

# When Depression Treatment Doesn't Work

## *What is treatment-resistant depression (TRD)?*

A person may have treatment-resistant depression when two or more antidepressant medications of adequate dose and duration don't produce response or remission.

We suggest, **at a minimum**, a prior trial of:

- ▶ Two different antidepressant classes (with adequate dose and duration of each)
- ▶ Regularly recurring psychotherapy or counseling:
  - **Six or more appointments**, best with the same psychotherapy provider.
  - Appointments at **least every two weeks**.
  - For patients who have not had access to the treatments above, MHCAG recommends the above options before you choose a treatment option below.

## **TMS (Transcranial magnetic stimulation)**

An electromagnetic coil is used to generate a targeted magnetic field in areas of the brain known to be underactive in people with depression. TMS is not the same as ECT (electroconvulsive therapy).

*Details:* Treatment sessions 5 days a week for 4-6 weeks, then the frequency tapers down on a set schedule. Sessions last 30-60 minutes and patients can drive themselves. There is no anesthesia involved.

*Notable adverse effects:* Headache

*Who might be a good fit?* Somebody with TRD who can take part in a treatment that requires 5 days a week regular involvement for a set period.

*Limitations:* Often limited to metropolitan areas. Covered by insurance. However, insurance providers may expect more treatment trials before they cover TMS. As of July 2021, TMS is not approved for children. It is under evaluation.

*How to get started:* Patients can refer themselves or ask for a provider referral. Most TMS clinics will evaluate the patient to see whether the treatment is a reasonable option.

## **ECT (electroconvulsive therapy)**

Today's ECT is notably different than what has historically been shown in the media – technology has advanced to reduce side effects. ECT is significantly underutilized, and for the right patients, it can be one of the most effective mental health treatments that exist.

Electrically conductive paddles are used to incite a 40-60-second-long seizure in a patient who has received anesthesia.

*Details:* 2-3 times per week for up to 12 sessions. Some patients receive maintenance treatment every 4-8 weeks after that.

*Notable adverse effects:* Sedation, confusion, headache for 12-36 hours after treatment. Short-term memory loss for things that occur around the time of treatment. It is very rare to forget events that occurred earlier in life.

*Who might be a good fit?* Somebody with severe symptoms who can use a treatment that may be incapacitating several times per week for the first several weeks.

*Limitations:* Must be done in a medical setting with anesthesiology and psychiatry both taking part.

*How to get started:* Refer for evaluation by an ECT program or a psychiatrist who performs ECT.

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## **Ketamine**

A medication that blocks N-Methyl-D-aspartic acid or N-Methyl-D-aspartate (NMDA) receptors (among others), can be added along with other antidepressant medication treatments. IV ketamine and esketamine nasal spray rely on essentially the same medication. However, the different routes result in some differences between the two. Evidence suggests IV ketamine may be more effective than esketamine nasal spray. However, because only esketamine nasal spray is FDA approved it is typically the only option covered by insurance<sup>1</sup>.

Notable adverse effects (common to both):

- |                 |             |                |                           |
|-----------------|-------------|----------------|---------------------------|
| ▶ Nausea        | ▶ Dizziness | ▶ Sedation     | ▶ Elevated blood pressure |
| ▶ Altered taste | ▶ Anxiety   | ▶ Dissociation |                           |

### **IV ketamine infusion:**

*Details:* 4 to 6 initial treatments over 2 weeks, booster treatment every 4-6 weeks sometimes recommended.

*Who might be a good fit?* Somebody with severe symptoms who can try a treatment that may require a full day, multiple times.

*Limitations:* Generally, not covered by insurance, with advertised cash prices per treatment ranging from \$400-500 as of 2021. Typically, only available in large cities.

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1 Bahji, A., Vazquez, G. H., and Zarate, C. A., Jr, 2021. Comparative efficacy of racemic ketamine and esketamine for depression: A systematic review and meta-analysis. *Journal of affective disorders*, 278(12473), pp. 542–555. <https://doi.org/10.1016/j.jad.2020.09.071>

*How to get started:* Patients may look for private clinics that offer the treatment. IV ketamine clinics typically require a referral from a mental health provider.

### ***Intranasal esketamine (Spravato®):***

FDA approved March 2019, as an adjunctive treatment for TRD. (**Must** maintain oral antidepressant during treatment). Approved in August 2020 for depression in patients with acute suicidal ideation or behavior.

*Details:* 2 times per week for 4 weeks, then 1 time per week for an additional 4 weeks, then 1 time every 1-2 weeks (duration of treatment is indefinite, based on clinical assessment).

- ▶ Two hours of supervision in a medical setting is required after each dose.

*Who might be a good fit?* Somebody with severe symptoms who can use a treatment that may require a half-day several times per week.

*Limitations:* There is a national Risk Evaluation and Mitigation Strategy (REMS) program that registers and tracks providers, pharmacies, and patients involved in esketamine nasal spray usage. Spravato® is not approved for use in children. FDA approval for Spravato® does not restrict to a maximum age. However, published research as of September 2021 does not show statistically significant benefits for 65 and older.

*How to get started:* Patients may self-refer to an identified prescribing provider, who will evaluate for whether the treatment is a reasonable option.

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## **Other psychedelics (examples: psilocybin, 3,4-Methylenedioxymethamphetamine (MDMA))**

Not currently a treatment option that medical providers can recommend. In November 2020, psilocybin-assisted therapy was made legal in Oregon. There are plans for a two-year implementation period. It is anticipated that legal psilocybin therapy will be available in January 2023. This is an area of active research.

*Who might be a good fit?* No patients at this time.

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