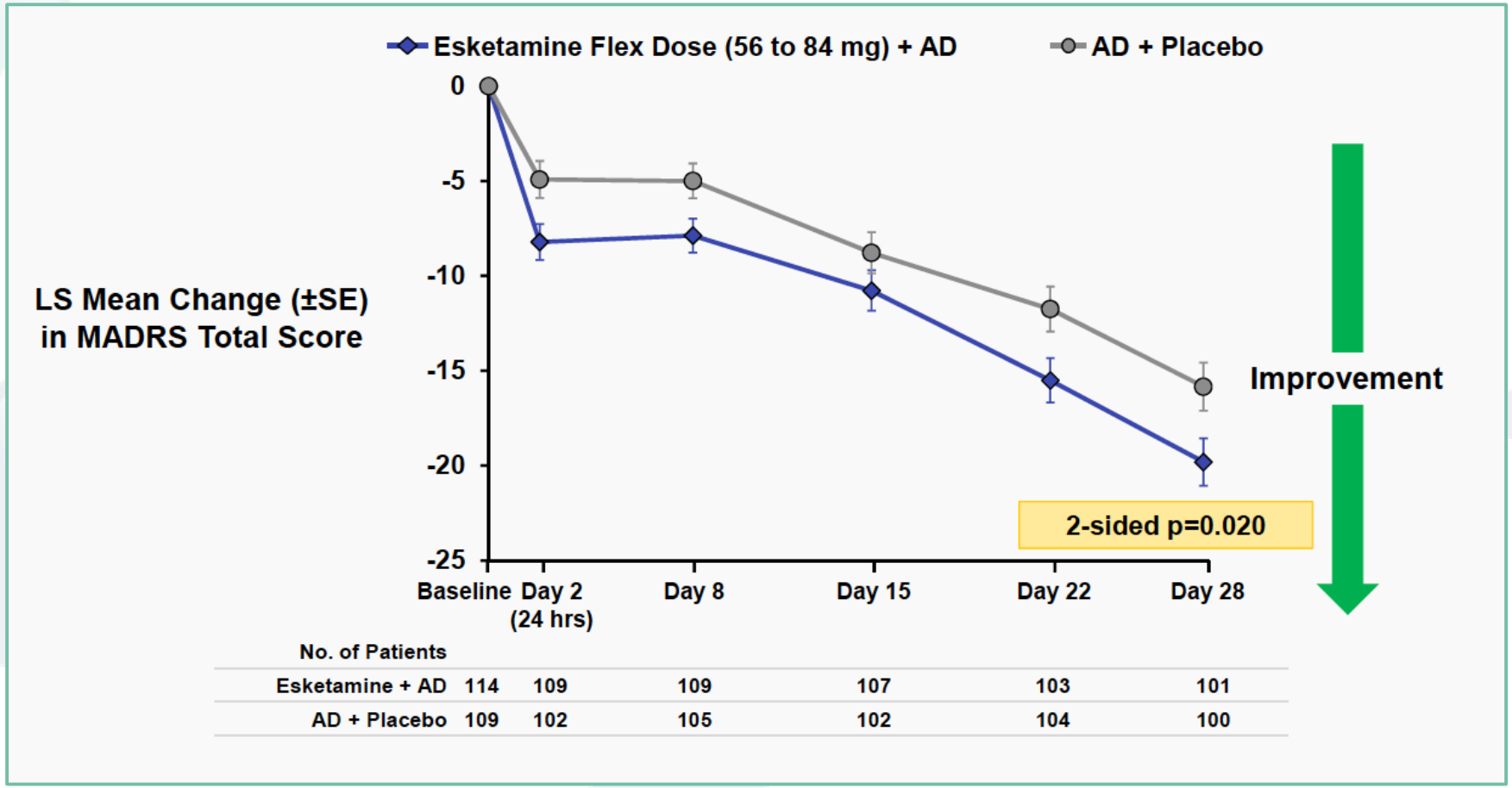
Acute, flexible dose study (3002, TRANSFORM-2)



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Elderly, acute, flexible dose study (3005, TRANSFORM-3)[5]	**Double-blind, active controlled**	**138**	**4-week induction**	**MADRS change at 4 weeks**

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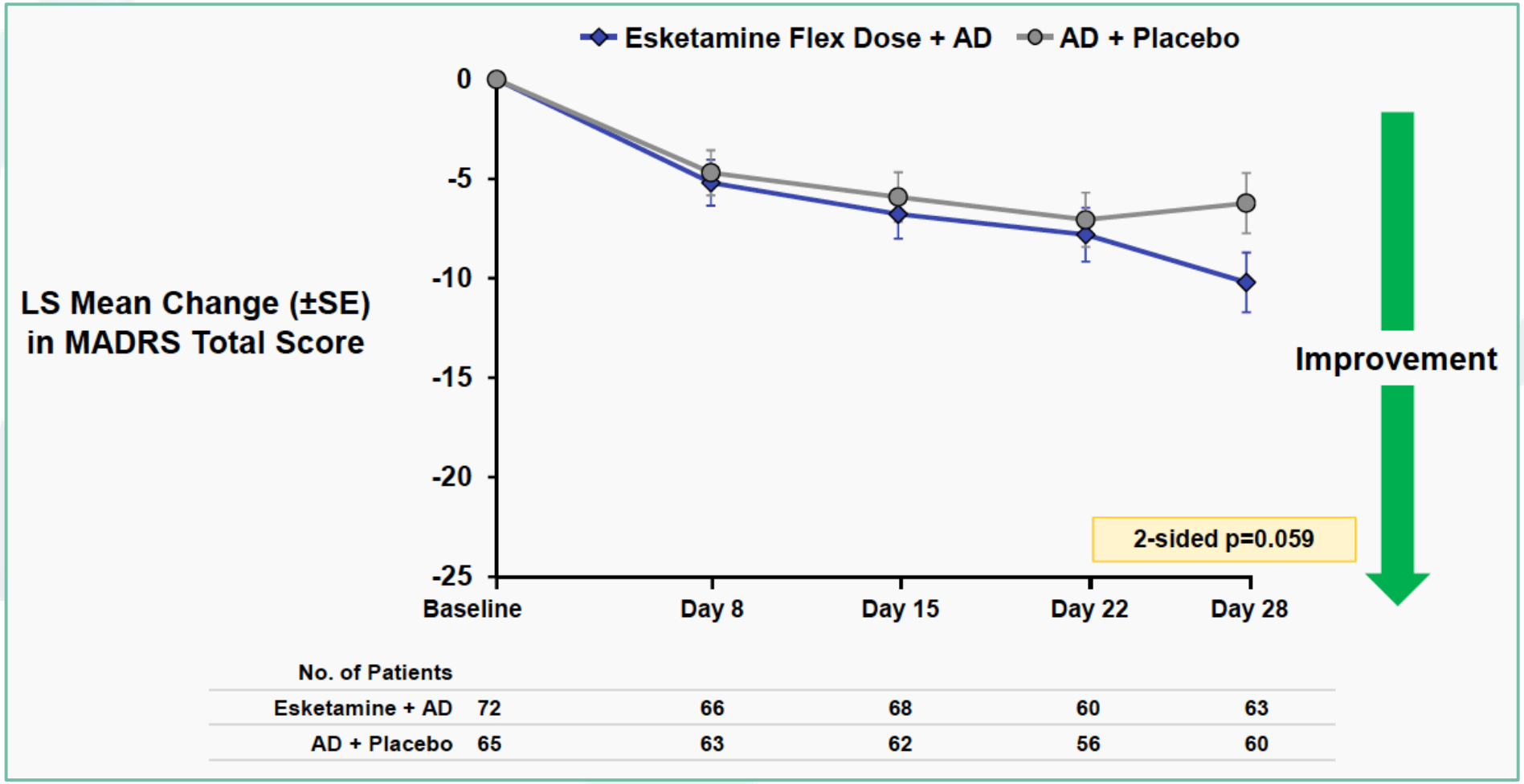
Elderly, acute, flexible dose study (3005, TRANSFORM-3)



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Maintenance, relapse prevention study (3003, SUSTaIN 1)[3]	**Open-label or double-blind induction (4-wks) and optimization (12-wks), followed by double-blind, active-controlled maintenance**	**705**	**Variable duration, longer term**	**Time to relapse; relapse in stable remitters; relapse in stable responders**

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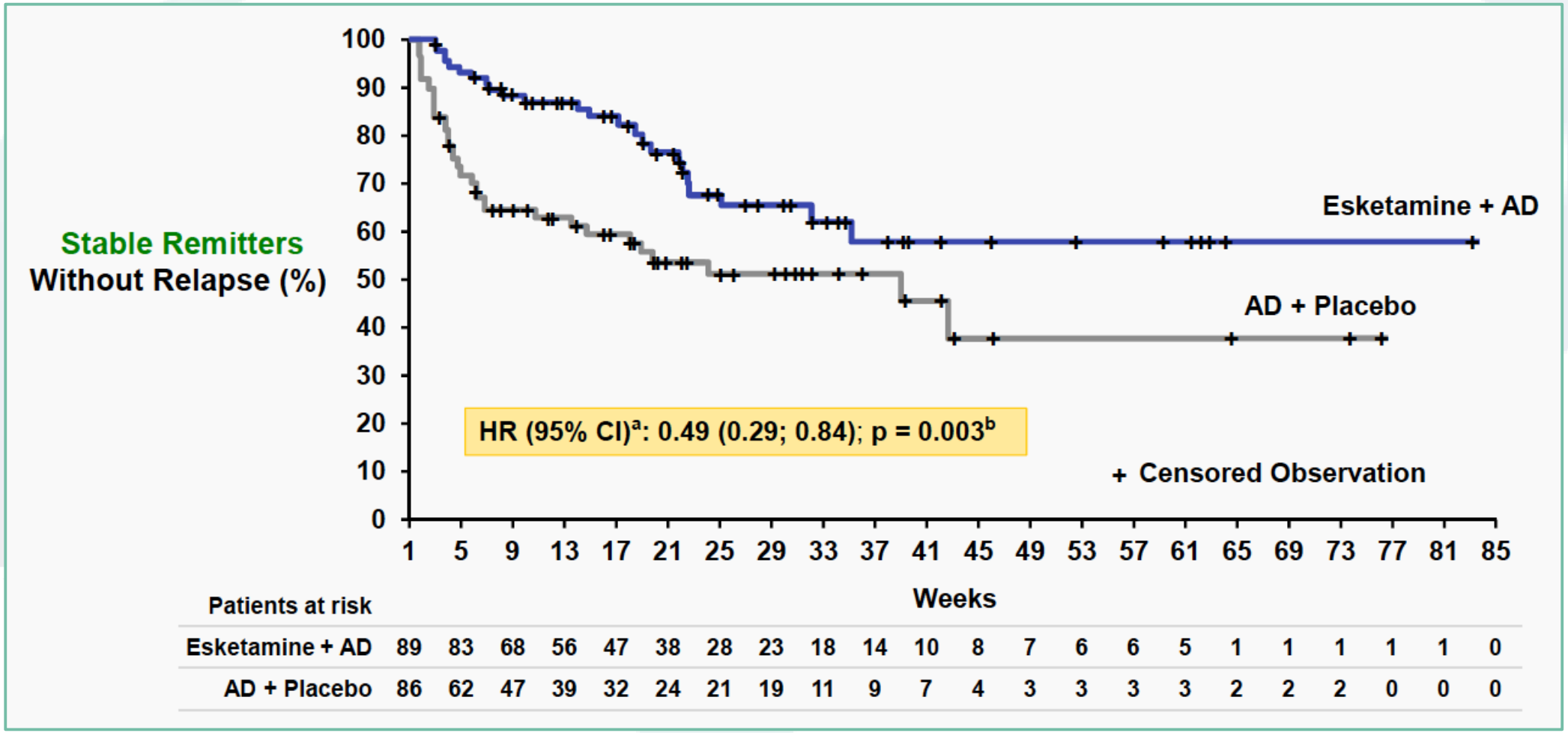

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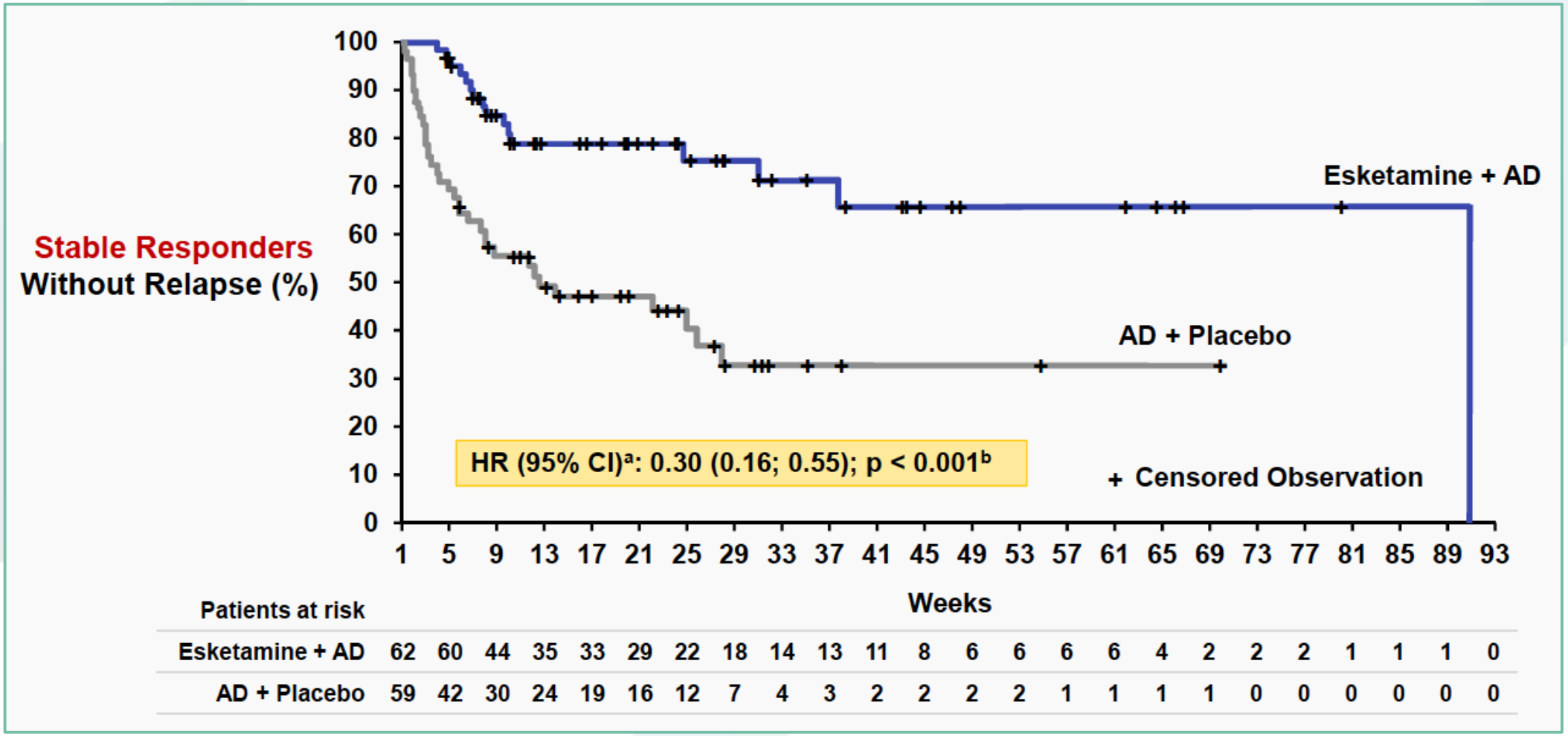

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Maintenance, safety study (3004, SUSTaIN 2)[4]	**Open-label**	**802**	**52-weeks**	**Safety and tolerability**

1. Fedgchin M, et al. *Poster presented at: the 9th Biennial Conference of the International Society for Affective Disorders (ISAD); September 20-22, 2018; Houston, TX.* 2. Popova V, et al. Poster presented at the *2018 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP);* May 29-June 1, 2018; Miami FL. 3. Daly EJ, et al. Poster presented at *the European College of Neuropsychopharmacology (ECNP) Congress*; October 7, 2018; Barcelona, Spain. 4. Wajs E, et al. Poster presented at *the European College of Neuropsychopharmacology (ECNP) Congress*; October 7, 2018; Barcelona, Spain. 5. Ochs-Ross R, et al. Poster presented at the *2018 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP);* May 29-June 1, 2018; Miami FL.

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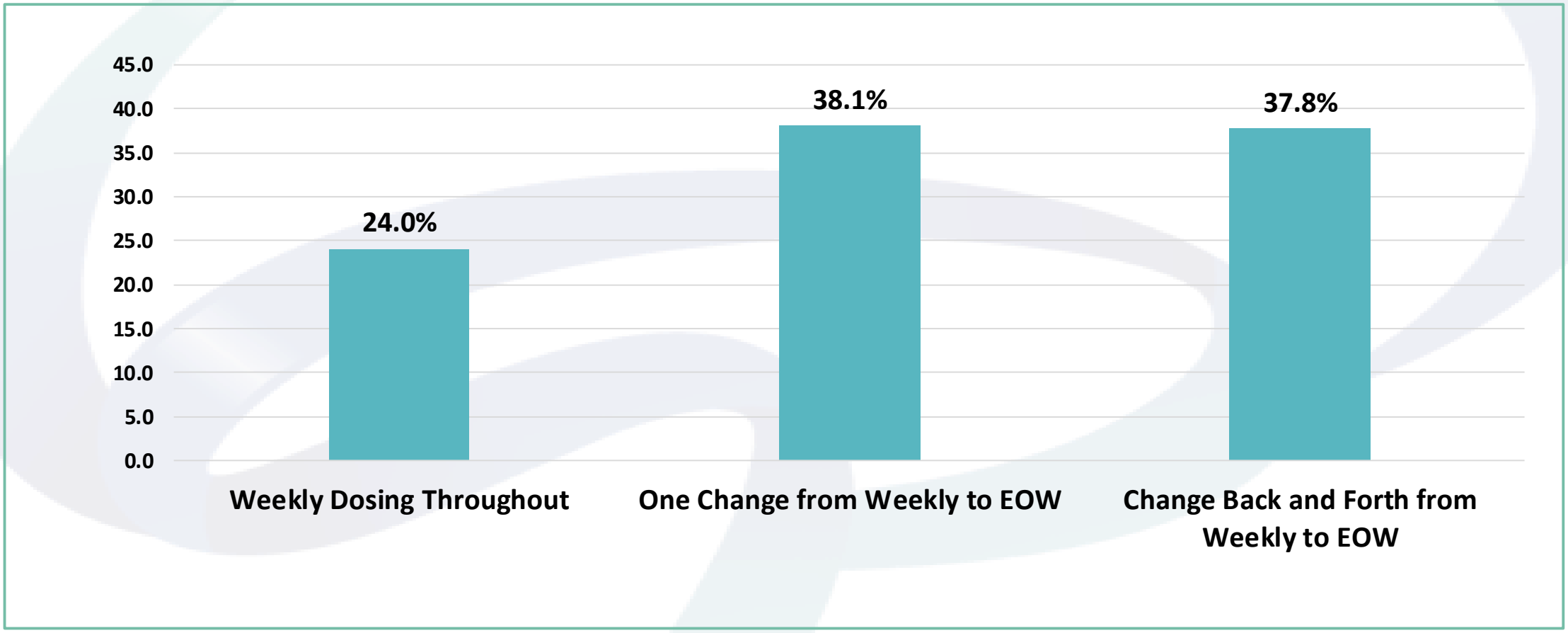


Wajs E, et al. Poster presented at *the European College of Neuropsychopharmacology (ECNP) Congress*; October 7, 2018; Barcelona, Spain.

Spravato (Esketamine)

FDA Approved: March 5, 2019

SPRAVATO™ is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist indicated, in a conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults.

INDUCTION
Weeks 1-4
(twice weekly)

- **Day 1:** 56 mg
- **Subsequent doses:** 56 mg or 84 mg

MAINTENANCE
Weeks 5-8
(once weekly)

- 56 mg or 84 mg once weekly

CONTINUATION
Weeks 9+
(once or EOW)

- 56 mg or 84 mg every 2 weeks or once weekly

SPRAVATO™ [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.

Adverse Events

	Spravato + AD (N=346)	Placebo + AD (N=222)
Dissociation	**142 (41%)**	**21 (9%)**
Dizziness	**101 (29%)**	**17 (8%)**
Nausea	**98 (28%)**	**19 (9%)**
Sedation	**79 (23%)**	**21 (9%)**
Vertigo	**78 (23%)**	**6 (3%)**
Headache	70 (20%)	38 (17%)
Dysgeusia	66 (19%)	30 (14%)
Hypoesthesia	63 (18%)	5 (2%)
Anxiety	45 (13%)	14 (6%)
Lethargy	37 (11%)	12 (5%)
↑Blood Pressure	36 (10%)	6 (3%)
Vomiting	32 (9%)	4 (2%)
Insomnia	29 (8%)	16 (7%)
Nasal Discomfort	23 (7%)	11 (5%)

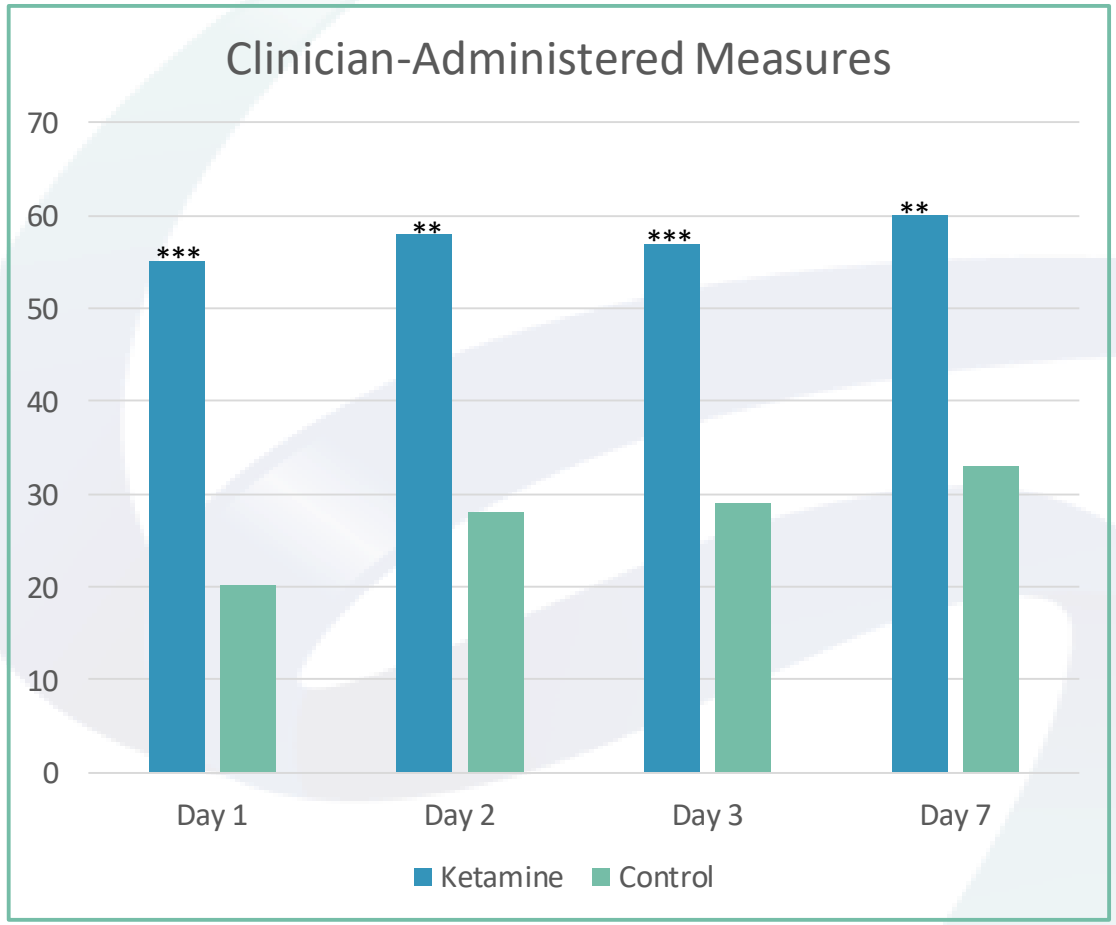
	Spravato + AD (N=346)	Placebo + AD (N=222)
Diarrhea	23 (7%)	13 (6%)
Throat Irritation	23 (7%)	9 (4%)
Feeling Drunk	19 (5%)	1 (0.5%)
Dry Mouth	19 (5%)	7 (3%)
Hyperhidrosis	14 (4%)	5 (2%)
Dysarthria	15 (4%)	0 (0%)
Pollakiuria	11 (3%)	1 (0.5%)
Oropharyngeal Pain	9 (3%)	5 (2%)
Mental Impairment	11 (3%)	2 (1%)
Tremor	12 (3%)	2 (1%)
Euphoric Mood	15 (4%)	2 (1%)
Constipation	11 (3%)	3 (1%)
Feeling Abnormal	12 (3%)	0 (0%)
Tachycardia	6 (2%)	1 (0.5%)

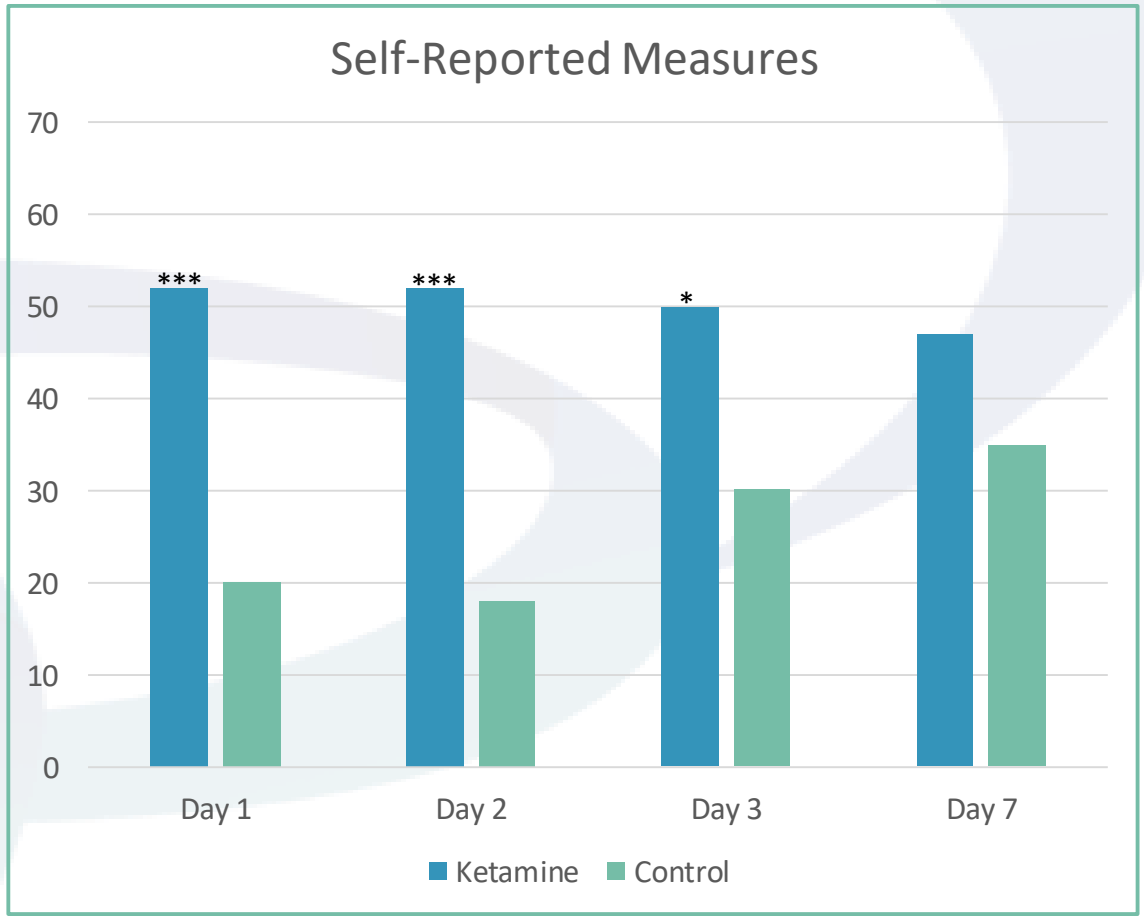
SPRAVATO™ [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.

Warnings & Precautions

- Sedation
- Dissociation
- Abuse and Misuse
- SPRAVATO Risk Evaluation and Mitigation Strategy (REMS)
- Suicidal Thoughts and Behaviors in Adolescents and Young Adults
- Increase in Blood Pressure
- Cognitive Impairment
- Impaired Ability to Drive and Operate Machinery
- Ulcerative or Interstitial Cystitis
- Embryo-fetal Toxicity

Ketamine and Suicidal Ideation

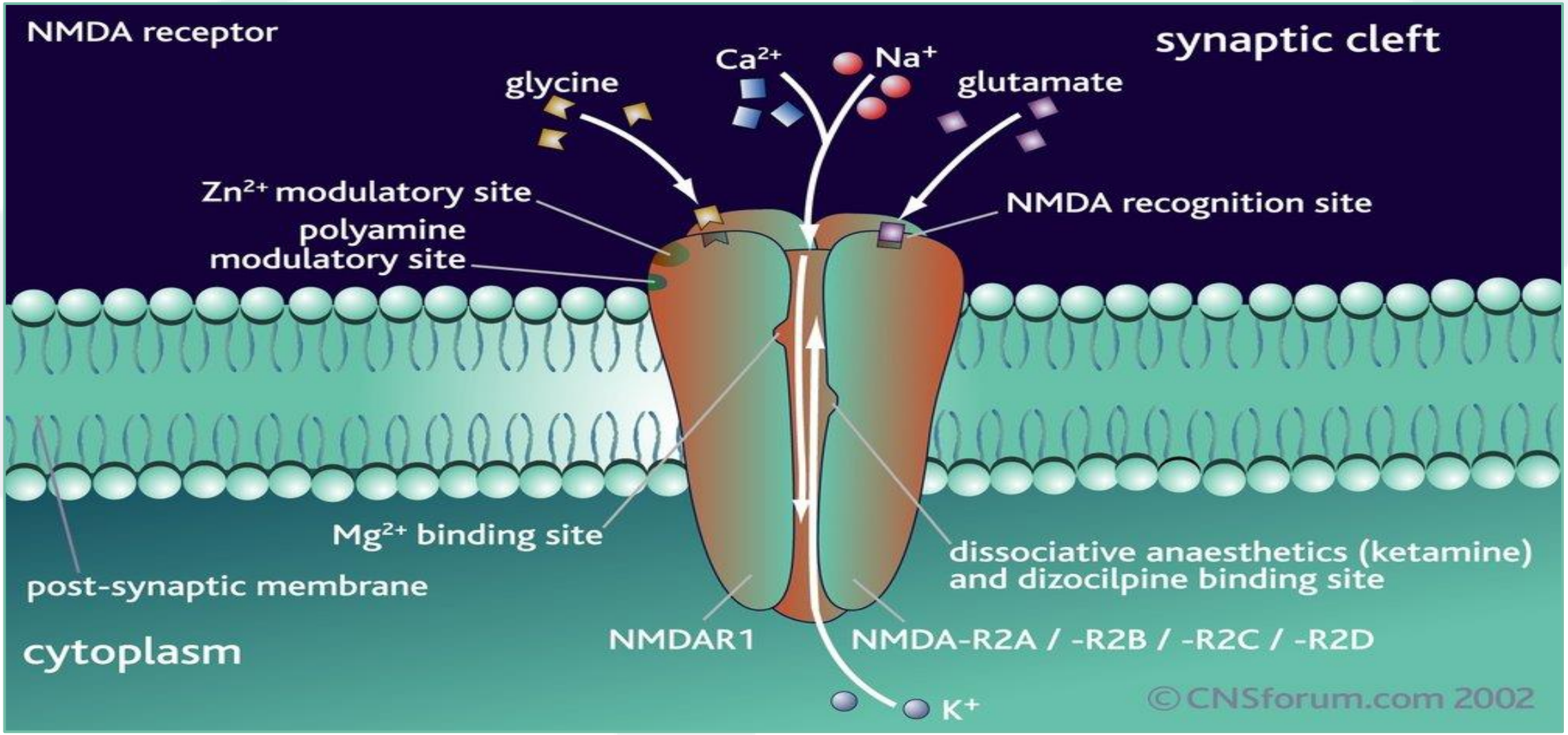




*p<0.05 **p<0.01 ***p<0.001

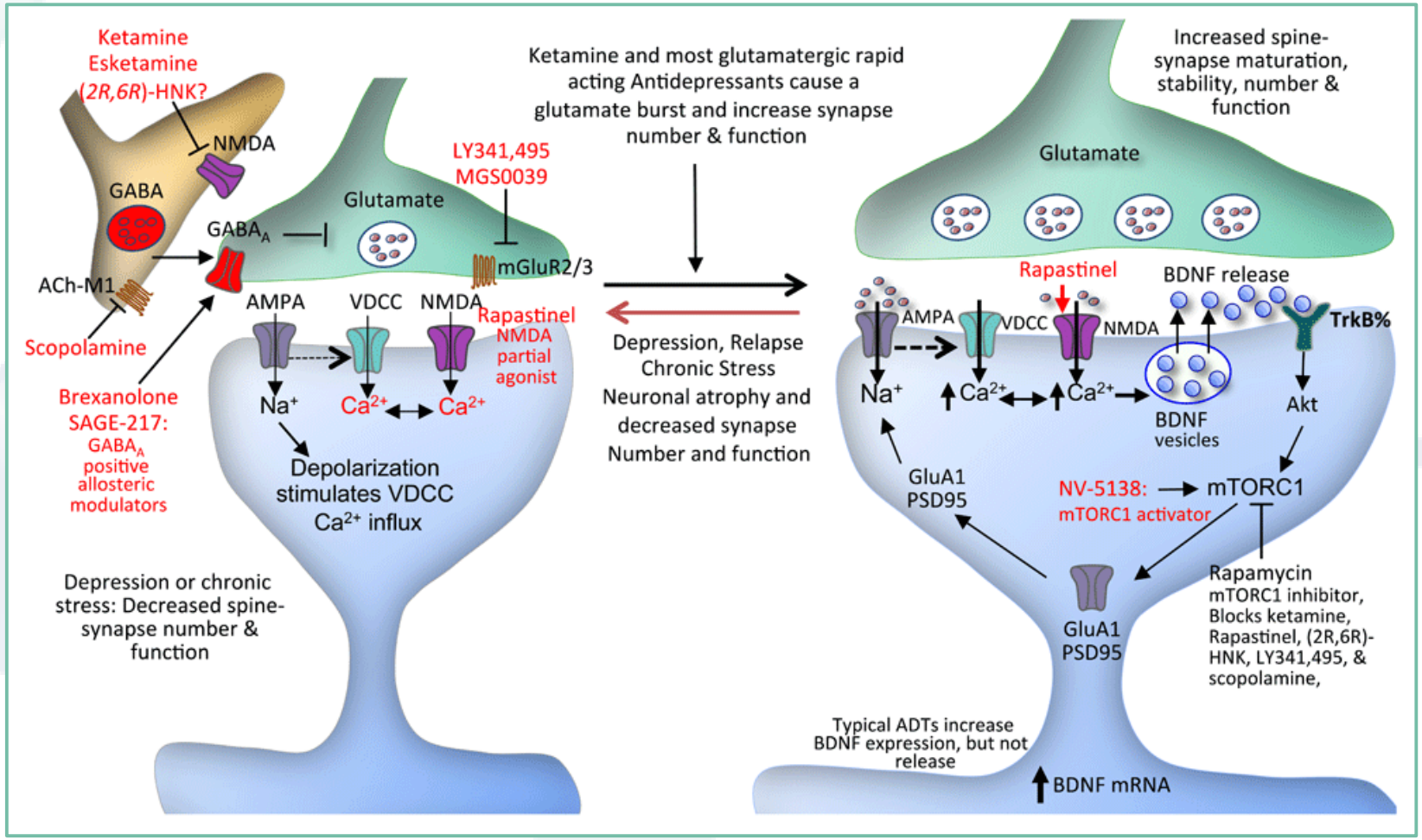
Wilkinson S, et al. *AM J Psychiatry* 2018; 175 (2): 150-158.

Ketamine and NMDA Receptor



Neill J et al. *European Neuropsychopharmacology.* 2014;24(5):822-835.

Suggested Mechanism of Action



Duman RS. Ketamine and rapid-acting antidepressants: a new era in the battle against depression and suicide [version 1; peer review: 3 approved]. *F1000Research* 2018, **7**(F1000 Faculty Rev):659 (https://doi.org/10.12688/f1000research.14344.1)

Thank You

Brain Health Consultants and TMS Center

“Forward Thinking, Evidence Based”