Psych Congress

EVOLVING MANAGEMENT STRATEGIES IN MAJOR DEPRESSIVE DISORDER:

Smarter Choices after Unsuccessful First-line Treatment

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- **Dr. Gus Alva:**Advisory Board, Consultant, Grant Research/Support, Speakers Bureau—AbbVie, Abbott, Acadia, Alkermes, Allergan, Amgen, Avanir, Biogen, Celgene, Cerevel Therapeutics, Cubist, Eisai, Ferring, Genentech, Janssen, Intra-Cellular Therapies, Inc., Liva Nova, Lundbeck, Merck, Myriad, Neurocrine Biosciences, Inc., Otsuka America Pharmaceutical, Inc., Sage Therapeutics, Shire, Elan, GlaxoSmithKline, Hospira, Pfizer, Bristol-Myers Squibb, Roche, Salix, Seattle Genetics, Takeda, Teva Pharmaceuticals.

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- **Vanessa Joy Walker** has disclosed no relevant financial relationship with any ineligible company (commercial interest).

Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).

- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

- This activity has been independently reviewed for balance.

Learning Objectives

- Implement strategies to improve the early identification and personalized treatment of patients with MDD in clinical practice
- Assess limitations of traditional antidepressants related to the suboptimal management of patients with MDD
- Evaluate the clinical safety and efficacy data associated with newer antidepressants for MDD
- Apply evidence-based and collaborative antidepressant switching strategies in clinical practice after first-line treatment failure for individualized MDD care

Pathophysiology, Prevalence and Burden of MDD

In 2020 ~21 Million Adults Experienced a Major Depressive Episode

~21 M

~8.4% of US adults experienced an MDE in 2020[1,†]

~13.8 M

~66% of US adults who experienced an MDE received treatment for MDD in 2020[1,†]

~7.9 M

~38% of US adults who experienced an MDE were prescribed at least 1 medication for MDD in 2022[1,2,‡]

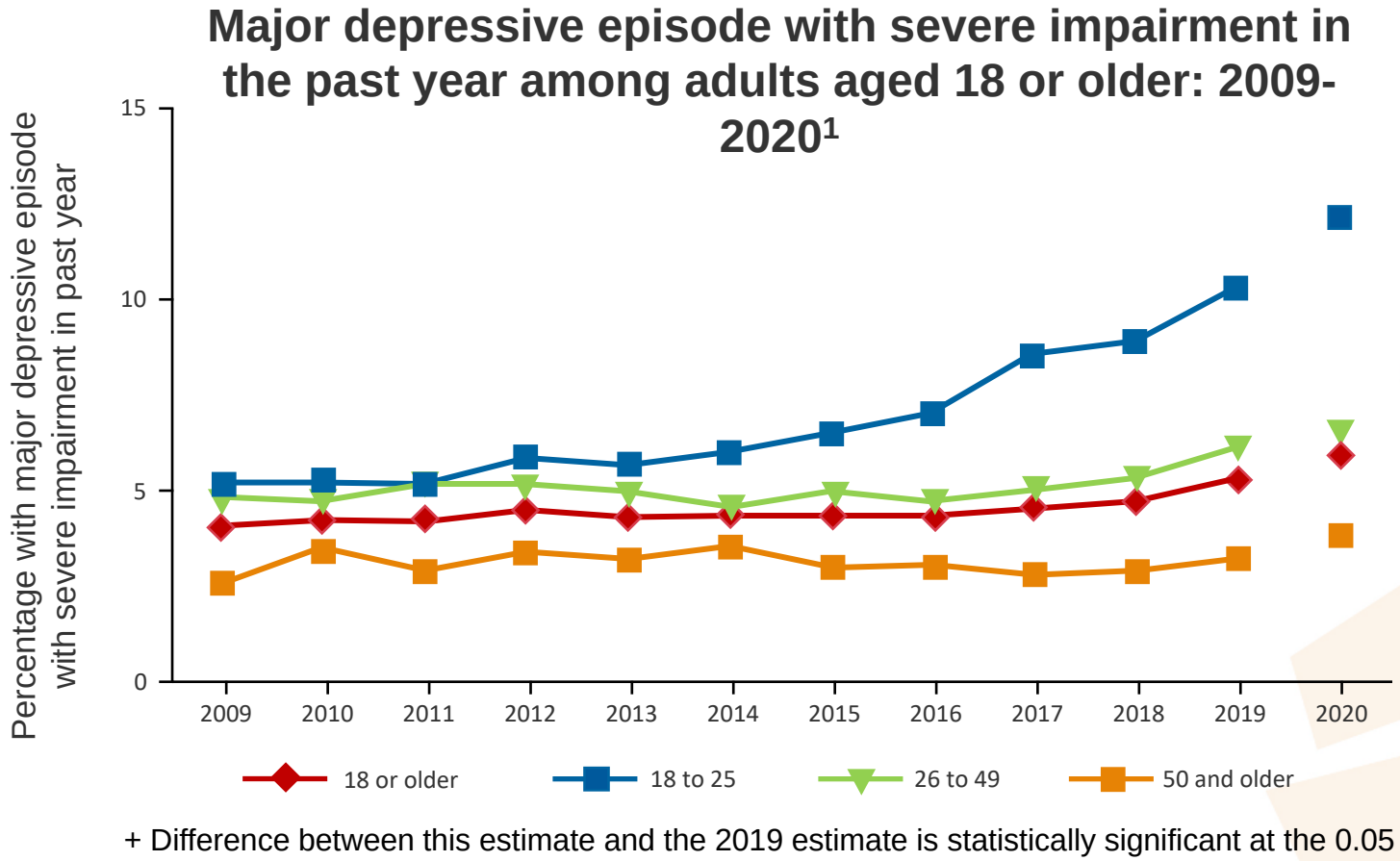
Prevalence of MDD in adults was highest among:

- Adult females (10.5%)[1,†]
- Adults aged 18-25 years (17%)[1,†]
- Adults with 2 or more races (15.9%)[1,†]

***Adults aged ≥18 years. †NSDUH 2020 data. ‡Values were calculated using 2020 rates applied to 2022 data. COVID-19, coronavirus disease 2019; M, million; MDD, major depressive disorder; NSDUH, National Survey of Drug Use and Health.**

1. Substance Abuse and Mental Health Services Administration. 2020 NSDUH detailed tables. Available at: https://www.samhsa.gov/data/report/2020-nsduh-detailed-tables. Accessed: Mar 2022. 2. Centers for Disease Control and Prevention. Mental health care household pulse survey. Available at: https://www.cdc.gov/nchs/covid19/pulse/mental-health.htm. Accessed: Mar 2022.

The Prevalence of MDD Is Increasing



+ Difference between this estimate and the 2019 estimate is statistically significant at the 0.05 level

Some factors associated with increased risk of depression include:

- Loss of spouse (widowed, divorced, or separated)[2]
- Family history of mental health disorder[2]
- Alcohol use[2]
- Unemployment[2]
- Poor access to health and mental health services[3]
- Social isolation/loneliness[3]
- Chronic disease[4]
- Chronic pain[4]
- Pandemic (COVID-19)[5,6]
- War/civil unrest[7]

1. Key substance use and mental health indicators in the United States: results from the 2020 national survey on drug use and health. US Department of Health and Human Services. https://www.samhsa.gov/data/sites/default/files/reports/rpt35325/NSDUHFFRPDFWHTMLFiles2020/2020NSDUHFFR1PDFW102121.pdf Accessed February 9, 2022. 2. Meng X et al. *BMJ Open*. 2017;7(6):e015156. doi:10.1136/bmjopen-2016-015156. 3. Aziz R, Steffens DC. *Psychiatr Clin North Am*. 2013;36(4):497-516. doi:10.1016/j.psc.2013.08.001. 4. Nabeshima T, Kim HC. *Exp Neurobiol*. 2013;22(4):235-243. doi:10.5607/en.2013.22.4.235. 5. Sher L. *QJM*. 2020;113(10):707-712. doi:10.1093/qjmed/hcaa202. 6. Pera A. *Front Psychol*. 2020;11:2263. doi:10.3389/fpsyg.2020.02263. 7. Musisi S, Kinyanda E. *Front Psychiatry*. 2020;11:20. doi:10.3389/fpsyt.2020.00020

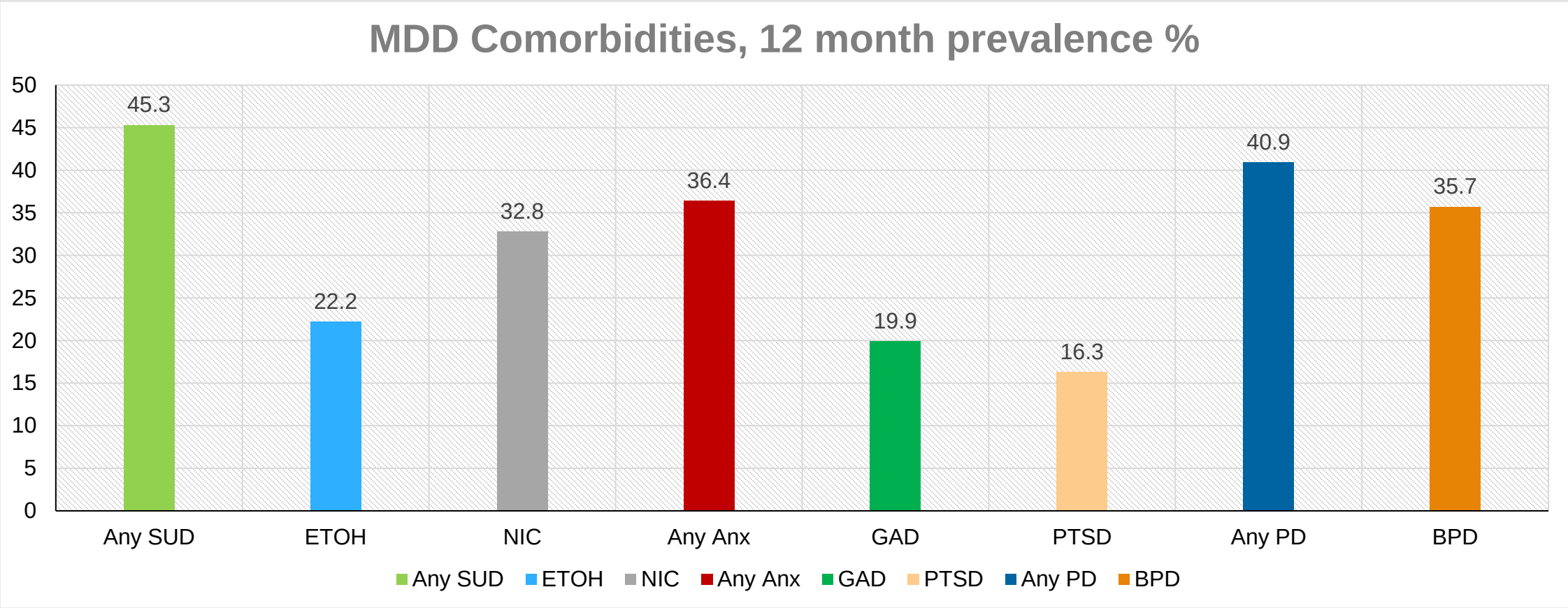
MDD: Societal and Personal Burden

- **Disability**
  - In the United States, depression is the **second leading cause of disability** after low back pain[1,2]
  - Depression* has been associated with a **higher rate of short-term work disability** compared to any other chronic condition in the United States[3]
- **Social/Emotional burden**
  - Individuals with MDD may experience increased **social irritability, financial strain**, and higher likelihood of **divorce**[3,4]
  - Increased chance of a **significant burden** on members of the **patient's family** and support group, including **effects on their mental health**[5]

***30-day prevalence of major depression. MDD, major depressive disorder.**

1. United States Burden of disease collaborators. JAMA. 2018;319(14):1444-1472. 2. World health organization. Global health estimates. Available at: https://www.who.int/data/global-health-estimates. Accessed: Nov 2021. 3. Kessler RC, et al. *Am J Psychiatry*. 1998;155(8):1092-1096. 4. Judd LL, et al. *Am J Psychiatry*. 1996;153(11):1411-1417. 5. Scazufca M, et al. *Soc Psychiatry Psychiatr Epidemiol.* 2002;37(9):416-422.

Psychiatric Comorbidities of MDD

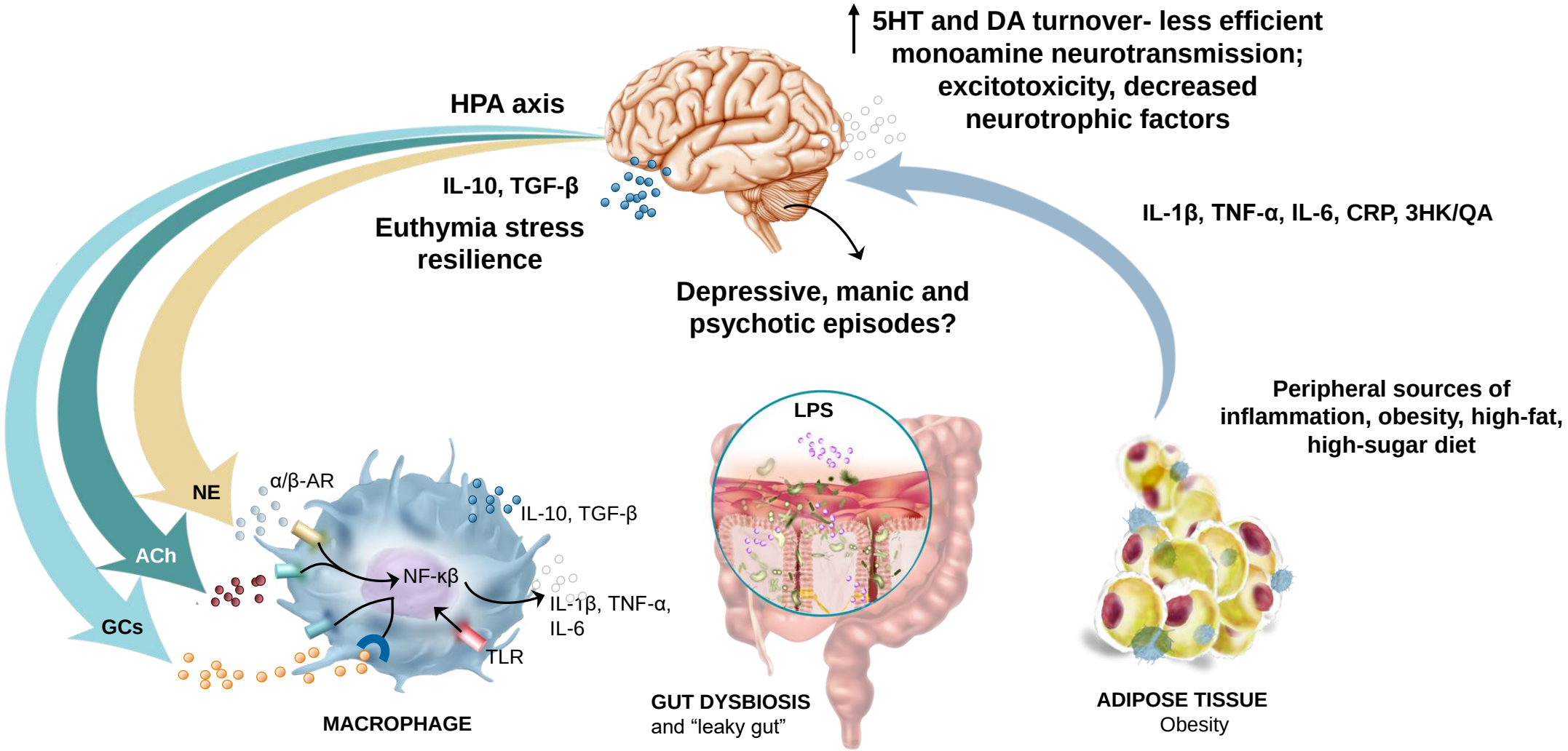


SUD = Substance use disorder; ETOH = Alcohol use disorder; NIC = Nicotine; GAD = Generalized anxiety disorder; PTSD = Post-traumatic stress disorder; PD = Personality disorder; BPD = Borderline personality disorder.

n = 36,309 adults who participated in the 2012-2013 National Epidemiologic Survey on Alcohol and Related Conditions III (NESARC-III).

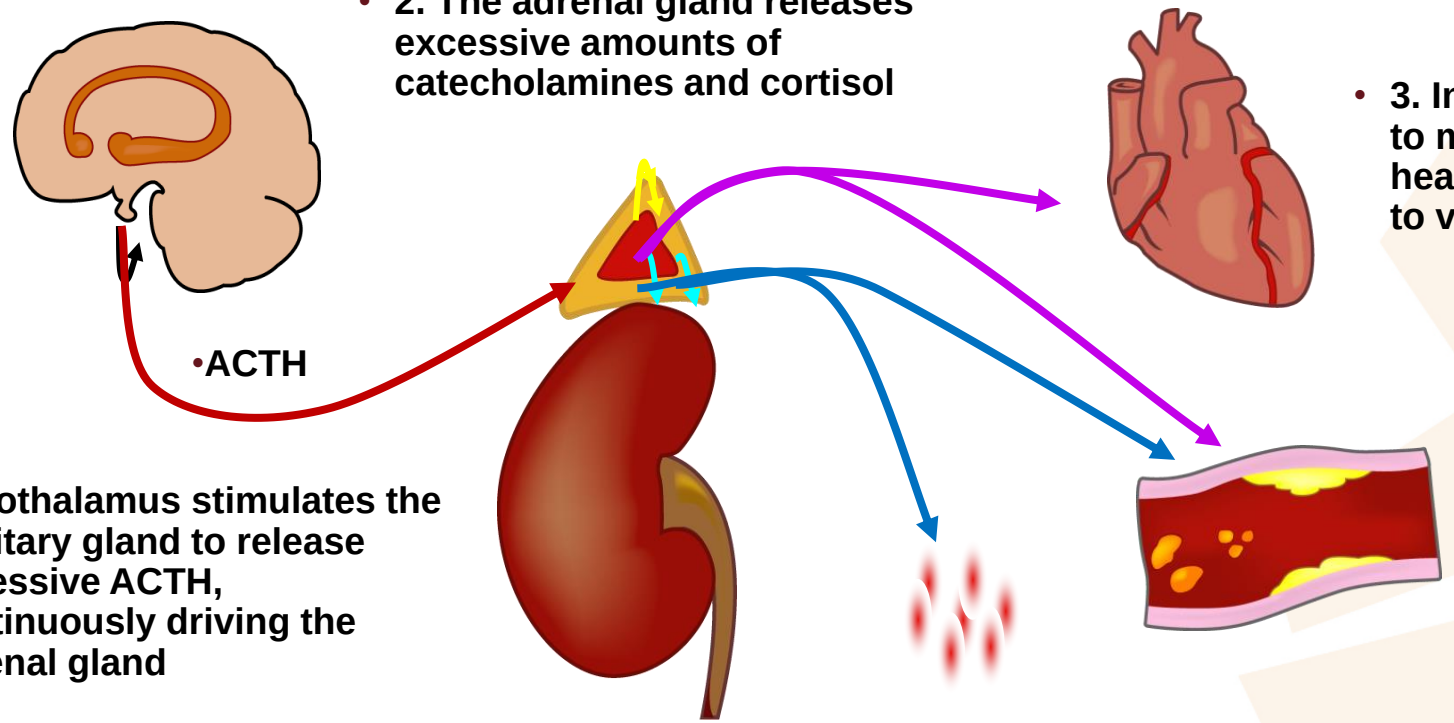
Hasin et al, 2018, *JAMA Psychiatry*. 75(4):336-346

Evolving Pathophysiology of Mood Disorders



Modified from: Maletic V, DeMuri-Maletic B.(2018) Bipolar Disorders and Their Clinical Management, Part I: Epidemiology, Etiology, Genetics, and Neurobiology. In: Black DW, ed. Scientific American Psychiatry. Hamilton: Decker; December 2018. DOI: 10.2310/7800.13099. Liang, et al, 2018, *Frontiers in Integrative Neuroscience*, Volume 12, Article 33. Lindqvist D, et al. *Biol Psychiatry*. 2009;66(3):287-292. Miller, et al, *Biol Psychiatry*. 2009;65: 732-741. Misiak, et al.2020, *Progress in Neuropsychopharmacology & Biological Psychiatry* 102: 109951.

Major Depressive Disorder May Have Systemic Consequences



- 2. The adrenal gland releases excessive amounts of catecholamines and cortisol

- 3. Increase in catecholamines can lead to myocardial ischemia, diminished heart rate variability, and can contribute to ventricular arrhythmias

- 4. Increase in catecholamines causes platelet activation; increase in cytokines and interleukins may also contribute to atherosclerosis and eventual hypertension

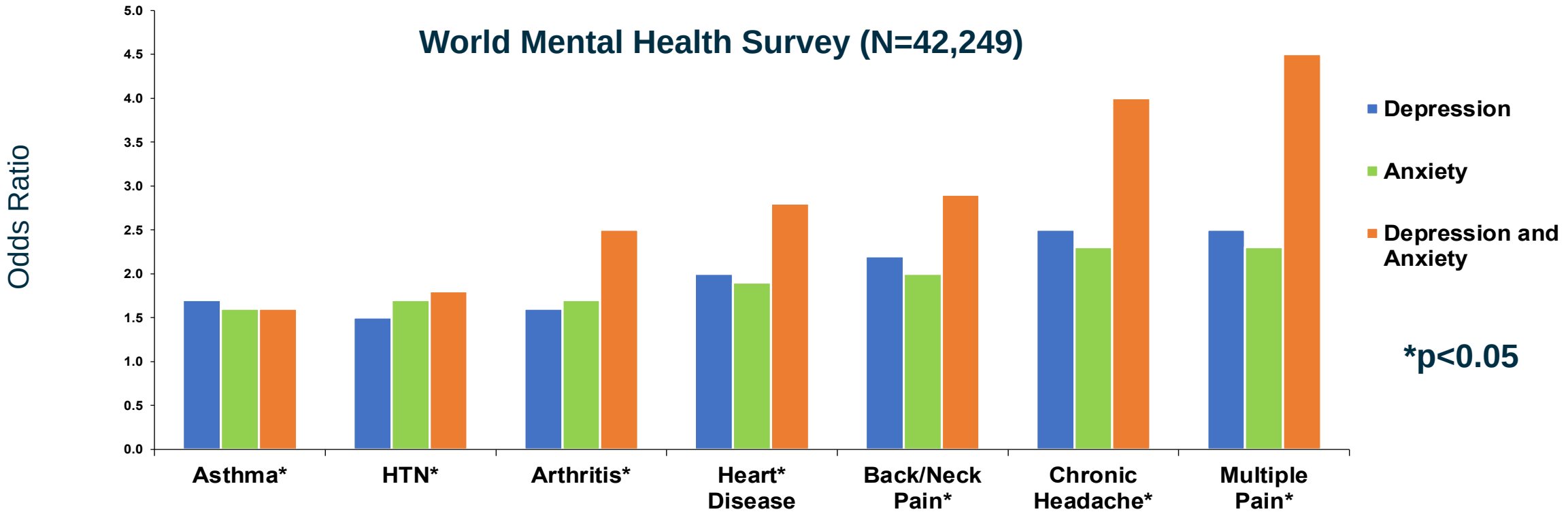
Hypothalamus stimulates the pituitary gland to release excessive ACTH, continuously driving the adrenal gland

- 5. Cortisol antagonizes insulin and contributes to dyslipidemia, type 2 diabetes, and obesity; increases in cortisol also suppress the immune system'

ACTH = Adrenocorticotropic hormone.

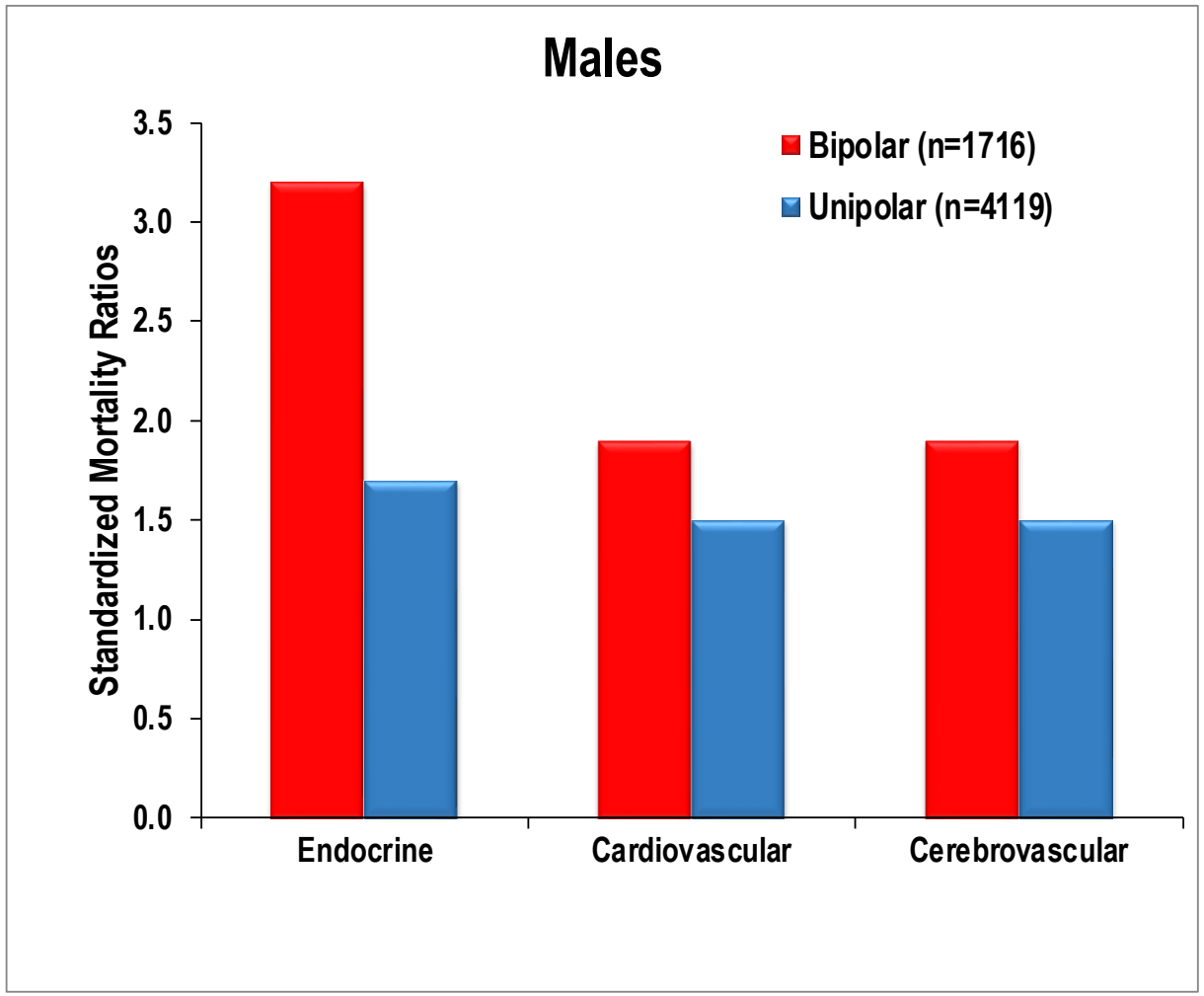
Adapted from Musselman et al. *Arch Gen Psychiatry* 1998;55(7):580–92.

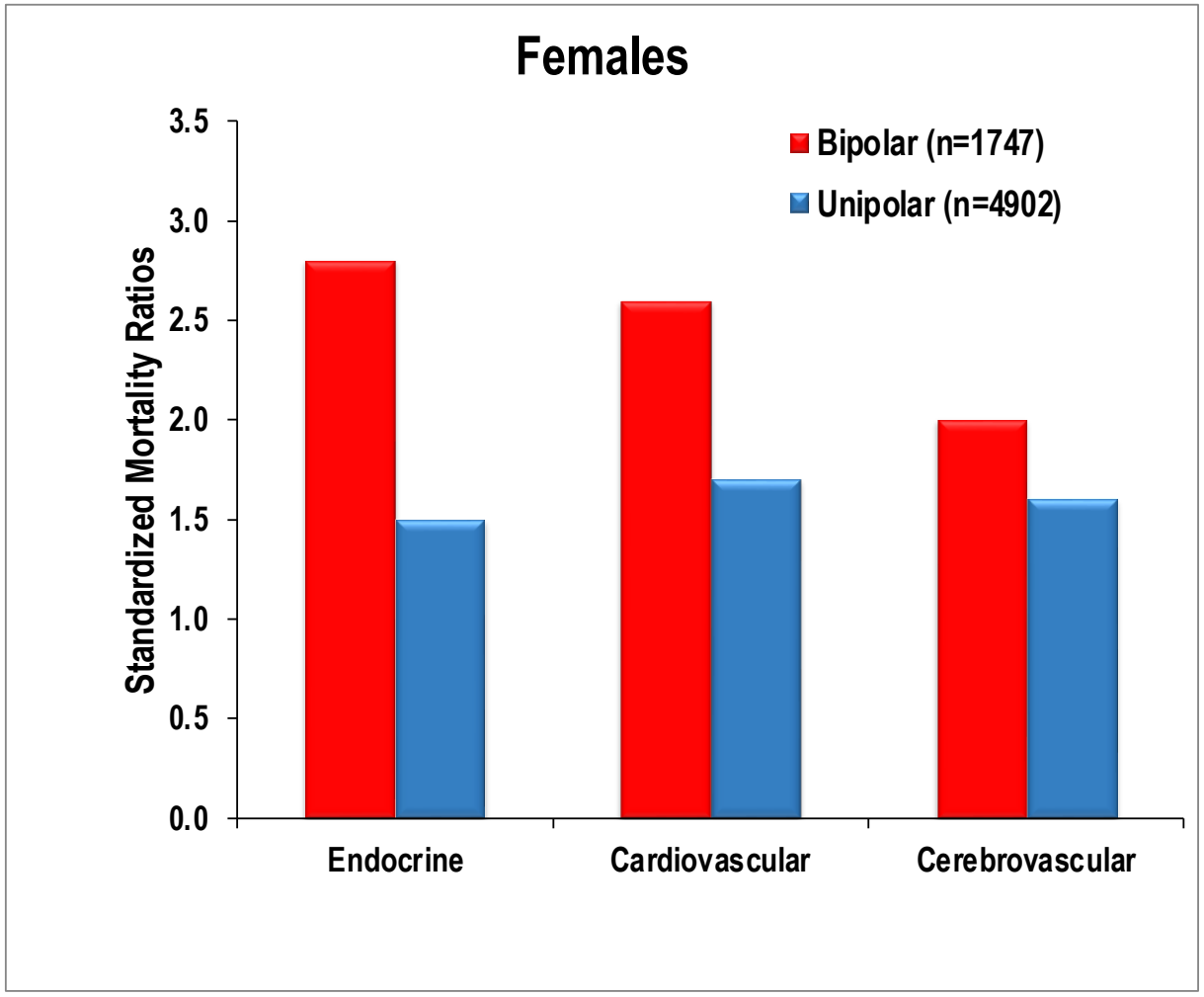
Association of Depression and Anxiety With Chronic Physical Conditions



Scott et al. 2007, *J Affect Disord*;103(1–3):113–20.

Increased Mortality in MDD and Bipolar Disorder Due to Natural Causes





Osby U, et al. *Arch Gen Psychiatry*. 2001;58(9):844-850.

Takeaways

- Prevalence of MDD is increasing with each subsequent age group
- MDD is associated with great individual suffering, loss of function and quality of life, as well as with substantial societal burden
- Multiple psychiatric comorbidities, such as substance use disorders, anxiety disorders and personality disorders, make treatment of MDD more challenging
- MDD has multiple somatic correlates, including HPA dysfunction, autonomic disturbances and immune dysregulation
- Somatic manifestations of MDD are linked to cardiometabolic derangements and shortened life expectancy

Patient Advocate:
The Burden of Treatment-Resistant MDD

Questions for patient advocate

- How long after disease onset did it take to arrive to correct diagnosis?
- Did you encounter any barriers in your pursuit of treatment?
- Have you experienced and physical symptoms associated with depressed mood?

Current Options in the Treatment of MDD

MDD is Primarily Treated with Pharmacotherapy and Psychotherapy

Primary Treatment Modalities[1-3]	 Pharmacotherapy	 Psychotherapy				
Secondary Treatment Modalities[1,4,5]	 Vagus nerve stimulation (VNS)	 Electroconvulsive treatment (ECT)*	 Transcranial magnetic stimulation (TMS)	 Other neurosurgical procedures		
Supportive Interventions[1,3,6]	 Mental health and therapy apps	 Peer support	 Lifestyle & exercise changes	 Dietary changes	 Meditation and/or mindfulness	

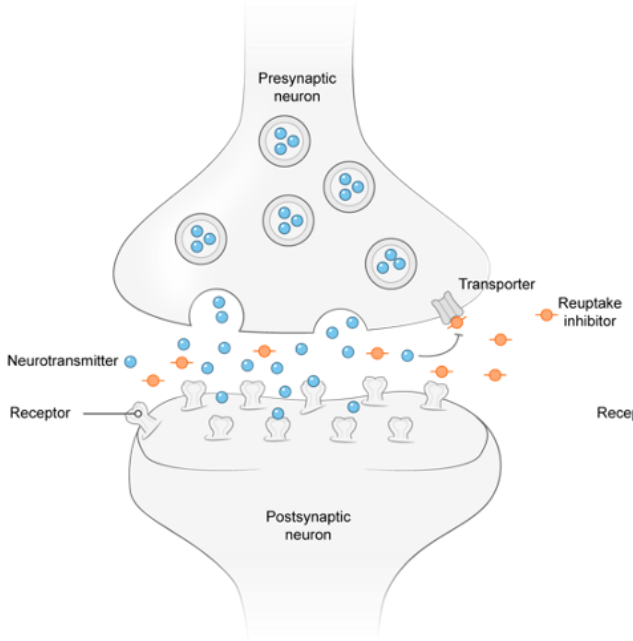
MDD = major depressive disorder.
***ECT is limited to patients with MDD whose depression is highly resistant to treatment or who present with psychosis.**

1. Gelenberg AJ, et al. *Am J Psychiatry*, 2010;167(10):1. 2. Kennedy SH, et al. *Can J Psychiatry*. 2016;61(9):540-560. 3. Parikh SV, et al. *Can J Psychiatry.* 2016;61(9):524-539. 4. Sonmez AI, et al. *Psychiatry Research*. 2019;273:770-781. 5. Fava M, et al. *Neuron.* 2000;28:335-341. 6. Ravindran AV, et al. Can J Psychiatry. 2016;61(9):576-587.

Monoamine-Modulating Antidepressants

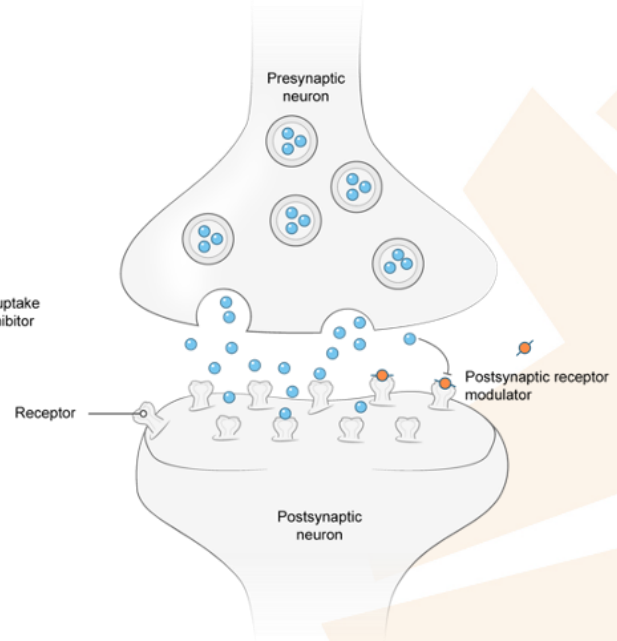
Monoamines
- Serotonin (5-HT)
- Epinephrine (E)
- Norepinephrine (NE)
- Dopamine (DA)

1. Reuptake inhibitors[1]



Adapted from Nedic-Erjavec, et al. Progress in Neuropsychopharmacology & Biological Psychiatry. 2021;105: 110139.

2. Receptor modulators[2]



Adapted from Skånland SS, Cieślar-Pobuda A. Eur J Pharmacol. 2019;865:172732.

3. Agents altering monoamine metabolism (monoamine oxidase inhibitors, MAOIs)[3]

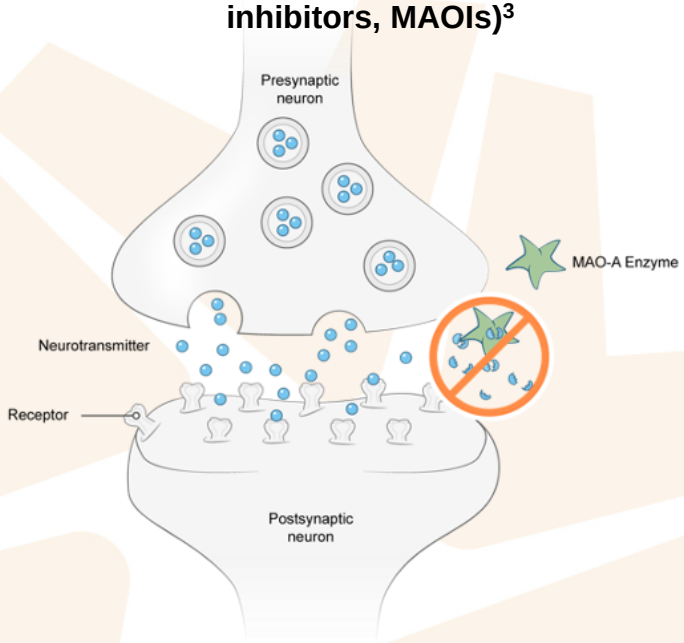
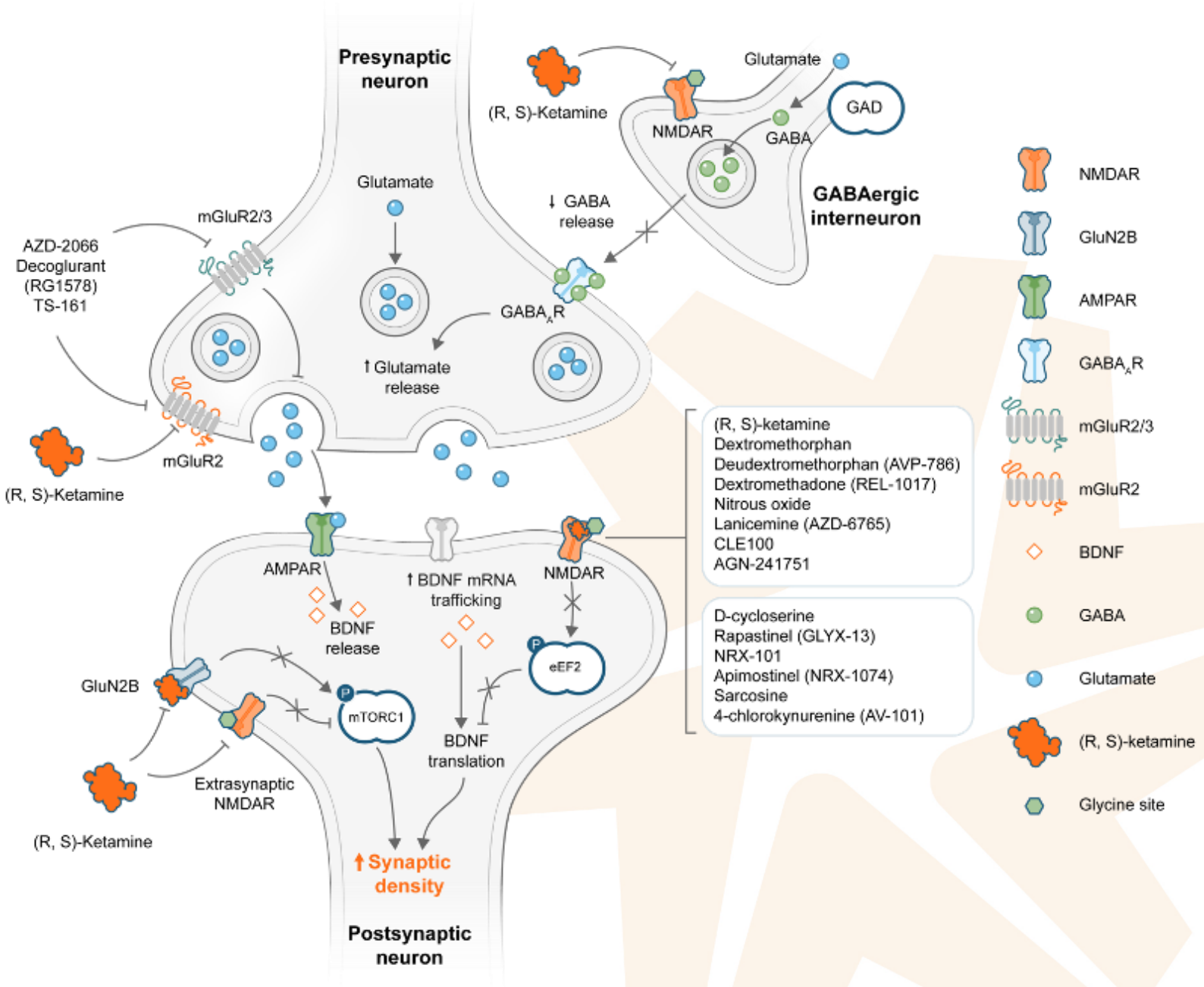


Illustration from Chamberlain SR, Baldwin DS. CNS Drugs. 2021;35(7):703-716.

DA = dopamine; E, = epinephrine; 5-HT = 5-hydroxytryptamine; MAO-A = monoamine oxidase type A; MAOIs = monoamine oxidase inhibitors; NE = norepinephrine..

1. Nedic-Erjavec, et al. *Progress in Neuropsychopharmacology & Biological Psychiatry*. 2021;105: 110139. 2. Skånland SS, et al. *Eur J Pharmacol.* 2019;865:172732. 3. Chamberlain SR, et al. *CNS Drugs*. 2021;35(7):703-716.

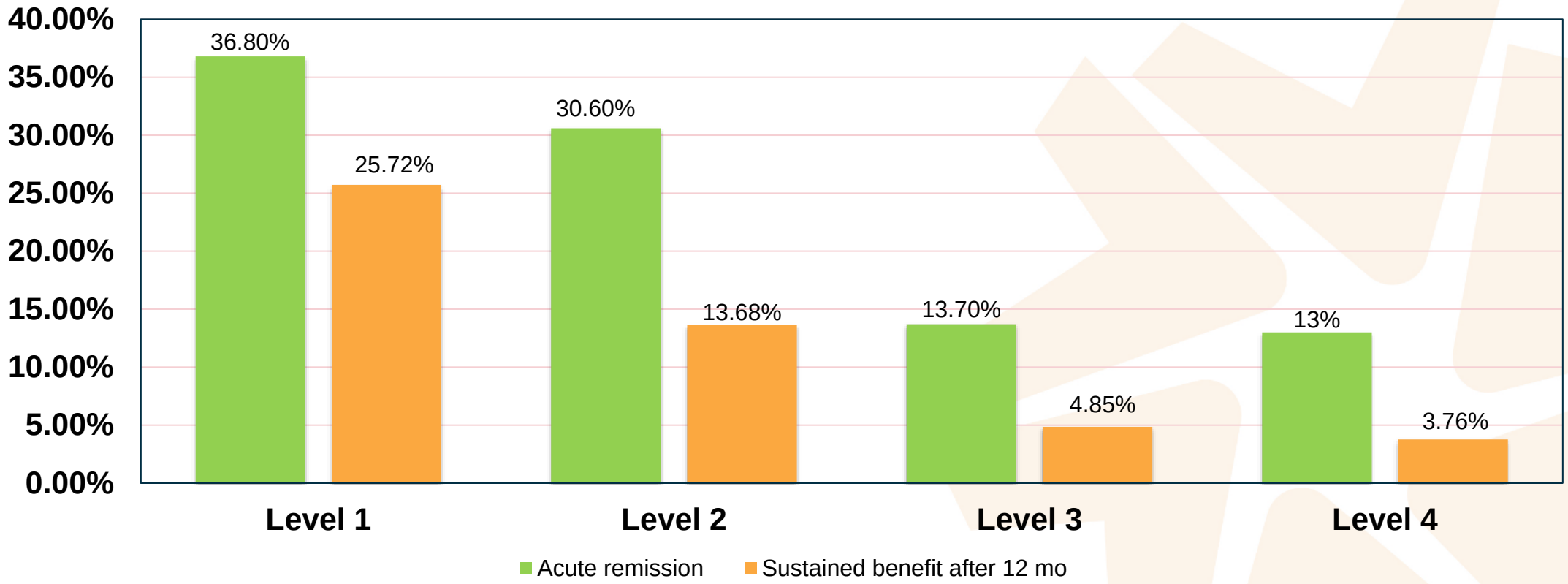
Mechanism of Action of Rapid-Acting Antidepressants



Henter et al. *CNS Drugs*. 2021; 35:527–543

How Durable was Remission in STAR*D?

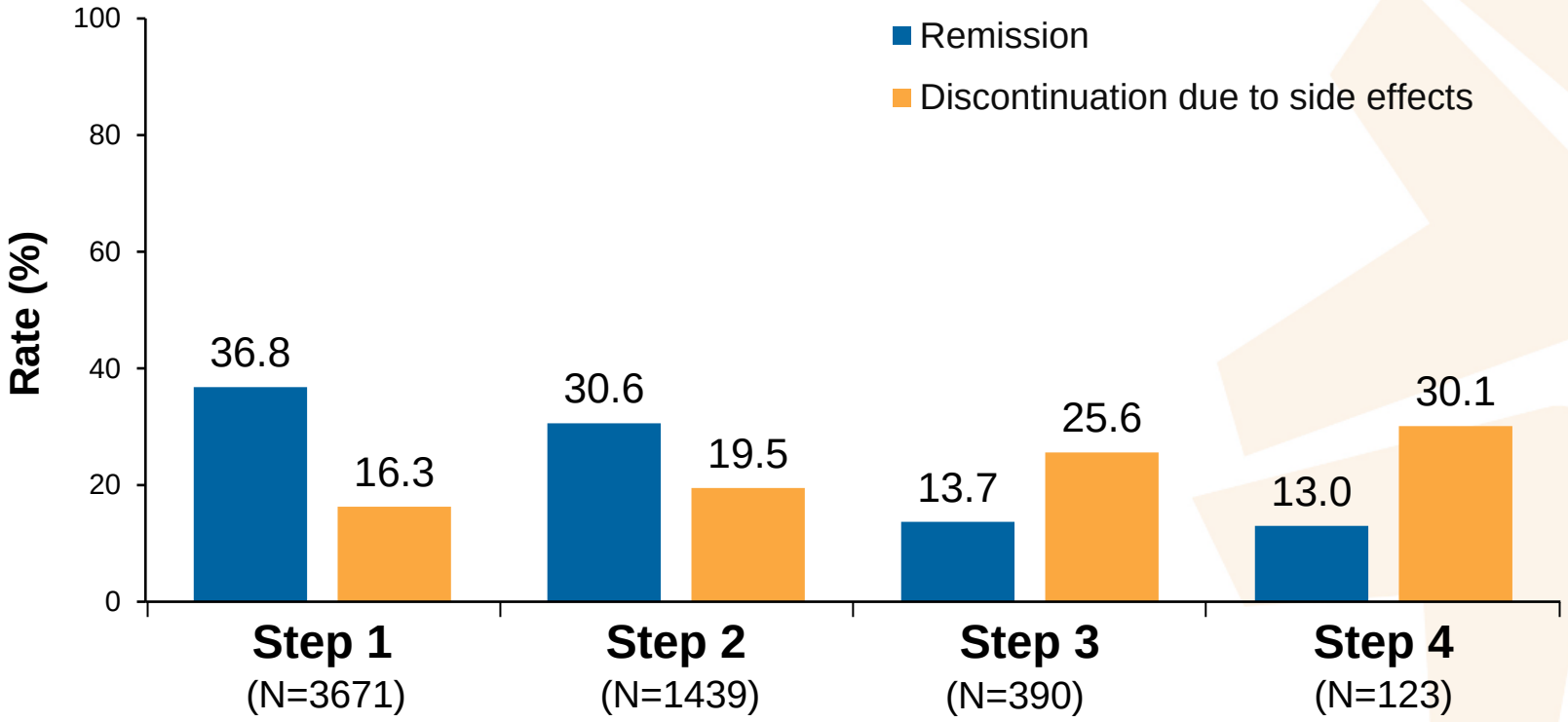
Rate of acute remission, and probability of sustained benefit over 12 months at each level of STAR*D



Acute remission: 12-week exit QIDS-SR16 ≤ 5.
Sustained benefit: Percentage of patients entering the step who have remained in remission after 12 months of naturalistic follow-up.
QIDS-SR = Quick Inventory of Depressive Symptomatology, Self-Report.
Sackeim HA. *Brain Stimul*. 2016;9(3):313-319.

Remission Rates Decreased with Discontinuation Due to Side Effects, and Increased with Each Additional Change in Therapy

Rates of remission and discontinuation due to intolerable side effects at each step exit in the STAR*D trial



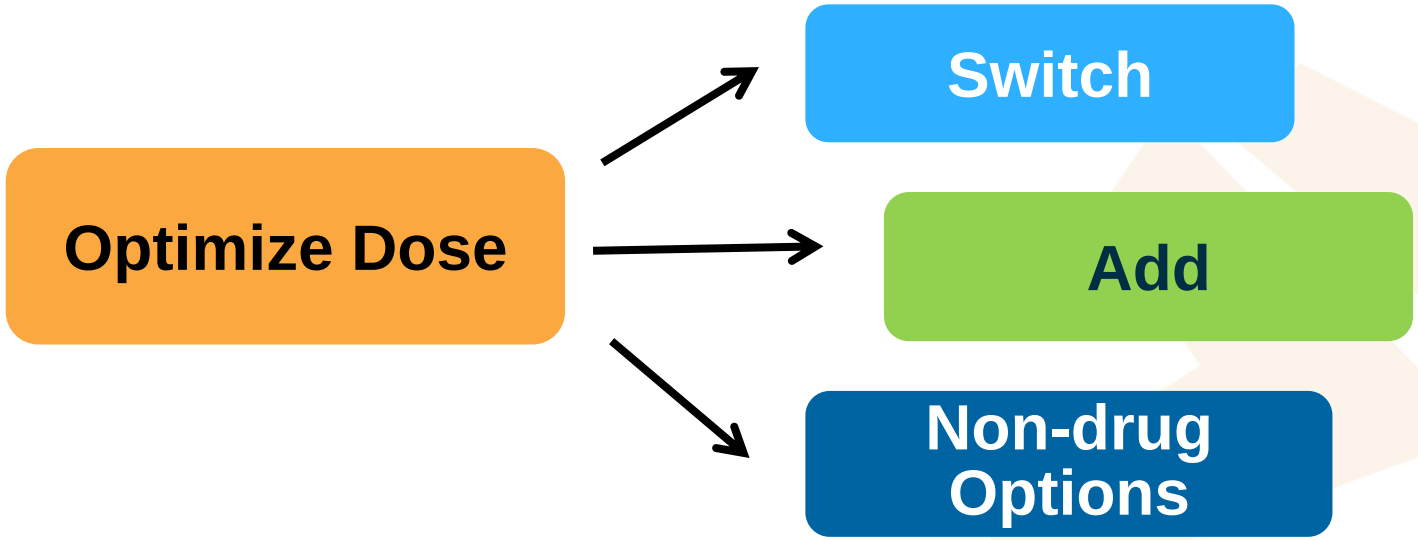
Each step of therapy included options to switch or augment.

Options included various SSRIs, SNRIs, lithium, T_3, and cognitive therapy.

SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; T_3 = triiodothyronine.

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

Strategies for Suboptimal Response



Combining 2 antidepressants

Guidelines: When MDD Treatment Fails

Guideline	Recommendations
APA[1]	▪ Consider change in treatment if patient has not fully responded to acute phase treatment over 4-8 weeks
CANMAT[2]	▪ If no early improvement after 2-4 weeks, consider switching or adding adjunctive treatments ▪ If early improvement, continue treatment for 6-8 weeks; if remission is not attained consider switching or treatment augmentation
Florida Best Practice Guideline[3]	▪ If initial treatment is ineffective or not tolerated, evaluate adherence, optimize dose ▪ If response is still insufficient, switch to different therapy or augment with psychotherapy, atypical antipsychotic FDA approved for MDD, another antidepressant (do not combine SSRI with SNRI), intranasal esketamine or intravenous racemic ketamine

1. American Psychiatric Association, Practice Guideline for the Treatment of Patients with Major Depressive Disorder, 3rd ed; 2010. 2. Kennedy. *Can J Psychiatry*. 2016;61:540. 3. 2019-2020 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults, Agency for Health Care Administration, State of Florida, 2020.

Adjunctive Therapies for MDD: Second-Generation Antipsychotic Agents

Agent	Indication[1]
Aripiprazole[1]	Adjunctive treatment for adults with MDD
Brexpiprazole[2]	Adjunctive therapy to antidepressants for MDD
Quetiapine XR[3]	Adjunctive therapy to antidepressants for adults with MDD
Olanzapine + fluoxetine[4]	Treatment-resistant depression*

***MDD in adults who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode.**

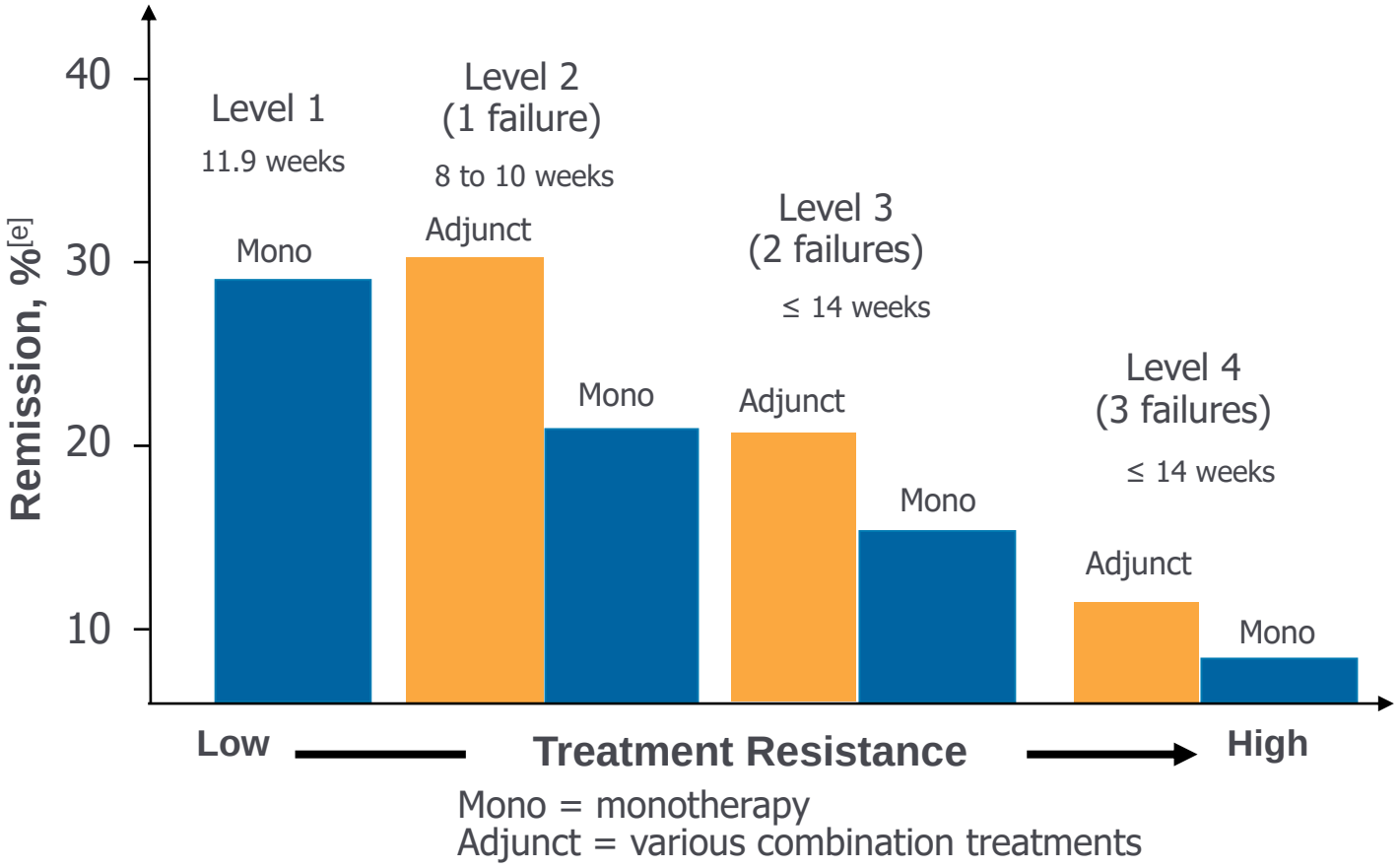
1. Aripiprazole PI. 2. Brexpiprazole PI. 3. Quetiapine XR PI. 4. Olanzapine/fluoxetine PI.

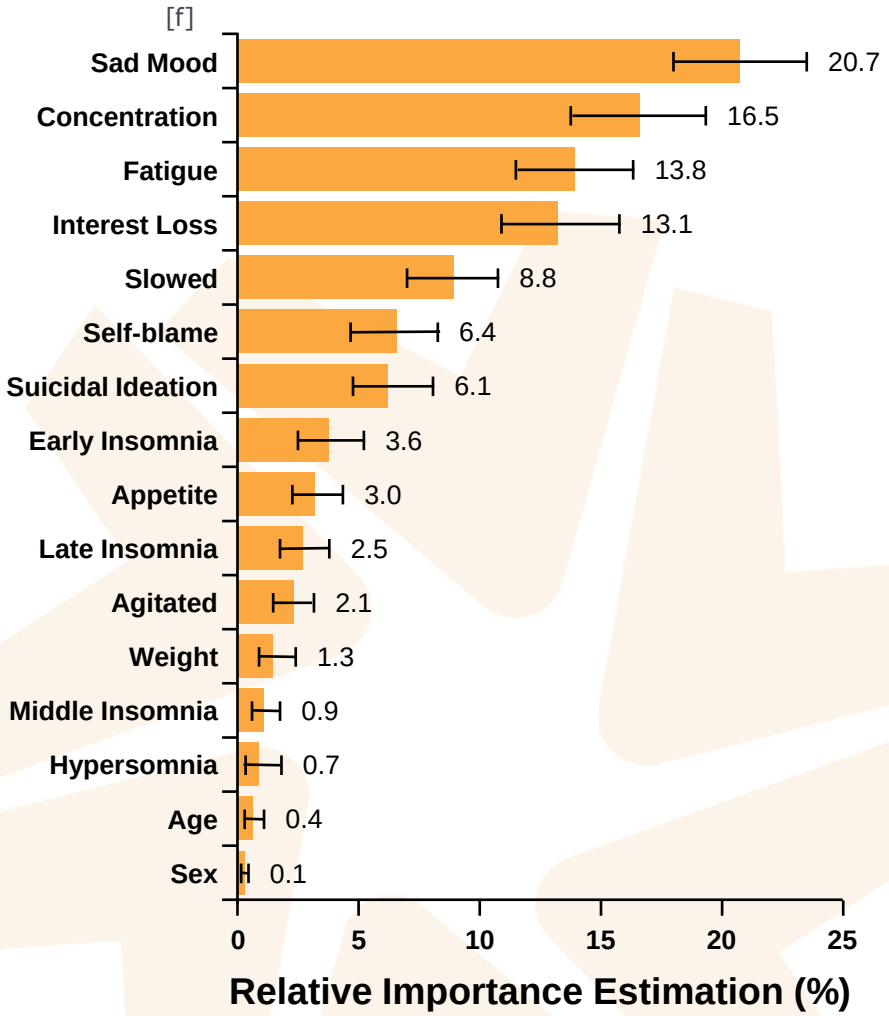
Adjunctive Therapies for MDD: Add-On Treatments[1,2]

Off Label	FDA Approved
▪ Lithium ▪ Psychostimulants ▪ Triiodothyronine (T3) ▪ Ziprasidone ▪ Risperidone ▪ L-methylfolate ▪ S-adenosylmethionine	▪ Esketamine (For TRD)

1. American Psychiatric Association, Practice Guideline for the Treatment of Patients with Major Depressive Disorder, 3rd ed; 2010.
2. 2019-2020 Florida Best Practice Psychotherapeutic Medication Guidelines for Adults, Agency for Health Care Administration, State of Florida, 2020. 3. Esketamine PI.

Mono vs. Adjunctive Therapies in STAR*D[a-f]

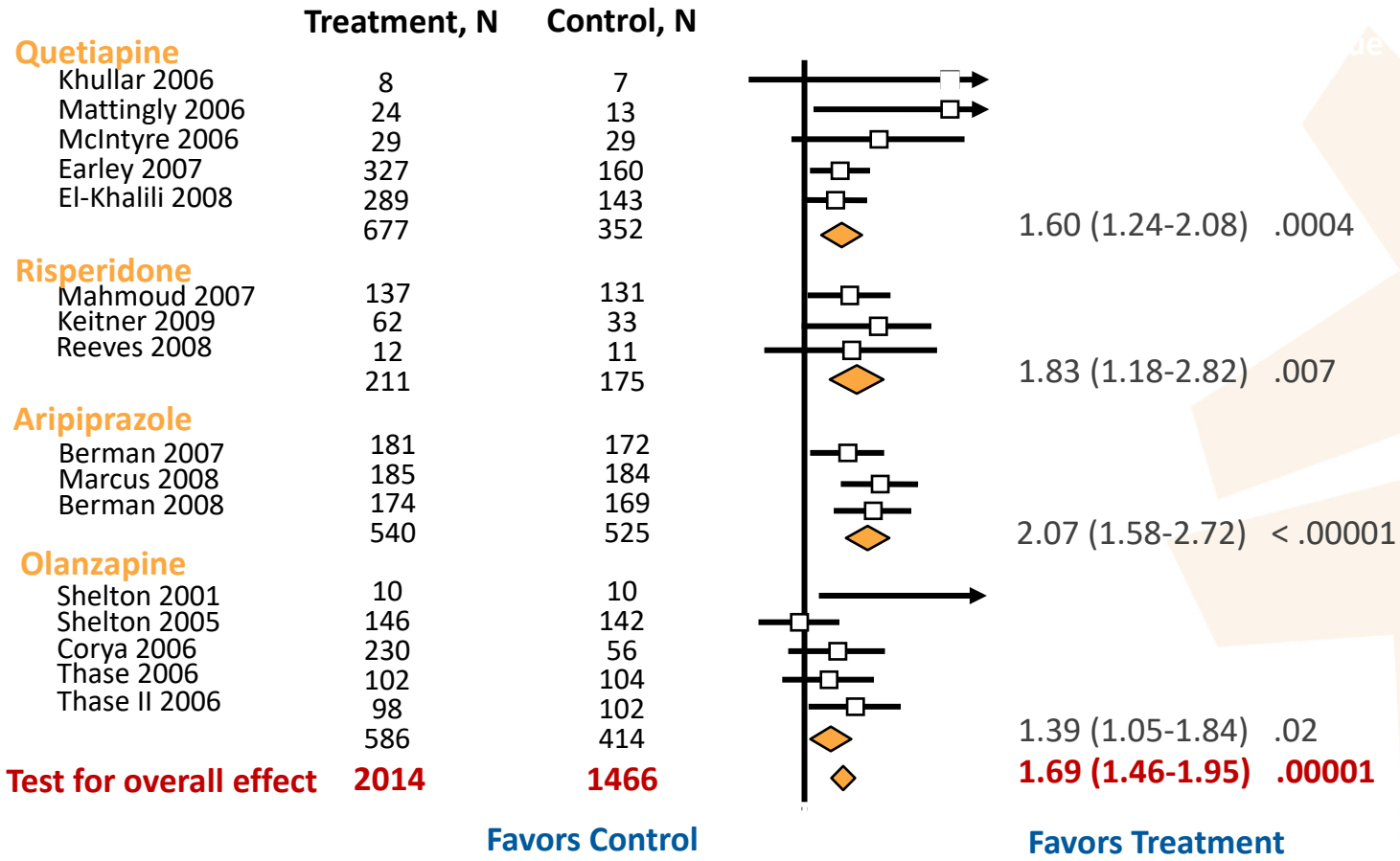




a. McGrath PJ, et al. *Am J Psychiatry*. 2006;163:1531-1541. b. Rush AJ, et al. *Am J Psychiatry.* 2006;163:1905-1917; c. Nierenberg AA, et al. *Am J Psychiatry.* 2006;163:1519-1530. d. Trivedi MH, et al. *J Clin Psychiatry*. 2006;67:1458-1465. e. Trivedi MH, et al. *N Engl J Med.* 2006;354:1243-1252. f. Fried EI, et al. *PLoS One*. 2014;9:e90311.

MDD Treatment Augmentation with Second-Generation Antipsychotics: 2009 Meta-Analysis

- Meta-analysis of 16 randomized, placebo-controlled trials of adjunctive second-generation antipsychotics in patients with treatment-resistant major depressive disorder (N = 3480)



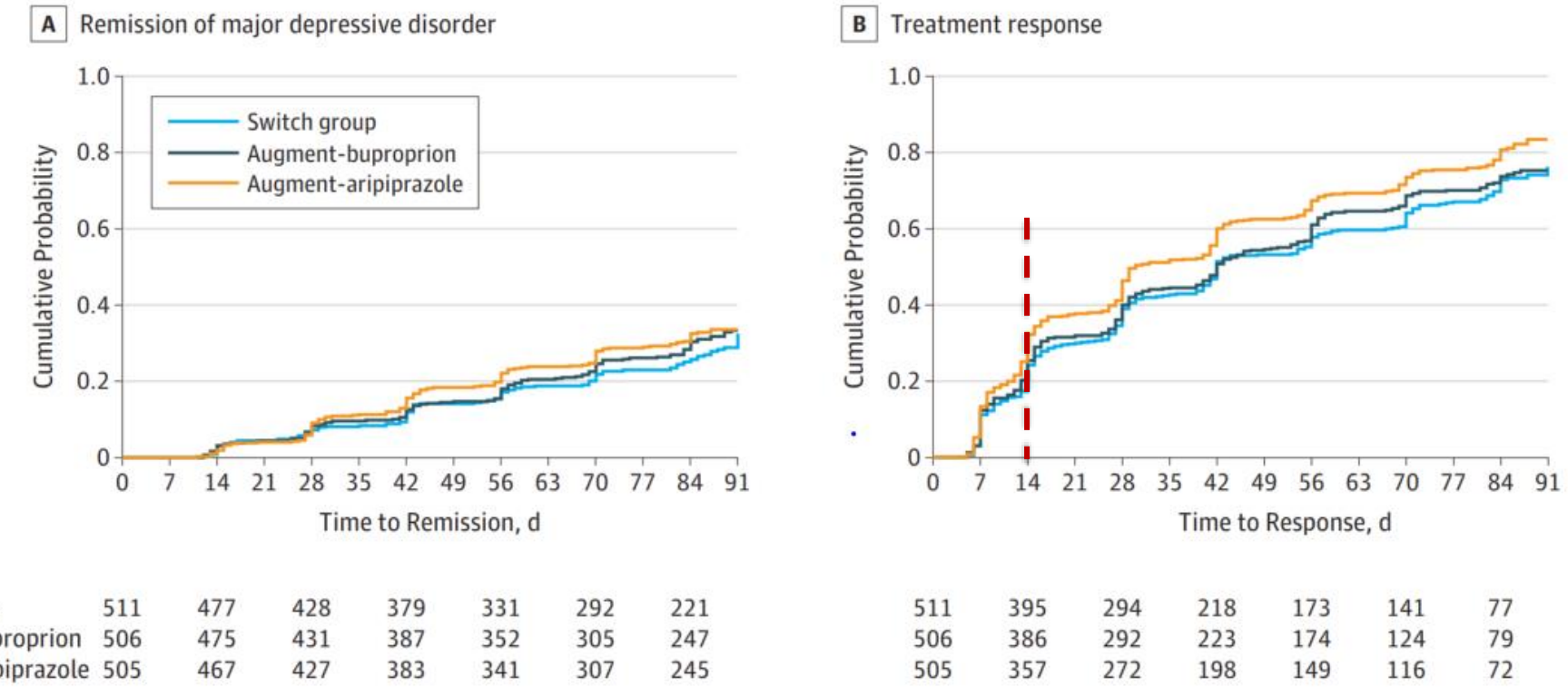
All agents:

- **More effective** than placebo
  - No differences in ORs among agents
- **Had higher rates of discontinuation** for adverse events than did placebo

VAST-D: MDD, Switching to Bupropion vs Augmentation with Bupropion or Aripiprazole

Cumulative Probability of Remission and Response Among Patients With Antidepressant-Resistant MDD, Acute Treatment Phase

VAST-D Sub-analysis:
Odds of achieving response and remission at week 12 are greater among individuals who exhibit improvement by the end of week 2:
OR= 7.7

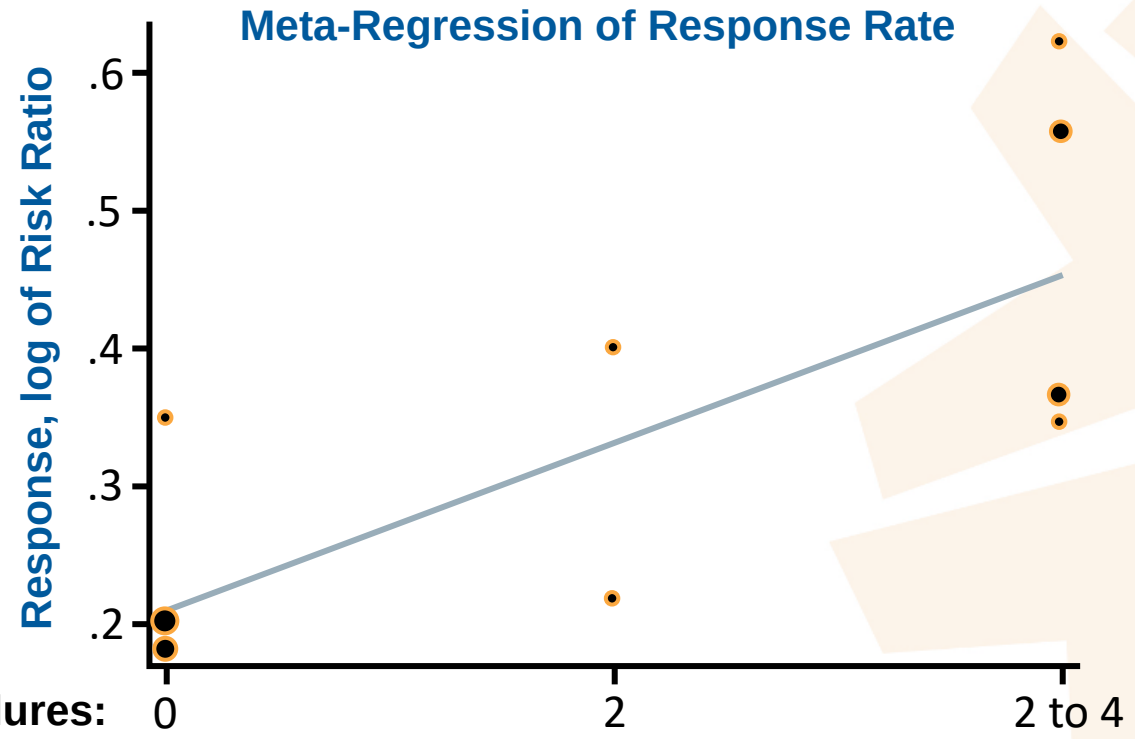


Among a predominantly male population with MDD unresponsive to antidepressant treatment, augmentation with aripiprazole resulted in a statistically significant but only modestly increased likelihood of remission during 12 weeks of treatment compared with switching to bupropion monotherapy.

Mohamed et al. JAMA. 2017;318:132; Hicks. Psych Res Clin Pract. 2019;1:58..

MDD Treatment Augmentation With Second-Generation Antipsychotics: Efficacy by Degree of Resistance

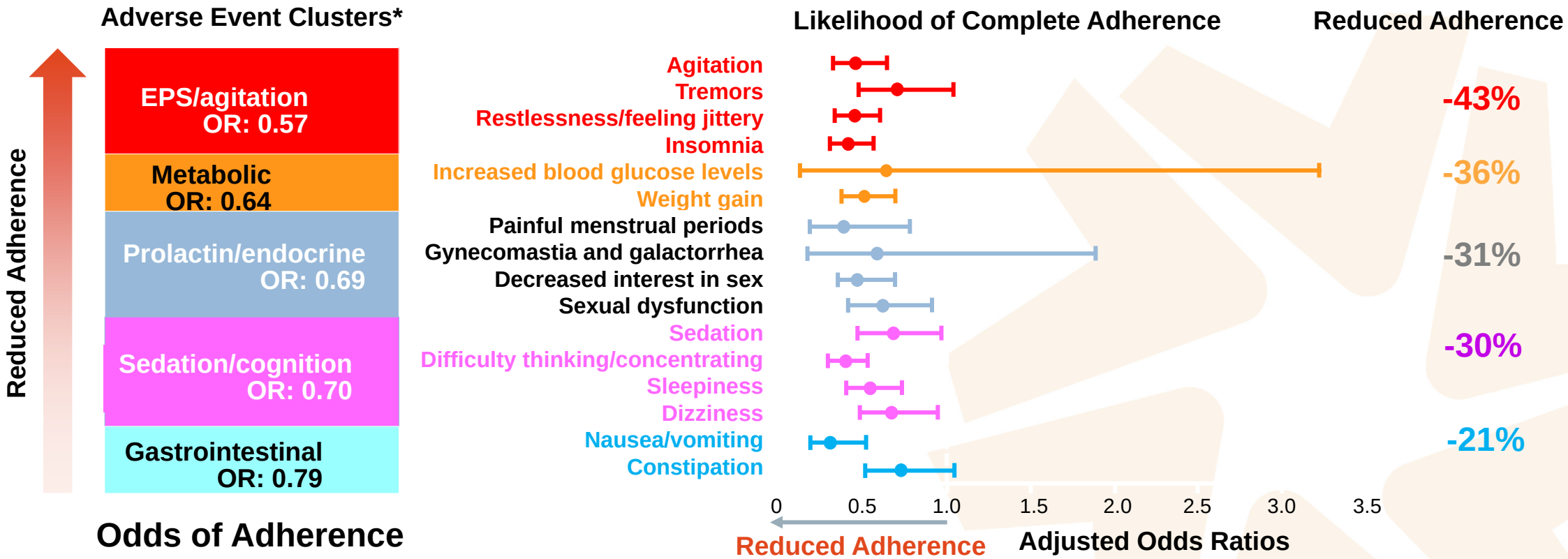
- Meta-analysis of 11 randomized, controlled trials of adjunctive second-generation antipsychotics in patients with treatment-resistant MDD (N = 3341)



- Improved efficacy with increasing rates of resistance

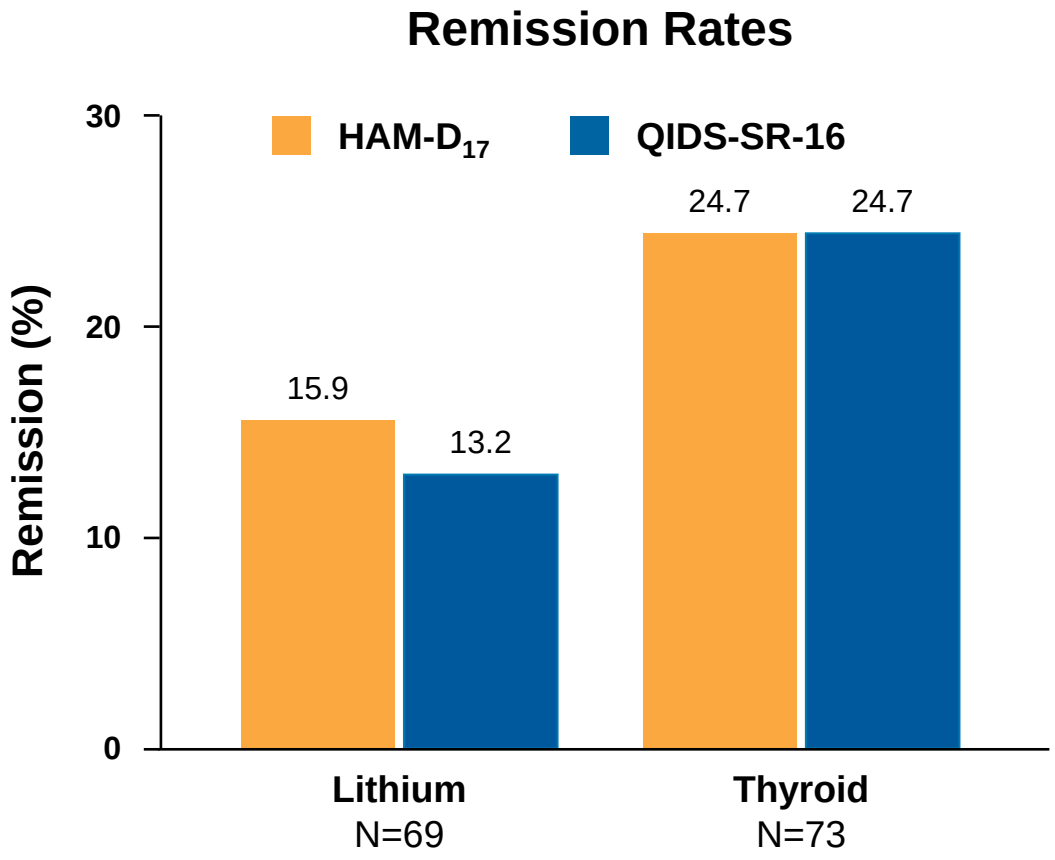
Wang. Int J Neuropsychopharmacol. 2015;18:pyv023.

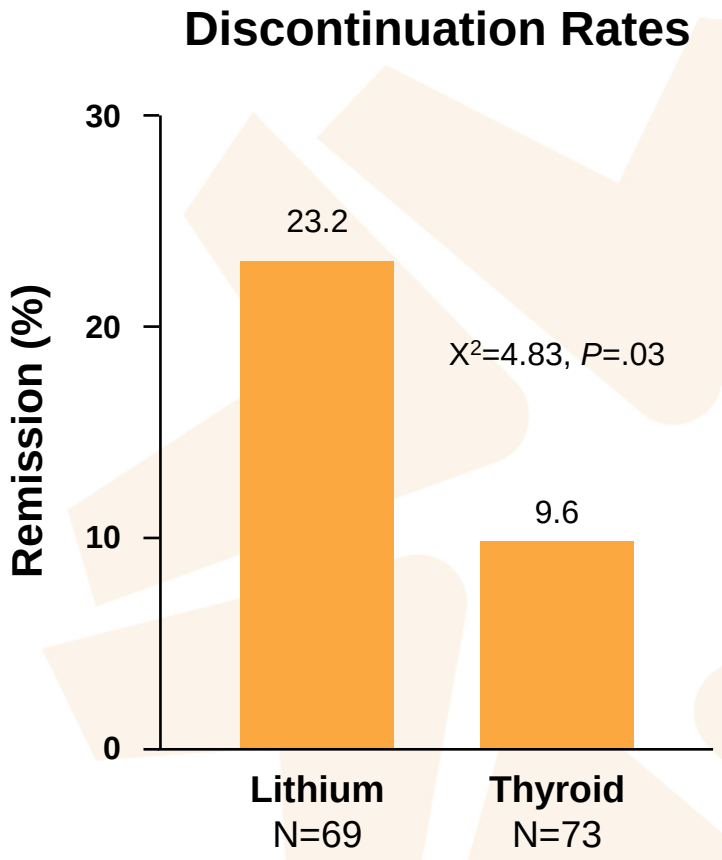
Impact of Antipsychotic Side Effects on Treatment Adherence



Survey of N=876 community-dwelling people with schizophrenia.
*ORs based on multivariable logistic regression with adherence as dependent variable.
Side effect was reported as present and "somewhat", "very", or "extremely bothersome".
DiBonaventura M, et al. *BMC Psychiatry*. 2012;12:20.

Adjunctive Therapy with Thyroid Hormone in STAR*D: *Results of Level 3 Comparison with Lithium*

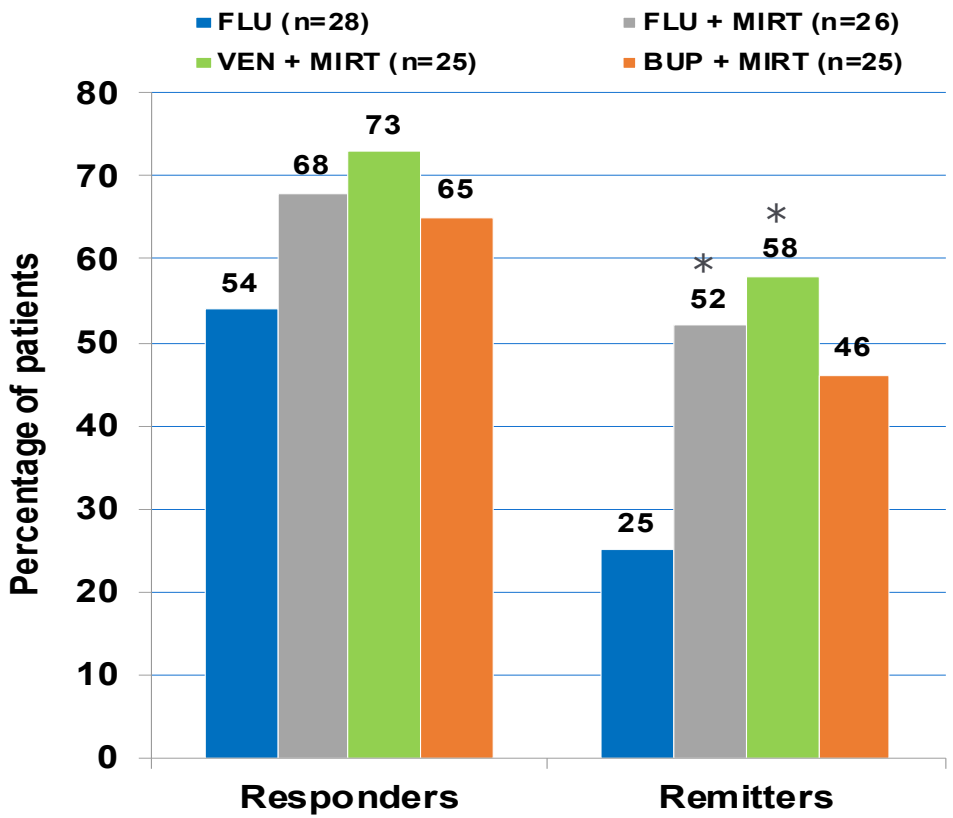




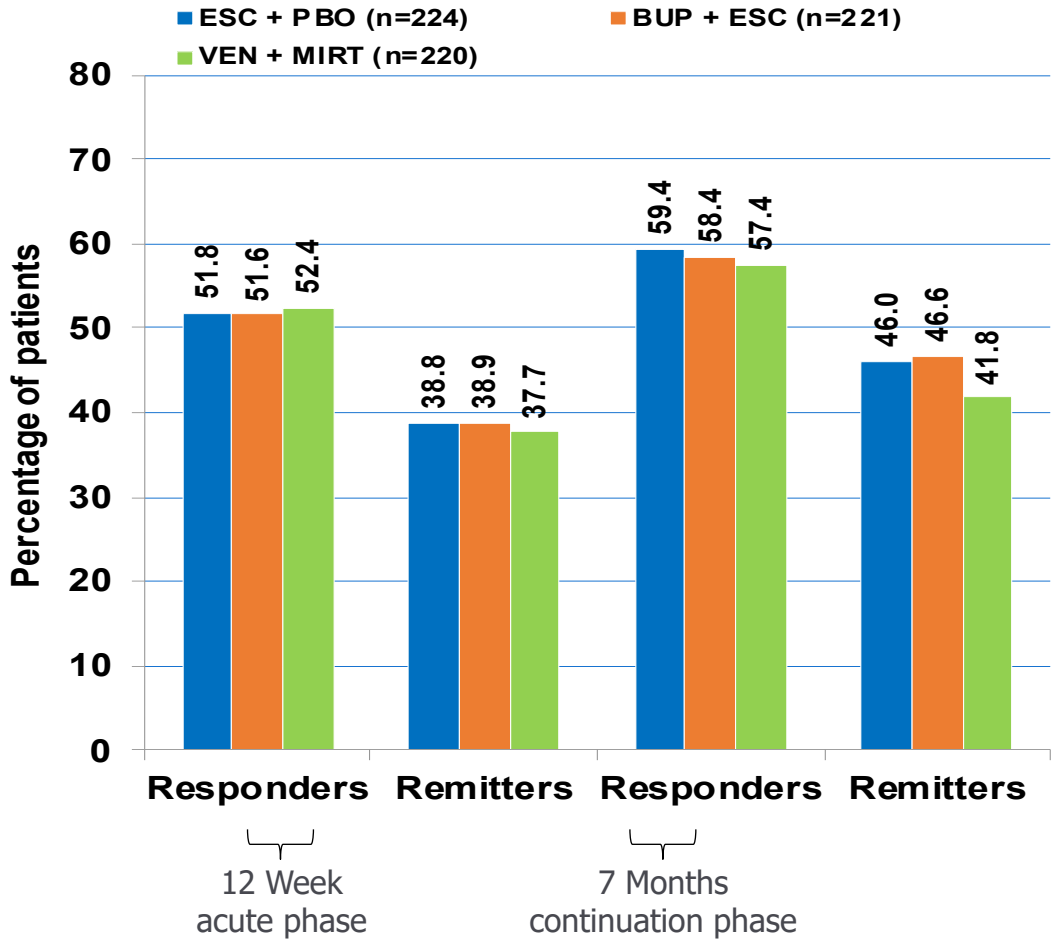
HAM-D-17 = 17-item Hamilton Rating Scale for Depression; QIDS-SR-16 = 16-item Quick Inventory of Depressive Symptoms Self-Report.
Nierenberg AA, et al. *Am J Psychiatry*. 2006;163(9):1519-1530.

Concurrent Combined Antidepressants
Contrasting Results of 2 RCTs

Blier et al (2010)[a]



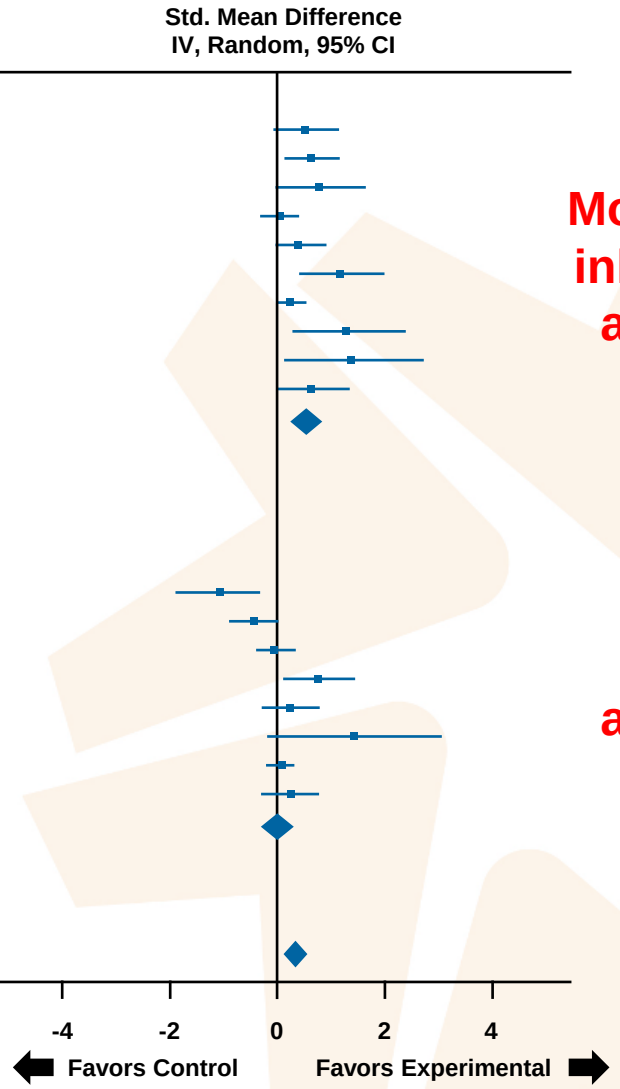
Rush et al (2011)[b]



***P* < .05.**
BUP = bupropion; ESC = escitalopram; FLU = fluoxetine; MIRT = mirtazapine; PBO= placebo; VEN = venlafaxine.
a. Blier P, et al. *Am J Psychiatry*. 2010;167:281-288; b. Rush AJ, et al. *Am J Psychiatry*. 2011;168:689-701.

Meta-Analysis of RCTs of Antidepressant Combinations - *Are All Antidepressant Combinations Created Equal?*

Study or Subgroup	Std. Mean Difference	SE	Experimental Total	Control Total	Weight (%)	Std. Mean Difference IV, Random, 95% CI
5.7.1 RI +a2						
Blier 2009	0.52	0.3204	21	40	5.4	0.52 (-0.11, 1.15)
Blier 2010	0.65	0.2715	77	28	6.3	0.65 (0.12, 1.18)
Carpenter 2002	0.83	0.4162	11	15	4.1	0.83 (0.01, -1.65)
Fang 2010/11	0.03	0.1866	47	150	7.9	0.03 (-0.34, 0.40)
Ferreri 2001	0.42	0.2458	32	71	6.7	0.42 (-0.06, 0.90)
Lauritzen 1992	1.2	0.4035	22	18	4.3	1.20 (0.41, 1.99)
Licht 2002	0.25	0.14	98	195	8.8	0.25 (-0.02, 0.52)
Maes 1996	1.33	0.5405	13	12	2.9	1.33 (0.27, 2.39)
Maes 1999	1.42	0.6656	11	12	2.1	1.42 (0.12, 2.72)
Medhus 1994	0.66	0.3388	18	19	5.2	0.66 (-0.00, 1.32)
Subtotal (95% CI)			**350**	**560**	**53.7%**	**0.54 (0.29, 0.79)**
Heterogeneity: Tau²=0.07; Chi²=16.95, df=9 (*P*=.05); I²=47%						
Test for overall effect: Z=4.22 (*P*<.0001)						
5.7.2 Non RI +a2						
Fava 1994	-1.08	0.4187	12	15	4.1	-1.08 (-1.90, -0.26)
Fava 2002	-0.43	0.2473	34	33	6.7	-0.43 (-0.91, 0.05)
Murphy 1977	-0.04	0.1874	58	115	7.9	-0.04 (-0.41, 0.33)
Nelson 2004	0.77	0.3519	13	26	5.0	0.77 (0.08, 1.46)
O'Brien 1993	0.24	0.2746	25	54	6.2	0.24 (-0.30, 0.78)
Raisi 2007	1.43	0.8325	23	22	1.5	1.43 (-0.20, 3.06)
Stewart 2013	0.06	0.1372	78	167	8.8	0.06 (-0.21, 0.33)
Tanghe 1997	0.25	0.2773	20	38	6.2	0.25 (-0.29, 0.79)
Subtotal (95% CI)			**263**	**470**	**46.3%**	**0.04 (-0.27, 0.35)**
Heterogeneity: Tau²=0.11; Chi²=19.14, df=7 (*P*=.008); I²=63%						
Test for overall effect: Z=0.25 (*P*=.80)						
Total (95% CI)			**613**	**1030**	**100.0%**	**0.33 (0.11, 0.54)**
Heterogeneity: Tau²=0.12; Chi²=46.73, df=17 (*P*=.0001); I²=64%						
Test for overall effect: Z=3.01 (*P*=.003)						
Test for subgroup differences: Chi²=6.04, df=1 (*P*=.01); I²=83.4%						

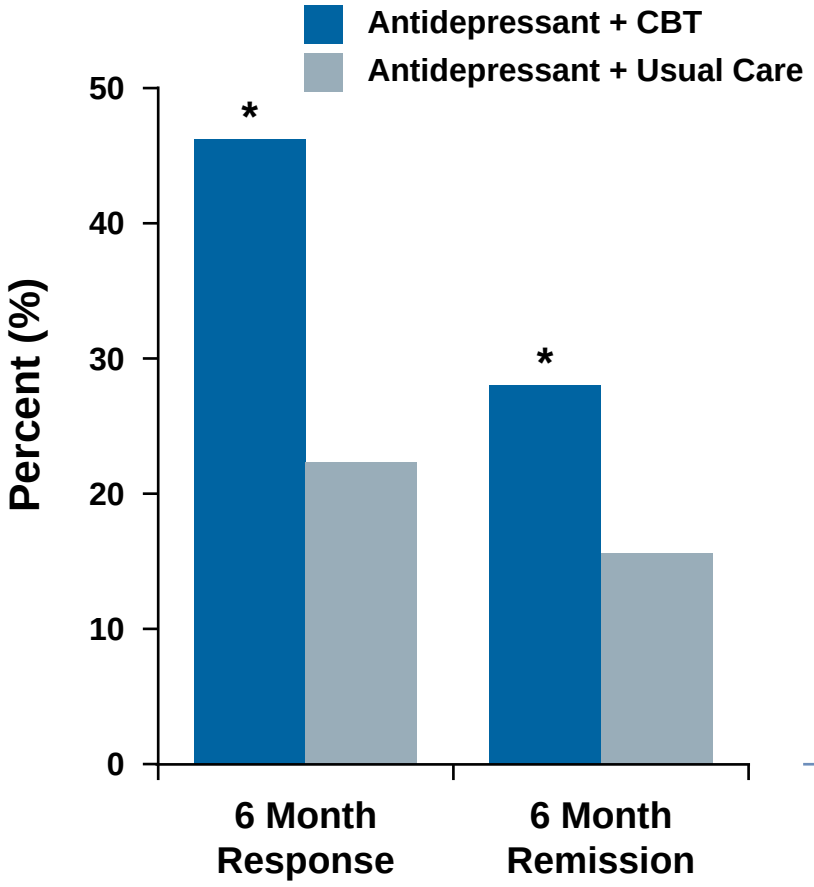


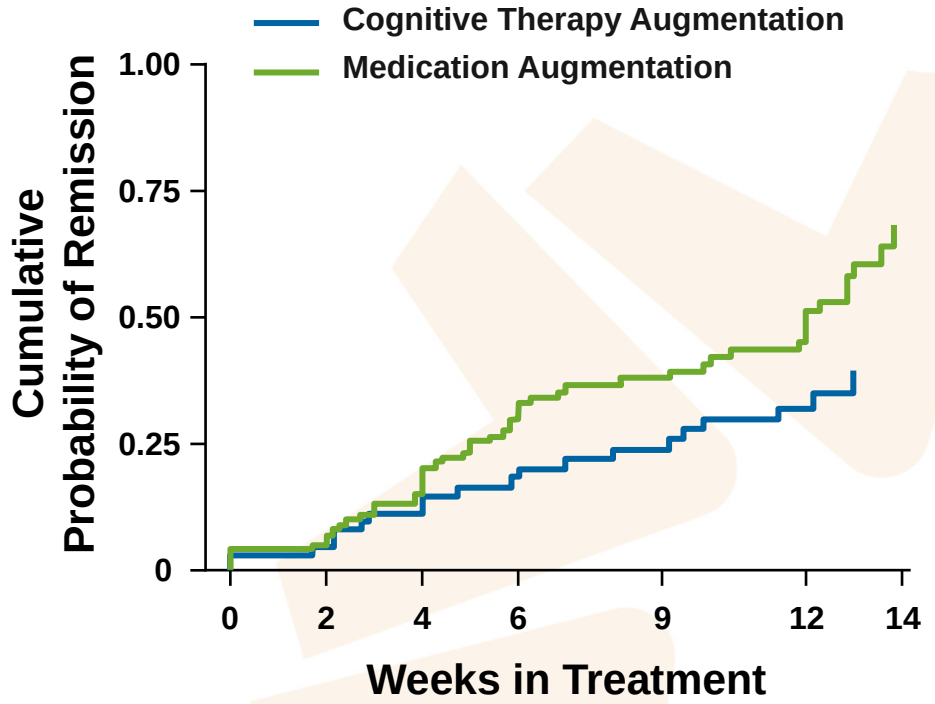
Monoamine reuptake inhibitor (RI) + α2AR antagonist combo

Non-RI + α2AR antagonist combo

Henssler J, et al. Can J Psychiatry. 2016;61:29-43.

Evidence Supporting Augmenting Antidepressants with Psychotherapy





Number:							
Cognitive	65	58	52	45	40	26	10
Medication	117	100	83	65	47	37	7
Total	182	158	135	110	87	63	17

Log-rank = 5.2124, *P* = .0224

***P* < .001.**
CBT = cognitive-behavioral therapy.
Wiles N, et al. *Lancet*. 2013;381(9864):375-384. Thase ME, et al. *Am J Psychiatry*. 2007;164(5):739-752.

Takeaways

- ADT's work in a similar manner but RAADs may change our treatment approach
- Tolerability is paramount for continued benefit of a medication
- If suboptimal response is encouraged guidelines abound, best evidence stands for augmentation with antipsychotic (eg. Aripiprazole)
- Mixed results abound for combining antidepressant agents

Patient Advocate: Life After the Successful Management of MDD with a Newer Treatment Option

When to Consider Switching?

Switch or Augment?
CANMAT 2016 MDD Guidelines

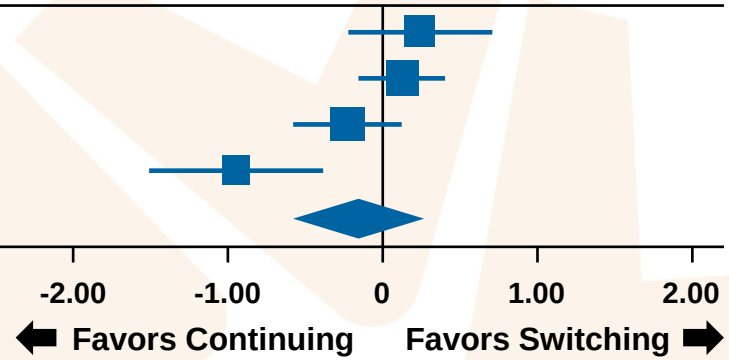
SWITCH to Another Antidepressant	AUGMENT with Another Medication
	2 or more failed antidepressant trials
Poorly tolerated side effects to initial antidepressant	Initial antidepressant well tolerated
< 25% improvement in symptoms on initial antidepressant (no response)	> 25% improvement in symptoms on initial antidepressant (partial response)
Less severe symptoms, functional impairment	More severe symptoms, functional impairment
Patient preference to switch	Patient preference for adding medication

Kennedy. *Can J Psychiatry*. 2016;61:540.

Switching to a New Antidepressant after Non-response to Initial Treatment

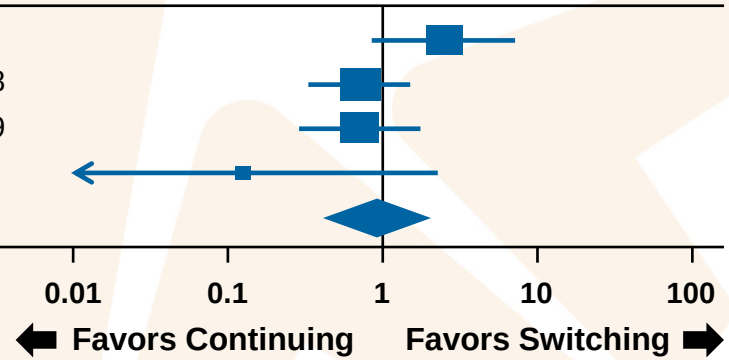
A. Standardized Mean Differences

Study / First Author	Standardized Mean Difference	Standard Error	Variance	Lower Limit	Upper Limit	*Z* Value	*P* Value	Sample Size (n) Switch	Sample Size (n) Continuation
Ferreri 2001[28]	0.245	0.239	0.057	-0.223	0.713	1.025	.305	33	38
Shelton 2005[30]	0.127	0.148	0.022	-0.162	0.416	0.862	.389	142	68
Corya 2006[29]	-0.229	0.184	0.034	-0.589	0.132	-1.244	.213	60	59
Souery 2011[27]	-0.948	0.289	0.083	-1.513	-0.382	-3.285	.001	20	39
Combined estimate	-0.165	0.219	0.048	-0.594	0.264	-0.756	.450		



B. Remission

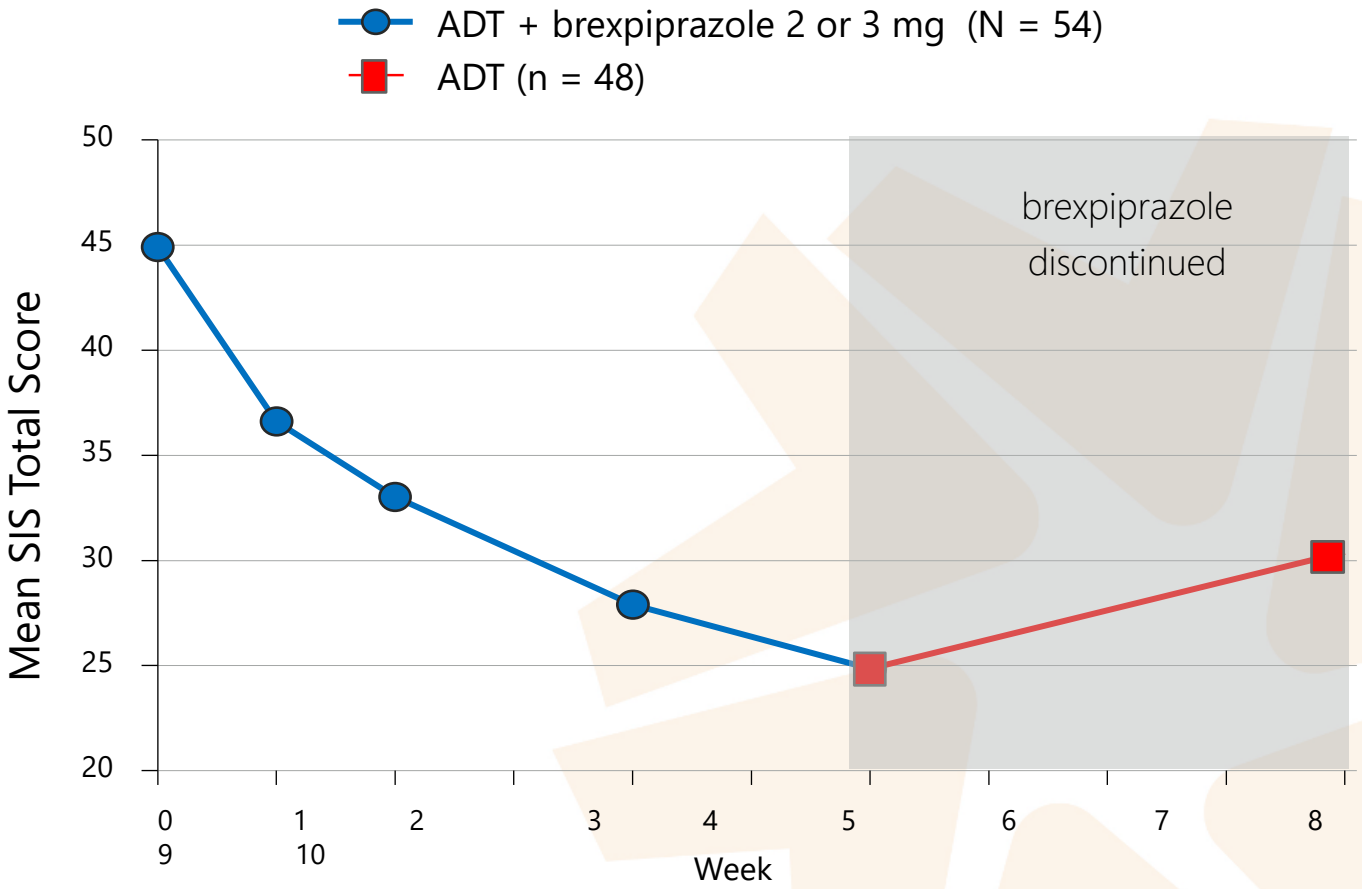
Study / First Author	Odds Ratio	Lower Limit	Upper Limit	*Z* Value	*P* Value	Remission (n) / Total (n) Switch	Remission (n) / Total (n) Continuation
Ferreri 2001[28]	2.531	0.856	7.484	1.678	.093	12 / 33	7 / 38
Shelton 2005[30]	0.721	0.328	1.586	-0.813	.416	19 / 142	12 / 68
Corya 2006[29]	0.708	0.283	1.770	-0.739	.460	10 / 60	13 / 59
Souery 2011[27]	0.126	0.007	2.351	-1.388	.165	0 / 20	6 / 39
Combined estimate	0.899	0.410	1.968	-0.267	.789		



Bschor et al. *J Clin Psychiatry*. 2018;79(1):11-18.

Does Augmentation with an SGA a_{1B} Antagonist Help Depression with Irritability?

Patients diagnosed with MDD according to DSM-IV-TR criteria who had inadequate response to antidepressant treatment continued treatment with their current antidepressant for 2 weeks. Patients still having inadequate response, and with irritability, received 6 weeks of open-label treatment with their current antidepressant at the same dose and adjunctive brexpiprazole (target dose: 3 mg/d)

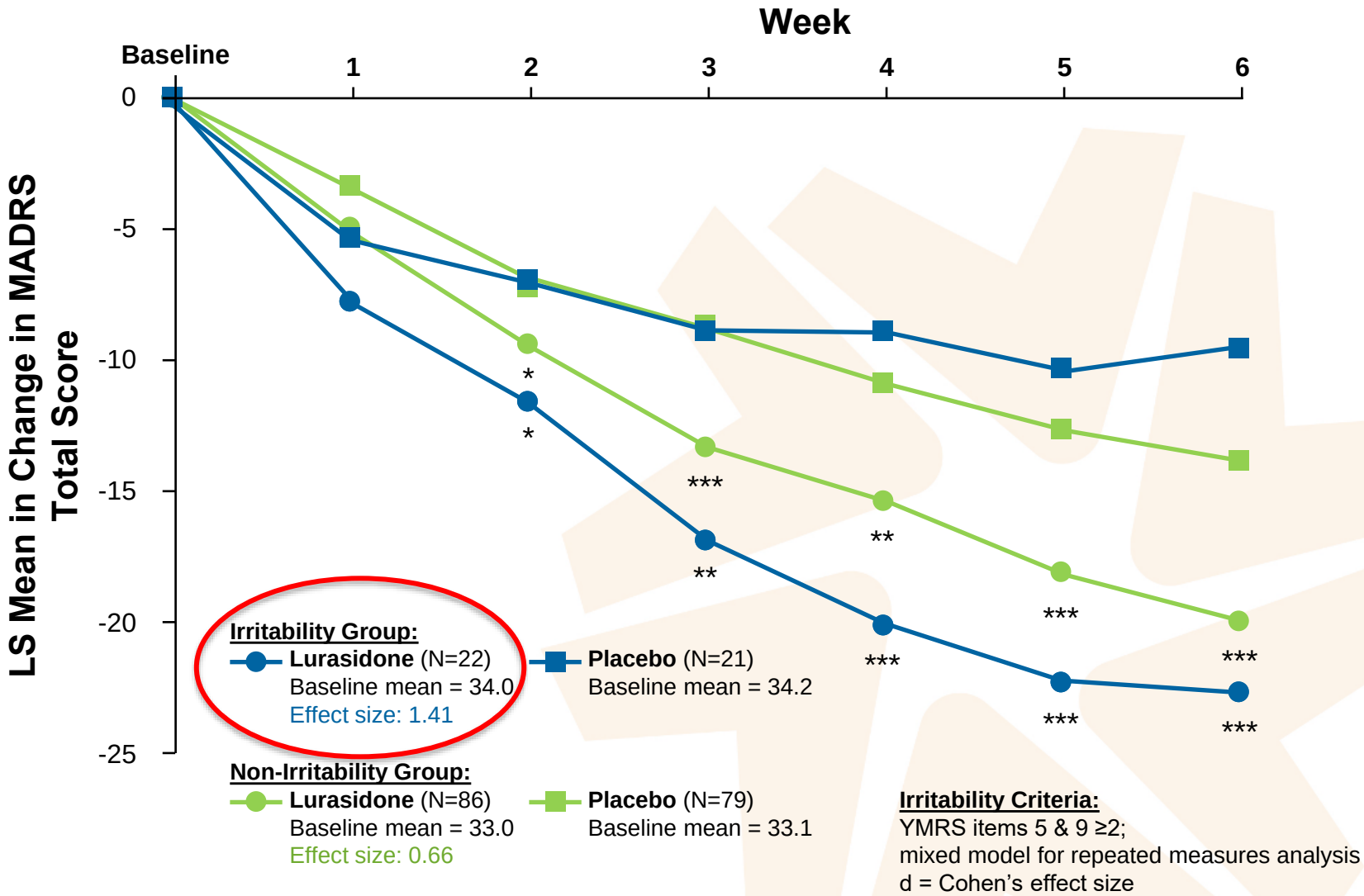


Sheehan Irritability Scale Total Score Change

Fava et al. *J Clin Psychiatry*. 2016;77(12):1695-1701.

Lurasidone is Effective Treatment for Irritability In MDD with Mixed Features

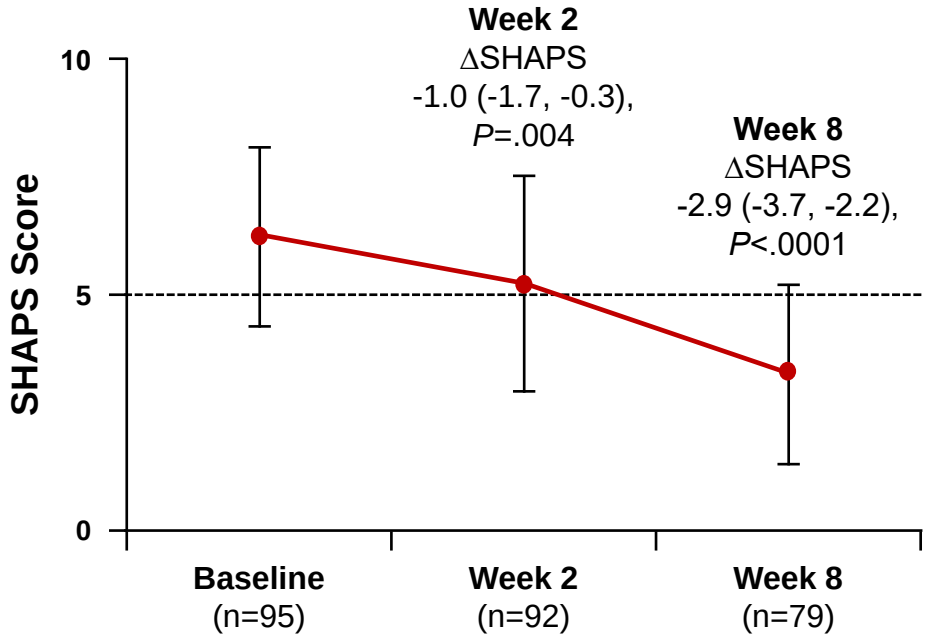
Patients meeting DSM–IV–TR criteria for unipolar MDD, with a Montgomery–Åsberg Depression Rating Scale (MADRS) total score ≥26, presenting with two or three protocol-defined manic symptoms, and who were randomized to 6 weeks of double-blind treatment with either lurasidone 20–60 mg/d (n = 109) or placebo (n = 100). "Irritability" was defined as a score ≥2 on both the Young Mania Rating Scale (YMRS) irritability item (#5) and the disruptive-aggressive item (#9).

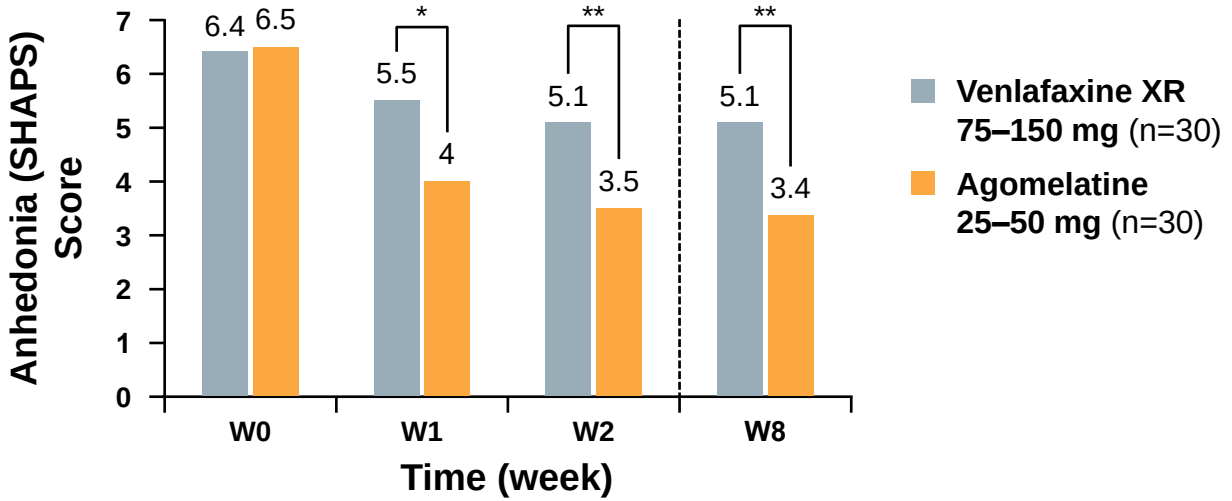


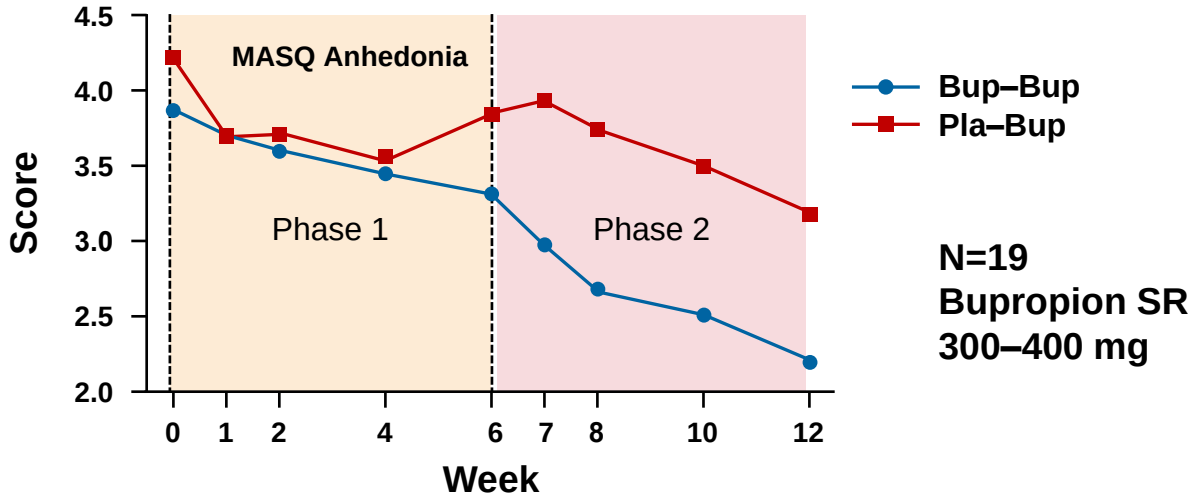
***P*<.05. ****P*<.01. *****P*<.001.

Swann et al.CNS Spectrums.2017;22: 228–235

Vortioxetine, Bupropion, and Agomelatine Significantly Improved Anhedonia in Major Depressive Disorder







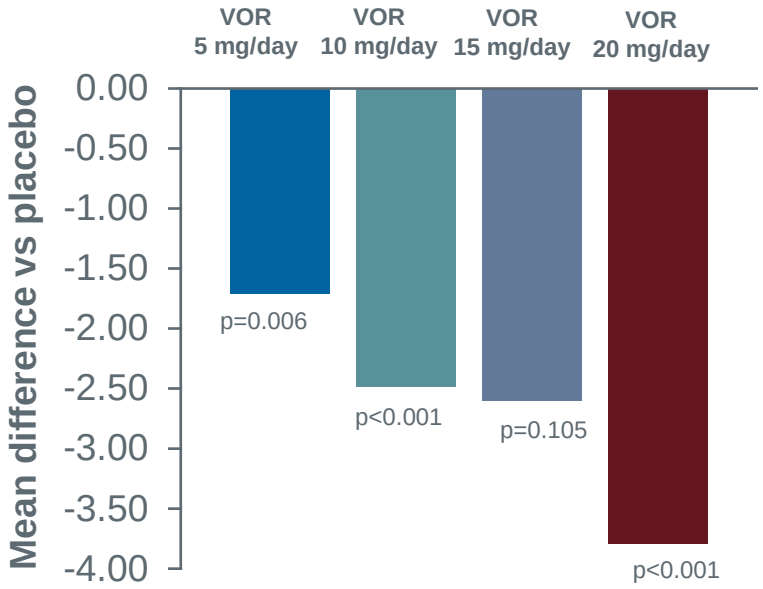
N = 100;
Open-label vortioxetine (10–20 mg/day, flexibly-dosed) for 8 weeks.
MASQ = Mood and Anxiety Symptoms Questionnaire;
SHAPS = Snaith–Hamilton Pleasure Scale.

Cao B, et al. *Front Psychiatry*. 2019;10:17. Di Giannantonio M, et al. *Eur Neuropsychopharmacol*. 2012;22 Suppl 3:S505-S510. Tomarken AJ, et al. *J Affect Disord*. 2004;78(3):235-241.

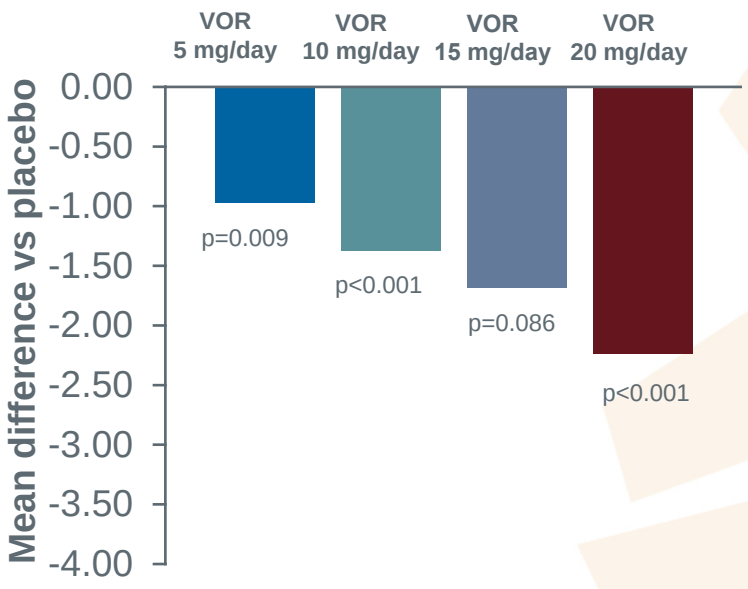
Vortioxetine Significantly Improved Depressive Symptoms (MADRS) Functioning (SDS) and Anhedonia (MADRS Anhedonia Score)

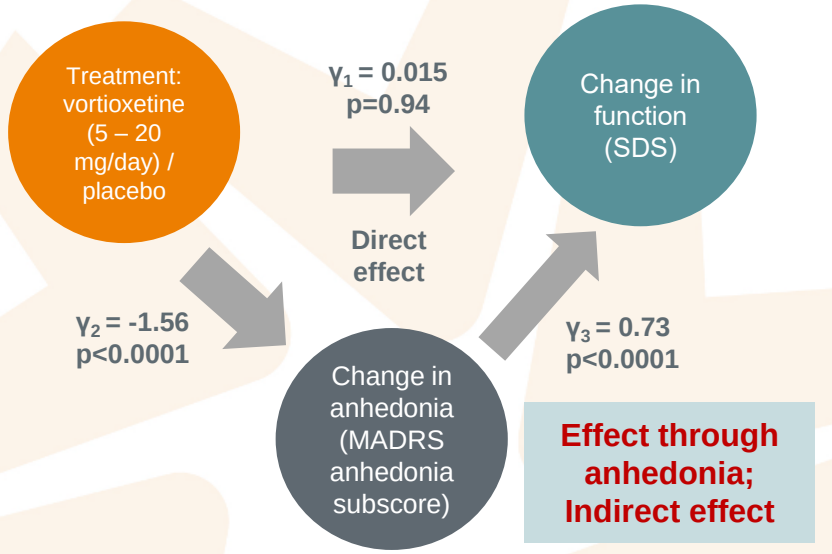
Pooled analysis of all 11 short-term, placebo-controlled studies

MADRS total score



MADRS anhedonia score





Vortioxetine-associated **improvements in functioning** appear to be **driven mostly by the effect** of vortioxetine **on anhedonia.**

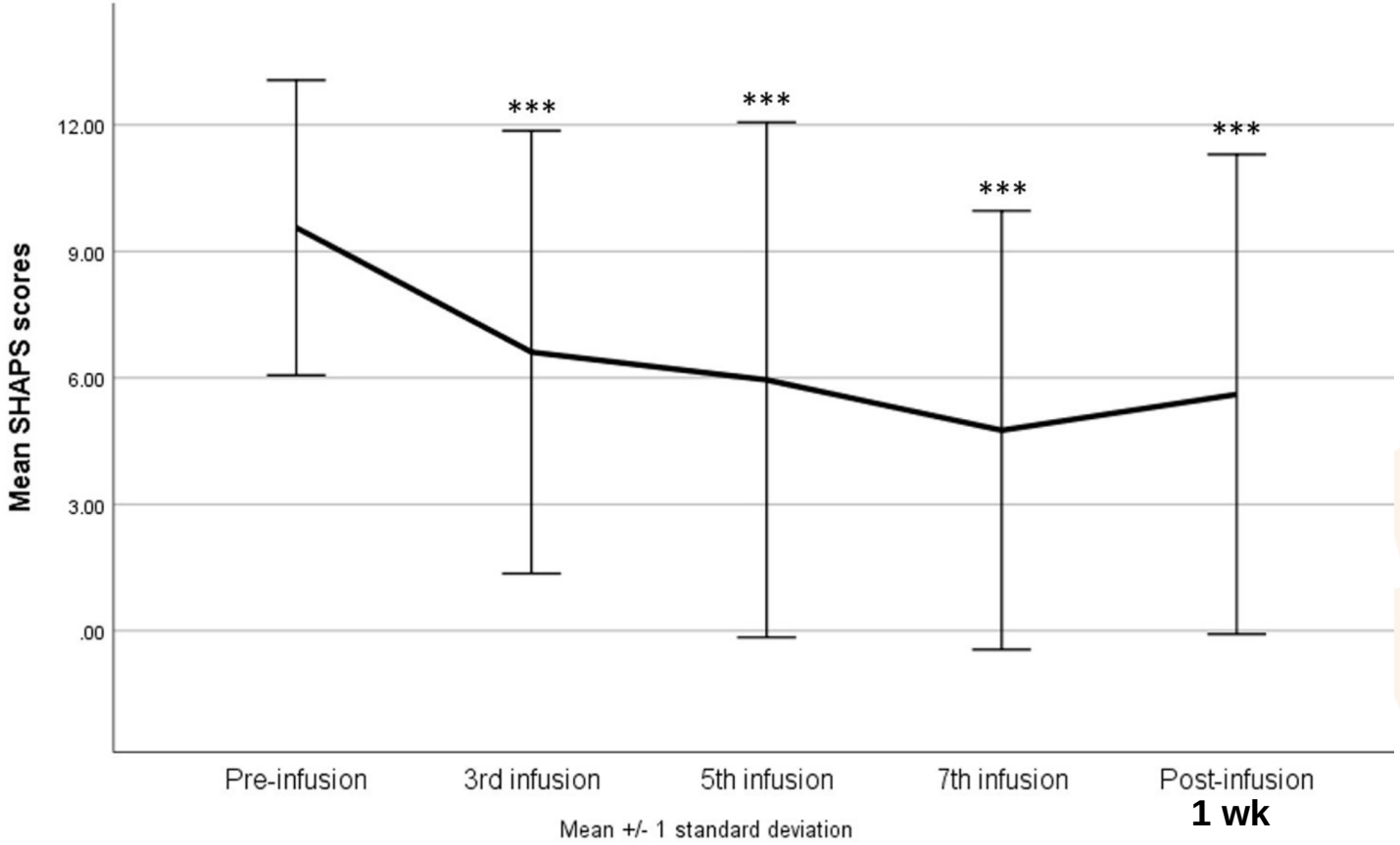
A total of 4988 patients with MDD were included in the placebo-controlled studies and 495 in the active-comparator study. In the placebo-controlled studies, improvements in functioning associated with vortioxetine appeared to be mostly driven by the effect of treatment on MADRS anhedonia factors.

SDS = Zung Self-Rating Depression Scale

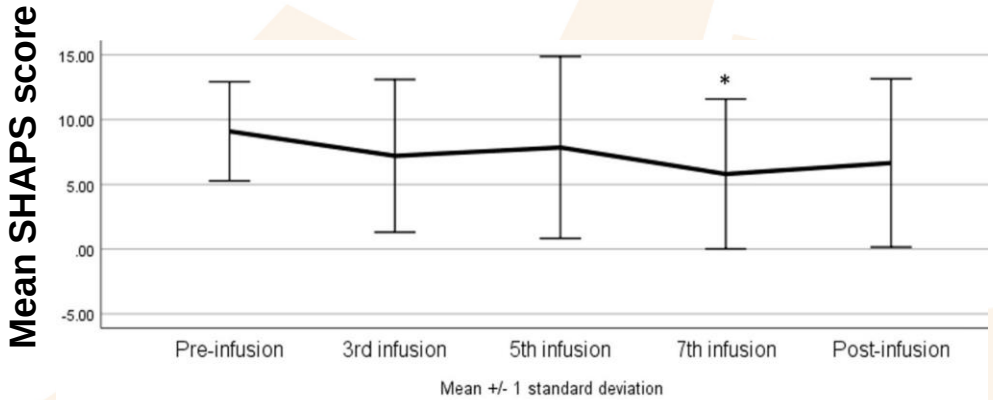
MADRS = Montgomery-Åsberg Depression Rating Scale. McIntyre RS et al. ***Neuropsychiatr Dis Treat.*** **2021;17:575-85**

Ketamine Improves Anhedonia in Treatment-resistant Depression Patients

Snaith–Hamilton Pleasure Scale (SHAPS) score change during ketamine treatment. ***$p < 0.001$ in comparison with baseline scores (pre-infusion).



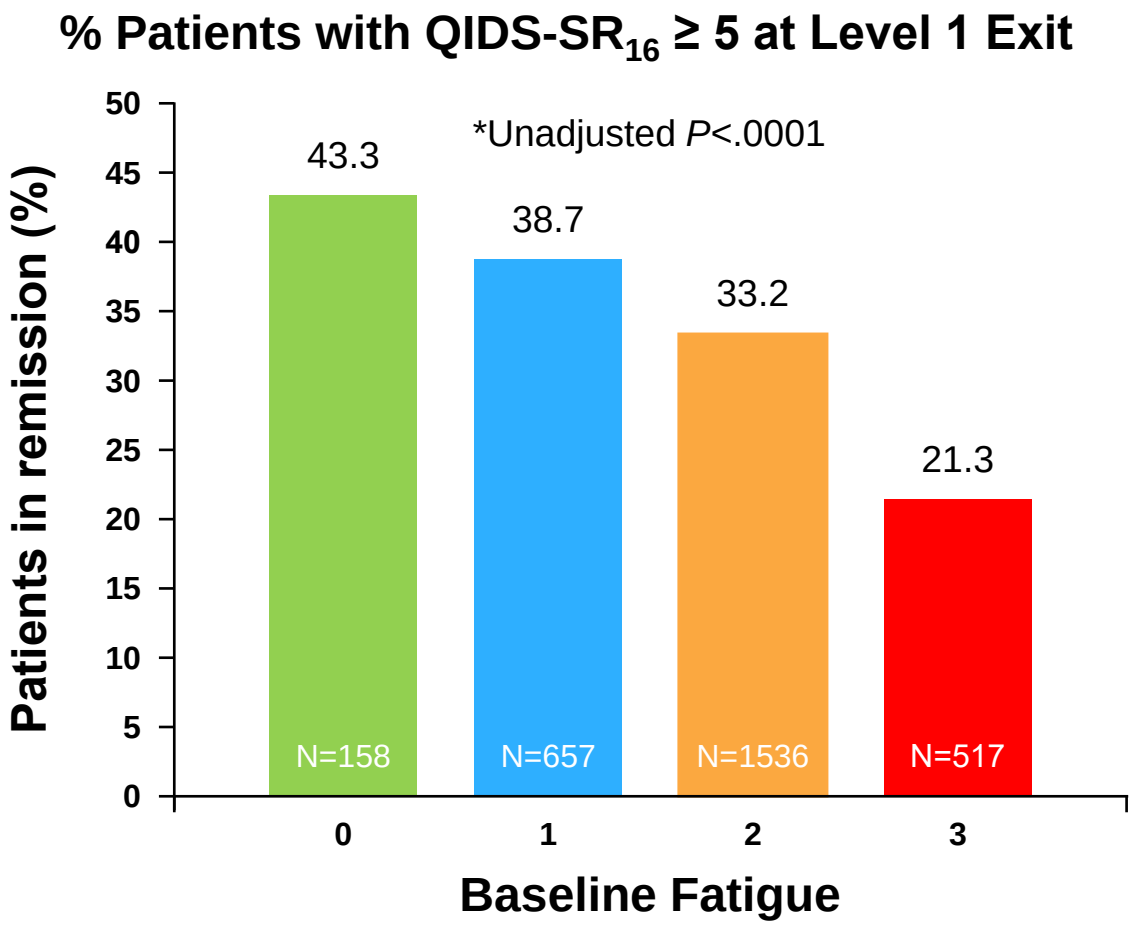
Patients using benzodiazepines during ketamine treatment.



Eight ketamine infusions over 4 weeks as an add-on treatment in 42 patients with treatment resistant depression. Ketamine was administered at a dose of 0.5 mg/kg based on the actual body weight of the patient and given as an intravenous infusion over 40 min.

Wilkowska A, et al. *Frontiers in Psychiatry*. 2021;Vol. 12: Article 704330.

Impact of Fatigue Severity on SSRI Response in STAR*D

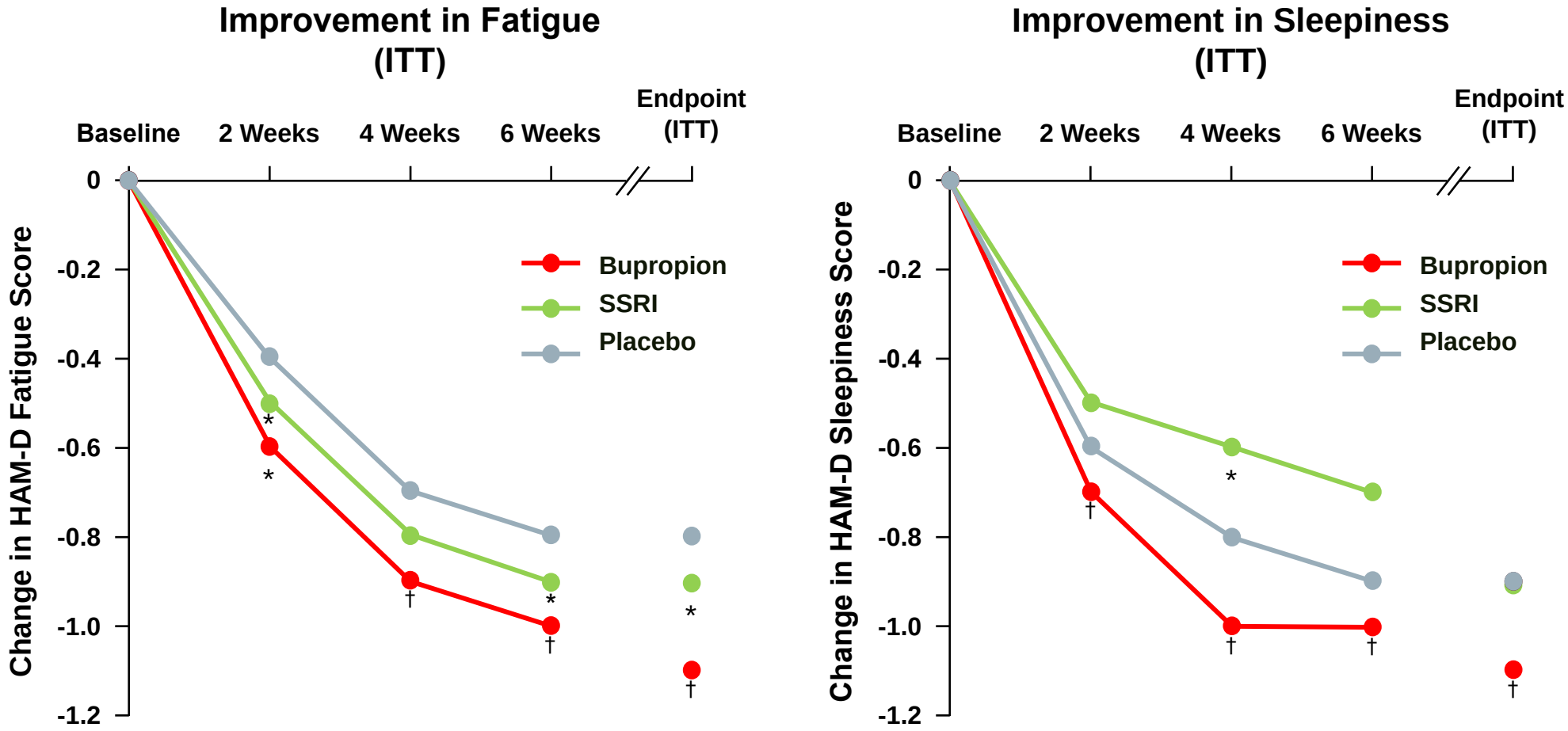


Item #14 - Energy level:

- **0 = There was no change in my usual level of energy.**
- **1 = I got tired more easily than usual.**
- **2 = I had to make a big effort to start or finish my usual daily activities (for example: shopping, homework, cooking or going to work).**
- **3 = I really couldn't carry out most of my usual daily activities because I just didn't have the energy.**

Level 1 remission (QIDS-SR16 score ≤ 5) outcome by baseline QIDS-SR16 (item 14) energy/fatigability score.
***Adjusted OR=.811 (*P*=.0001; 95% CI [.73, .90]). Adjusted for number of Axis I comorbidities, baseline HAM-D-17, and anxious features.**
QIDS-SR16 = 16-item Quick Inventory of Depressive Symptomatology, Self-Report; HAM-D-17 = 17-item Hamilton Rating Scale for Depression.
Ferguson M, et al. *Curr Med Res Opin*. 2014;30(10):2109-2118.

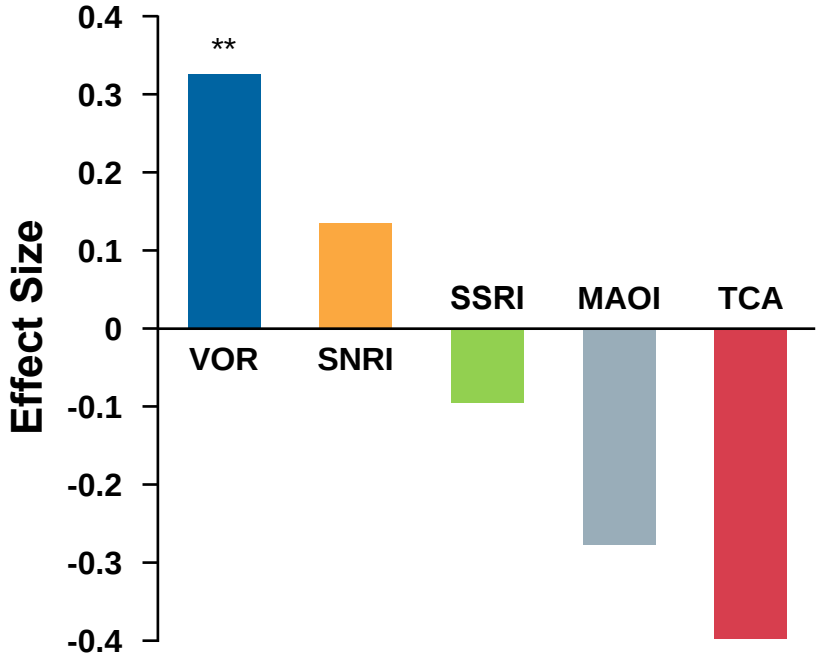
Presence of Sleepiness and Fatigue Might Influence our Treatment Choice



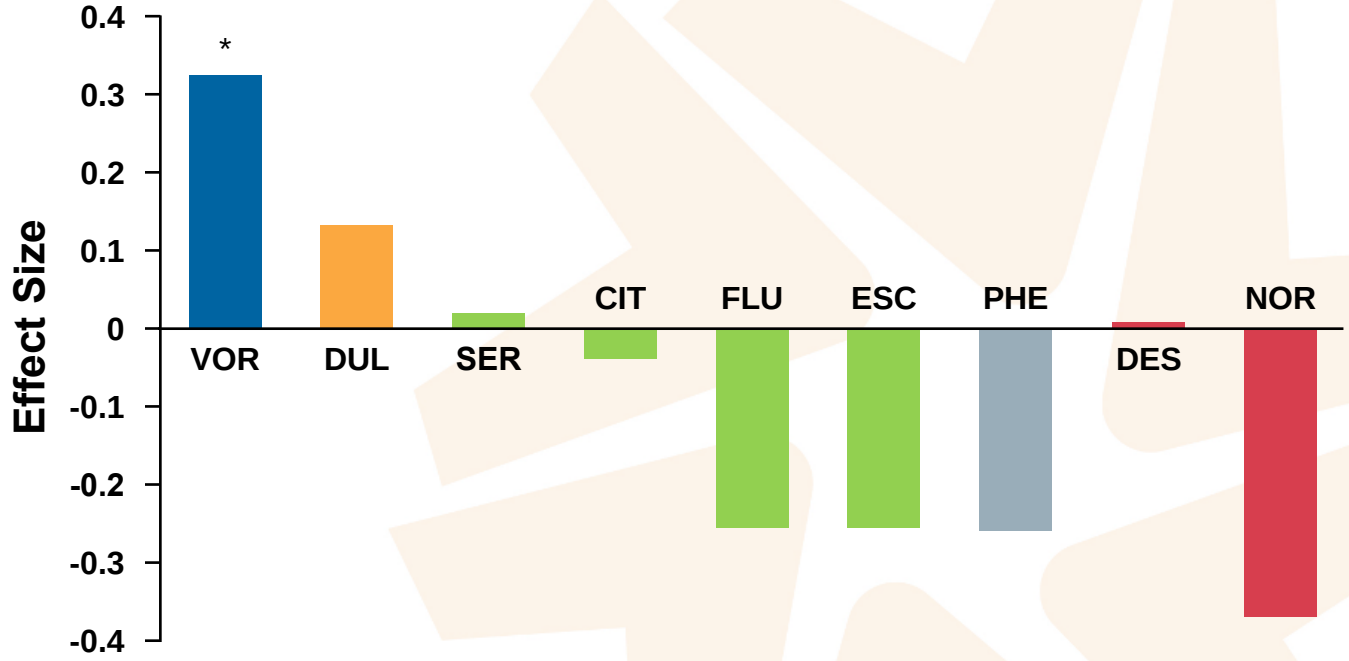
Left: **P*<.05 vs placebo, †*P*<.01 vs SSRIs and placebo; Right: **P*=.07 vs placebo, †*P*<.01 vs SSRIs and placebo.
HAM-D = Hamilton Rating Scale for Depression.
Papakostas GI, et al. *Biol Psychiatry*. 2006;60(12):1350-1355.

Improvement in Cognitive Dysfunction in MDD as Assessed by the DSST

Standardized Effect Size Relative to Placebo by Antidepressant Therapeutic Classes



Standardized Effect Size Relative to Placebo by Individual Antidepressants

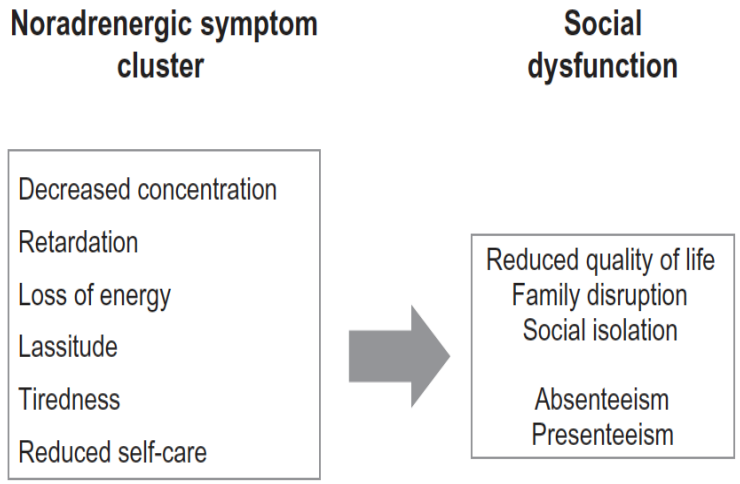


***P*<.05; ****P*<.01**

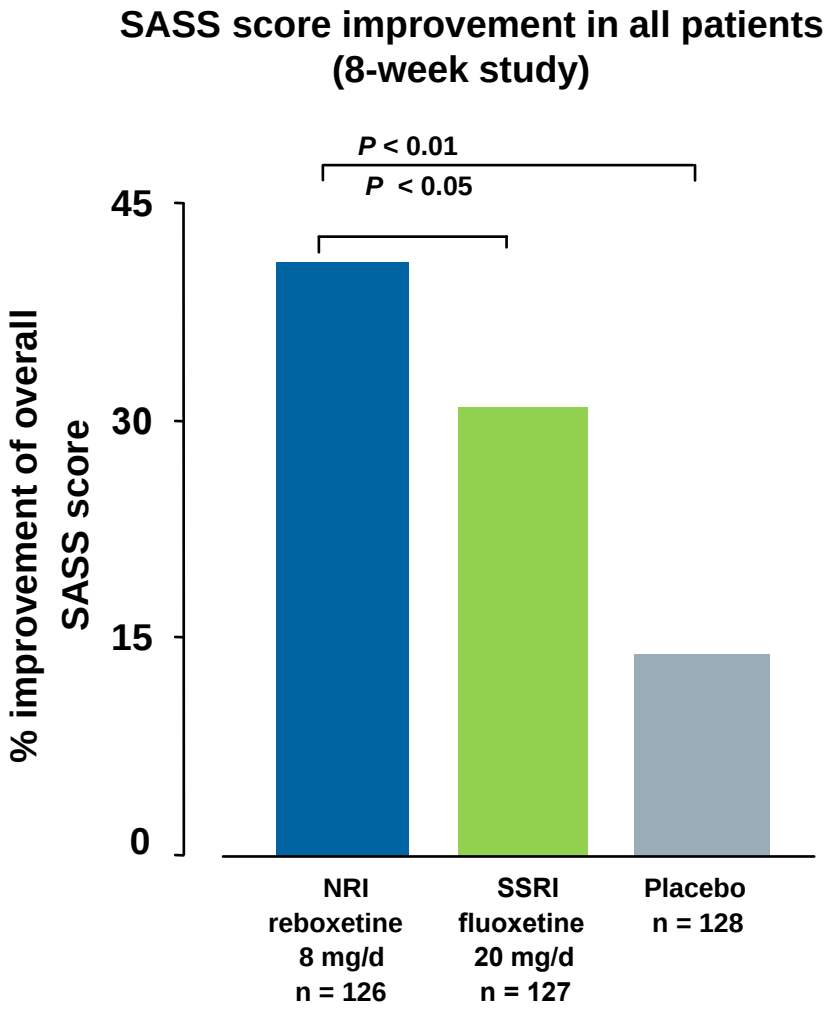
DSST = Digit Symbol Substitution Test; CIT = citalopram; DES = desipramine; DUL = duloxetine; ESC = escitalopram; FLU = fluoxetine; NOR = nortriptyline; PHE = phenelzine; SER = sertraline; TCA = tricyclic antidepressant; VOR = vortioxetine.

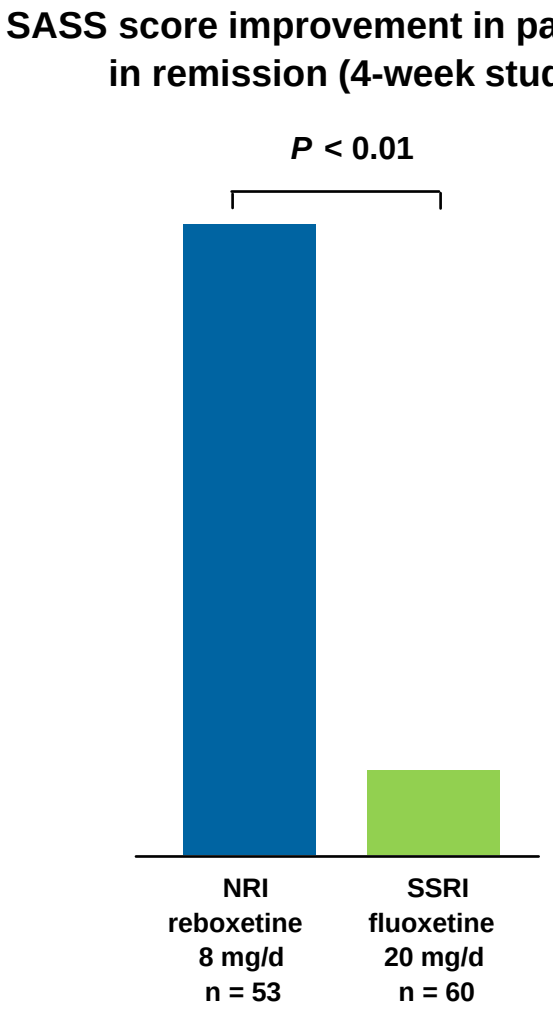
Baune BT, et al. *Int J Neuropsychopharmacol*. 2018;21(2):97-107.

Improvement in Social Functioning may be Related to Noradrenergic Antidepressant Effect



Improvement in Social Adaptation Self-evaluation Scale (SASS) score during antidepressant therapy.

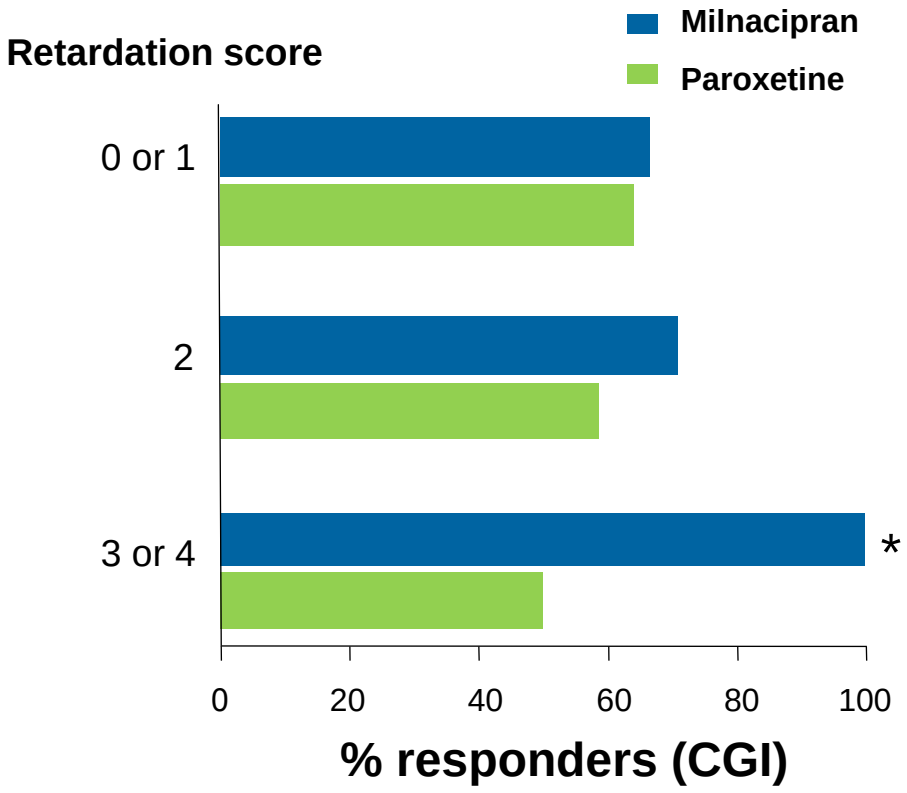




NRI = norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

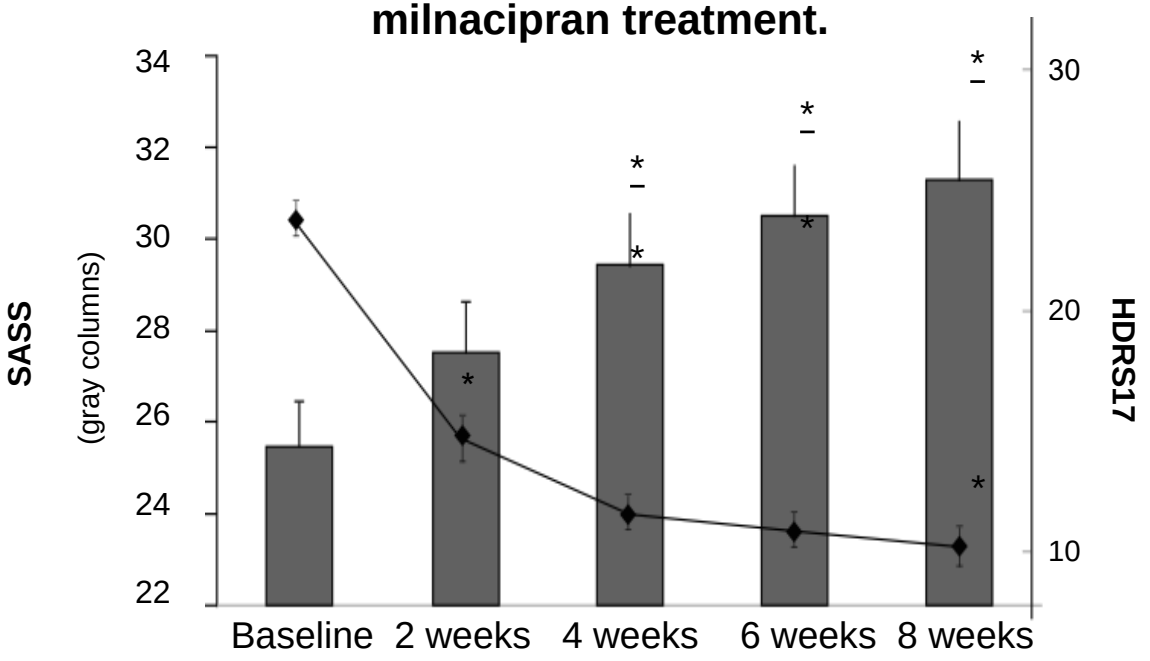
Kasper et al. *Neuropsychiatric Disease and Treatment.* 2011;7(Suppl 1): 21–27.

Improvement in Social Functioning and Retardation may be Related to Noradrenergic Antidepressant Effect



Retardation score = the score on item 8 of the Hamilton Depression Rating Scale.
***P* 0.05 compared with paroxetine-treated patients with retardation scores of 3 or 4.**
CGI = Clinical Global Improvement.
Kasper et al. *Neuropsychiatric Disease and Treatment*. 201177 (Suppl 1): 21–27.

Depression and social function during milnacipran treatment.



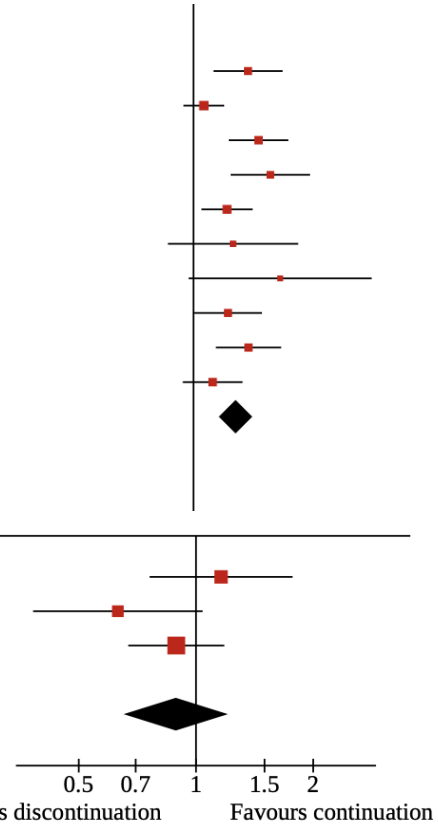
Depression ratings (black lozenges and line) are the mean Hamilton Depression Rating Scale (HDRS 17) scores. Social function ratings are the mean Social Adaptation Self-evaluation Scale (SASS) scores (standard error of the mean).
***P < 0.01 compared with respective baseline values; n = 101 used for intention-to-treat analysis.**

How to Safely Discontinue an Antidepressant?

Abrupt discontinuation, no co-intervention: HR of relapse: 2.09

Discontinuation with high-intensity psychological interventions versus continuation: HR of relapse: 0.89 n.s.

Study or Subgroup	log[Hazard Ratio]	SE	Abrupt discontinuation Total	Continuation Total	Weight	Hazard Ratio IV, Random, 95% CI
1.1.2 No co-intervention follow-up > 24 weeks						
Gilaberte 2001	0.9555	0.3086	70	70	10.3%	2.60 [1.42 , 4.76]
Kane 1982	0.1823	0.182	6	6	15.5%	1.20 [0.84 , 1.71]
Klysner 2002	1.1394	0.2657	61	60	11.9%	3.12 [1.86 , 5.26]
Kornstein 2006	1.3455	0.3543	65	73	8.8%	3.84 [1.92 , 7.69]
Montgomery 1988	0.5878	0.2286	112	108	13.4%	1.80 [1.15 , 2.82]
Peterson 2010	0.6931	0.5814	16	14	4.5%	2.00 [0.64 , 6.25]
Rapaport 2001	1.5173	0.8167	89	92	2.5%	4.56 [0.92 , 22.60]
Rouillon 2000	0.6043	0.3033	110	104	10.5%	1.83 [1.01 , 3.32]
Terra 1998	0.9632	0.2914	94	110	10.9%	2.62 [1.48 , 4.64]
Wilson 2003	0.3365	0.2667	57	56	11.8%	1.40 [0.83 , 2.36]
Subtotal (95% CI)			**680**	**693**	**100.0%**	**2.09 [1.59 , 2.74]**
Heterogeneity: Tau² = 0.09; Chi² = 18.59, df = 9 (P = 0.03); I² = 52%						
Test for overall effect: Z = 5.33 (P < 0.00001)						
Bockting 2018	0.1484	0.2157	43	100	30.1%	1.16 [0.76 , 1.77]
Kuyken 2008	-0.462	0.2557	61	62	23.9%	0.63 [0.38 , 1.04]
Kuyken 2015	-0.1165	0.1449	212	212	46.0%	0.89 [0.67 , 1.18]
Total (95% CI)			**316**	**374**	**100.0%**	**0.89 [0.66 , 1.19]**
Heterogeneity: Tau² = 0.03; Chi² = 3.33, df = 2 (P = 0.19); I² = 40%						
Test for overall effect: Z = 0.80 (P = 0.42)						
Test for subgroup differences: Not applicable						



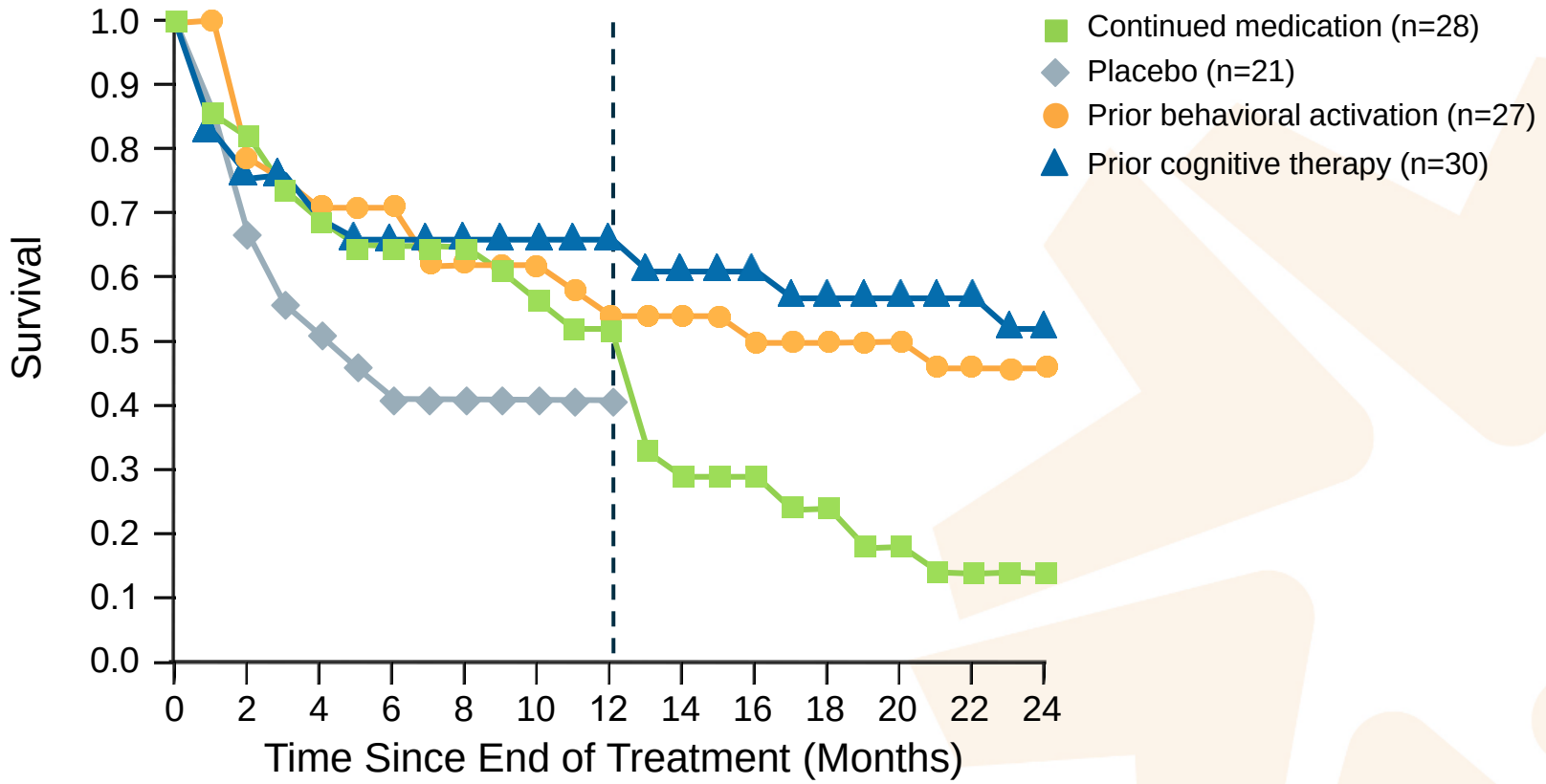
Van Leeuwen, et al. *Cochrane Database of Systematic Reviews.* 2021;Issue 4. Art. No.: CD013495.

Takeaways

- In general, unless patient has no response to treatment, adjunctive therapies provide more favorable outcomes than therapy switches
- Treatment switches are appropriate if patient has significant side-effects, or initial treatment leads to worsening of clinical state
- Certain pharmacological strategies have established advantage for certain symptom domains, such as irritability, mixed features, anhedonia, fatigue, cognitive difficulties or diminished social functioning
- Appropriate psychosocial strategies minimize the risk of mood destabilization associated with treatment switches

Non-Pharmacological Options and Collaborative Care

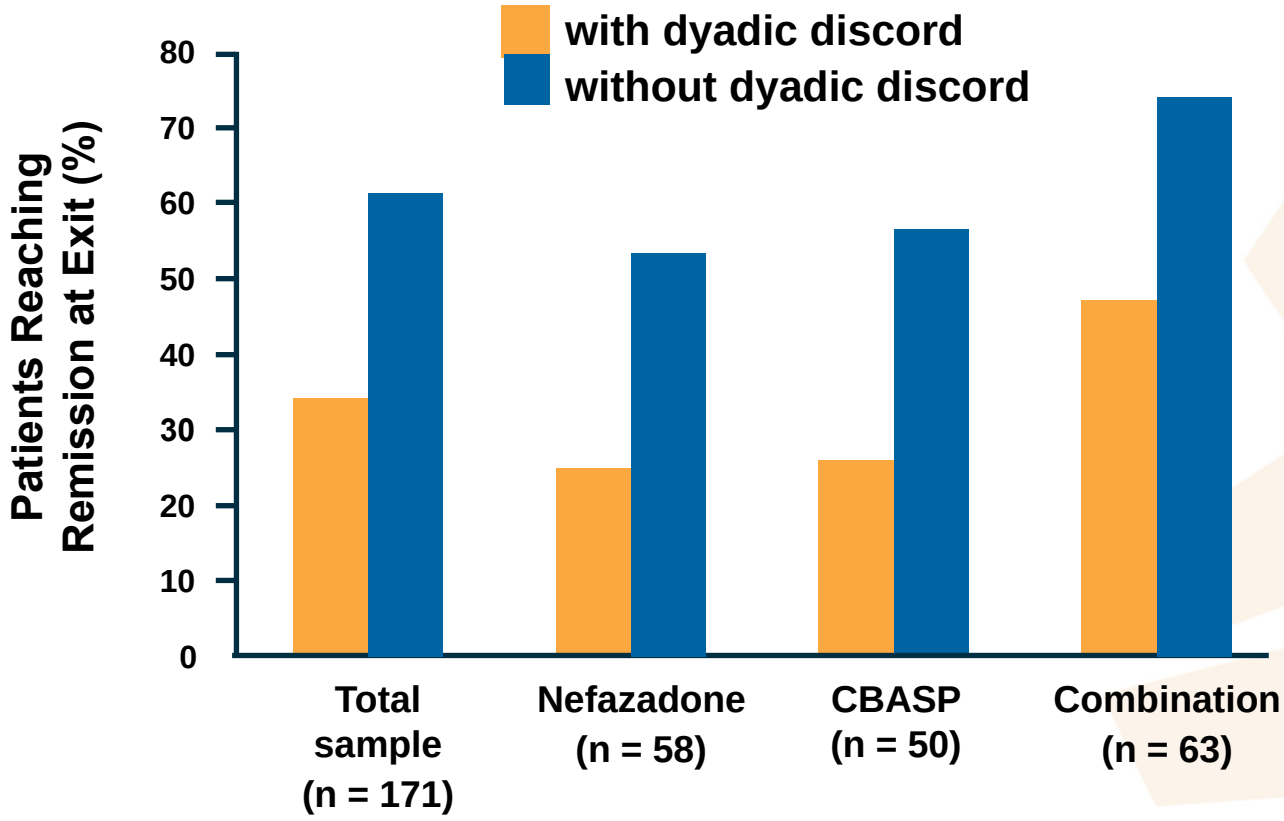
Cognitive Therapy and Behavioral Activation Were Advantageous in Delaying Relapse



Participants were initially assigned to 16 weeks of antidepressant treatment (n=100), cognitive therapy (n=45), and behavioral activation (n=43); treatment responders on antidepressants were randomized to continue with medication or placebo; relapse was defined as a HAM-D score of ≥14; recurrence was defined with the same criteria during the second year of follow-up.

Adapted from Dobson KS, et al. *J Consult Clin Psychol.* 2008;76(3):468-477.

Dyadic Discord is Associated with Lack of Remission in MDD

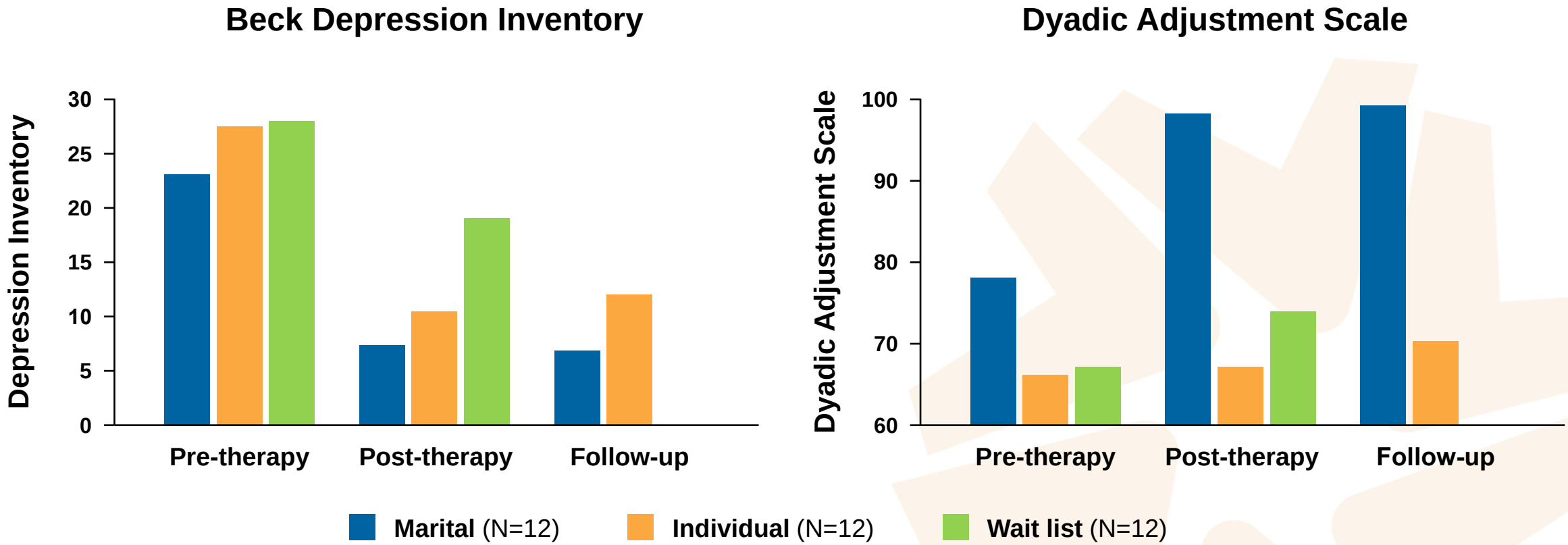


- Comparing exit rates of remission for patients with and without dyadic discord at baseline
- Remission was defined as an IDS-SR30 score of ≤14 at study exit

CBASP = cognitive behavioral analysis system of psychotherapy; IDS-SR30 = inventory of depressive symptomatology-self report.

Denton WH, et al. *Psycho Med*. 2010;40(3):415-424.

Is Marital Therapy a Viable Treatment for Depression?

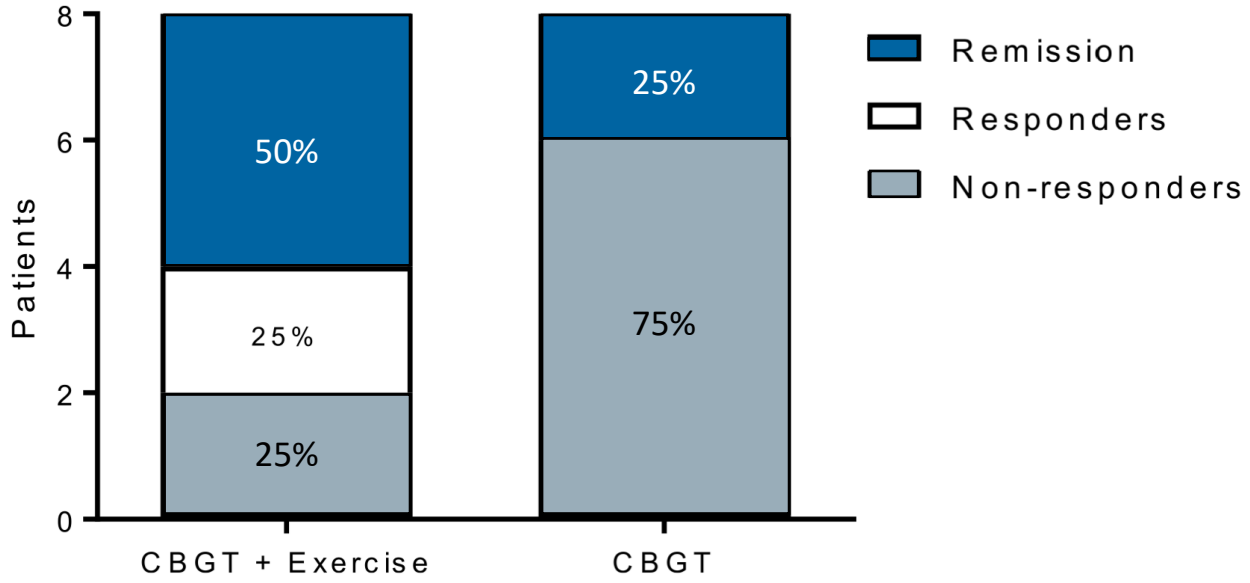


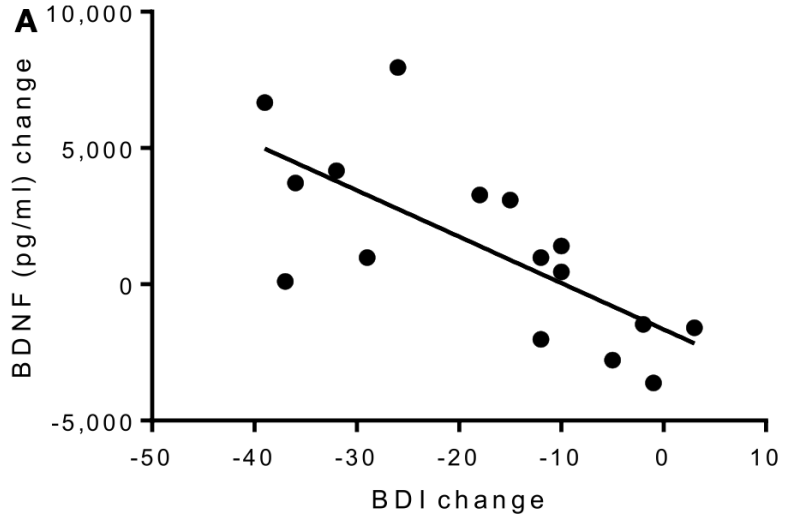
Changes in depression inventory and marital satisfaction scores in women given 15 weeks of **marital** therapy or **individual cognitive therapy** and women in a waiting-list control group.

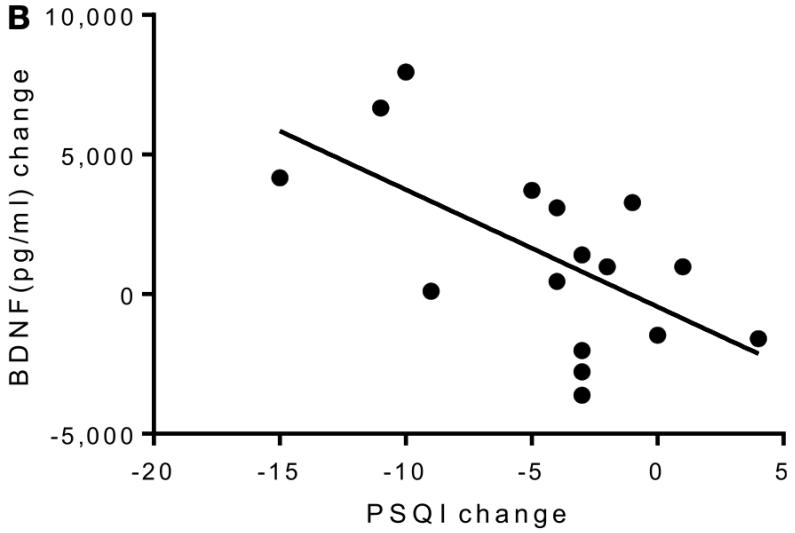
No medications were used. N=36 couples.

O'Leary KD, et al. *Am J Psychiatry*. 1990;147(2):183-186.

Prescribing Exercise Dramatically Improves the Outcome and Biological Markers of MDD Treatment







N=16, low-active MDD patients were recruited from a mental health day treatment program at a local hospital. Eight medicated patients performed an 8-week exercise intervention in addition to CBGT, and eight medicated patients attended the CBGT only. Exercise resulted in greater reduction in depression symptoms (p = 0.007, d = 2.06), with 75% of the patients showing either a therapeutic response or a complete remission of symptoms vs. 25% of those who did not exercise.

CBGT=cognitive behavioral group therapy; BDI = Beck Depression Inventory; BDNF = brain-derived neurotropic factor; PSQI = Pittsburgh Sleep Quality Index.

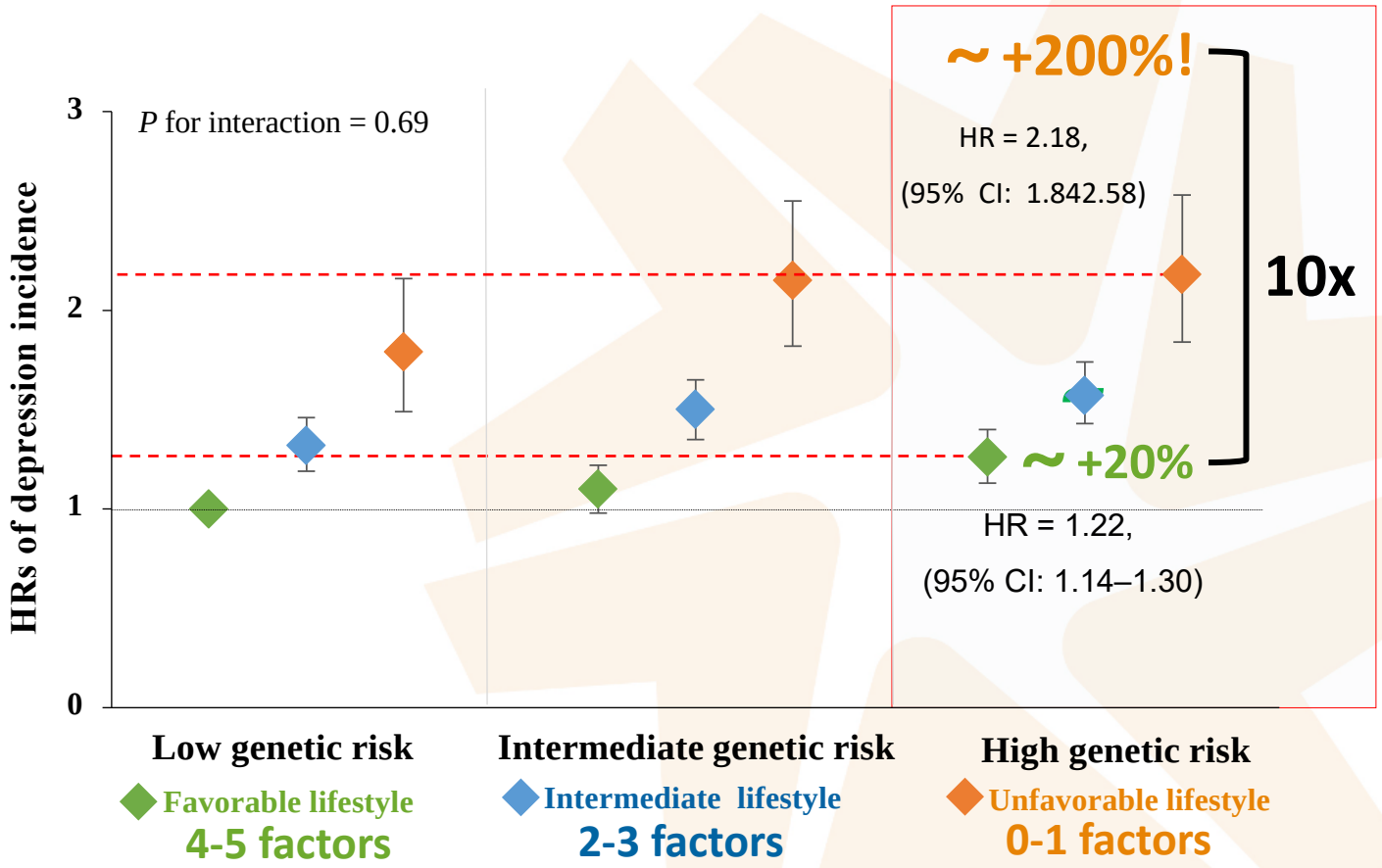
Polygenic Risk Score and Lifestyle Factors Influence The Risk of Depression: Is it modifiable? YES!

The **risk of depression was only 22% higher** among those at high genetic risk compared with those at low genetic risk (HR = 1.22, 95% CI: 1.14–1.30) if they had a low-risk lifestyle.

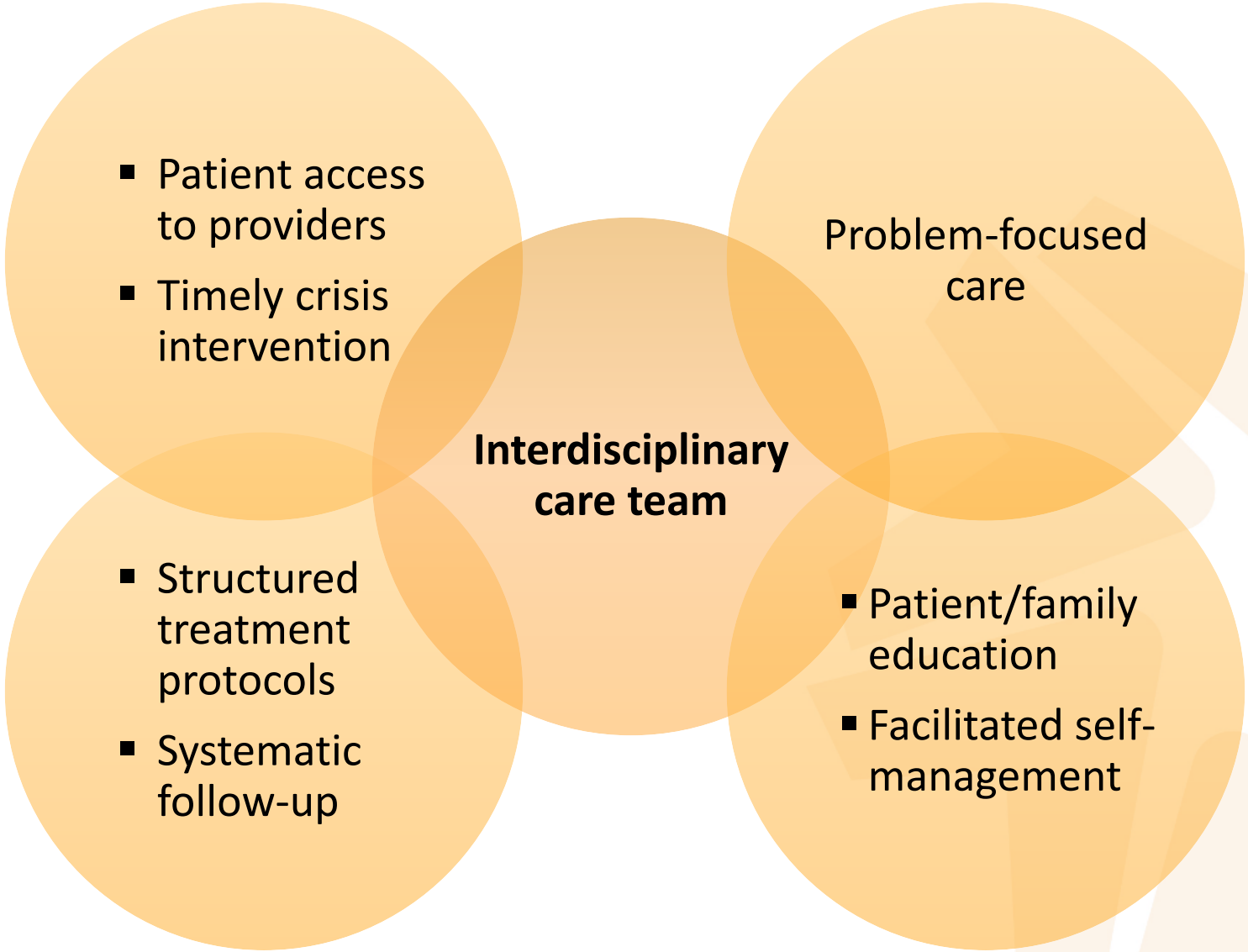
Data were obtained from the UK Biobank and consisted of 339,767 participants (37–73 years old) without depression between 2006 and 2010. Genetic risk was categorized as low, intermediate, or high according to polygenic risk score for depression.

Five healthy lifestyle factors were based of the American Heart Association (AHA) guidelines:

1. **Moderate alcohol intake (**0–28 g/d for men and 0–4 g/d for women**)**
2. **No current smoking**
3. **Healthy diet (**≥2 of increased consumption of fruit, vegetables, and fish, as well as the decreased consumption of processed meats and red meats**);**
4. **BMI < 30 kg/m²**
5. **Regular physical activity (**at least 150 min of moderate-intensity activity weekly or 75 min of vigorous activity weekly).



MDD: Integrated Care Model



VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorders, 2016.

Patient Advocate: Improved Outcomes After Clinician-Patient Collaboration

Q&A