



Exploring Treatment Options in Major Depressive Disorder (MDD) and Unmet Treatment Needs

Disease State Education

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Crisis Text Line

741-741

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Objectives

Provide a brief discussion on treatment options for MDD



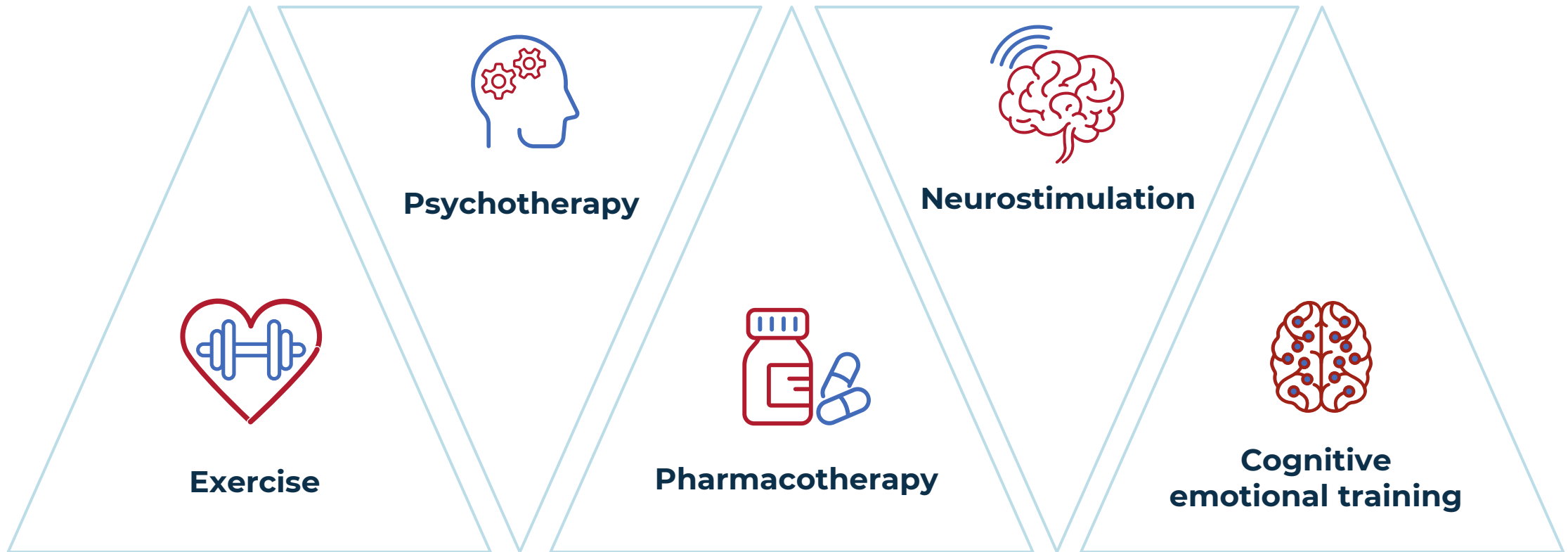
Explore the neuroplastic effects of treatments for MDD



Describe the still unmet needs for Treatment of Depression

Treatment Options for MDD

Current and Investigational MDD Treatments Span Multiple Modalities¹⁻⁴

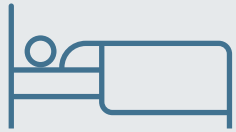


MDD, major depressive disorder.

1. Murri MB, et al. *Front Psychiatry*. 2019;9:762.
2. American Psychiatric Association. *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*. 3rd ed. 2010.
3. Müller HHO, et al. *Front Neurosci*. 2018;12:239.
4. Iacoviello BM, Charney DS. *Eur Psychiatry*. 2015;30(1):75-81.

Exercise May Help Ease Symptoms of Depression

Physical activity is good for the body *and* the brain¹



It can **improve sleep** quality and duration¹



It can help **decrease stress**¹



It can **decrease inflammation**, which has been implicated in depression^{1,2}



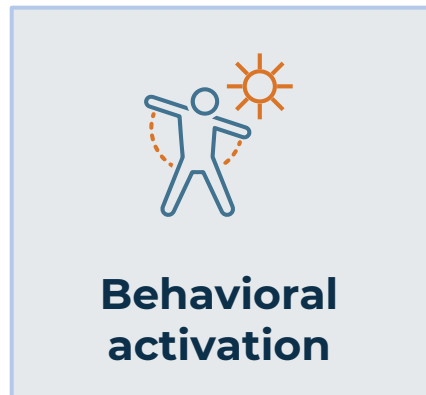
It is associated with **neuroplastic changes**²

1. Murri MB, et al. Front Psychiatry. 2019;9:762.
2. Kandola A, et al. Neurosci Biobehav Rev. 2019;107:525-539.

Psychotherapy Helps Individuals Resolve the Factors Triggering Their Depression

Psychotherapy, also known as “talk therapy,” can be delivered one-on-one, in groups, by telephone, or through the internet/apps^{1,2}

There are different types of psychotherapy, including^{1,3}:

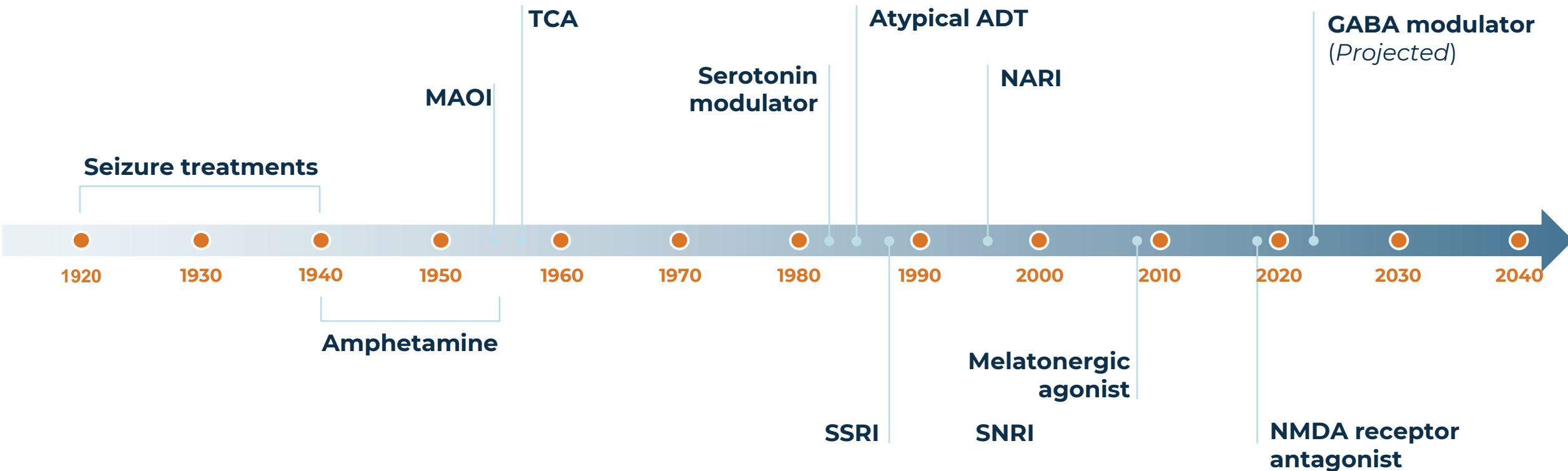


Learn more about these types of psychotherapy in the slide notes field

All of them help patients **modify their behaviors, cognition, emotions, and/or other personal characteristics** to help treat their depression¹

1. Cuijpers P, et al. *Curr Psychiatry Rep.* 2019;21(12):129.
2. National Institute of Mental Health. Accessed December 9, 2022. <https://www.nimh.nih.gov/health/topics/psychotherapies>.
3. Feldman G, et al. *Behav Ther Res.* 2009;47(4):316-321.

Pharmacologic Treatments for MDD Have Advanced Over the Last 100 Years¹⁻⁷



ADT, antidepressant therapy; GABA, gamma-aminobutyric acid; MAOI, monoamine oxidase inhibitor; NARI, noradrenaline reuptake inhibitor; NMDA, N-methyl-D-aspartate; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

1. Hirschfeld RMA. J Clin Psychiatry. 2012;73(suppl 1):5-9.
2. D'Agostino A, et al. P T. 2015;40(1):36-40.
3. Moore TJ, et al. Pharmacotherapy. 2022;42(7):567-579.
4. Formulary Watch. Accessed December 20, 2022. <https://www.formularywatch.com/view/fda-approves-rapid-acting-augmenting-for-major-depression>.

5. Pharmacy Times. Accessed December 19, 2022. <https://www.pharmacytimes.com/view/fda-to-evaluate-zuranolone-for-major-depressive-disorder-postpartum-depression>.
6. Kelland K. Reuters. October 12, 2010. Accessed February 20, 2023. <https://www.reuters.com/article/health-us-pfizer-reboxetine/pfizer-depression-drug-ineffective-may-be-harmful-study-idUKTRE69B6MR20101012>.
7. De Bodinat C, et al. Nat Rev Drug Discov. 2010;9(8):628-642.

ADT Targets the Monoamine Neurotransmitters

Second-generation ADTs are often the **first choice** for pharmacotherapy¹

Older ADTs may be **less commonly used**¹



There are different classes of ADT

SSRI²

Inhibits the reuptake of serotonin

SNRI²

Inhibits the reuptake of serotonin and norepinephrine

TCA²

Inhibits the reuptake of serotonin and norepinephrine

Serotonin modulator²

Inhibits the reuptake of serotonin; modulates serotonin receptors

Atypical ADT²

Broad class that includes drugs that do not fit into the other classes

MAOI²

Inhibits the breakdown of monoamine neurotransmitters

Examples of medications in each class are listed in the slide notes field 

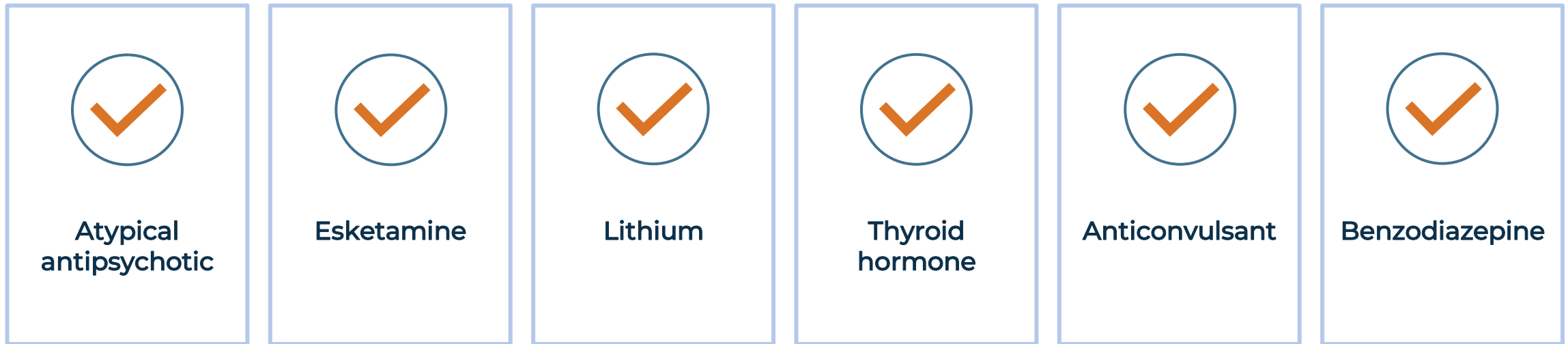
If a patient does not adequately respond to ADT, next steps for pharmacotherapy include: **increase** the dose of the ADT, **switch** to a different ADT, **combine** ADTs from different classes, or **augment** with a non-antidepressant medication²

ADT, antidepressant therapy; MAOI, monoamine oxidase inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

1. Rush AJ. UpToDate. Accessed December 9, 2022. <https://www.uptodate.com/contents/depression-treatment-options-for-adults-beyond-the-basics>.
2. Ruberto VL, et al. Pharmaceuticals (Basel). 2020;13(6):116.

Pharmacologic Augmentation Involves Adding a Non-Antidepressant Medication to Current ADT

Different agents can be used to augment ADT¹⁻³



Augmentation may provide **additive or synergistic effects** due to the different mechanisms of action⁴

ADT, antidepressant therapy.

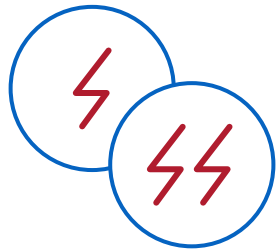
1. Taylor RW, et al. *Int J Neuropsychopharmacol*. 2020;23(9):587-625.
2. Ruberto VL, et al. *Pharmaceuticals (Basel)*. 2020;13(6):116.
3. American Psychiatric Association. *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*. 3rd ed. 2010.
4. Nelson JC, et al. *Neuropsychiatr Dis Treat*. 2008;4(5):937-948.

ADT and Psychotherapy Have Additive Effects

In a meta-analysis including 22 studies on MDD¹:



Combination therapy with ADT and psychotherapy was found to be **more effective than ADT alone** for the treatment of MDD



This effect was not associated with disease severity, which supports the use of **combination therapy even in patients with mild or moderate MDD**

ADT and CBT are associated with **unique, treatment-specific changes in brain connectivity**, providing a biological basis for combination therapy²

ADT, antidepressant therapy; CBT, cognitive behavioral therapy; MDD, major depressive disorder.

1. Cuijpers P, et al. World Psychiatry. 2014;13(1):56-67.
2. Dunlop BW, et al. Am J Psychiatry. 2023;180(3):218-229.

Neurostimulation Is an Augmenting Strategy Used for Severe or Treatment-Resistant Depression



ECT¹

- An electric current stimulates brain regions to **induce a seizure**
- It is not fully understood how this relieves the symptoms of depression



TMS

- Magnetic pulses delivered to certain regions of the brain **depolarize the brain tissue**¹
- As the primary target is the DLPFC, TMS is believed to cause **neuroplastic changes** in the **cognitive control network**²



VNS¹

- The vagus nerve is repeatedly stimulated, which **sends impulses to the brain**
- This **modulates the concentration of neurotransmitters**, making VNS **similar to ADT**

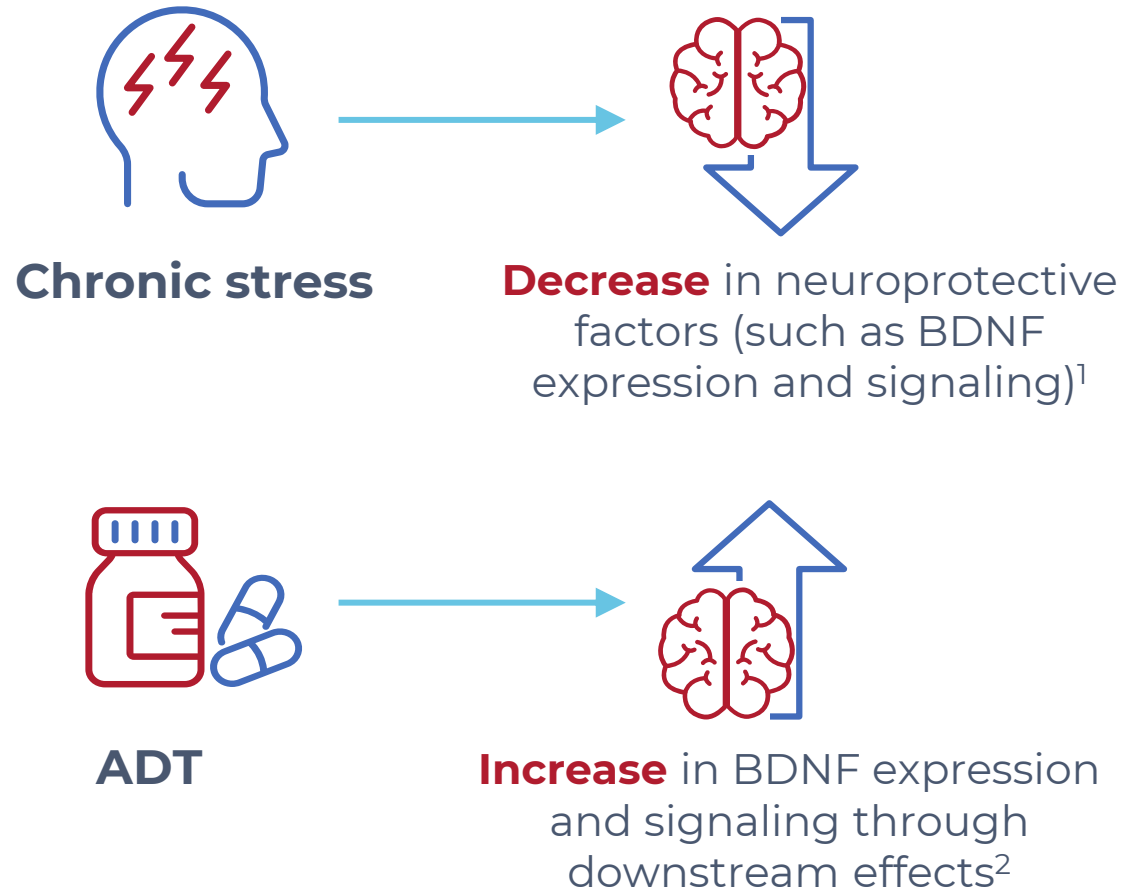
ADT, antidepressant therapy; DLPFC, dorsolateral prefrontal cortex; ECT, electroconvulsive therapy; TMS, transcranial magnetic stimulation; VNS, vagal nerve stimulation.

1. Müller HHO, et al. Front Neurosci. 2018;12:239.

2. Wilkinson ST, et al. Biol Psychiatry. 2019;85(6):454-465.

Neuroplastic Effects of Treatment

ADT May Indirectly Mitigate Maladaptive Neuroplasticity



This **indirect effect** may explain the **delayed response** to ADT that is observed in many patients²

ADT, antidepressant therapy; BDNF, brain-derived neurotrophic factor.

1. Price RB, Duman R. Mol Psychiatry. 2020;25(3):530-543.
2. Casarotto PC, et al. Cell. 2021;184(5):1299-1313.

Other Modes of MDD Treatment May Affect Neuroplasticity



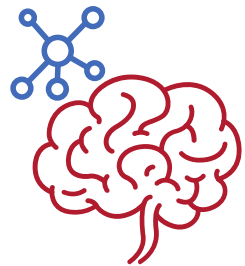
ECT¹

Changes in **hippocampal and amygdala volume, peripheral BDNF, and default mode network connectivity** have been observed



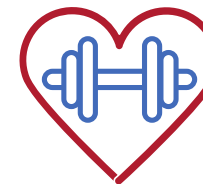
TMS¹

Hypothesized to alter activity in the **cognitive control network**



CBT²

Altered connectivity between the mPFC and ACC has been observed



Exercise³

Changes in **hippocampal function** have been observed following consistent physical activity

ACC, anterior cingulate cortex; CBT, cognitive behavioral therapy; ECT, electroconvulsive therapy; MDD, major depressive disorder; mPFC, medial prefrontal cortex; TMS, transcranial magnetic stimulation.

1. Wilkinson ST, et al. Biol Psychiatry. 2019;85(6):454-465.
2. Yoshimura S, et al. J Affect Disord. 2017;208:610-614.
3. Gourgouvelis J, et al. Neural Plast. 2017;2017:8305287. doi:10.1155/2017/8305287

Cognitive Emotional Training Is an Investigational Treatment That Leverages Neuroplasticity

Cognitive emotional training addresses the **hypoactive cognitive processing** and **hyperactive emotion processing** seen in MDD¹

In the **Emotional Faces Memory Task**, patients are asked to recognize and remember photos of emotional faces¹



This simultaneously stimulates **cognitive processing** (via demands on working memory) and **emotion processing** (from viewing emotional faces)¹



This may induce short-term **neuroplastic changes**, with altered connectivity between the **cortical and limbic brain regions**²



These changes are associated with an **improvement in depressive symptoms**²

MDD, major depressive disorder.

1. Iacoviello BM, Charney DS. *Eur Psychiatry*. 2015;30:75-81.
2. Hoch MM, et al. *Chronic Stress (Thousand Oaks)*. 2019;3:2470547019877880.

Unmet Needs in the Treatment of Depression

There Are Barriers to Accessing Mental Health Care



Shortage and uneven geographic distribution of mental health care providers^{1,2}

- **2 out of 5** Americans live in areas with a **shortage of mental health care providers**³
- **16 of 22** EU member states reported that **insufficient availability** of mental health care providers affected access to care⁴



Cost/reimbursement

- Cost to the patient¹
- Insufficient reimbursement for mental health services²



HCP time constraints

There may be insufficient time to address mental health, especially in the primary care setting¹



Stigma

Patients may avoid talking to their HCP about their mental health concerns due to stigma¹



Health disparities

Access issues may be magnified in racial and ethnic minorities, the LGBTQ community, and lower socioeconomic classes⁵⁻⁷

HCP, healthcare professional; LGBTQ, lesbian, gay, bisexual, transgender, and queer.

1. Unützer J, Park M. Prim Care. 2012;39(2):415-431.

2. Knickman J, et al. National Academy of Medicine. September 19, 2016. Accessed November 19, 2022. <https://nam.edu/wp-content/uploads/2016/09/Improving-Access-to-Effective-Care-for-People-Who-Have-Mental-Health-and-Substance-Use-Disorders.pdf>.

3. South Jersey Behavioral Health Innovation Collaborative. Accessed November 19, 2022. <http://www.njha.com/media/399452/SJBHIC-Year-One-Final-Report09092016Final.pdf>.

4. Barbato A, et al. EU Compass for Action on Mental Health and Well-Being. Accessed November 19, 2022. <https://www.lisboninstituteegmh.org/assets/files/Access%20to%20mental%20health%20care%20in%20Europe.pdf>.

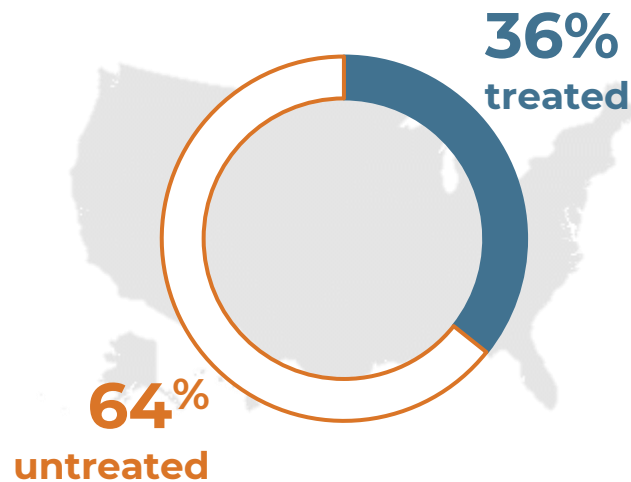
5. Blue Cross Blue Shield Association. May 21, 2022. Accessed November 19, 2022. https://www.bcbs.com/sites/default/files/file-attachments/health-of-america-report/Racial-Disparities-in-Diagnosis-and-Treatment-of-Major-Depression_2.pdf.

6. American Psychiatric Association. Accessed February 21, 2023. <https://www.psychiatry.org/File%20Library/Psychiatrists/Cultural-Competency/Mental-Health-Disparities/Mental-Health-Facts-for-LGBTQ.pdf>.

7. Sadowska K. Stanford J Public Health. 2018;7:16-18.

Individuals With MDD May Receive No or Delayed Treatment

In the US, only **1 in 3 individuals initiated ADT and/or PT** within 90 days of diagnosis^{1,a}



Minimally adequate treatment ranges from **4%** in LMICs to **23%** in HICs^{2,b}



Individuals with MDD may experience a **delay in treatment of almost 4 years**³



a, Study data were obtained from 5 US healthcare systems: Kaiser Permanente regions of Southern California, Washington, Colorado, and Hawaii, and HealthPartners in Minnesota.

b, Minimally adequate treatment represents the combination of treatment strategies established by research to be minimally sufficient in treating those with depression.

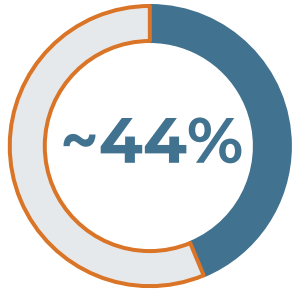
ADT, antidepressant therapy; HIC, high-income country; LMIC, low- and middle-income country; MDD, major depressive disorder; PT, psychotherapy.

1. Waitzfelder B, et al. J Gen Intern Med. 2018;33(8):1283-1291.

2. Moitra M, et al. PLoS Med. 2022;19(2):e1003901.

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

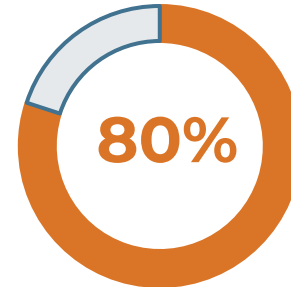
Many Patients Do Not Respond to ADT or Psychotherapy



Only **~44%** of patients using ADT for at least 3 months **are in remission**¹



The presence of **residual symptoms** is a **major predictor of relapse/recurrence**²



Relapse and recurrence rates may be as high as **80%**³



Only **~1/3** of patients **achieve remission on psychotherapy**⁴

ADT, antidepressant therapy.

1. Mojtabai R, et al. J Clin Psychiatry. 2021;82(6):21m13988.
2. Zajecka J, et al. J Clin Psychiatry. 2013;74(4):407-414.
3. Masand PS. Clin Ther. 2003;25(8):2289-2304.
4. Cuijpers P, et al. Acta Psychiatr Scand. 2021;144(3):288-299.

Nonadherence to ADT Is Common

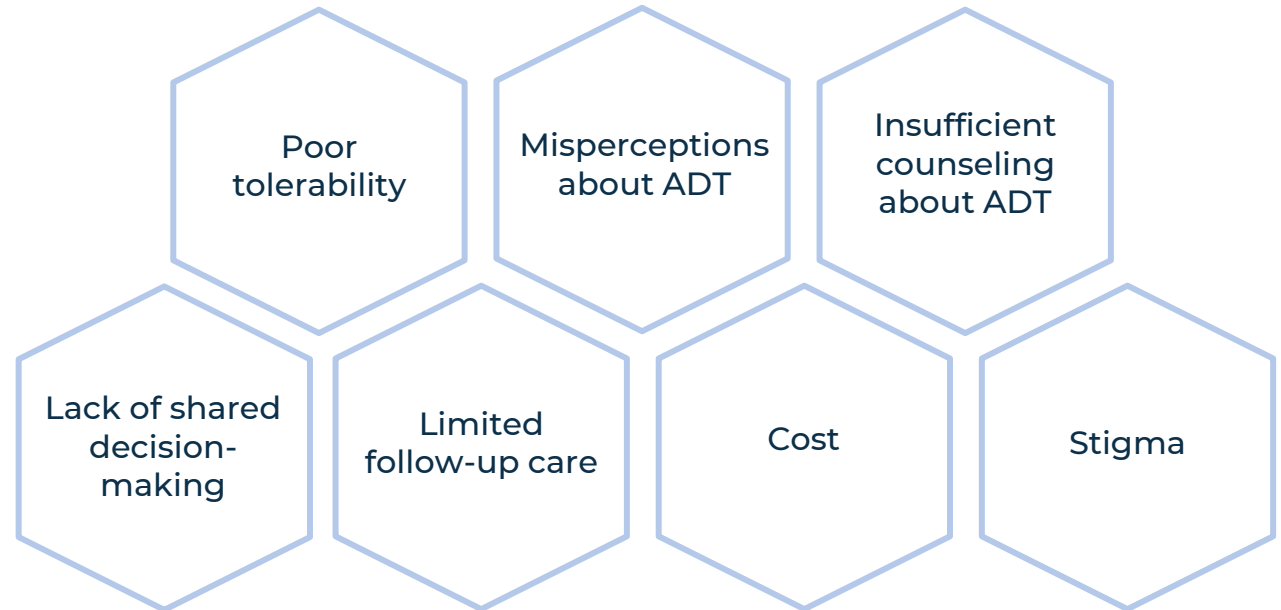
MORE THAN HALF OF PATIENTS WITH MDD HAVE POOR ADHERENCE TO ADT¹



55%

of adults discontinue ADT within **6 months²**

Patients prematurely discontinue ADT due to¹:



ADT, antidepressant therapy; MDD, major depressive disorder.

1. Dell'Osso B, et al. Ann Gen Psychiatry. 2020;19:61.
2. Bushnell GA, et al. J Affect Disord. 2016;196:138-147.

The Patient Perspective Is Often Overlooked When Defining Treatment Goals

Restoring life engagement and function is more important to patients than simply reducing symptom burden—patients want to return to their former sense of **well-being**

“

Like a light switch turned on and I had my old life back

“

I felt like myself again

“

It's like sunshine

“

I've been feeling pretty awesome; I've completed more projects in the last 2 weeks than I have in the last 5 years because I have been feeling better

The patient perspective should be factored into treatment goals and treatment selection

1. Correll CU, et al. J Clin Psychiatry. 2022;83(5):LU21112AH3.

Novel Treatment Modalities and Delivery Methods May Help Address Unmet Needs



Digital therapeutics (DTx) deliver software-based interventions to patients to treat, manage, or prevent a disease or disorder¹

DTx are backed by **clinical data and real-world evidence**

They can be used **independently or in combination with medications, devices, or other therapies**

Regulatory clearance/certification is required to support claims of risk, efficacy, and intended use



Some investigational therapies such as **cognitive emotional training** may be delivered through **DTx²**

In addition, DTx may offer **accessibility and convenience³**

1. Digital Therapeutics Alliance. November 2019. Accessed February 7, 2023. https://dtxalliance.org/wp-content/uploads/2021/01/DTA_DTx-Definition-and-Core-Principles.pdf.
2. Iacoviello BM, et al. *Depress Anxiety*. 2014;33(8):699-706.
3. National Institute of Mental Health. Accessed January 5, 2023. https://www.nimh.nih.gov/health/topics/technology-and-the-future-of-mental-health-treatment#part_2443.

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