# Depression Drug Treatments: What is in the Pipeline?

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# Disclosures 4/2021

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* Asterisk denotes consulting activity undertaken on behalf of Massachusetts General Hospital.

# Introduction

- MDD (DSM-5) is highly prevalent in US
- 12-month prevalence of 10.4%
- 12-month prevalence of 20.6%
- 13.6% with lifetime MDD attempted suicide
- 4.7% with 12-month MDD attempted suicide
- 46.9% with lifetime MDD never treated with an antidepressant
- 73.1% with MDD the past 12 months never treated with an antidepressant.
- Those with lifetime MDD who received any treatment waited approximately 52.5 months.



Hason DS, et al. JAMA Psychiatry. 2018 Apr; 75(4): 336–346.

# Introduction

- 73.1% with MDD the past 12 months never treated with an antidepressant.
- Those with lifetime MDD who received any treatment waited approximately 52.5 months.
- Barriers?
  - Stigma
  - Access to diagnosis and treatment
  - Risk/ benefit of existing antidepressants
- Present talk will focus on breakthroughs in this third area.



Hason DS, et al. JAMA Psychiatry. 2018 Apr; 75(4): 336–346.

# NMDA-Focused

# AXS-5 (Oral)

- Dextromethorphan and bupropion
- Dextromethorphan (DM)
  - NMDA receptor antagonism
  - Sigma-1 receptor agonism
  - Rapidly cleared by CYT 2D6
- Bupropion (BUP)
  - NE reuptake inhibition
  - DA (weak) reuptake inhibition
  - CYT 2D6 inhibitor



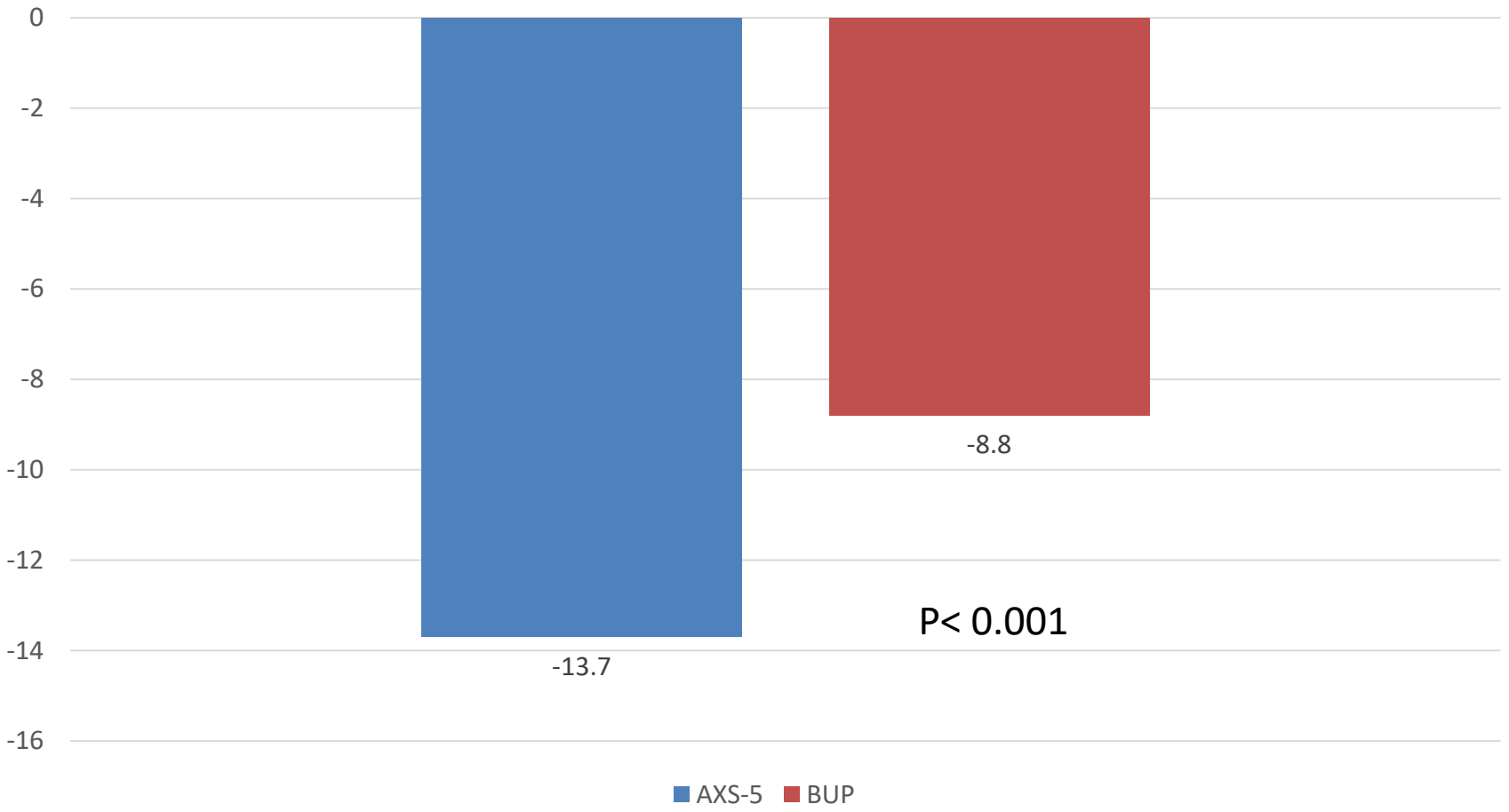
Ionescu D and Papakostas GI. Curr Behav Neurosci Rep. 2016 ;3(2):185-191.

# ASCEND (Assessing Clinical Episodes in Depression) Trial (Phase 2)

- NCT03595579
- Monotherapy in MDD
- 6 week double-blind period
- Active: 45mg DM and 105mg BUP (N=43)
- Control: 105mg BUP (N=37)
- Mean baseline MADRS score 31.8, 32.2

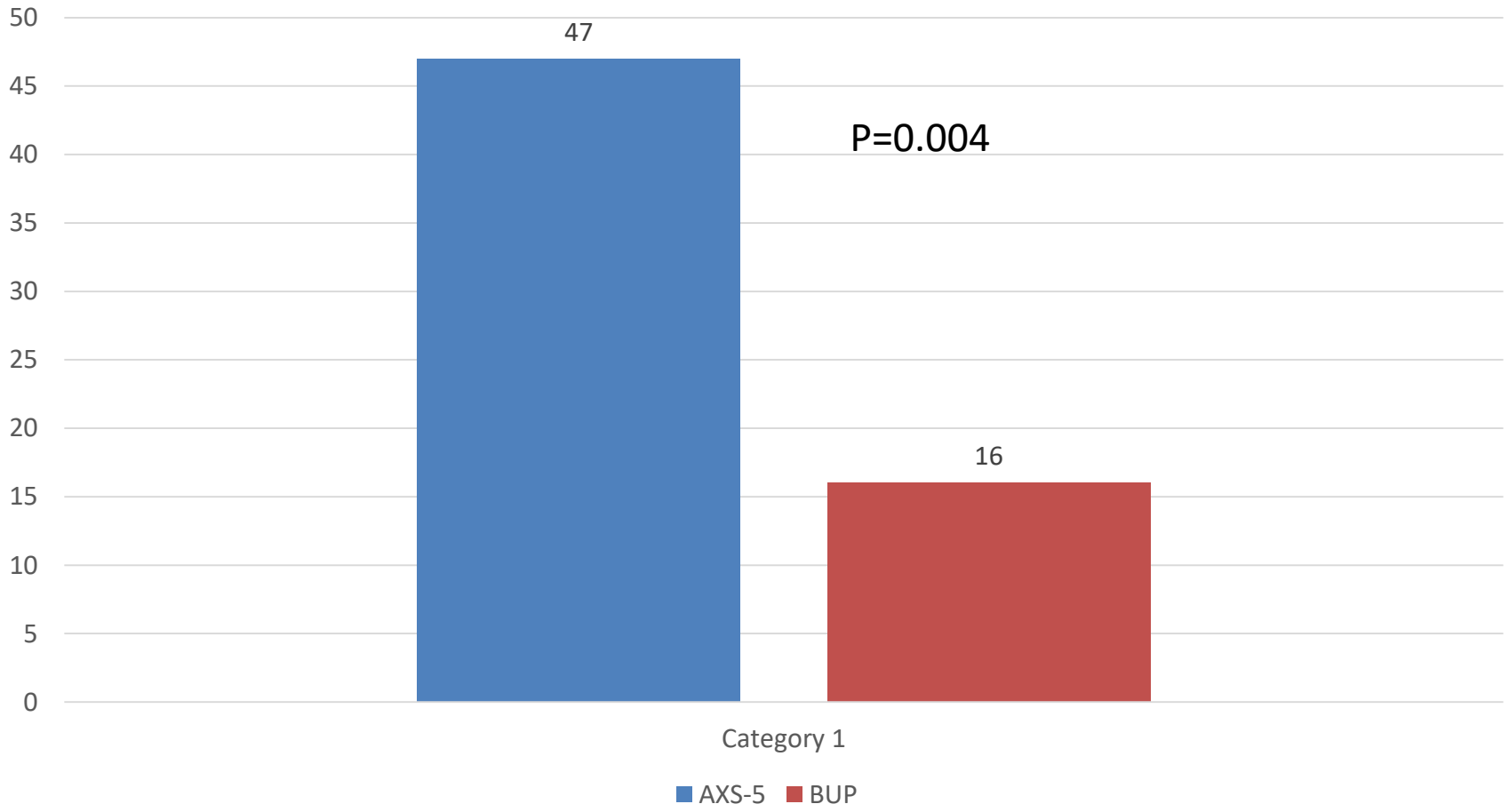
Anderson A, Iosifescu DV, Jacobson M, Jones A, Kennon K, O'Gorman C, Stahl SM, Tabuteau H. Efficacy and Safety of AXS-05, an Oral NMDA Receptor Antagonist with Multimodal Activity, in Major Depressive Disorder: Results of a Phase 2, Double-Blind, Active-Controlled Trial. ASCP Annual Meeting 2019.

# ASCEND: Change in MADRS Scores




Anderson A, et al. ASCP Meeting. 2019.

# Remission (%) (MADRS≤10)




Anderson A, et al. ASCP Meeting. 2019.

# Tolerability and Safety

- There were no reported serious adverse events.
- The most commonly reported adverse events in the AXS-05 arm were nausea, dizziness, dry mouth, decreased appetite and anxiety.
- The rate of discontinuations due to adverse events was approximately 12% for each treatment group.
- Treatment with AXS-05 was not associated with psychotomimetic effects, weight gain, or increased sexual dysfunction.



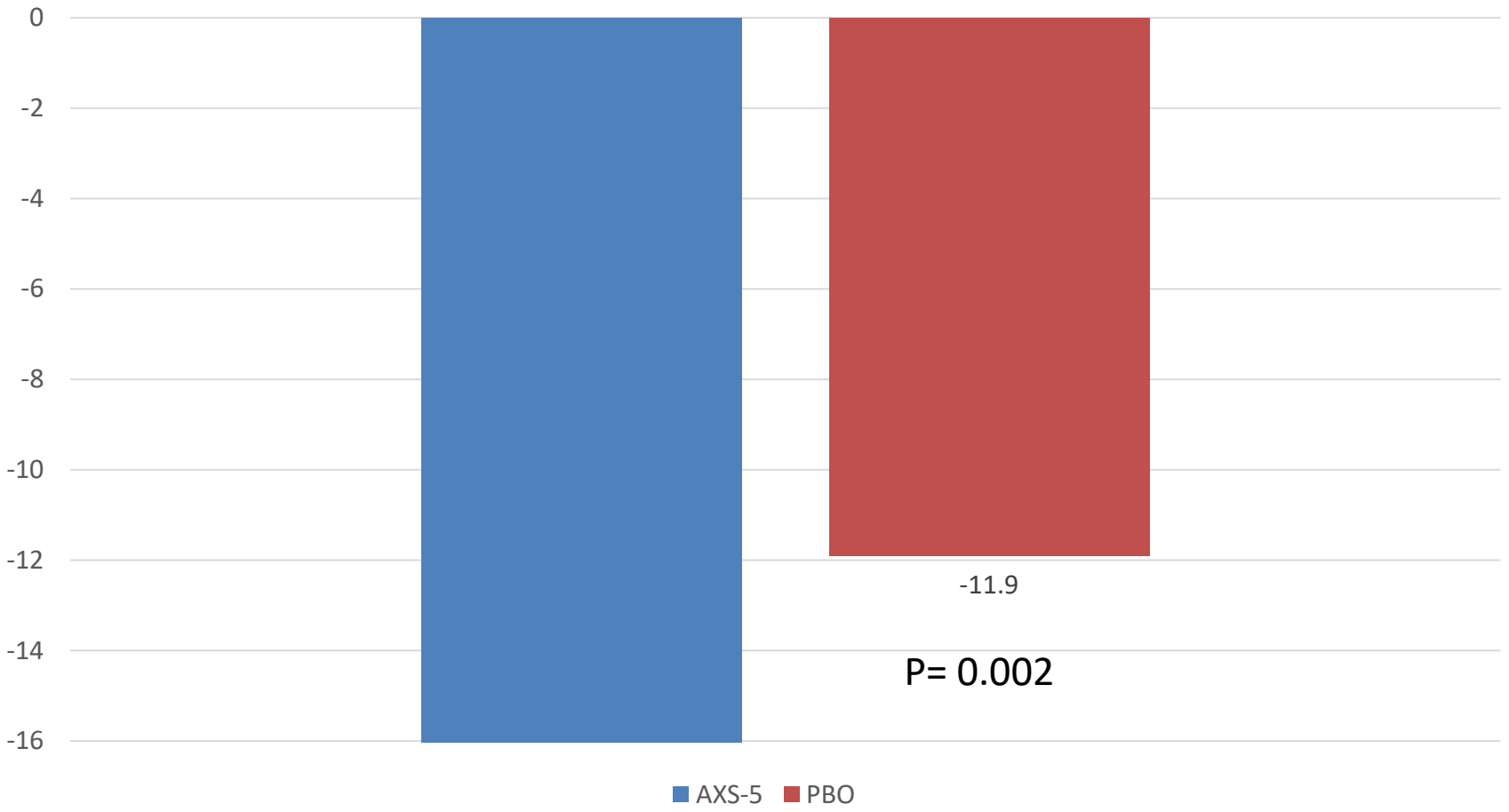
Anderson A, et al. ASCP Meeting. 2019.

# GEMINI (Phase 3)

- NCT04019704
- Monotherapy MDD
- 6-week double-blind period
- Active: 45mg DM and 105mg BUP BiD (N=163)
- Control: Placebo (Pbo) (N=164)
- Mean baseline MADRS score 33.6, 33.2

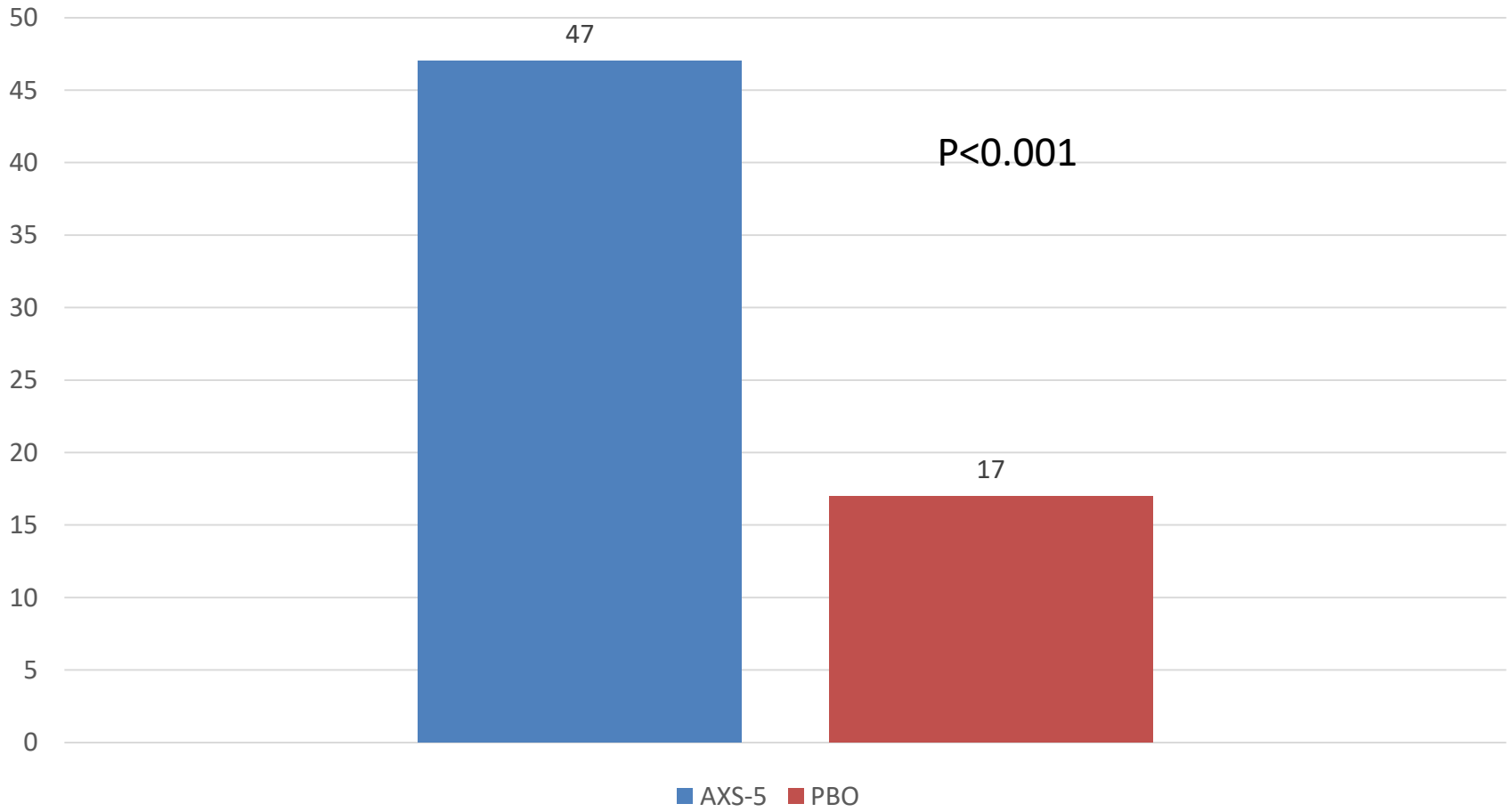
O'Gorman C, Jones A, Iosifescu DV, Fava M, Tabuteau H. Efficacy and Safety of AXS-05, an Oral NMDA Receptor Antagonist with Multimodal Activity, in Major Depressive Disorder. ECNP Annual Meeting. 2020.

# GEMINI: Change in MADRS Scores




O'Gorman C, et al. ECNP Annual Meeting. 2020.

# Remission (%) (MADRS≤10)




O'Gorman C, et al. ECNP Annual Meeting. 2020.

# Tolerability and Safety

- There were no drug-related reported serious adverse events.
- The most commonly reported adverse events in the AXS-05 arm were nausea, dizziness, headache, diarrhea, somnolence, dry mouth.
- • Rates of discontinuation due to adverse events were low in both groups, 6.2% and 0.6%, for AXS-05 and placebo, respectively
- Treatment with AXS-05 was not associated with psychotomimetic effects, weight gain, or increased sexual dysfunction.

O'Gorman C, et al. ECNP Annual Meeting. 2020.

# AXS-5 Program

- Ongoing
  - NCT04634669
    - Open-label TRD
    - N=150 for 12 months
    - Due 5/2022
  - NCT04608396
    - Relapse prevention
    - N=50 for up to 52 weeks
    - Due 9/2021

# AXS-5 Program

- Completed
  - NCT02741791
    - TRD (STRIDE-1) Phase 3
    - N=312
    - 6 weeks open-label BUP
    - 6 weeks double-blind AXS-5 vs BUP
    - MADRS 1o outcome

# Dextromethadone (D-methadone)

- REL-1017
- Oral NMDA receptor antagonist (1)
- 10–30-fold lower affinity for the μ and δ-opioid receptor subtypes compared with *l*-methadone (2, 3)
- Not associated with typical opioid-induced effects in humans at doses predict to exert antidepressant activity (4).

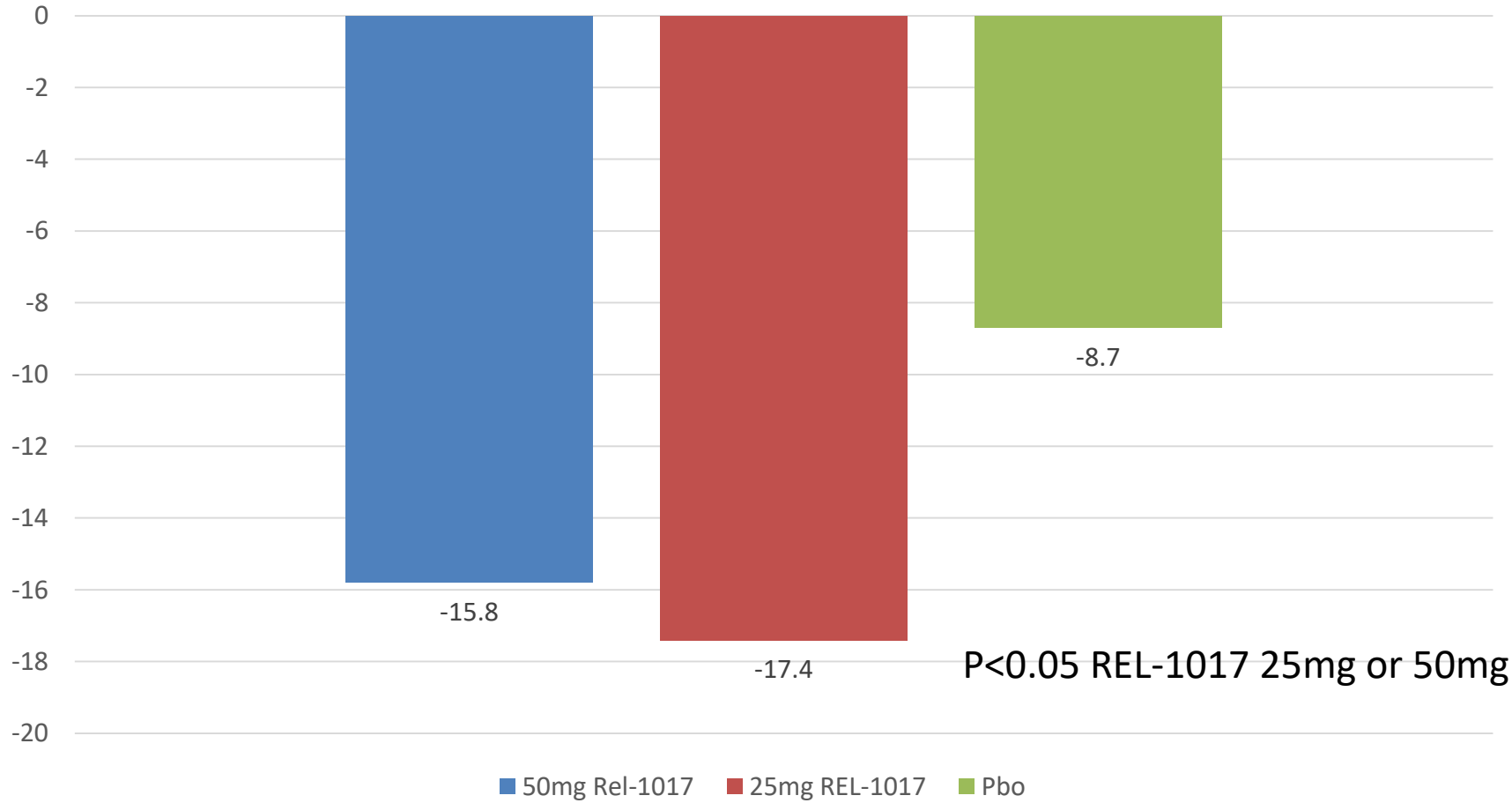
1. Callahan RJ, et al. Anesth Analg. 2004;98:653–9.
2. Kristensen K, Life Sci. 1995;56:PL45–50.
3. Gorman AL, Neurosci Lett. 1997;223:5–8.
4. Bernstein G et al, J Clin Psychopharmacol. 2019;39:226–37

# NCT03051256 (phase 2)

- 25mg (N=19) vs 50mg (N=21) REL-1017
- vs Pbo (N=22)
- Adjunctive treatment in MDD
- Primary outcome at 7 days post-randomization

https://www.clinicaltrials.gov/ct2/show/results/NCT03051256?term=relmada&draw=2&rank=4

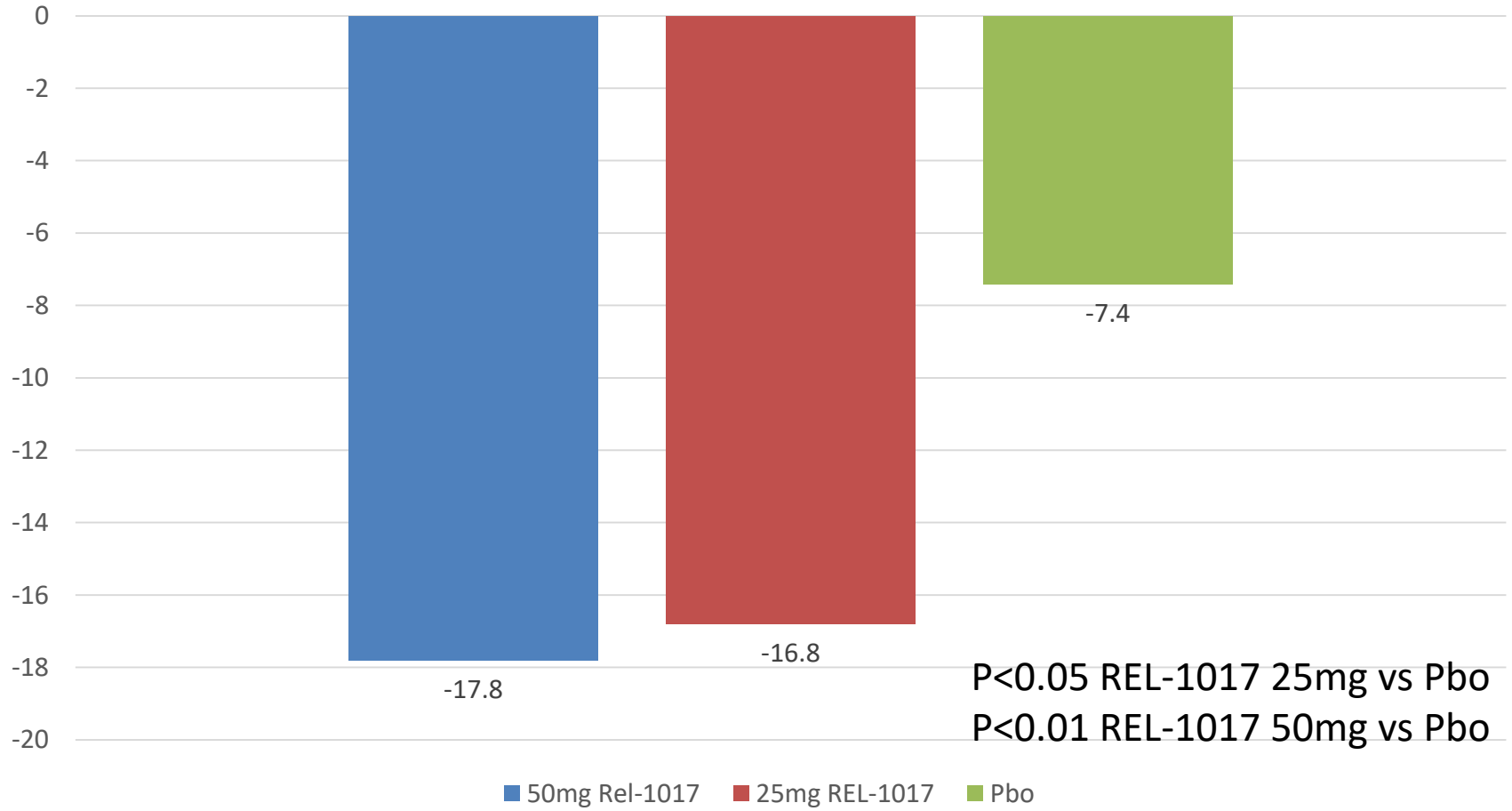
# Change in MADRS Scores day 7




P<0.05 REL-1017 25mg or 50mg vs Pbo

https://www.clinicaltrials.gov/ct2/show/results/NCT03051256?term=relmada&draw=2&rank=4

# Change in MADRS Scores day 14




P<0.05 REL-1017 25mg vs Pbo
P<0.01 REL-1017 50mg vs Pbo

https://www.clinicaltrials.gov/ct2/show/results/NCT03051256?term=relmada&draw=2&rank=4

# Safety and tolerability

- Constipation, nausea, somnolence, sedation similar to placebo
- No SAEs

https://www.clinicaltrials.gov/ct2/show/results/NCT03051256?term=relmada&draw=2&rank=4

# REL-1017 Program

- Ongoing
  - NCT04688164 (RELIANCE-1)
  - Adjunctive MDD
  - Phase 3
  - 25mg vs Pbo
  - Change MADRS baseline to day 28

# NMDA Development: Phase 3

- NCT03185819
  - JNJ
  - IN Esketamine
  - Pediatric MDD with SI

# NMDA Development: Phase 2

- NCT04669665
  - Seelos Therapeutics, Inc
  - Intranasal racemic ketamine
  - Adjunctive MDD wth suicidal thoughts
- NCT04103892
  - CLE-100
  - Clexio Biosciences Ltd.
  - Oral NMDA Antagnosis
  - Adjunctive MDD
- NCT04722666
  - MIJ821
  - Novartis Pharmaceuticals
  - IV NMDA Antagonist
  - MDD with prominent SI

# HPA-Focused

# Seltorexant (JNJ42847922/MIN-202)

- Orexin Receptor-2 (OXR-2) Antagonist (1)
- OXR-2 relates to Hypothalamic-Pituitary-Adrenal (HPA)-axis activation (2)
- HPA-axis hyperactivation relating to MDD (3)

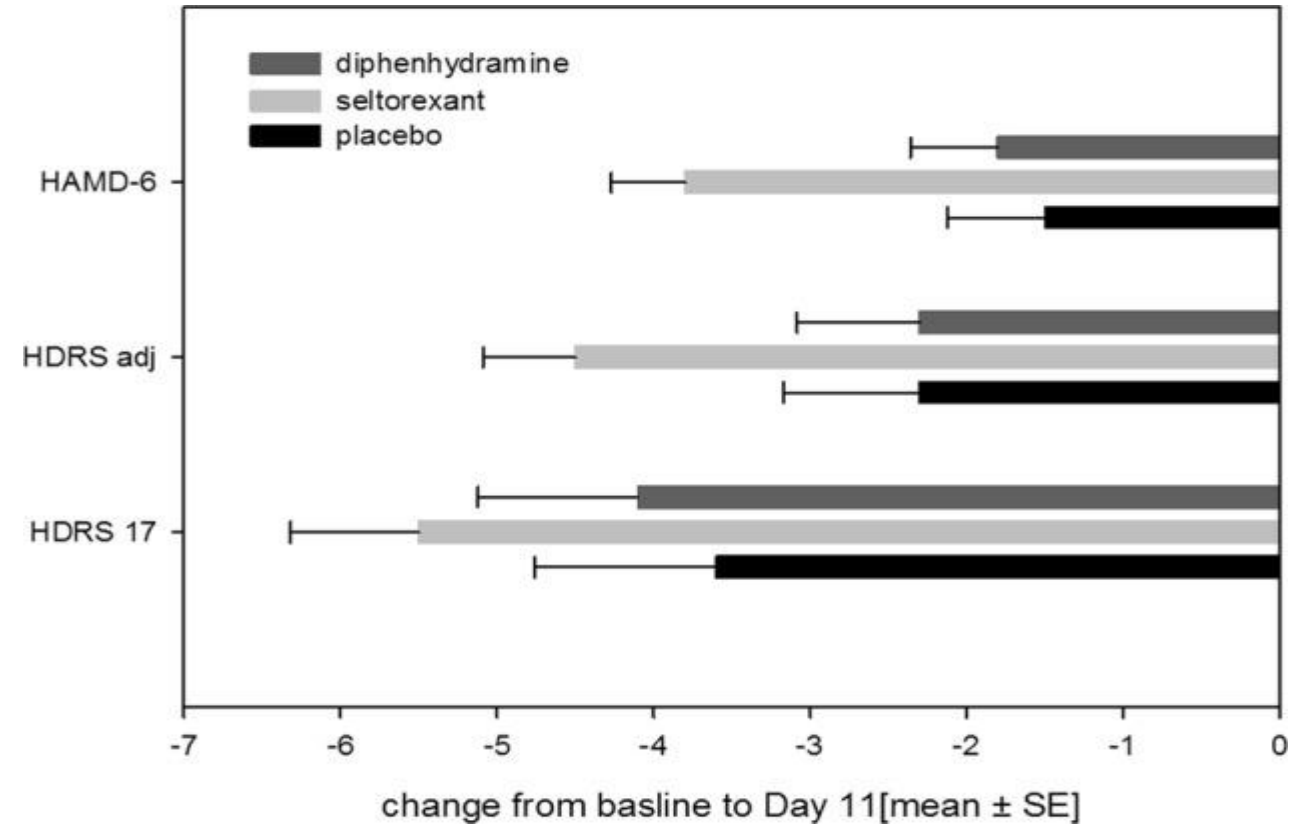
1. Bonaventure, P. et al. et al. J. Pharmacol. Exp. Ther. 354, 471–482 (2015).
2. Yun, S. et al. Behav. Neurosci. 11, 83 (2017)
3. Pariante CM, Miller AH. Biol Psychiatry. 2001;49(5):391-404.

# NCT02476058

- 2:1:1
- Seltorexant 20mg  (N=22)
- Diphenhydramine 25mg (N=13)
- Placebo (N=12)
- MDD
- Monotherapy or adjunctive

Recourt K et al. Transl Psychiatry. 2019 Sep 3;9(1):216.

# Difference in Change in HAMD17 Scores day 11




Significant larger reduction in the adjusted HDRS17 and HAMD-6 scores for seltorexant versus placebo (least-squares means difference −2.2, 95% CI [−4.35; −0.05], $p < 0.05$ and least-squares means difference −2.5, 95% CI [−4.14; −0.80], $p < 0.01$, respectively).

Recourt K et al. Transl Psychiatry. 2019 Sep 3;9(1):216.

# Seltorexant Program

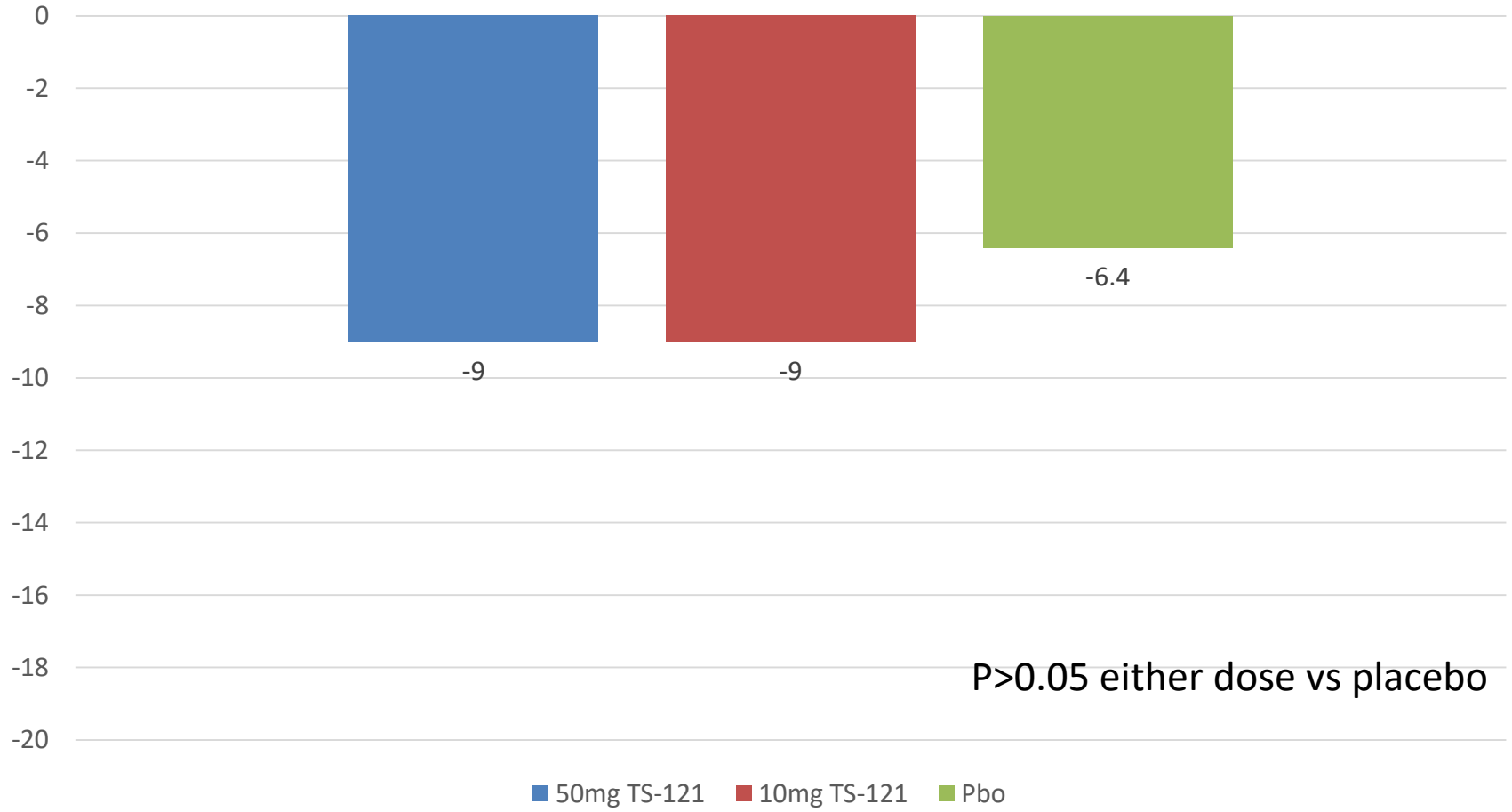
- Ongoing
  - NCT04532749, NCT4533529
    - Adjunctive therapy 20mg versus placebo
    - MDD with insomnia
  - NCT04513912
    - Adjunctive therapy 20mg versus Quetiapine versus placebo
- Completed
  - NCT03321526 (adjunctive MDD)
    - Seltorexant 20mg
    - Seltorexant 40mg
    - Quetiapine 150mg
    - Quetiapine 300mg
    - Placebo
  - NCT03227224 (adjunctive MDD)

# TS-121

- Vasopressin 1b (V1B) receptor antagonist (1)
- V1b receptor implicated in HPA-axis regulation (2)
- NCT03093025
- Adjunctive oral TS-121 10mg (N=16) vs 50mg (N=16)
- Vs Pbo (N=18)
- 1o outcome MADRS week 6

1. Kamiya M et al, J Psychiatr Res. 2020 Sep;128:43-51 (Epub ahead)
2. Roper J et al, Stress. 2011 Jan;14(1):98-115.

# Difference in Change in MADRS Scores week 6




1. Kamiya M et al, J Psychiatr Res. 2020 Sep;128:43-51

# Other Novel Mechanisms

# Ezogabine

- Opens voltage-gated potassium channel coded by gene KCNQ2/3 (1)
- Such agents have been proposed for mood and anxiety disorders due to their role in regulating neuronal excitability (2)

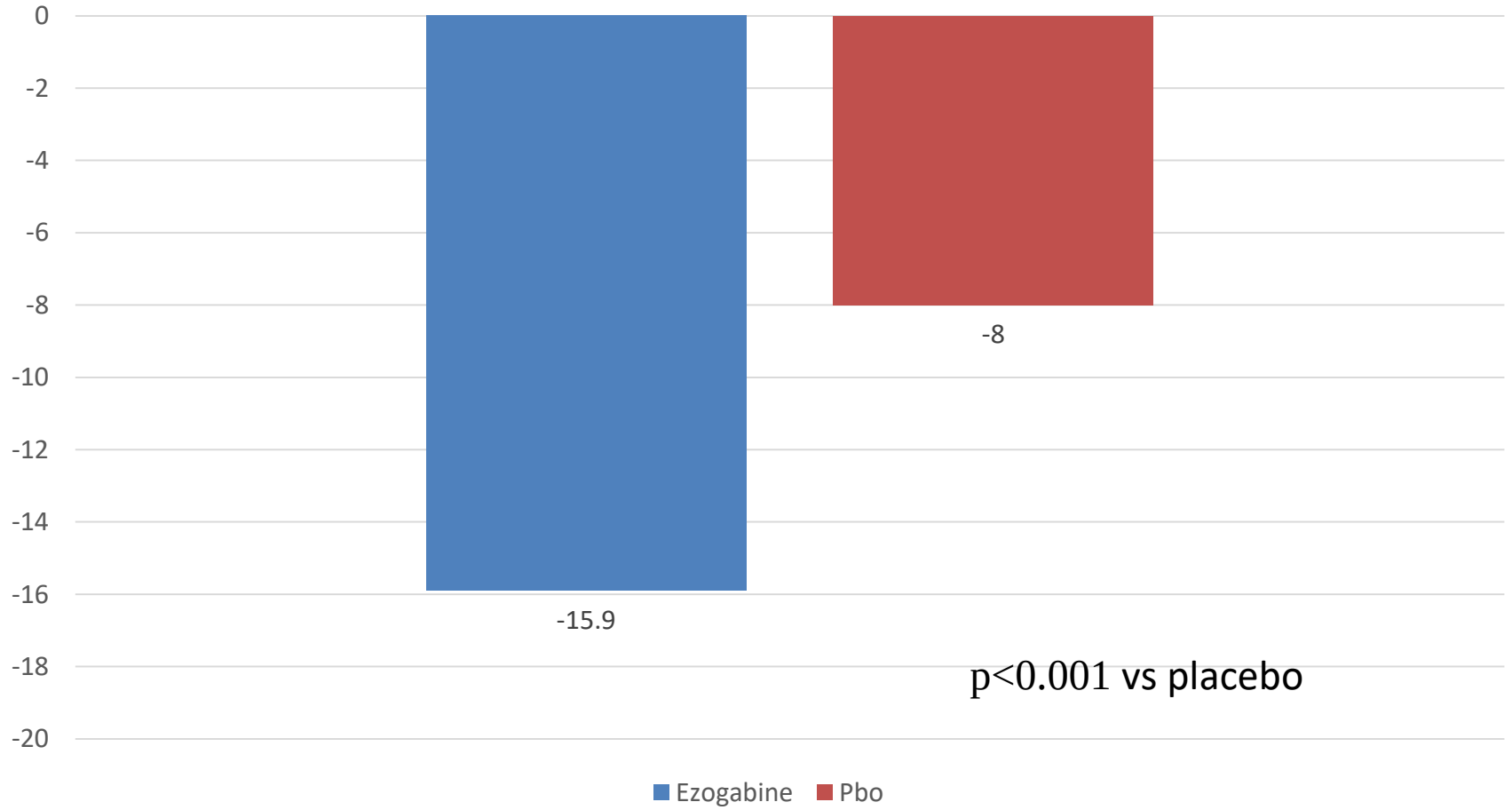
1.Li et al. Mol Cell. 2021 Jan 7;81(1):25-37.e4.
2. Surti TS and Jan LY. Curr Opin Investig Drugs. 2005 Jul;6(7):704-11.

# NCT03043560

- MDD with prominent anhedonia
- Ezogabine (n=21) 900mg versus placebo (n=24)
- 5-weeks
- MADRS primary outcome

Murrough J et al, AM J Psychiatry. 2021 Mar 3;appiajp202020050653

# Difference in Change in MADRS Scores week 5




Murrough J et al, AM J Psychiatry. 2021 Mar 3;appiajp202020050653

# Development of KCNQ channel openers

- NCT03043560 Phase 2
- XEN1101 (Xenon Pharmaceuticals)
- XEN1101 20mg oral versus placebo
- N=60
- 8 weeks- MADRS

Bialer M et al, Epilepsia. 2020 Nov;61(11):2340-2364.

# Gamma Aminobutyric acid receptor A subtype (GABAA) positive allosteric modulator (PAM)

- PRAX 114
- NCT04832425 Phase 2/3
- Praxis Precision Medicines
- PRAX 114 40mg versus placebo
- Total duration 28 days
- Primary outcome 14 days

# Kappa Opioid Receptor (KOR) antagonist development

- NCT04221230
- BTRX-335140- Blackthorn Therapeutics
- Phase 2
- MDD with anhedonia
- 8 weeks
- HAMD17



Guerrero M et al, J Med Chem. 2019 Feb 28;62(4):1761-1780.

# JNJ-54175446

- Oral P2X7 Antagonist (1)
- P2X7 is present on several  immune cells types and plays a role in the regulation of inflammatory molecules during stress (2,3).
- Phase 2
- NCT04116606
- N=142
- MDD adjunctive
- Week 8 MADRS scores

1.Jacobson K et al. Biochem Pharmacol. 2020 Oct 29:114311.
2. Su WJ et al, Front Cell Neurosci. 2018 Nov 13;12:412.
3. Dao-Ung P et al. Purinergic Signal. 2015 Dec;11(4):481-90.

# Monoaminergic Agents

# Psilocybin

- 5HT2A-receptor agonist (1)
- NCT03866174
  - Usona Institute
  - MDD
  - 25mg Psilocybin versus Niacin 100mg
  - N=80
- NCT04670081
  - Multi-sponsored including Usona
  - MDD (TRD)
  - Psilocybin (5mg or 25mg) versus Nicotinamide 100mg
  - N=144

De Sangtos RG e al, J Psychopharmacol. 2021 Mar 19:269881120986422.

# Others

- Mescaline
- MDMA (3,4-Methylenedioxymethamphetamine)
- LSD (Lysergic acid diethylamide)

# Traditional Agents

- OPC 64005 (Otsuka)
  - SNDRI
  - NCT04244253
    - 10mg vs 20mg vs Pbo in MDD
    - 1o outcome MADRS week 6
- Cariprazine (Allergan)
  - Atypical Antipsychotic
  - NCT03738215, NCT03739203
    - Adjunctive MDD

# Conclusion

- Urgent need to expand on existing therapeutic models in MDD pharmacotherapy.
- NMDA and HPA axis are two areas of investigation.
- Opioidergic, GABAergic and anti-inflammatory agents also in phase 2.
- Several monoaminergic agents.