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The Potential Role of Neurosteroid Antidepressants For Intermittent Treatment of MDD

Gus Alva, MD, DFAPA

Medical Director, ATP Clinical Research
Medical Director, Senior Brain Health, Hoag Hospital
Assistant Professor, Department of Psychiatry and Neuroscience
University of California, Riverside, CA

Rakesh Jain, MD, MPH

Clinical Professor
Department of Psychiatry
Texas Tech University School of Medicine
Midland, Texas

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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

CME = continuing medical education

Learning Objectives

- Assess how barriers to MDD recognition and treatment and limitations of conventional treatment options can affect patient outcomes
- Describe the neurobiological mechanisms of MDD as currently understood and associated implications for therapeutic targeting along with differentiating acute vs. chronic treatment of depression
- Evaluate the clinical role of novel therapies for the treatment of MDD based on mechanisms of action and safety and efficacy data

DEFINITION AND KEY SYMPTOMS

Emotional Symptoms

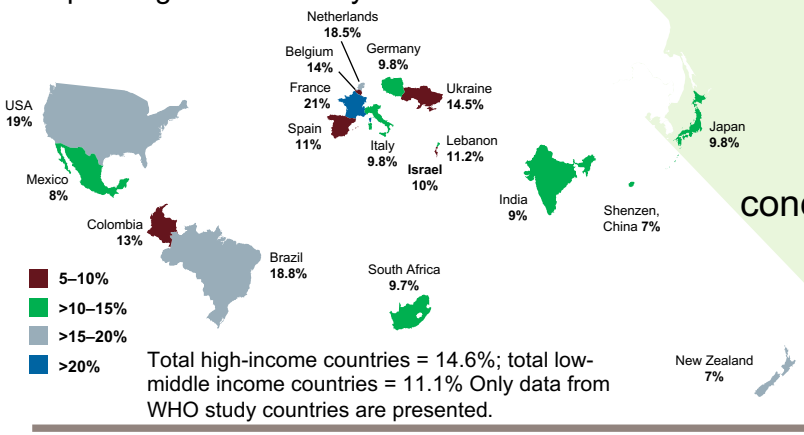
Sadness, hopelessness, loss of energy and interest in activities you once enjoyed, as well as suicidal thoughts [3]

Physical and cognitive symptoms

Sexual dysfunction, anhedonia and cognitive problems, including difficulties with memory, concentration and planning.[3]

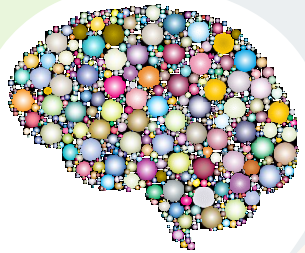
Average lifetime prevalence of major depressive episode[1]

The lifetime prevalence of MDD is 6.5–21%, depending on the country[1]



Total high-income countries = 14.6%; total low-middle income countries = 11.1% Only data from WHO study countries are presented.

More than 300 million people worldwide suffer from depression[2]



UNMET NEEDS

Tolerance Issues[4]

Lack of adherence to treatment

- Gastrointestinal Symptoms
- Insomnia
- Changes in Body Weight
- Sexual Dysfunction
- Emotional Numbing

Persistent symptoms in partial responders[5]

- Interrupted Sleep[6]
- Anhedonia
- Cognitive Impairment

Low remission rates in "real world" patients[6]

Treatment Resistant Depression

BURDEN OF DISEASE

High morbidity and mortality[7]

Decreased ability to interact with friends, family, and colleagues[7]

3,000 deaths by suicide every day worldwide[7]

Largely driven by workplace productivity losses[8]

Serious financial burden on patients and society8

1 in 20 people reported having had an episode of depression in the past year[7]

Leading cause of disability globally[7]

1. Bromet E et al. BMC Med 2011;9:90; 2. World Health Organization. Depression and Other Common Mental Disorders. Global health estimates. 2017. Available at: https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017. 2-eng.pdf?sequence=1&isAllowed=y; 3. American Psychiatric Association. DSM-5. American Psychiatric Publishing, 2013; 4. Kelly K et al. *Dialogues Clin Neurosci*. 2008;10:409-18; 5. Zajecka JM. *J Clin Psychiatry*. 2013;74(Suppl 2):9-13; 6. Gaynes BN et al. *Cleve Clin J Med*. 2008;75:57-66; 7.Marcus M et al. depression. A Global Public Health Concern. 2016. Available at: https://www.who.int/mental_health/management/depression/who_paper_depression_wfmh_2012.pdf; 8. Krol Met al. *Pharmacoeconomics*. 2011:29:601-19.

MDD is One of the Most Common Mental Disorders in the United States[1]

Lifetime Prevalence

of MDD in adults in the United States is **16.6%**[2*]

59.3% of people with 12-month MDD assessed by CIDI reported

Either Severe or Very Severe Role Impairment[3]

MDD Is One of the Most Common Mental Disorders in the United States[1]

Women

have higher rates of lifetime MDD compared with men[2]

The Burden of MDD

Includes Increases in the Relative Risk of various diseases, such as heart disease, diabetes mellitus, and cancer[4,5]

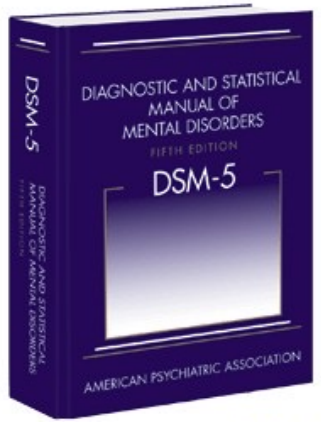
CIDI = Composite International Diagnostic Interview.
***As of 2009.**

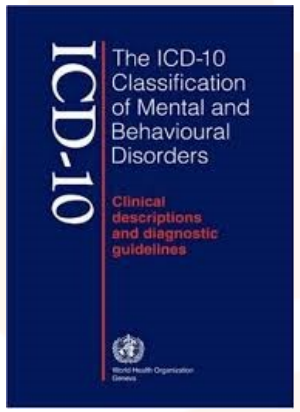
1. Major depression among adults. National Institute of Mental Health website. https://www.nimh.nih.gov/health/statistics/prevalence/major depression-among-adults.html . Accessed July 7, 2017. 2. Kessler RC et al. *Epidemiol Psychiatr Sci*. 2015;24(3):210-226. 3. Kessler RC et al. *JAMA*. 2003;289(23):3095-3105. 4. Otte C et al. *Nat Rev Dis Primers*. 2016;2:16065. doi:10.1038/nrdp.2016.65. 5. Penninx BWJH et al. *BMC Med*. 2013;11:129. doi:10.1186/1741-7015-11-129.

DSM-5 and ICD-10 Identify Cognitive Symptoms as Criteria for Depression

- **Five (or more) of the following symptoms have been present during the same 2-week period** and represent a change from previous functioning; at least one of the symptoms is either **(1) depressed mood or (2) loss of interest or pleasure.** **Note:** Do not include symptoms that are clearly attributable to another medical condition.
  - **Depressed mood most of the day**, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (**Note:** In children and adolescents, can be irritable mood.)
  - **Markedly diminished interest or pleasure** in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
  - **Significant weight loss** when not dieting or weight gain (e.g., change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (**Note:** In children, consider failure to make expected weight gain.)
  - **Insomnia or hypersomnia** nearly every day.
  - **Psychomotor agitation or retardation** nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
  - **Fatigue or loss of energy** nearly every day.
  - **Feelings of worthlessness or excessive or inappropriate guilt** (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
  - **Diminished ability to think or concentrate**, or indecisiveness, nearly every day (either by subjective account or as observed by others).
  - **Recurrent thoughts of death** (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

- The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The episode is not attributable to the physiological effects of a substance or another medical condition.
- The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
- There has never been a manic episode or a hypomanic episode.



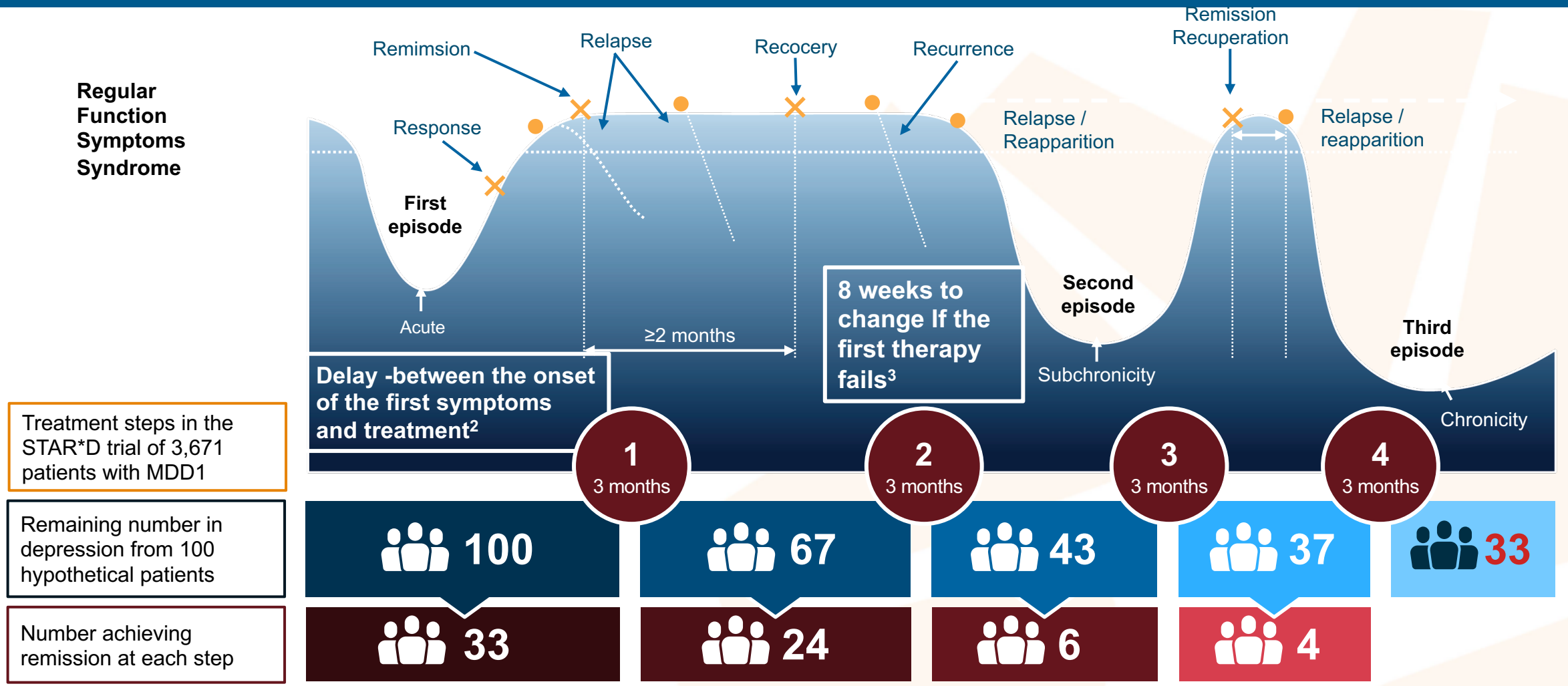


DSM-5, Diagnostic and Statistical Manual of Mental Disorders 5th Edition; ICD-10, International Classification of Diseases 10th Revision;

1. American Psychiatric Association. DSM-5. American Psychiatric Publishing, 2013;

2. WHO. ICD-10. 2010. Available at: http://apps.who.int/classifications/icd10/browse/2010/en

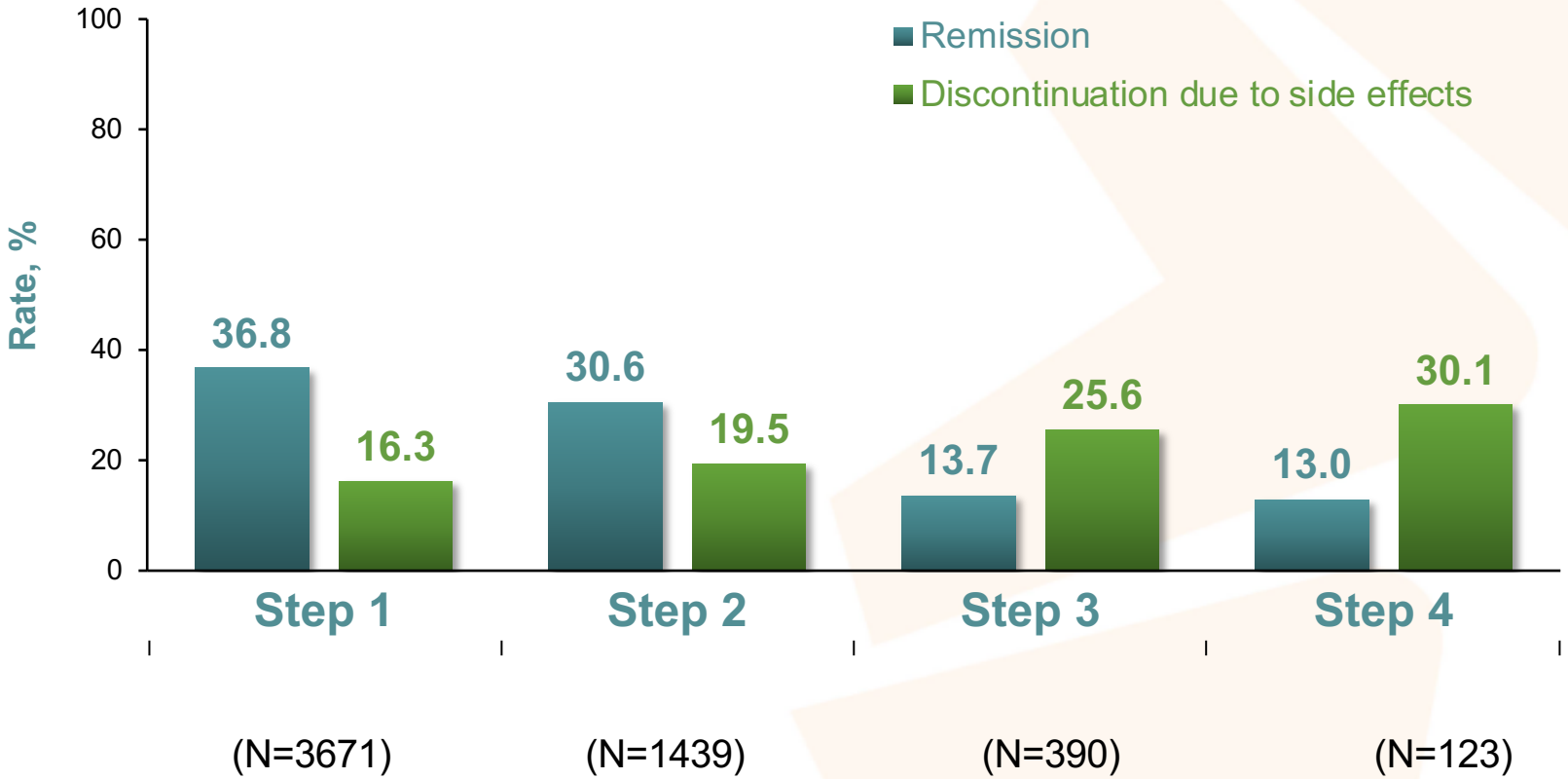
MDD Clinical Course



STAR*D, Sequenced Treatment Alternatives for Alleviating Depression. 1. Gaynes BN et al. *Cleve Clin J Med.* 2008;75:57-66; 2. Hasin DS et al. *JAMA Psychiatry*. 2018:75:336–346; 3. Patient Flow, US, IMS LifeLink November 2012 to October 2016.

Remission Rates Decreased While Discontinuation Due to Side Effects 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 Study



Each step of therapy included options to switch or augment.

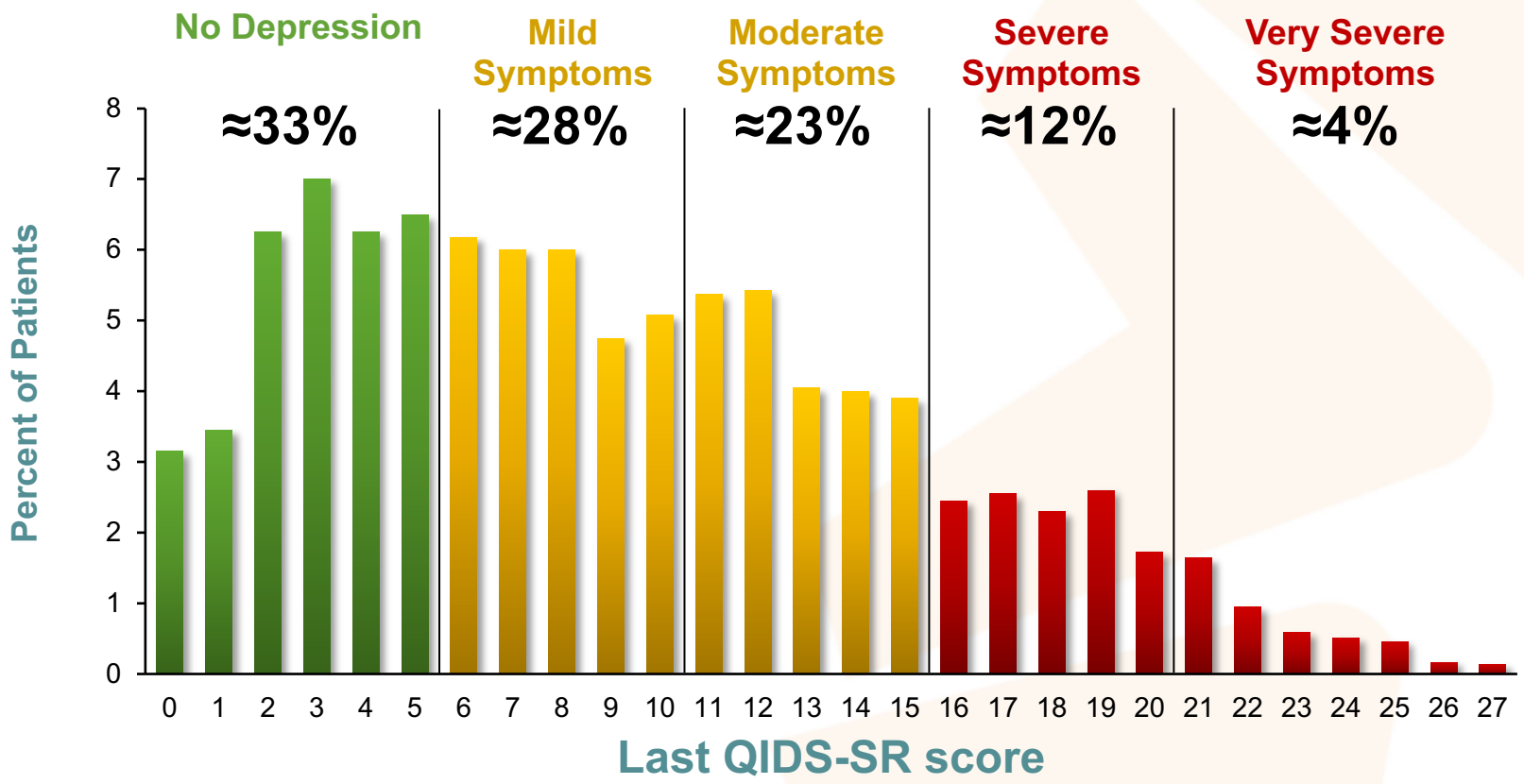
Options included various SSRIs, SNRIs, lithium, T_3, and cognitive therapy.

SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; STAR*D = Sequenced Treatment Alternatives to Relieve Depression; T_3, triiodothyronine.

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

The Majority of Patients Remained Symptomatic Despite Treatment with a First-line Antidepressant Monotherapy

Total distribution of exit scores on QIDS-SR for outpatients with MDD (N=2876)



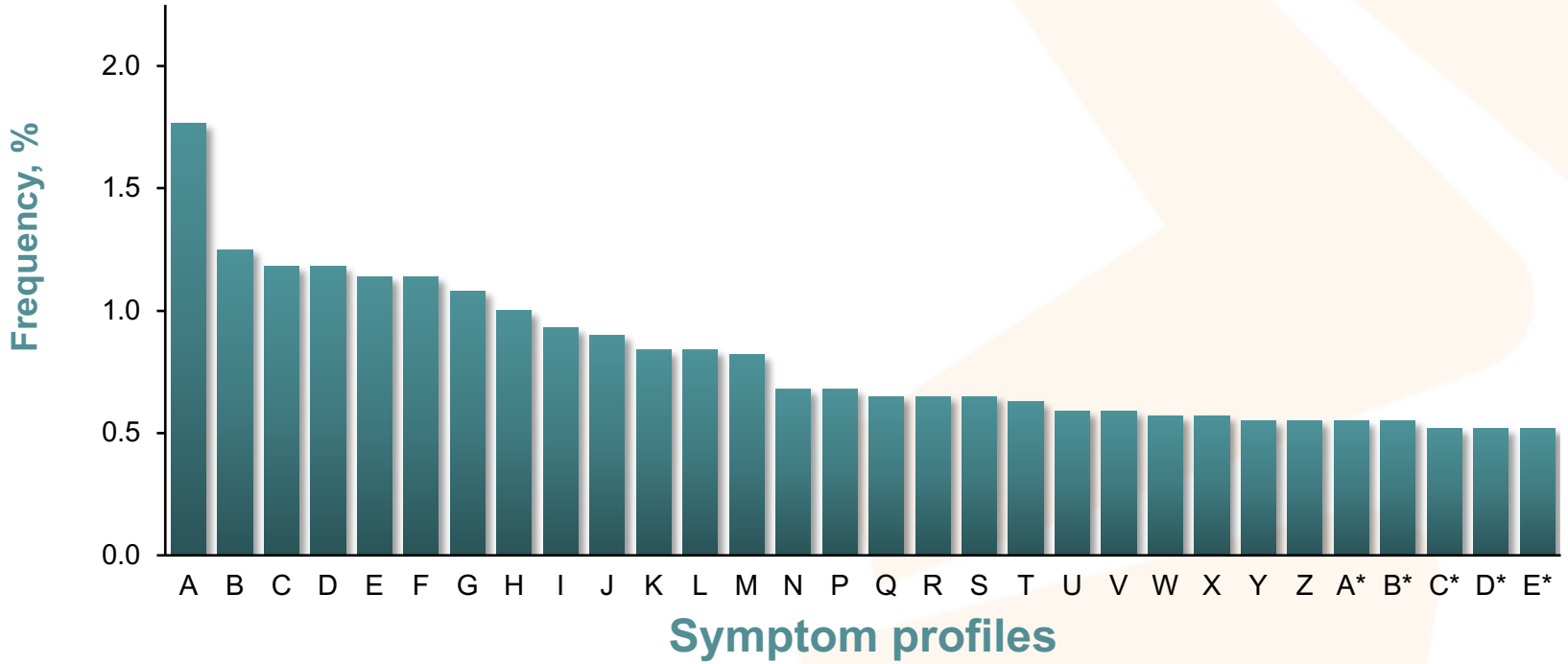
The majority of patients remained symptomatic after receiving a first-line antidepressant monotherapy for up to 14 weeks.

QIDS-SR = Quick Inventory of Depressive Symptomatology, Self-Report.

Trivedi MH et al. *Am J Psychiatry*. 2006;163(1):28-40.

Symptomatic Profiles in MDD are Highly Heterogeneous

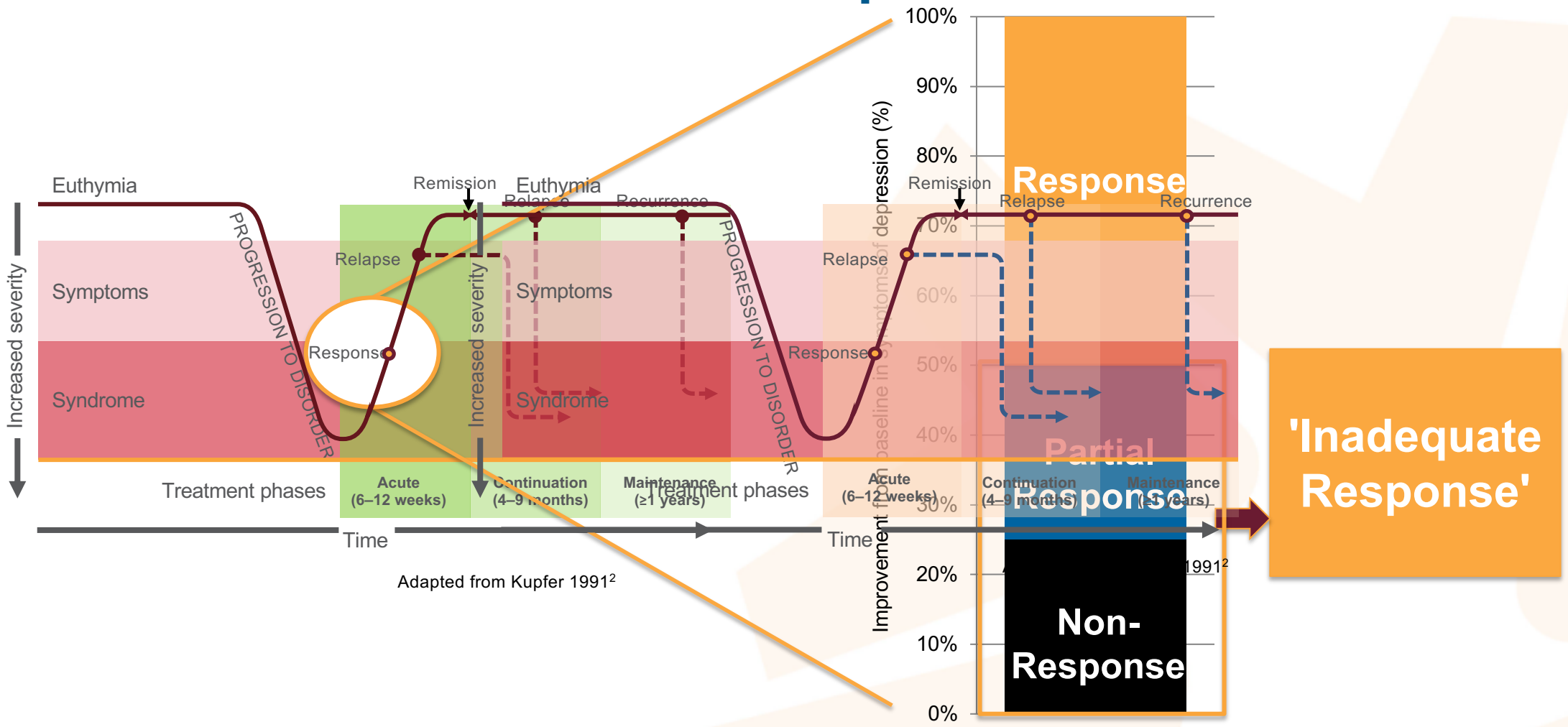
Frequency of the 30 most common depression symptom profiles at the beginning of the first treatment stage of the STAR*D study (N=3703)



Of the 1030 unique symptom profiles identified in the STAR*D study, the most common symptom profile occurred in **<2% of patients.**

Reproduced with permission from: Fried EI, Nesse RM. *J Affect Disord*. 2015;172:96-102.

Traditionally, There are Three Types of Treatment Response in MDD[1]



1. Nierenberg AA et al. *J Clin Psychiatry.* 2001;62(Suppl. 16):5–9; 2. Kupfer DJ. *J Clin Psychiatry.* 1991;52(Suppl.):28–34.

The Definition of Treatment Success in Depression Has Evolved

Response
Many symptoms remain

Remission
Some symptoms may persist

Full functional recovery
Symptoms are essentially absent; patient returns to pre-morbid functional status

1970s

Reduction of symptoms (e.g. ≥50% of MADRS or HAM-D score)[2,3]

1990s

Commonly defined as MADRS score ≤10[2] or HAM-D17 score ≤7[1,3]

Current

Direct questioning combined with a clinical impression to assess patient-specific functioning and quality of life[4]

Nearly half of depressed patients who achieve 'remission' do not consider themselves to be in remission[1,2]

MADRS=Montgomery-Åsberg Depression Rating Scale; HAM-D=Hamilton Depression Rating Scale

1. Zimmerman M, et al. *J Clin Psychiatry*. 2012;73:790–5; 2. Hawley CJ, et al. *J Affect Disord*. 2002;72:177–84; 3. Nierenberg AA, DeCecco LM. *J Clin Psychiatry*. 2001;62(Suppl 16):5–9; 4. Saltiel PF, Silvershein DI. *Neuropsychiatr Dis Treat*. 2015;11:875–88

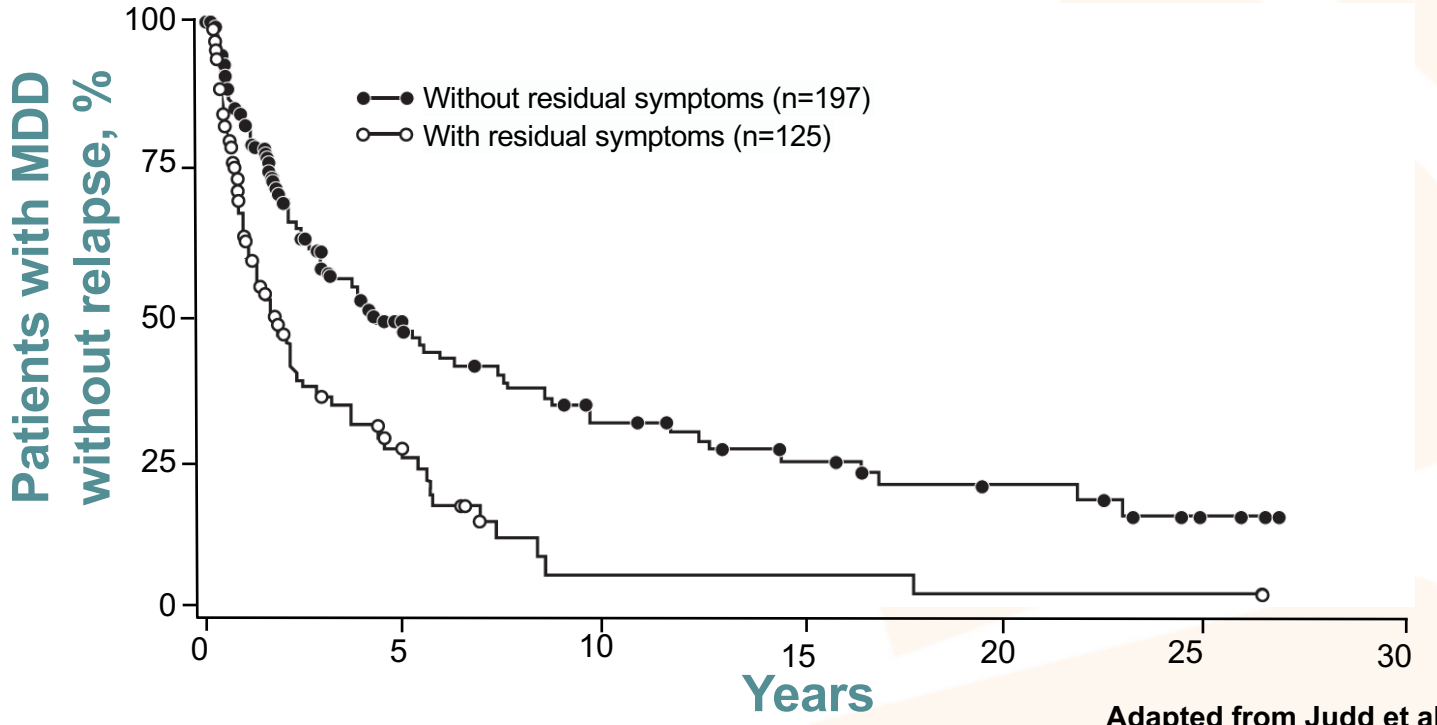
Common Residual Symptoms in Patients with MDD Despite Receiving Treatment

- Depressed mood/ Diminished interest[1,2]
- Cognitive problems[1,2]
- Insomnia[1-3]
- Fatigue[1-4]
- Anxiety[3,5]
- Anhedonia[3,4]
- Irritability[3,5]
- Dysfunctional attitude[3,5]
- Interpersonal friction[3,5]
- Inhibited communication[5]
- Social maladjustment[5]
- Change in weight/appetite[2,4]
- Guilt and lowered self-esteem[2,3]
- Excessive reactivity to social stress[3]

1. Conradi HJ, et al. *Depress Anxiety*. 2012;29(7):638-645. 2. Nierenberg AA, et al. *Psychol Med*. 2010;40(1):41-50. 3. Nierenberg AA, et al. *J Clin Psychiatry*. 2001;62(suppl 16):5-9. 4. Shelton RC, et al. *Psychiatr Serv*. 2001;52(11):1469-1478. 5. Fava GA. *Psychol Med*. 1999;29(1):47-61.

Having Residual Symptoms Can Increase Risk of Relapse, Among other Serious Consequences

Time to onset of first MDE relapse or recurrence in patients with and without residual symptoms in a 31-year longitudinal study (*P*<.0001)[1,*]



Adapted from Judd et al.[1]

Consequences of not reaching remission may include

- Recurrent episodes of MDD[2]
- Faster relapse rate[2]
- More chronic future course[2]
- Significant psychosocial disability, including work impairment[2,3]

MDE, major depressive episode.
*Open and closed circles indicate censored data.

1. Judd LL, et al. *J Clin Psychiatry*. 2016;77(8):1065-1073. 2. American Psychiatric Association. *Practice guideline for the treatment of patients with major depressive disorder, third edition*. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Published October 2010. Accessed July 14, 2017. 3. Miller IW, et al. *J Clin Psychiatry*. 1998;59(11):608-619.

MDD is Primarily Treated with Pharmacotherapy and Psychotherapy

Primary Treatment Modalities[1-3]	 Pharmacotherapy	 Psychotherapy	Pharmacological Augmentation		
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.

The Primary Targets of FDA-Approved Antidepressants are Monoaminergic

	Monoamines		
	Serotonin	Norepinephrine	Dopamine
TCAs[1-3]	✓	✓	
MAOIs[4]	✓	✓	✓
SSRIs[5]	✓		
NDRIs[6]		✓	✓
SNRIs[7]	✓	✓	
Adjunctive atypical antipsychotics[8]	✓	✓	✓
Multimodal[9]	✓		

1. Amitriptyline [prescribing information]. Sandoz Inc; 2014. 2. Norpramin [prescribing information]. Sanofi-Aventis US LLC; 2014. 3. Imipramine [prescribing information]. Excellium Pharmaceutical Inc; 2012. 4. Emsam [prescribing information]. Somerset Pharmaceuticals Inc; 2014. 5. Zoloft [prescribing information]. Pfizer Inc; 2017. 6. Wellbutrin XL [prescribing information]. Valeant Pharmaceuticals North America LLC; 2017. 7. Cymbalta [prescribing information]. Lilly USA LLC; 2017. 8. Seroquel [prescribing information]. AstraZeneca Pharmaceuticals LP; December 2009. 9. Viibryd [prescribing information]. Allergan USA Inc; 2017.

First Line Antidepressant Therapies: Current Clinical Guidelines

APA, 2010[1]

SSRI
SNRI
NDRI
NaSSA

RANZCP, 2015[2]

SSRI
NARI
NaSSA
Melatonin agonist
NDRI

CANMAT, 2016[3]

SSRI
SNRI
NDRI
Melatonin agonist
Serotonin modulator
NaSSA

NICE, TBC[4]

SSRI
TCA
Moclobemide

These recommendations are made on the basis of meta-analyses, systematic reviews, and randomised clinical trials

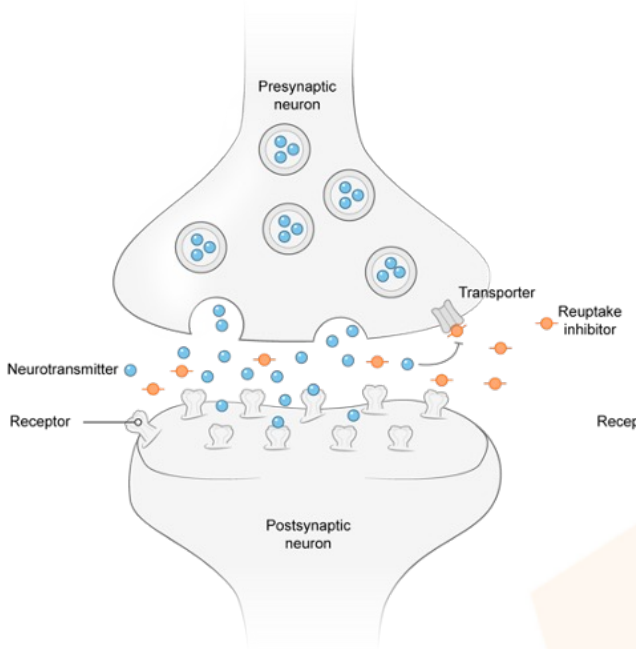
CANMAT=Canadian Network for Mood and Anxiety Treatments; NARI=selective Nor-Adrenaline Reuptake inhibitors; NaSSA=noradrenergic and specific serotonergic antidepressants; NDRI=norepinephrine–dopamine reuptake inhibitor; NICE=National Institute for Health and Care Excellence; RANZCP=Royal Australian and New Zealand College of Psychiatrists; SNRI=serotonin–norepinephrine reuptake inhibitors; TBC=to be confirmed.

1. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder. 3rd ed. Arlington, VA 2010; 2. Malhi GS, et al. *Aust NZ J Psychiatry*. 2015;49:1087–206; 3. Kennedy SH, et al. *Can J Psychiatry*. 2016;61:540–60; 4. National Institute for Health and Care Excellence (NICE) Depression in adults: treatment and management. Draft for consultation, July 2017. Available at: https://www.nice.org.uk/guidance/gid-cgwave0725/documents/short-version-of-draft-guideline-2 Last accessed September, 2022.

Monoamine-Modulating Antidepressants

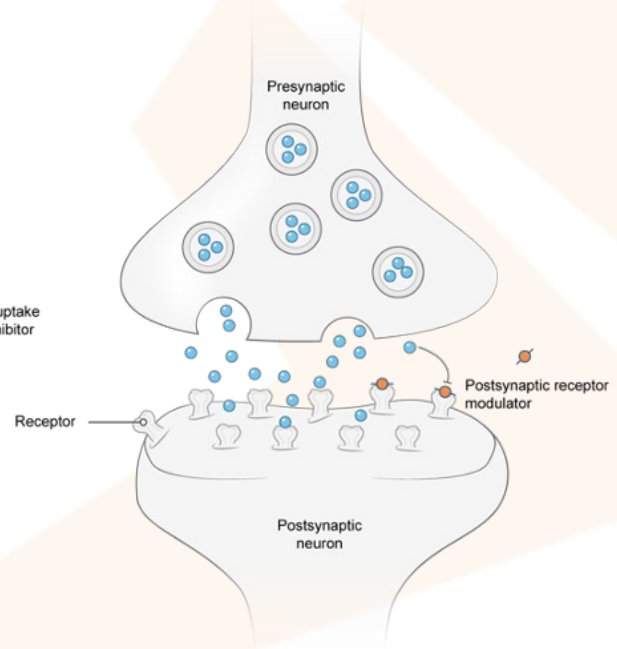
Monoamines
- Serotonin (5-HT)
- Epinephrine (E)
- Norepinephrine (NE)
- Dopamine (DA)

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]

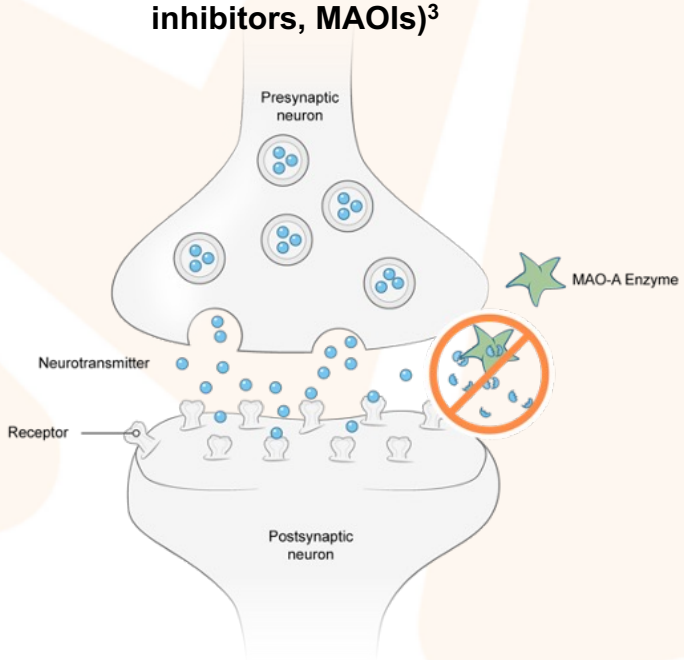


Illustration from Chamberlain SR, Baldwin DS. CNS Drugs. 2021;35(7):703-716.

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.

STAR-D Step 2: Switch or Augment?

	Response
Step 2 (N = 1439)	28.5
Switch strategy (N = 789)	27.3
Bupropion SR (N = 239)	26.1
Cognitive therapy (N = 62)	30.6
Sertraline (N = 238)	26.7
Venlafaxine XR (N = 250)	28.2
Augmentation strategy (N = 650)	29.9
Bupropion (N = 279)	31.8
Buspirone (N = 286)	26.9
Cognitive therapy (N = 85)	34.1

Response
28.5% Switch
29.9% Augment

Rush AJ, et al. *Am J Psychiatry*. 2006;163:1905.

Pharmacologic Treatments for Depression

Antidepressants

- SSRIs (fluoxetine, sertraline, paroxetine, citalopram, and escitalopram)
- SNRIs (venlafaxine, desvenlafaxine, duloxetine)
- Others (bupropion, mirtazapine, vortioxetine, vilazodone, levomilnacipran, trazodone)
- Tricyclic and tetracyclics, MAOIs

Second-generation antipsychotics (as augmentation)

Intranasal esketamine

Off-label and experimental: nutraceuticals, ketamine, pramipexole, anti-inflammatory medications

MAOI = monoamine oxidase inhibitor; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Jha MK, et al. Experimental Therapies for Treatment-Resistant Depression: Deciding When to Go to an Unproven or Experimental Therapy. *Focus*. 2018;16(3):279-284.

MDD Treatments May Not be Meeting Current Needs

- Characteristics of current medications include:
  - Delayed Onset of Action[1]
  - Delayed Functional Improvements
  - High Relapse Rates[2]
  - Low Remission Rates[2]
  - Side Effects[2]

1.Liu B, et al. *Front Cell Neurosci*. 2017;11:305 2. Rush AJ, et al. *Am J Psychiatry.* 2006;163(11):1905-1917

What Can We Aspire to for an Effective Antidepressant?

- Highly sought after characteristics[1,2]:
  - Rapid Symptom Reduction
  - Rapid Improvement in Quality of Life
  - Low Side Effect burden
  - High Remission Rates
  - Sustained Efficacy

1.Dzevlan A, et al. *Mater Sociomed*. 2019;31(1):14-18; 2.Kennedy S, et al. *J Psychiatry Neurosci*. 2002;27(4):269-280

Early, Effective Treatment is Important – An Increasing Duration of Depression has a Negative Impact on Patient Outcomes

Decreased likelihood of recovery

An increasing duration of depression reduces the probability of recovery[2,3]

Increased comorbidities

Untreated symptoms of depression predict future cardiovascular disease and stroke[4]

Greater risk of relapse

Chronic mood symptoms lasting for 2 years or longer may double the risk of relapse[2]

Impaired functioning

Workers with persistent depression are seven times more likely to be less effective at work[5]

1.McIntyre RS, et al. *Can J Psychiatry.* 2004;49(Suppl. 1):10S–16S; 2.Lin E, et al. *Arch Fam Med.* 1998;7:443–449; 3.Keller M, et al. *Arch Gen Psychiatry.* 1992;49:809–816; 4.Tranter R, et al. *J Psychiatry Neurosci.* 2002;27:241–247; 5.Druss B, et al. *Am J Psychiatry.* 2001;158:731–734.

Consequence of Lingering Depression

In a prospective, longitudinal, observational study, patients with early response to treatment (≥50% reduction from baseline in the 17-item Hamilton Depression Rating Scale [HAMD-17] total score after 6 weeks of antidepressant treatment) had a ≥4-fold higher likelihood of achieving remission (HAMD-17 total score ≤7) in the first 6 months and remaining in remission until the end of the 12-month follow-up period compared with patients who failed to achieve early response[1].

Patients who experience a shorter time to response and/or remission experience fewer mental, physical, and financial hardships compared with those who experience a longer time to response/remission[2-5].

In a literature analysis examining the timing of onset of effect of SOC treatment options for MDD, improvements in treatment outcomes (mean change from baseline [CFB] in HAMD-17 scores [164 studies], response [105 studies], and remission [69 studies]) were generally observed between 1 and 6 weeks after starting SOC therapy (6). However, treatment efficacy was lower at earlier timepoints, with approximately 51% of maximum mean CFB, 23% of maximum response, and 19% of maximum remission achieved by Week 2, compared with the maximum improvement observed at Week 10.

Treatment benefits for most patients stabilized after Week 5 or Week 6, and the interval between starting treatment and achieving maximal effect suggests an opportunity to benefit from treatments that achieve maximal effect at earlier timepoints[6].

1.Ciudad A, et al. ***J Clin Psychiatry*****. 2012 Feb;73(2):185-91. doi: 10.4088/JCP.10m06314. Epub 2011 Oct 4. PMID: 22053897; 2.Arnaud A, et al.** ***J Affect Disord.*** **2021 Apr 15;285:112-119. doi: 10.1016/j.jad.2021.02.027. Epub 2021 Feb 10. PMID: 33640861; 3.Nierenberg AA, et al.** ***Psychol Med*****. 2010 Jan;40(1):41-50. doi: 10.1017/S0033291709006011. Epub 2009 May 22. PMID: 19460188; PMCID: PMC5886713; 4.Romera I, et al.** ***BMC Psychiatry*****. 2013 Feb 11;13:51. doi: 10.1186/1471-244X-13-51. PMID: 23398902; PMCID: PMC3575400; 5.Rush AJ, et al.** ***Am J Psychiatry*****. 2006 Nov;163(11):1905-17. doi: 10.1176/ajp.2006.163.11.1905. PMID: 17074942; 6.Smith KS, et al.** ***Nutritional Neuroscience*****. 2021;24(12):963-977. doi: 10.1080/1028415X.2019.1701220.**

HRQoL in Patients who Fail Multiple Treatments

Prolonged treatment and time to remission also have effects on the patient's health-related quality of life (HRQoL), negatively affecting their employment, education, relationships, and self-care[1-3].

Although a return to a usual level of functioning is rated by patients as one of the most important goals of treatment (American Psychiatric Association, 2010), ≥50% of patients experience severely impaired HRQoL after trying multiple lines of therapy[4].

An increased number of treatment steps and time to remission are also associated with higher incidence of concurrent psychiatric disorders (obsessive-compulsive disorder, posttraumatic stress disorder, anxiety, panic disorder, and social phobia) and decreased patient well-being and functioning[5].

Patients who do not experience early remission (not meeting MDD criteria per DSM-IV-TR and HAMD-17 ≤7 during the first 6 weeks of antidepressant treatment) may require 1 year to regain average normal functioning, whereas those achieving early remission may achieve normal functioning as quickly as 6 weeks[6].

HRQoL = health-related quality of life.

1.American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders: Fifth Edition. Arlington, VA: American Psychiatric Association, 2013; 2.Esch, T. (2014). The Neurobiology of Meditation and Mindfulness. In: Schmidt, S., Walach, H. (eds) Meditation – Neuroscientific Approaches and Philosophical Implications. Studies in Neuroscience, Consciousness and Spirituality, vol 2. Springer, Cham. https://doi.org/10.1007/978-3-319-01634-4_9; 3.Proudman D., et al. Pharmaco Economics. 2021;39:619–625. https://doi.org/10.1007/s40273-021-01040-7; 4.IsHak et al. Acta Psychiatrica Scandinavica. January 2015;131(1):51-60; 5. Rush AJ, et al. Am J Psychiatry. 2006 Nov;163(11):1905-17. doi: 10.1176/ajp.2006.163.11.1905. PMID: 17074942; 6. Ciudad A, et al. J Clin Psychiatry. 2012 Feb;73(2):185-91. doi: 10.4088/JCP.10m06314. Epub 2011 Oct 4. PMID: 22053897.

Consequences of Not Having Rapid Effect

- Risk of suicide
- Nonadherence
- Treatment costs
- Greater disease burden

Underlying Biological Processes and Potential Intervention Points

Reward Biology

Neurotransmitter Dysregulation

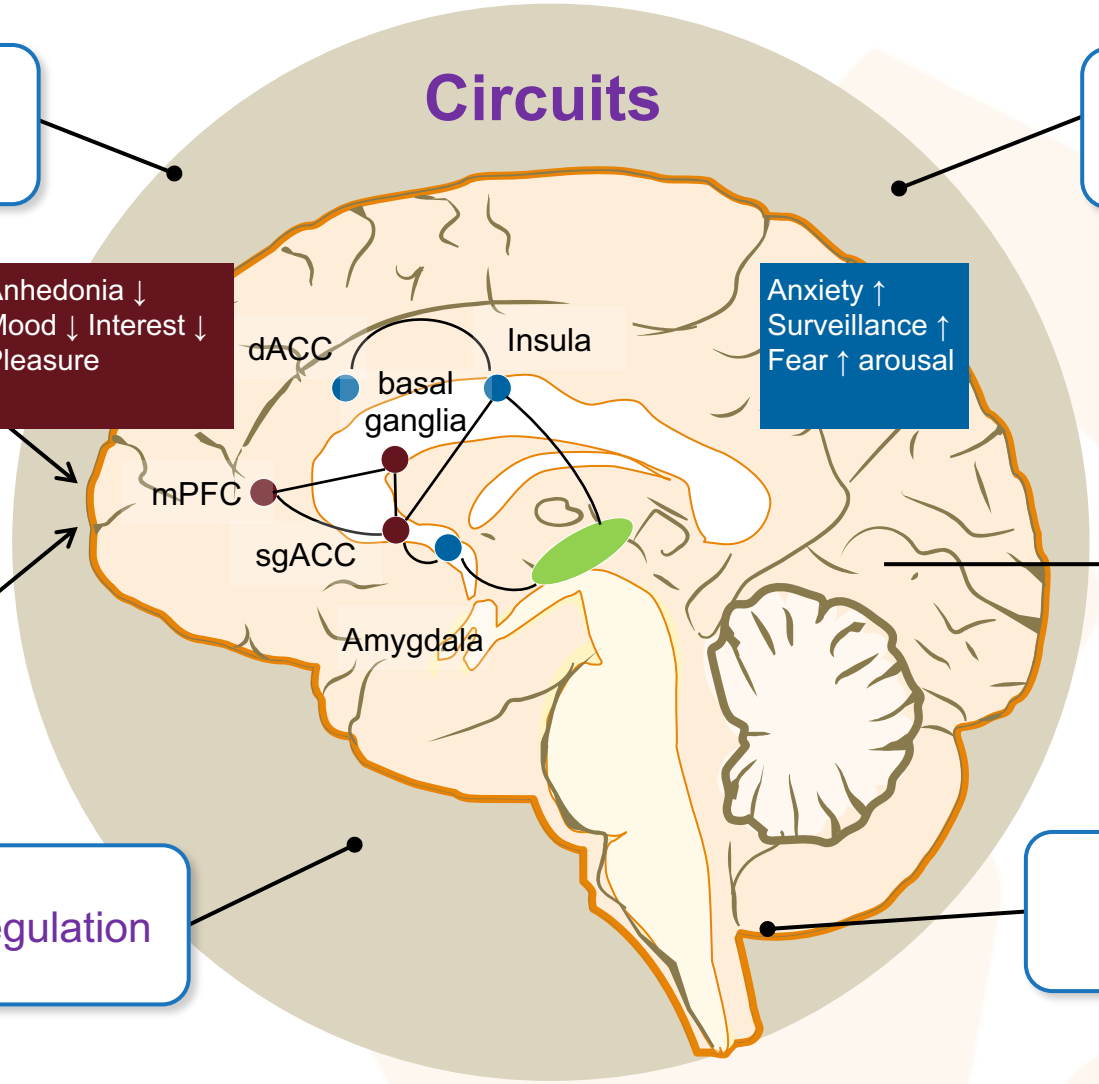
Environmental

Genetics

Glutamate Dysregulation

Neuroinflammation / Biology of Stress

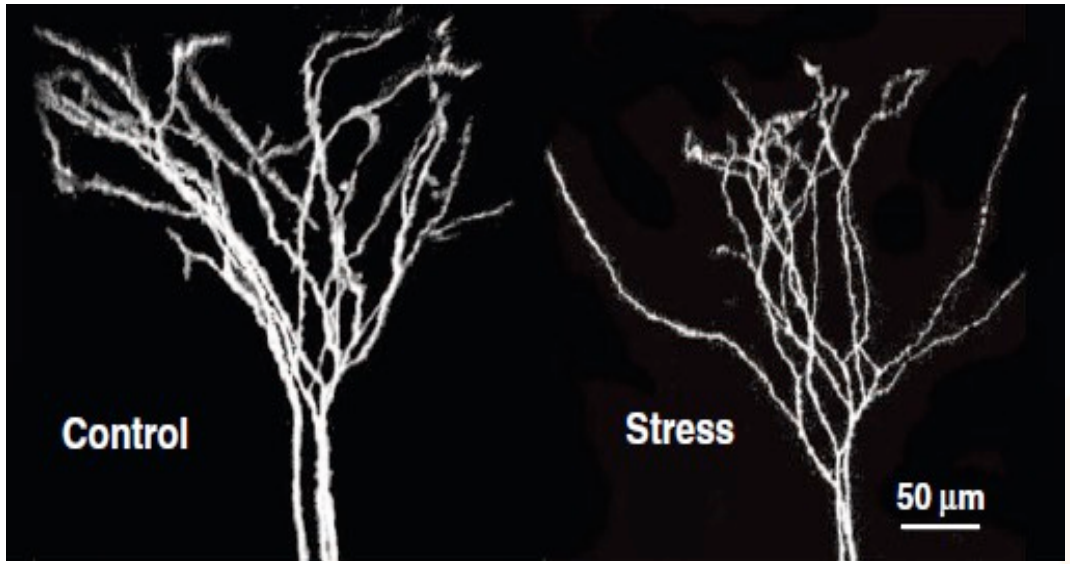
Symptoms



dACC = dorsal anterior cingulate cortex; mPFC = medial prefrontal cortex; sgACC = subgenual anterior cingulate cortex

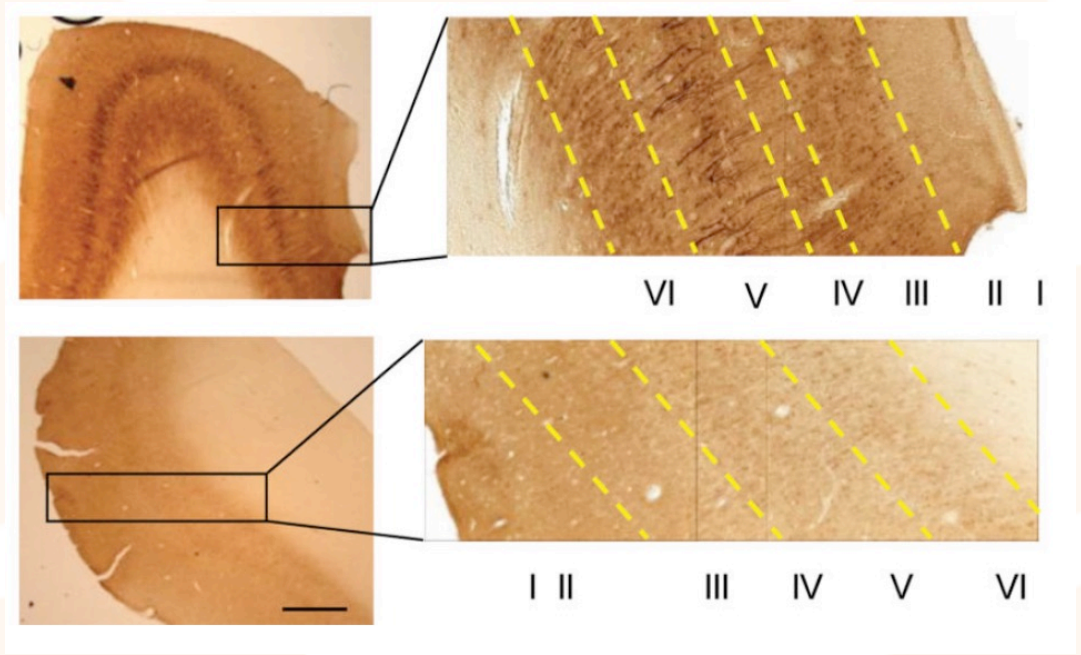
Reduced Neuronal Plasticity and Synaptogenesis are Associated with Depressive States and MDD

Chronic stress, as a model for depression, reduced dendrite length and branching in the PFC of rodents[1]



Reproduced with permission from Duman et al.[1]

Number of dendritic branches were decreased in the dlPFC of patients with MDD[2]



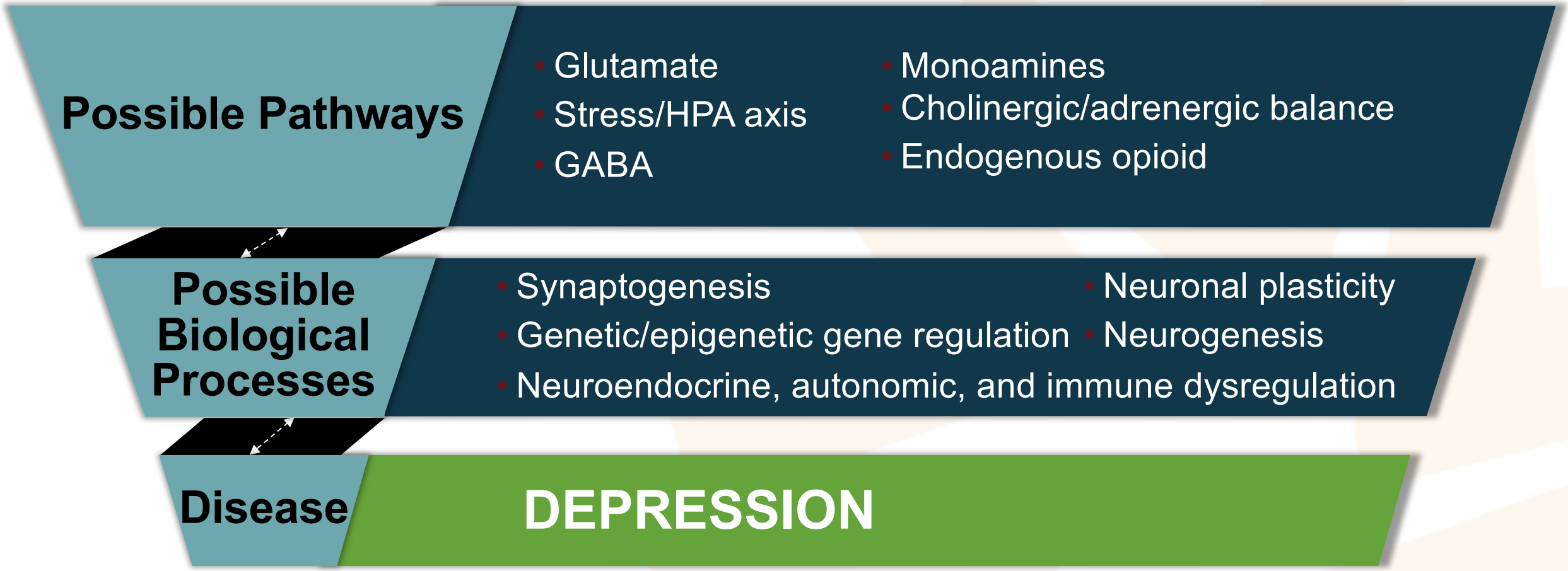
MAP2 antibody was used to label dendrites in postmortem human brain slices.

Reproduced with permission from Kang et al.[2]

dlPFC = dorsolateral prefrontal cortex; PFC = prefrontal cortex; MAP2 = microtubule-associated protein 2.

1. Duman RS, et al. *Science*. 2012;338(6103):68-72. 2.Kang HJ, et al. *Nat Med*. 2012;18(9):1413-1417.

Numerous Pathways and Biological Processes May be Involved in the Biology of MDD[1,2]

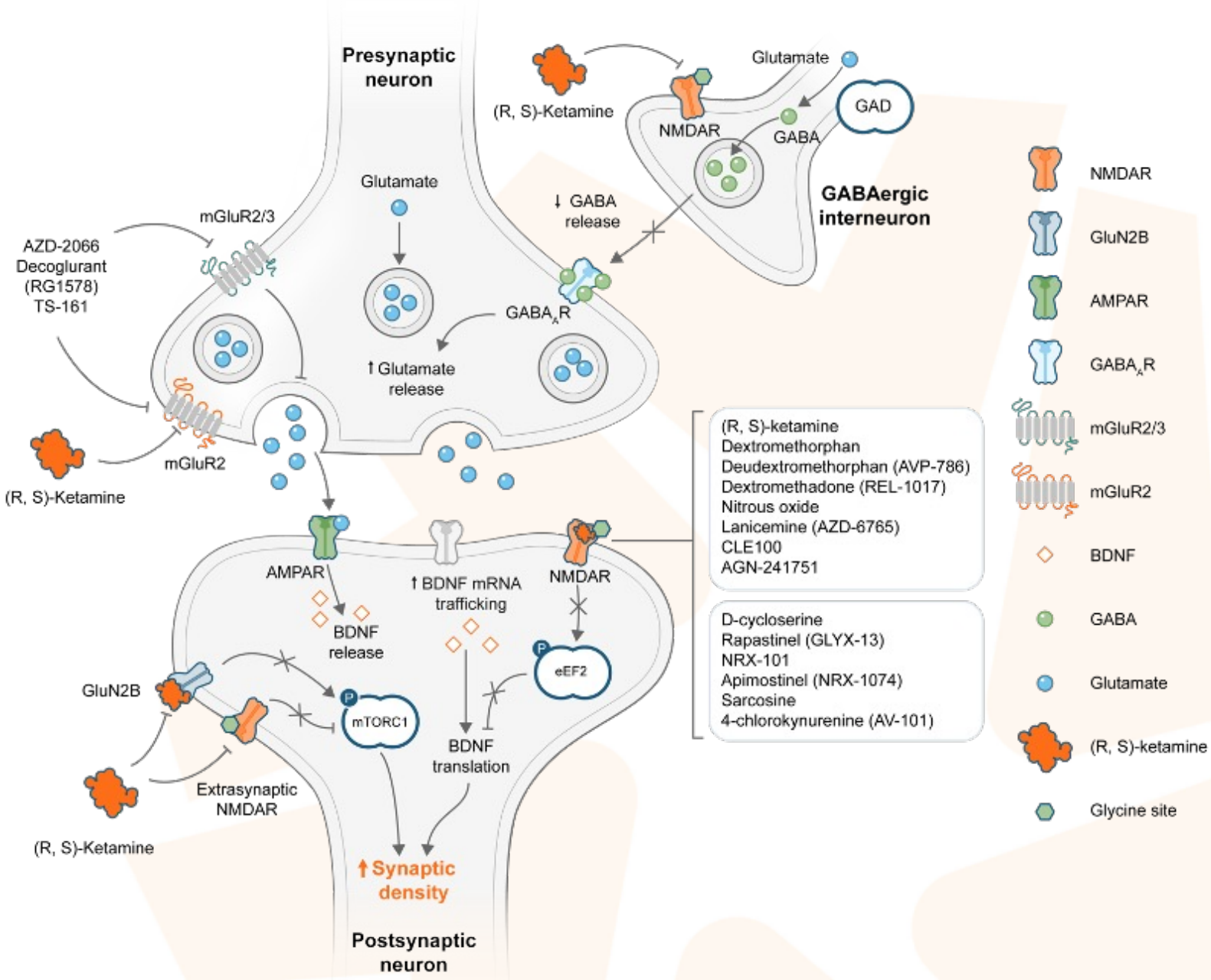


Adapted from Dale et al.[1]

GABA, gamma-aminobutyric acid; HPA, hypothalamic-pituitary-adrenal.

1.Dale E, et al. *Biochem Pharmacol*. 2015;95(2):81-97. 2.Maletic V, et al. *Front Biosci*. 2009;14:5291-5338.

Mechanism of Action of Rapid-Acting Antidepressants



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

Currently Available Treatments with Rapid Response in MDD

Agent	Class	Approval status/indication	Earliest time to efficacy	Safety concerns	Supporting references
Approved treatments					
ECT	Non-pharmacologic	Patients aged ≥13 years with severe MDE associated with MDD	Week 1	Headache, memory complaints, and elevations in heart rate and blood pressure	Husain MM et al. (Husain et al., 2004)
TMS	Non-pharmacologic	Adults with MDD who have failed 1 prior ADT	Week 1	Headache and scalp pain	Wang Y et al. (Wang et al., 2017)
Esketamine	Intranasal NMDA receptor antagonist	For use in conjunction with oral ADT in adults with TRD	Within 24 hours	Dissociative symptoms, sedation, dizziness, and abuse potential	Popova V et al. (Popova et al., 2019)
		For use in conjunction with oral ADT in adults with MDD with acute suicidal ideation or behavior	Within 4 hours		Ionescu DF, et al. (Ionescu et al., 2021); Fu DJ, et al. (Fu et al., 2020)
Aripiprazole	Second-generation antipsychotics	Adjunctive therapy in adults with MDD	Week 1	Akathisia and weight gain	Berman RM et al. (Berman et al., 2007)
Brexpiprazole	Second-generation antipsychotics	Adjunctive therapy in adults with MDD	Week 1	Akathisia and weight gain	Thase ME et al. (Thase et al., 2015)
Auvelity	Oral NMDA receptor antagonist	Adults with MDD	Week 1	Seizure, Bulimia, Dizziness, Nausea	Tabuteau, M.D. et al (Tabuteau et al, 2022)

Rapid being defined as a timeframe of < or equal to 7 days

Currently Available and Investigational Treatments with Rapid Response in MDD

Off-label treatments					
Ketamine	NMDA receptor antagonist	Treatment-resistant MDD	Within 24 hours	Dissociative symptoms, sedation, dizziness, transient blood pressure changes, and abuse potential	Murrough JW et. al. (Murrough et al., 2013)
Investigational drugs					
Psilocybin	5-HT_{2A} receptor agonist	Adults with MDD	Week 1	Headache, nausea, migraine, fatigue, feeling jittery, vomiting, palpitations, sleep disorder, and diarrhea	Davis AK et al. (Davis et al., 2021)
AXS-05	NMDA receptor antagonist	Adults with MDD	Week 1	Dizziness, nausea, headache, diarrhea, somnolence, and dry mouth	Iosifescu et al. (Iosifescu et al., 2022)
REL-1017	NMDA receptor antagonist	Adjunctive therapy in adults with MDD	Day 4	Headache, constipation, nausea, and somnolence	Fava et al. (Fava et al., 2022)
Zuranolone	$GABA_A$ PAM NAS	Adults with MDD	Day 2	Somnolence, dizziness, headache, and sedation	Gunduz-Bruce H et al. (Gunduz-Bruce et al., 2019)

5-HT_{2A} = 5-hydroxytryptamine type 2A; ADT = antidepressant therapy; ECT = electroconvulsive therapy; $GABA_A$ = gamma aminobutyric acid type A; MDD = major depressive disorder; MDE = major depressive episode; NAS = neuroactive steroid; NMDA = N-methyl-D-aspartate; PAM = positive allosteric modulator; TMS = transcranial magnetic stimulation; TRD = treatment-resistant depression.

Rapid being defined as a timeframe of < or equal to 7 days

Psychological Resilience in Depression

- Psychological resilience is a trait described as “adapting well in the face of adversity, trauma, tragedy, threats, or significant sources of stress” or ‘bouncing back’ from difficult experiences.”[1]
- Individuals who suffer from depression are believed to be genetically vulnerable to a chronically stressful environment, leading to impairments of GABAergic neurons, whereas individuals who are resilient to chronic stress do not experience major depression/GABAergic impairment.[2]
- In animal models, it has been shown that the functional state of GABAergic neurons in the brain correlates to resilience versus vulnerability to chronic stress for the development of major depression.[2,3]
- Because defects in GABAergic inhibition that are induced by stress create a self-perpetuating cycle, mechanisms such as those produced by neurosteroid antidepressants are believed to confer stress resilience.[3]

1.American Psychological Association. The road to resilience. https://www.apa.org/topics/resilience. Accessed September 27, 2022; 2.Zhu Z, et al. GABAergic neurons in nucleus accumbens are correlated to resilience and vulnerability to chronic stress for major depression. *Oncotarget.* 2017;8(22):35933-35945; 3.Lüscher B, et al. Brexanolone, a neurosteroid antidepressant, vindicates the GABAergic deficit hypothesis of depression and may foster resilience. *F1000Research.* 2019;8:751. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6544078/pdf/f1000research-8-20548.pdf. Accessed March 23, 2022.

Mechanisms that promote resilience to stress hold the promise of enabling the development of more efficacious antidepressant therapies.[1]

1 Lüscher B, et al. Brexanolone, a neurosteroid antidepressant, vindicates the GABAergic deficit hypothesis of depression and may foster resilience. *F1000Research.* 2019;8:751. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6544078/pdf/f1000research-8-20548.pdf. Accessed March 23, 2022.

The GABAergic Deficit Hypothesis

- The “GABAergic deficit hypothesis” of depression posits that defects in GABAergic and neurosteroid neural transmission may be one of the more prominent causes of MDD phenotypes.[1]
- According to this perspective, the effects of currently used monoaminergic antidepressants are the result of downstream alterations in GABAergic transmission. GABA level deficits in plasma, cerebrospinal fluid, and brain concentration, as shown by proton magnetic resonance spectroscopy, have been reported in patients with MDD in support of this theory.[1]
- While genetic links have been associated with GABA-A receptor dysfunctions, modulation of these receptors by chronic stress, both in early life and adulthood, seems to represent a major risk factor of depressive disorders.[2]

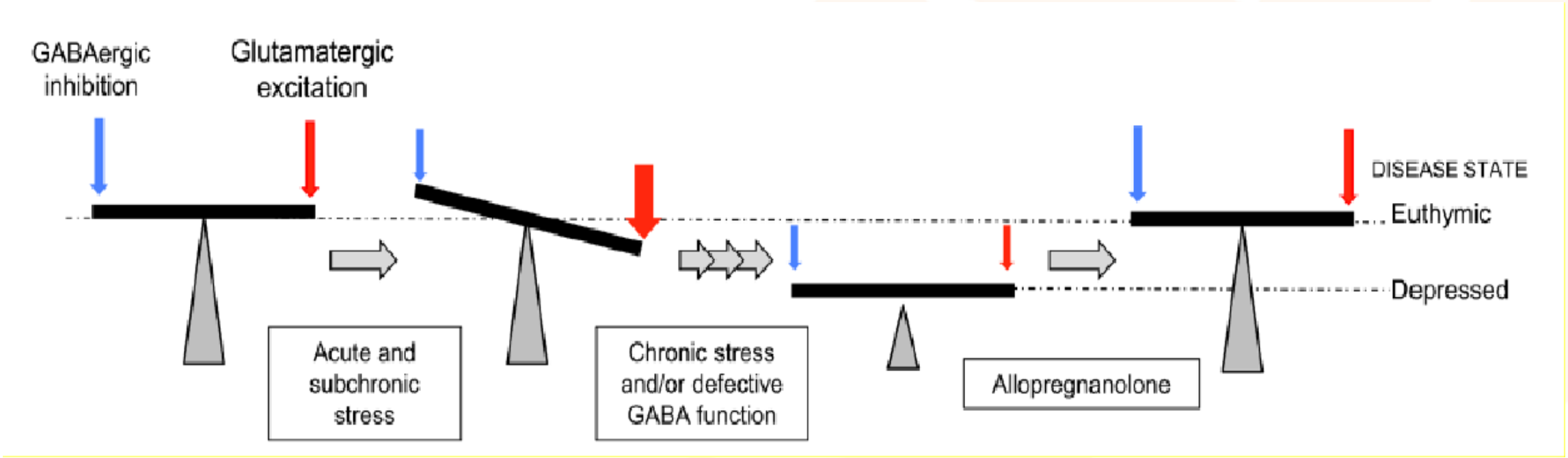
1.Luscher B, et al. The GABAergic Deficit Hypothesis of major depressive disorder. *Mol Psychiatry.* 2011;16(4):383- 406; 2.Lüscher B, et al. Brexanolone, a neurosteroid antidepressant, vindicates the GABAergic deficit hypothesis of depression and may foster resilience. *F1000Research.* 2019;8:751. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6544078/pdf/f1000research-8-20548.pdf. Accessed March 23, 2022.

The Role of Neurosteroids in GABAergic Transmission

- Neurosteroids, which are synthesized in the central nervous system by glia cells and neurons, are known to moderate nervous system function, inflammation and neuroplasticity.[1]
- Multiple neurosteroids have been identified, but currently allopregnanolone is of the greatest interest because of its role in MDD.[1]
- Allopregnanolone is a potent positive allosteric modulator (PAM) of GABA-A receptors, enhancing the efficacy of GABA.[1]
- Chronic stress reduces serum and brain levels of allopregnanolone in animal models.[2]
- In patients with MDD, allopregnanolone levels were reduced in both plasma and cerebrospinal fluid, and selective serotonin reuptake inhibitors and other antidepressants have been shown to normalize allopregnanolone levels while reducing depressive symptoms

1. Zorumski CF, Pauet al. Neurosteroids as novel antidepressants and anxiolytics: GABA-A receptors and beyond. *Neurobiol Stress.* 2019;11:100196; 2. Lüscher B, et al. Brexanolone, a neurosteroid antidepressant, vindicates the GABAergic deficit hypothesis of depression and may foster resilience. *F1000Research.* 2019;8:751. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6544078/pdf/f1000research-8-20548.pdf. Accessed March 23, 2022.

Chronic Stress and GABAergic Deficit-Induced Downregulation of Glutamatergic Transmission and Recovery By Allopregnanolone



Exogenous neurosteroids, or neuroactive steroids (NASs), have been shown to have potent GABA-A receptor effects.
Zorumski CF, et al. Neurosteroids as novel antidepressants and anxiolytics: GABA-A receptors and beyond. *Neurobiol Stress.* 2019;11:100196.

Neurosteroids in the Treatment of MDD

- Allopregnanolone agonists demonstrate a novel mechanism of action in the treatment of depressive symptoms,[1] and these agents may find a clinical role in the treatment of MDD.
- **Brexanolone** was the first NAS, or synthetic allopregnanolone, to be developed for relief from depressive symptoms and is currently approved as a treatment for postpartum depression (PPD),[1,2] Administered by intravenous infusion over 60 hours, brexanolone was shown to be effective and safe for the treatment of PPD in two 4-week clinical studies.[3]
- Brexanolone has a risk evaluation and mitigation strategy (REMS) program because of the side effects of excessive sedation and possible loss of consciousness during administration.[2]
- Brexanolone is not indicated for the treatment of MDD.[2]

1.Walkery A, et al. Review of allopregnanolone agonist therapy for the treatment of depressive disorders. *Drug Design Dev Ther*. 2021;15:3017-3026; 2.ZULRESSO (brexanolone) [package insert]. Cambridge, MA: Sage Therapeutics, Inc. Revised June 2019; 3.FDA approves first treatment for post-partum depression [press release]. U.S. Food & Drug Administration web site. Accessed September 28, 2022: https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-post-partum-depression. March Luscher B, et al. The GABAergic Deficit Hypothesis of major depressive disorder. *Mol Psychiatry.* 2011;16(4):383- 406.19,

Neurosteroids in the Treatment of MDD (cont.)

- An orally bioavailable positive allosteric modulator (PAM) of GABA-A receptors, **zuranolone** (SAGE-217) is being evaluated for the treatment of MDD.

- In the phase 3 CORAL study, zuranolone met the primary and key secondary endpoints in the treatment of patients with MDD. Reduction in depressive symptoms has been observed by day 3 in 6 out of 6 studies and has been shown to provide ongoing efficacy over the 2- weeks of administration. Zuranolone was administered to the study group with an open-label standard- of-care antidepressant (ADT) and compared with patients taking ADT + placebo. Patients in the study group demonstrated a significantly greater mean change from baseline in Hamilton Rating Scale for Depression (HAMD-17) total score of -8.9 compared with -7.0 in patients in the ADT + placebo group. The key secondary endpoint of treatment effect over the 2-week treatment period of mean change in treatment effect also was significantly greater, with a -11.7 change for patients in the study group compared with -10.1 for patients in the ADT + placebo group.[1]

- Positive results also were observed in the 1-year ongoing open-label SHORELINE study of patients with MDD. Of patients who responded to an initial 14-day course, nearly 80% only needed 1 or 2 treatment courses over the course of the year, demonstrating rapid and sustained improvements in MDD symptoms.[2]

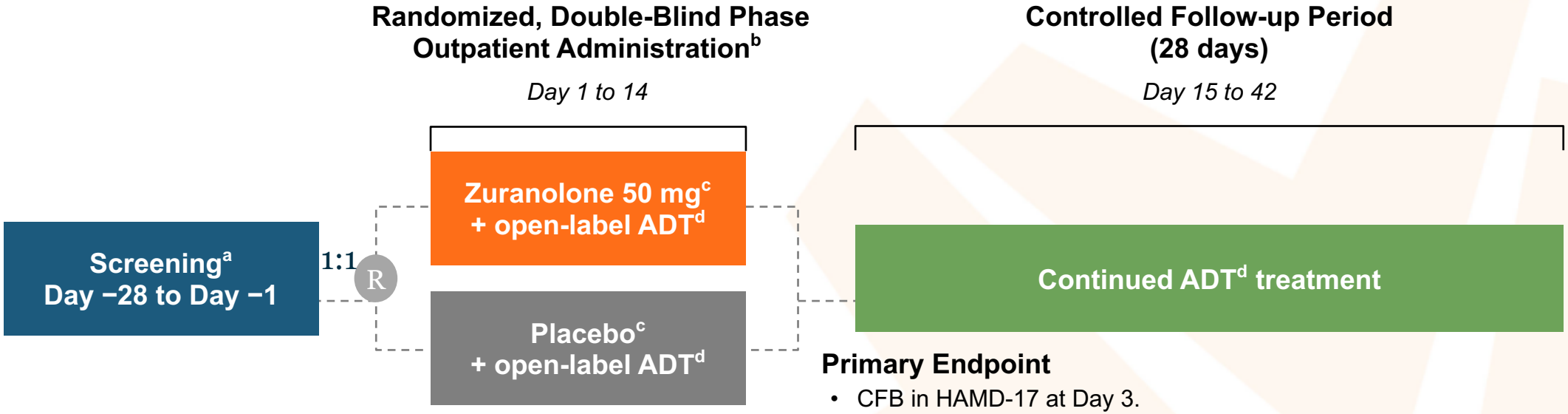
- Zuranolone was generally well tolerated in both studies. Based on these results, zuranolone may have the potential to offer more rapid relief from MDD symptoms than current standard of care.

1. Sage Therapeutics and Biogen announce the phase 3 CORAL study met its primary and key secondary endpoints—comparing zuranolone 50 mg co-initiated with standard of care antidepressant vs standard of care co-initiated with placebo in people with MDD [press release]. Biogen web site. http://media.biogen.com/news-releases/news-release-details/sage-therapeutics-and-biogen-announce-phase-3-coral-study-met. February 16, 2022. Accessed March 22, 2022; 2.Sage Therapeutics and Biogen announce positive, one-year zuranolone 50 mg data in the ongoing open-label SHORELINE study in patients with MDD [press release]. Sage Therapeutics web site. https://investor.sagerx.com/news-releases/news-release-details/sage-therapeutics-and-biogen-announce-positive-one-year. December 1, 2021. Accessed March 22, 2022.

Zuranolone

- Zuranolone is an oral positive allosteric modulator of both synaptic and extrasynaptic GABA type A receptors under investigation as a once-daily, 14-day treatment for adults with major depressive disorder and postpartum depression.
- The LANDSCAPE zuranolone clinical development program has been ongoing with the hopes of fast acting antidepressant effects.
- Across several studies, patients with MDD taking zuranolone have shown improvements in depressive symptoms in as little as 2 doses, with improvements maintained across study visits and for weeks after the end of a 14-day treatment.
- Most completed studies investigated zuranolone as a monotherapy or add-on to an existing antidepressant regimen.

CORAL Study Design



Eligibility

- Adults aged 18–64 years.
- MDD diagnosis for ≥4 weeks.
- HAMD-17 ≥24 at screening and prior to dosing on Day 1.
- No psychosis, treatment-resistant depression, or significant risk of/attempted suicide in current episode.

Primary Endpoint

- CFB in HAMD-17 at Day 3.

Key Secondary Endpoint

- CFB in HAMD-17 over the blinded treatment period, with equal weight given to each study visit at Days 3, 8, 12, and 15.

Additional Secondary Endpoints

- CFB in HAMD-17 at Day 15 and Day 42.
- HAMD-17 response (defined as ≥50% reduction in HAMD-17 from baseline at Day 15 and Day 42).
- HAMD-17 remission (defined as HAMD-17 ≤7) at Day 15 and Day 42.

Safety was assessed by the incidence and severity of TEAEs.

[a]Day −28 to Day −1 refer to timing relative to first day of dosing with zuranolone.
[b]Self-administration (zuranolone 50 mg or placebo) orally once daily in the evening with fat-containing food for 14 days.
[c]Dose reduction to 40 mg or matching placebo permitted due to perceived intolerance of higher dose, at the discretion of the investigator.
[d]ADTs were co-initiated with zuranolone 50 mg or placebo and included selective serotonin reuptake inhibitors (sertraline, escitalopram, citalopram) and serotonin and norepinephrine reuptake inhibitors (duloxetine, desvenlafaxine).
ADT = antidepressant therapy; CFB = change from baseline; HAMD-17 = 17-item Hamilton Rating Scale for Depression total score; MDD = major depressive disorder; TEAE = treatment emergent adverse event.

Patient Disposition *(all patients)*

	Zuranolone + ADT N=220	Placebo + ADT N=220
Dosed, n	212	218
Completed study, n (%)	180 (84.9)	177 (81.2)
Discontinued study, n (%)	32 (15.1)	41 (18.8)
Reasons for discontinuation, n (%)		
Withdrawal by patient	16 (7.5)	20 (9.2)
Adverse events	11 (5.2)	10 (4.6)
Lost to follow-up	4 (1.9)	7 (3.2)
Physician decision	1 (0.5)	1 (0.5)
Protocol deviation	0	2 (0.9)
Non-compliance with study drug	0	1 (0.5)

ADTs included selective serotonin reuptake inhibitors (sertraline, escitalopram, citalopram) and serotonin and norepinephrine reuptake inhibitors (duloxetine, desvenlafaxine). Zuranolone or placebo + ADT denotes co-initiation with an ADT.
ADT = antidepressant therapy.

Demographics and Patient Characteristics

	Zuranolone + ADT n=212	Placebo + ADT n=218
Age, mean ± SD, years	38.6 ± 12.7	37.7 ± 12.3
Female, n (%)	129 (60.8)	140 (64.2)
Race, n (%)		
White	153 (72.2)	168 (77.1)
Black or African American	46 (21.7)	31 (14.2)
Asian	6 (2.8)	12 (5.5)
BMI, mean ± SD, kg/m^2	29.1 ± 6.3	29.9 ± 6.4
HAMD-17, mean ± SD	26.8 ± 2.5	26.6 ± 2.6
Assigned ADT use*, n (%)		
SSRI	156 (74.3)	159 (72.9)
SNRI	54 (25.7)	59 (27.1)
History of any antidepressant use†, n (%)	115 (54.2)	120 (55.0)

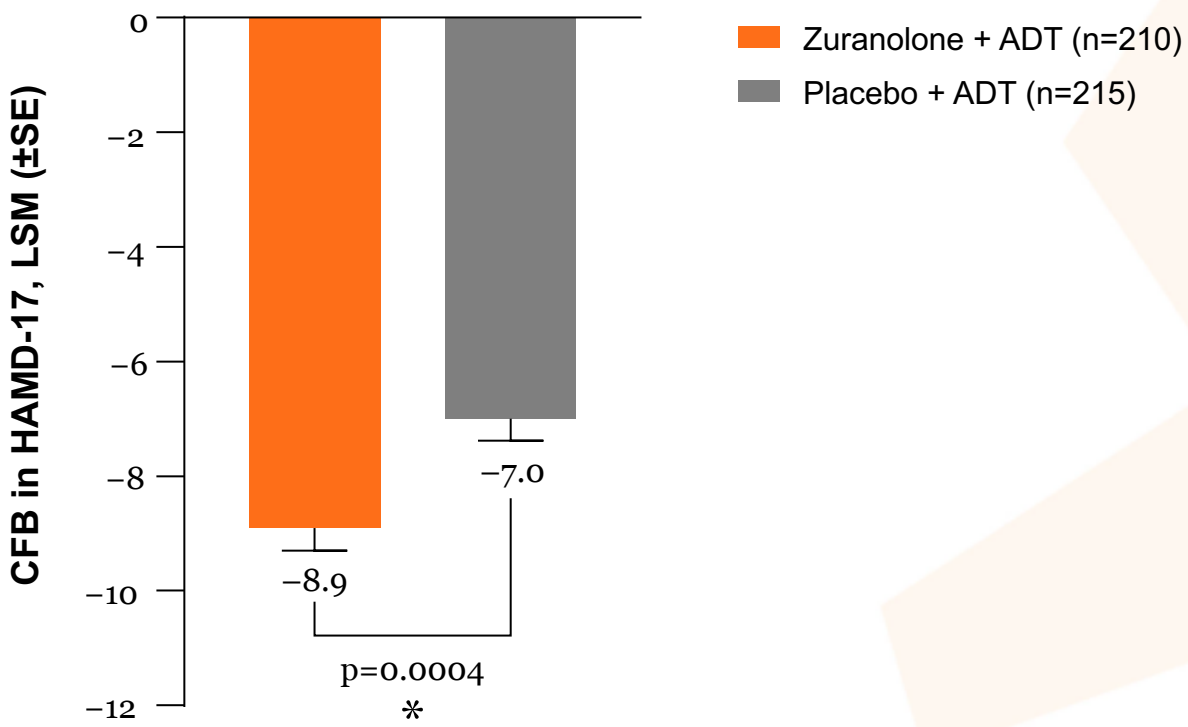
Baseline demographics and patient characteristics were comparable between the zuranolone + ADT group and the placebo + ADT group.

***SSRIs included sertraline, escitalopram, and citalopram; SNRIs included duloxetine and desvenlafaxine. †Antidepressant use was recorded within 6 months prior to screening. Zuranolone or placebo + ADT denotes co-initiation with an ADT.**

ADT = antidepressant therapy; BMI = body mass index; HAMD-17 = 17-item Hamilton Rating Scale for Depression total score; MDD = major depressive disorder; SD = standard deviation; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Primary Endpoint

Change from Baseline in HAMD-17 at Day 3 *(full analysis set)*



Patients who received zuranolone + ADT demonstrated significantly greater improvements in depressive symptoms compared with patients who received placebo + ADT at Day 3.

***p<0.05 for difference. p-values were calculated by a mixed effects model for repeated measures. The full analysis set was defined as all randomized patients administered blinded zuranolone 50 mg or placebo with a valid baseline and ≥1 valid post-baseline efficacy endpoint assessment.**

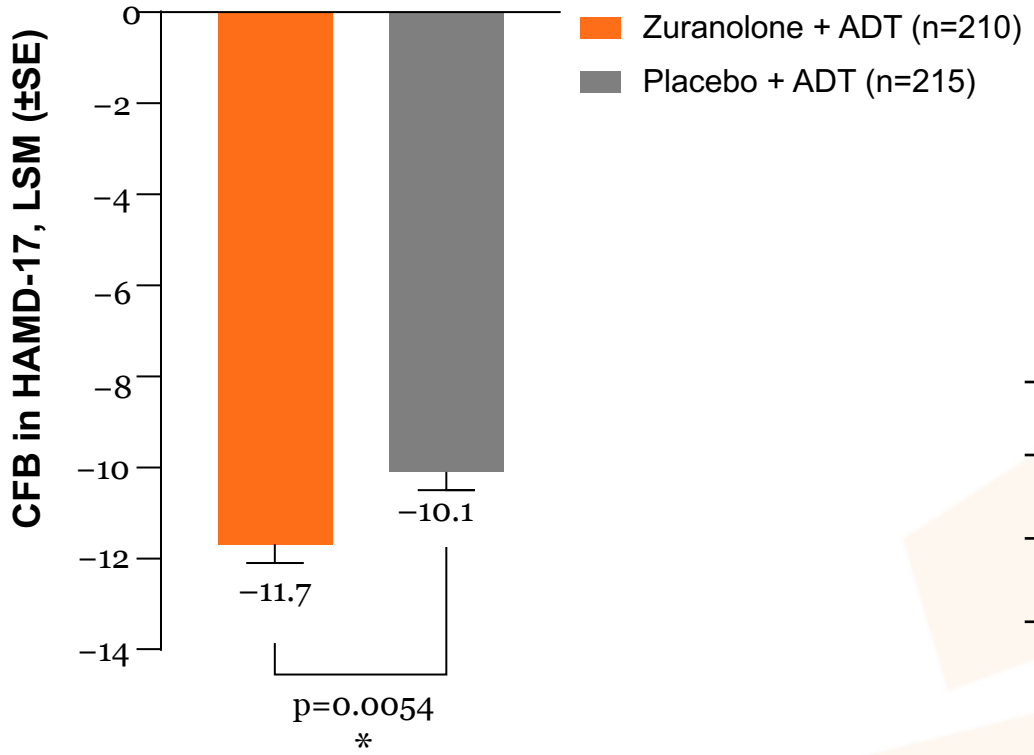
ADT = antidepressant; CFB = change from baseline; HAMD-17 = 17-item Hamilton Rating Scale for Depression total score; LSM = least squares mean; SE = standard error.

Key Secondary Endpoint

Change from baseline in HAMD-17 using equal weights over Days 3, 8, 12, and 15 *(full analysis set)*

Applied to Calculate the Key Secondary Endpoint

LSM CFB in HAMD-17 at Days 3, 8, 12, and 15[1,2]

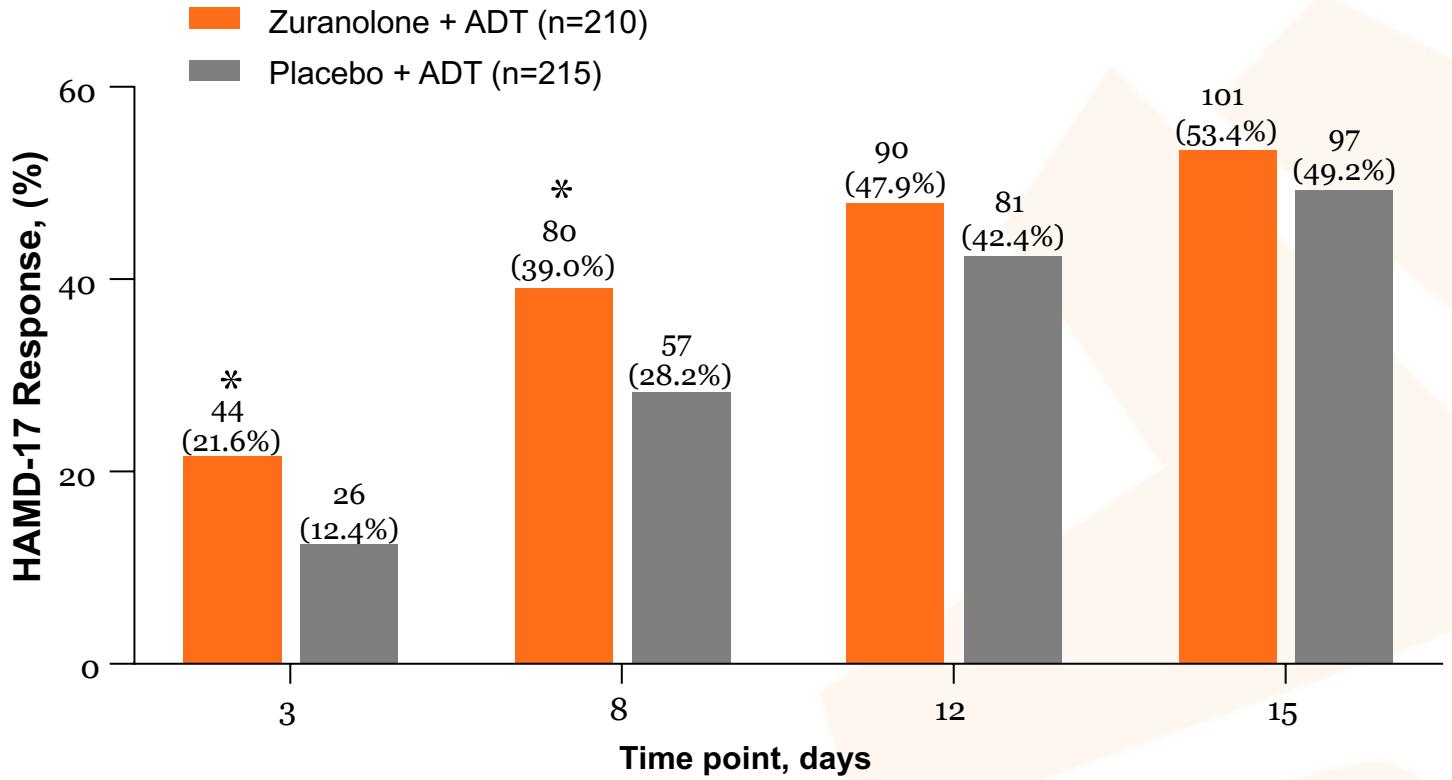


Day	Zuranolone 50 mg co-initiated with an ADT (n=210) CFB in HAMD-17	Placebo co-initiated with an ADT (n=215) CFB in HAMD-17	p-value
3	−8.9	−7.0	0.0004*
8	−11.3	−9.2	0.0012†
12	−12.8	−11.4	0.0381†
15	−13.7	−12.9	0.2477

*p<0.05 for difference. p-values were calculated by a mixed effects model for repeated measures. †Nominal p-value not adjusted for multiplicity. Equal weights were given to Days 3, 8, 12, and 15. The full analysis set was defined as all randomized patients administered blinded zuranolone 50 mg or placebo with a valid baseline and ≥1 valid post-baseline efficacy endpoint assessment.

ADT = antidepressant therapy; CFB = change from baseline; HAMD-17 = 17-item Hamilton Rating Scale for Depression total score; LSM = least squares mean; SE = standard error.

HAMD-17 Response Rate *(full analysis set)*

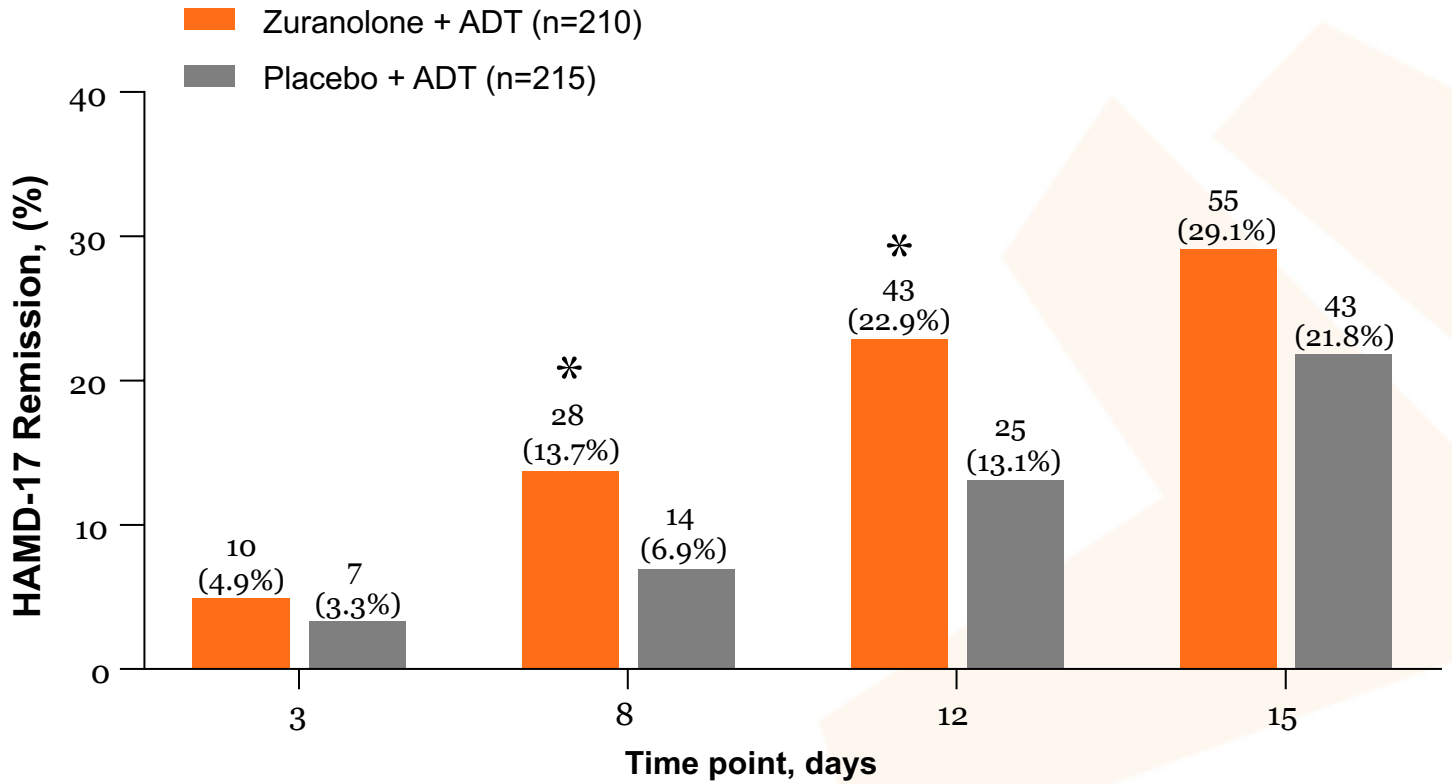


Zuranolone + ADT, n =	204	205	188	189
Placebo + ADT, n =	210	202	191	197

Patients receiving zuranolone + ADT achieved a higher rate of HAMD-17 response by Day 3 compared with patients who received placebo + ADT. A numerical advantage was maintained at all study visits in the blinded treatment period.

***p<0.05 for difference. p-values are nominal and were not adjusted for multiplicity. Response was defined as a ≥50% reduction from baseline in HAMD-17. The full analysis set was defined as all randomized patients administered blinded zuranolone 50 mg or placebo with a valid baseline and ≥1 valid post-baseline efficacy endpoint assessment.**
ADT = antidepressant; HAMD-17 = 17-item Hamilton Rating Scale for Depression total score.

HAMD-17 Remission Rate *(full analysis set)*



Zuranolone + ADT, n =	204	205	188	189
Placebo + ADT, n =	210	202	191	197

A higher proportion of patients receiving zuranolone + ADT achieved remission compared with patients who received placebo + ADT.

***p<0.05 for difference. p-values are nominal and were not adjusted for multiplicity. Remission was defined as HAMD-17 ≤7. The full analysis set was defined as all randomized patients administered blinded zuranolone 50 mg or placebo with a valid baseline and ≥1 valid post-baseline efficacy endpoint assessment.**
ADT = antidepressant; HAMD-17 = 17-item Hamilton Rating Scale for Depression total score.

Safety Summary *(safety set)*

- The majority of TEAEs in either group were mild to moderate in severity.
- Top TEAEs leading to study withdrawal:
  - Zuranolone + ADT: sedation and dizziness.
  - Placebo + ADT: diarrhea and nausea.
- No deaths were reported during the study.

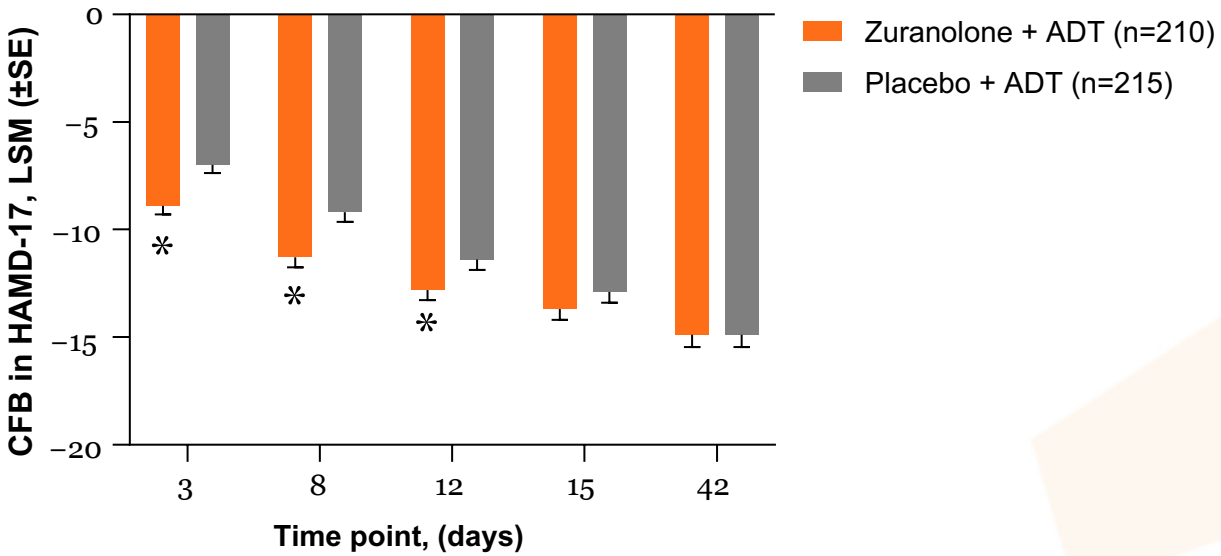
Safety parameters, n (%)	Zuranolone + ADT n=212	Placebo + ADT n=218
Any TEAE	157 (74.1)	143 (65.6)
Mild	76 (35.8)	83 (38.1)
Moderate	73 (34.4)	55 (25.2)
Severe	8 (3.8)	5 (2.3)
Dose reduction due to TEAE	20 (9.4)	6 (2.4)
Treatment discontinuation due to TEAE	9 (4.2)	7 (3.2)
Study withdrawal due to TEAE	11 (5.2)	10 (4.6)
Most common TEAEs (>5% in any group)		
Somnolence	39 (18.4)	18 (8.3)
Dizziness	28 (13.2)	16 (7.3)
Headache	25 (11.8)	32 (14.7)
Insomnia	21 (9.9)	17 (7.8)
Dry mouth	20 (9.4)	19 (8.7)
Nausea	19 (9.0)	51 (23.4)
Fatigue	18 (8.5)	11 (5.0)
Diarrhea	13 (6.1)	21 (9.6)
Decreased appetite	12 (5.7)	7 (3.2)
Sedation	12 (5.7)	6 (2.8)
Tremor	11 (5.2)	3 (1.4)

TEAEs were ordered by descending incidence in the zuranolone + ADT group. The safety set was defined as all randomized patients administered blinded zuranolone 50 mg or placebo.

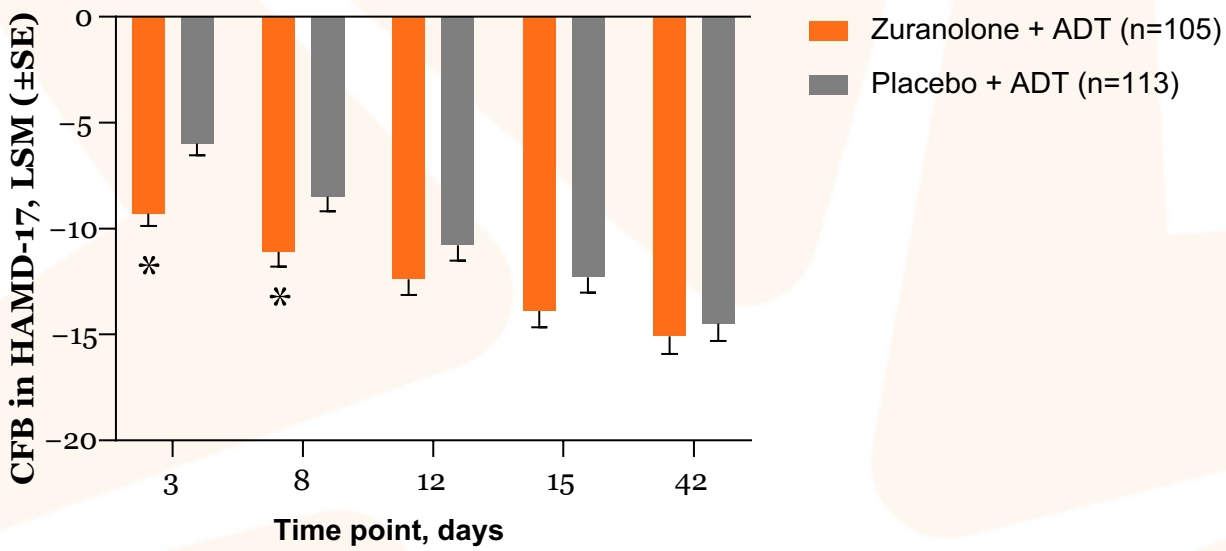
ADT = antidepressant therapy; TEAE = treatment-emergent adverse event.

CORAL Study: Analysis of MDD With Elevated Anxiety *(full analysis set)*

MDD overall



MDD with elevated anxiety HAM-A ≥20



***p<0.05 (p values are nominal and not adjusted for multiplicity, except at Day 3 for MDD overall). The full analysis set was defined as all randomized patients administered blinded zuranolone 50 mg or placebo with a valid baseline and ≥1 valid post-baseline efficacy endpoint assessment. The term "elevated anxiety" is being used only in reference to or as a symptom of depression.**
ADT = antidepressant therapy; BL = baseline; CFB = change from baseline; HAM-A = Hamilton Anxiety Rating Scale total score; HAMD-17 = 17-item Hamilton Rating Scale for Depression total score; LSM = least squares mean; MDD = major depressive disorder.

What Outcomes Are Patients Trying to Achieve? Remission from the Patient Perspective

Factors identified as "very important" by >70% of patients included

1. Presence of positive mental health (eg, optimism, vigor, self-confidence)
2. Feeling like your usual, normal self
3. Returning to usual level of function at work, home, and school
4. Feeling in control of emotions
5. Participating in and enjoying relationships with family and friends
6. Absence of symptoms of depression

Zimmerman M, et al. *Am J Psychiatry*. 2006;163(1):148-150.

Conclusions

- The CORAL study met its primary endpoint, with patients who received zuranolone co-initiated with an ADT demonstrating significantly greater improvements in depressive symptoms at Day 3 compared with those who received placebo co-initiated with an ADT.
- Zuranolone was generally well tolerated, with no new safety signals in this study compared with previous studies of zuranolone.[1–4]
- Zuranolone was effective at improving depressive symptoms in patients with MDD, including those who experienced MDD with elevated anxiety.
- The results of the CORAL study suggest that zuranolone co-initiated with an ADT may offer a more rapid improvement in depressive symptoms than ADTs alone, supporting zuranolone as a potential add-on therapy for adults with MDD.

Zuranolone is an investigational drug and is not approved by the Food and Drug Administration or any other regulatory agency as safe and effective for any use.

ADT = antidepressant therapy; MDD = major depressive disorder; SF-36v2 = 36-Item Short Form Survey version 2.

1.Gunduz-Bruce H, et al. *N Engl J Med*. 2019;381(10):903−911. 2.Clayton A, et al. Presented at: New Medication Symposium. 34th European College of Neuropsychopharmacology Hybrid Congress. Lisbon, Portugal. 2021. 3.Mittal A, et al. Poster presented at: American Academy of Neurology. 2020. 4.Cutler AJ, et al. Poster presented at: American Society of Clinical Psychopharmacology Annual Meeting; Virtual Congress. 2021.

Practical Take-Aways

- MDD is a common and disabling affliction that incurs a heavy personal and financial burden and is increasing in incidence. Despite the devastating consequences of MDD, many patients remain untreated or undertreated.
- There is a clear need for additional effective therapies with different MoAs and instances where rapidity of onset may be of crucial importance to the patient and “fast acting agents. Changes in current treatment guidelines are needed to evolve from the “start low, go slow” approach associated with the current SOC ADTs to one that focuses on rapid and sustained response. Agents that allow for rapid response in MDD present support for re-evaluation of the current standards in clinical practice.
- No single MDD treatment is effective in all patients, and the discovery of the role of GABAergic transmission in MDD pathophysiology has led to the development of new and emerging neurosteroid antidepressant drugs that improve allopregnanolone levels and reduce depressive symptoms.

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Q&A