Major Depressive Disorder (MDD)

Definium THERAPEUTICS

What is MDD?

Major Depressive Disorder, or MDD, is the second-most common mental health disorder in the U.S., with over 21 million adults experiencing a major depressive episode (MDE) each year.[1,2] This disorder, a leading cause of disability worldwide,[3] consists of depressed mood, persistent feelings of worthlessness, fatigue, and, in some instances, recurrent thoughts of death,[4] and it increases long-term mortality risk by 40%.[5]

MDD also carries a $326 billion annual economic burden in the U.S., driven by healthcare costs and lost productivity.[6]

What causes MDD?

There is no single cause of MDD, which can develop as a result of a variety of factors, including genetic, environmental, psychological, and biochemical. The risk of MDD is higher in people with a family history of depression, trauma, significant life changes, chronic stress, or serious physical illnesses like cancer and diabetes. In some cases, depression can be a side effect of certain medications.[7]

How is MDD diagnosed?

A clinician, such as a primary care doctor, psychiatrist, or psychologist, makes the diagnosis through a clinical interview and evaluation, applying recognized criteria and ruling out other medical conditions.

As defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), depression symptoms occur within the same two-week period, represent a change from the patient's previous mental state, and cause significant distress or functional impairment. Core symptoms include depressed mood or anhedonia, which is defined as markedly diminished interest or pleasure in all or almost all activities. Additional symptoms often include appetite or weight change, sleep disturbance, increased or decreased psychomotor activity, fatigue, feelings of worthlessness or guilt, poor concentration, or suicidality.[8]

The U.S. Preventive Services Task Force (USPSTF) recommends screening for depression in the adult population, including during pregnancy and the postpartum period, as well as in people who are 65 and older.

Precise science. Boundless impact.

Definium is developing a new generation of therapeutics intended to address the underlying causes of psychiatric and neurological disorders. The mission of Definium Therapeutics is to forge a new era of psychiatry by applying scientific rigor to psychedelics, with the goal of developing accessible treatments that unlock healing at scale.

Definium is currently advancing controlled clinical trials of DT120 Orally Disintegrating Tablet (ODT) – its proprietary, pharmaceutically optimized form of LSD. Currently, four Phase 3 clinical trials are underway to explore the potential of DT120 ODT for the treatment of GAD and MDD, with a fifth trial in PTSD planned, all without adjunctive psychotherapeutic interventions.

How is MDD treated?

There are a variety of treatment options that usually involve antidepressant medications, psychotherapy, and changes to day-to-day activities or some combination of the three.

While there are numerous approved medications for MDD, the treatment paradigm is characterized by critical unmet needs. Too often, existing treatments for MDD fall short, leading many patients to be treated with multiple medications without lasting relief. Fewer than one-third of patients reach remission with first-line treatments,[9] and the onset of meaningful improvement can take weeks to months,[10,11] often with poor tolerability,[12,13] and frequent switching between medications, augmentation, and discontinuation of pharmacotherapy.[14] Treatment-resistant depression (TRD), defined by the U.S. Food and Drug Administration as inadequate response to at least two antidepressants, affects at least an estimated 30% of patients with MDD.[15]

What is the relationship between MDD, Generalized Anxiety Disorder (GAD), and Posttraumatic Stress Disorder (PTSD)?

Mental health conditions like MDD, generalized anxiety disorder (GAD), and posttraumatic stress disorder (PTSD) often co-occur. More than 50% of patients with GAD also have MDD. Co-occurring MDD and GAD is associated with increases in mean annual per-patient inpatient visits, office visits, emergency department visits, annual drug costs, and total medical costs.[16] Approximately 80% of individuals with PTSD meet the criteria for another psychiatric diagnosis, underscoring the interconnection across these disorders and the urgent need for more effective treatment options.[17]

References

1. National Institute of Mental Health (NIMH). "Major Depression: Prevalence of Major Depressive Episode Among Adults." Updated 2024.
2. Substance Abuse and Mental Health Services Administration (SAMHSA). "2023 National Survey on Drug Use and Health (NSDUH)."
3. World Health Organization (WHO). "Depression Fact Sheet." Updated 2023.
4. American Psychiatric Association. "Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)." 2013.
5. Cuijpers, P., et al. "Long-Term Mortality Risk in Depression: A 20-Year Follow-Up Study." JAMA Psychiatry, 2023.
6. Greenberg, P. E., et al. "The Economic Burden of Adults with Major Depressive Disorder in the United States (2020)." Journal of Clinical Psychiatry, 2024.
7. Substance Abuse and Mental Health Services Administration. (2023, April 24). Depression. U.S. Department of Health and Human Services. https://www.samhsa.gov/mental-health/what-is-mental-health/conditions/depression
8. American Psychiatric Association. (2022). Diagnostic and statistical manual of mental disorders (5th ed., text rev.). American Psychiatric Association Publishing.
9. Hasin, D. S., et al. "Epidemiology of Adult DSM-5 Major Depressive Disorder and Its Specifiers in the United States." JAMA Psychiatry, 2018.
10. Rush, A. J., et al. "Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report." American Journal of Psychiatry, 2006.
11. APA. Practice Guideline for the Treatment of Patients with Major Depressive Disorder. Published 2010.
12. Alemi F, Min H, et al. Effectiveness of common antidepressants: A post market release study. eClinicalMedicine. 2021;41.
13. Cipriani A, et al. Comparative Efficacy and acceptability of 21 antidepressant drugs for the Acute Treatment of Adults with Major Depressive Disorder: A Systematic Review and Network Meta-analysis. Lancet. 2018;391(10128):1357-66.
14. Braund TA, Tillman G, et al. Antidepressant Side Effects and Their Impact on Treatment Outcome in People with Major Depressive Disorder: An Ispot-D Report. Transl Psychiatry. 2021;11①:417.
15. McIntyre RS, Alsuwaidan M, Baune BT, et al. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. World Psychiatry. 2023 Oct;22②:394-412.
16. Armbrecht, E., Shah, R., Poorman, G. W., Luo, L., Stephens, J. M., Li, B., Pappadopulos, E., Haider, S., & McIntyre, R. S. (2021). Economic and humanistic burden associated with depression and anxiety among adults with non communicable chronic diseases (NCCDs) in the United States. Journal of Multidisciplinary Healthcare, 14, 887–896. https://doi.org/10.2147/JMDH.S280200
17. Brady, K. T., Killeen, T. K., Brewerton, T., & Lucerini, S. (2000). Comorbidity of psychiatric disorders and posttraumatic stress disorder. Journal of Clinical Psychiatry, 61(Suppl 7), 22–32.