New Treatments for Depression: Ketamine, Propofol, Nitrous Oxide, Psychedelics and Transcranial Magnetic Stimulation. What Is the Evidence?

By

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In 2020, an estimated 8.4% of the US adult population (21 million adults) and 12% of the U.S. population aged 12 to 17 (2.9 million adolescents) had at least one major depressive episode. Depression with severe impairment is defined by a two week or more period of depressed mood or loss of interest or pleasure in daily activities, with many associated symptoms such as problems with sleeping, eating, energy, concentration, or self-worth.[1]

Depression is typically treated with a combination of antidepressants and psychotherapy. However, only 40 to 70% of depressed patients respond to these treatments, and about 10% to 30% of patients with a major depressive disorder develop severe treatment resistant depression (TRD).[2] In the past, electroconvulsive therapy (ECT) was used as the main treatment when other methods had failed. Recently, other modalities such as ketamine, propofol, nitrous oxide, psychedelics, and transcranial

magnetic stimulation have been evaluated as alternative treatments for severe TRD to avoid the potentially severe side effects of ECT. This article will look at how successful those modalities are in treating TRD, and the level of scientific evidence for their usefulness.

Ketamine

Ketamine is an anesthetic agent with analgesic properties that has been utilized for procedural sedation in emergency departments and operating rooms. It was first synthesized in the 1960s as a derivative of phencyclidine. Ketamine rapidly produces a hypnotic state with profound analgesia and anesthesia without reducing respirations. It may produce amnesia, with the eyes typically remaining open, and the patient feeling disconnected from their body in a condition called dissociative anesthesia. Ketamine has potential central nervous system (CNS) side effects including hallucinations, intense dreams, delusions, and as the patient awakens, emergence delirium.[3] Laryngospasm, another potential adverse effect may require expert airway management skills during intravenous therapy.

Ketamine is a potent NMDA antagonist.[4] Research points to the N-methyl-D-aspartate (NMDA) and gamma-aminobutyric acid (GABA) receptors as factors in the pathophysiology of major depression, and locations where antidepressant treatments work to improve depressive symptoms. Inhibition of NMDA receptors and activation of GABA receptors are thought to be factors in the improvement of depressive symptoms.[5]

Ketamine for injection consists of two enantiomers (molecules that are mirror images of each other), the S and R forms of ketamine. S-ketamine (esketamine) has four-times the affinity of R-ketamine (arketamine) for the NMDA receptor, and arketamine appears to have fewer psychotropic side effects. The two compounds have been found to have differing effects on some areas of the brain in animal studies. In some pre-clinical studies arketamine has been found to possibly be a better and longer acting agent for depression than esketamine, which is the form currently being used.[6,7] One study using a mixture of ar- and esketamine found the mixture caused less side effects than esketamine used alone, with similar results in treating depression. The authors of that study suggest more clinical studies are needed, but an ar- and esketamine mixture may be a better combination to use rather than esketamine alone.[6].

In a pilot study published in 2000, nine subjects with major depression were given either ketamine or a placebo. Intravenous ketamine treatment produced significantly greater reductions on a depression rating scale than saline treatment.[4] In 2016, a placebo-

controlled study of 30 patients found that intravenous esketamine reduced depression symptoms in 64%-67% of the subjects (results varied by dosage of ketamine used) compared to 0% of the controls.[8] Based partially on that study, intranasal esketamine was approved by the FDA for the treatment of TRD.[3] However, only two of the five studies submitted to the FDA by the manufacturer in the approval process actually demonstrated a benefit from intranasal esketamine.[6] A 66-subject proof-of-concept trial of intranasal esketamine versus placebo, given in addition to standard-of-care treatment, found that it may produce both rapid improvement in depressive symptoms and suicidal ideation.[9]

Patients receiving intranasal esketamine must be observed in a monitored environment for at least two hours due to some potential side effects including sedation, reduced attention, dissociation (judgment and thinking alteration, depersonalization and derealization), misuse, abuse, or suicidal thoughts.[3]

One systematic review of the literature concluded that ketamine appears to be effective in reducing depressive symptoms in TRD patients, and has a reasonable safety profile based on the results of the clinical trials. However, the authors noted that the clinical relevance of the treatment effect, and the safety demonstrated by many clinical trials, cannot be guaranteed in the real-world setting.[10] Another systematic review of the long-term effects of esketamine found mixed results for long-term effectiveness after termination of therapy. The authors' conclusion was that the level of proof of esketamine's efficacy in long-term TRD treatment remains low, and more randomized controlled trials with larger sample sizes and active comparators were needed. It is possible that continued therapy might be needed to prevent relapses.[11] A Cochrane Review of the literature on ketamine for depression concluded that ketamine and esketamine may be more efficacious than placebo for treatment of TRD at 24 hours, but how those findings translated into clinical practice was not entirely clear.[12] A review of a total of 83 trials, and both systemic reviews and meta-analyses in the literature on ketamine treatment concluded there was a large amount of evidence for a rapid and transient antidepressant effect from ketamine in unipolar and bipolar depression, and TRD. Repeated doses appeared to increase the duration of effectiveness. The authors also concluded that in numerous studies ketamine was found to have short-lived anti-suicidal properties. The authors did warn that the conclusions should be interpreted with caution because of the high risk of bias in the experimental design of many of the included studies.[13]

Propofol

Propofol is an intravenous general anesthetic that potentiates the function of GABA receptors, and inhibits the function of NMDA receptors. In one pilot study of 10 patients who received 10 treatments, 60% of the patients responded positively with no serious side effects. One of the 6 responders relapsed a few months after the final propofol treatment while the other 5 remained well for at least 3 months of follow-up.[14] Further published studies on the effectiveness of propofol for depression were not found on internet searches.

Nitrous Oxide

It has been postulated that inhaled nitrous oxide is a NMDA antagonist that may be useful in treating TRD.

A proof-of-concept trial with 20 patients comparing inhaled nitrous oxide versus placebo for severe TRD found that nitrous oxide had rapid antidepressant effects in some patients. In two one-hour intervals one week apart each patient received an inhalation treatment of either 50% nitrous oxide or a 50% nitrogen-50% oxygen placebo. All patients received both the nitrous oxide and placebo in random order. Nitrous oxide treatment resulted in a treatment response in 20% of patients with TRD and remission in an additional 15%. The antidepressant effects were sustained for at least 24 hours, and in some patients for one week. Some patients experienced adverse events such as nausea, anxiety, or vomiting requiring a short interruption or discontinuation of treatment.[15]

A phase-two trial was performed which with 24 patients who each received 50% nitrous oxide, 25% nitrous oxide or a placebo in a randomly chosen sequence, with a one-hour treatment once a month for three months. At the end of three months, 85% of patients had improved with a decreased Hamilton depression rating scale (HDRS- the most commonly used depression scale), 55% had a treatment response, saying their depression was less intense, and 40% were in remission, with a HDRS$\leq$7. There was no significant difference in the efficacy of depression treatment between the 25% or 50% nitrous oxide, both being significantly better than placebo, but 25% nitrous oxide had a markedly lower rate of adverse side effects compared to 50% nitrous oxide. It was suggested by the authors that the antidepressant effects of nitrous oxide may last between 2 and 4 weeks in responders.[16]

Psychedelics

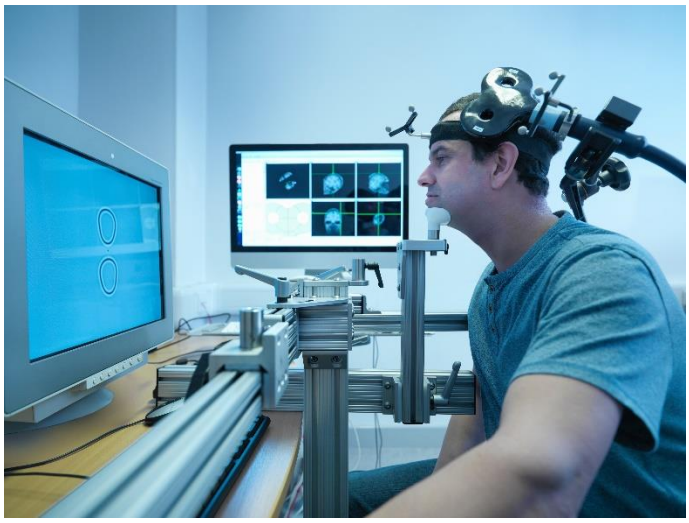
Lysergic acid diethylamide (LSD) and psilocybin are psychedelic drugs that produce perceptual distortions and mind-altering effects, mainly by being agonists of the serotonin 5-HT2A brain receptor.[17] Long term pessimism also known as "trait" pessimism seen in severe depression, has been linked to deficient 5-HT2A receptor stimulation.[17]

For depression therapy, microdoses of psychedelics are administered at approximately one tenth of the dose that causes hallucinogenic effects.[18] In most trials of psychedelics, an assessment is necessary to determine if the patient is suitable for psychedelic therapy. Currently, people with a personal or family history of psychosis and bipolar disorder are excluded, as are those with significant health issues such as significant hypertension, because psychedelics transiently increase blood pressure. Certain medications should be stopped or reduced before the treatment, because they can block or attenuate the effect of the psychedelic. Medications that block 5-HT2A receptors including amitriptyline, olanzapine, quetiapine, risperidone, and trazodone should be withdrawn. Serotonin reuptake inhibitors ideally should be stopped or, if that is not feasible, tapered down, because they can also decrease the sensitivity of the 5-HT2A receptor.[19]

An MRI study found psilocybin caused a significant decrease in the connectivity between the medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC), and decreased activity in the anterior cingulate cortex and mPFC. These results suggested that the subjective effects of psychedelic drugs are caused by decreased activity and connectivity in the brain's key connector hubs, enabling a state of unconstrained cognition (mind-altering effects). Activity in and connectivity with the mPFC is known to be elevated in depression, which becomes normalized after effective treatment. The results of this study suggested that psilocybin works by decreasing mPFC activity via 5-HT2A receptor stimulation and increasing GABA transmission.[17]

One meta-analysis of eight studies of psychedelic use for depression found a significant decrease in depression on day one as well as at six months. No serious adverse effects were reported in any included studies. A transient increase of the heart rate, blood systolic, and diastolic pressure were found after psychedelic administration compared with placebo.[20] Another trial found that 71% of psilocybin treated patients still had significant antidepressant effects at 4-weeks post therapy. [21] However, a 59-patient trial of psilocybin versus escitalopram found that psilocybin was no better at improving TRD symptoms than the antidepressant.[22]

Transcranial Magnetic Stimulation



Transcranial Magnetic Stimulation

People with depression do not produce enough of some neurotransmitters, such as serotonin and dopamine, and electrical impulses to the brain can stimulate production of those neurotransmitters. Repetitive transcranial magnetic stimulation (rTMS) uses highly focused repetitive magnetic pulses to induce an electrical current two to three centimeters deep, typically in the left prefrontal section of the cerebral cortex. That region of the brain acts as an emotion modulator, and appears to underproduce neurotransmitters in depression. Typically, rTMS protocols consist of treatments over four to six weeks in daily high frequency stimulation sessions to the left dorsolateral prefrontal cortex.[23] rTMS is FDA-approved for major depressive disorder in patients who have not responded to an adequate antidepressant trial.[24] Standard rTMS is seldom useful in acutely suicidal patients because of a delayed time-to-response.[23]

The most common side effects of rTMS include transient headache, scalp discomfort and a tapping sensation of the head in time with the magnetic pulses during sessions. The most concerning adverse side effect is the potential of grand mal seizures.[25] The risk of grand mal seizure varies, but is thought to be 0.003% for standard rTMS, .02% for Theta burst TMS, and 1.4% to 2.9% in patients with an underlying seizure disorder.[26]

Attempts are being made to try to increase the efficacy of TMS by varying the administration of the treatment. It can be administered in a number of different ways; high or low frequency, unilateral or bilateral, with priming doses, accelerated, with theta-burst impulses, or synchronized with alpha waves.[27] In accelerated TMS (aTMS), the time intervals between treatments are shortened, so that it takes days rather than weeks to complete. Another method is combining rTMS and theta burst stimulation (TBS)

where the TMS mimics endogenous hippocampal theta patterns.[23] In synchronized rTMS, three magnets provide low energy stimulation, the frequency of which is based on and synchronized to an individual patient's own alpha wave frequency.[28]

The literature on rTMS has produced mixed results, with some trials showing a statistically significant benefit over sham treatment, and others no benefit. Part of the issue might be that there are a number of manufacturers of TMS machines,[29] as well as many different ways to administer the therapy. Almost all the meta-analyses suggested larger trials were needed to resolve how effective TMS actually is.

In 2007, the first trial of TMS versus sham treatment found a significant improvement of depression with TMS over placebo, and the FDA approved the first device for administering TMS based on that study.[29,30] A National Institute of Mental Health trial found that 14% of patients with drug-resistant major depressive disorder experienced a remission of symptoms after repetitive transcranial magnetic stimulation (rTMS) while a control group reported only a 5% rate of remission. However, some authorities felt those results were similar to the success rate of antidepressants alone.[25,31] In a Cochrane review of the literature, 14 trials were analyzed and most comparisons did not show differences between repetitive (rTMS) and other interventions. The authors concluded that there was no strong evidence for the efficacy of transcranial magnetic stimulation for the treatment of depression, although the results did not exclude the possibility of benefit.[32] A number of other meta-analyses found no evidence of a difference between rTMS and sham therapy,[33,34] while other trials and meta-analyses found it was significantly better than sham therapy.[23,35,36,37] One of those meta-analyses looked at high-frequency rTMS (HF-rTMS) and found 29.3% of the subjects responded to the therapy, and 18.6% went into remission, compared with 10.4% responders and 5% remission rates in the sham group.[36]

TMS has also been compared to ECT. One study of ECT versus rTMS found no statistically significant difference between the two procedures.[38] In a systemic review and meta-analysis ECT was found to be superior to HF-rTMS in terms of response (64.4% vs. 48.7%) and remission (52.9% vs. 33.6%) of depressive symptoms. The superiority of ECT was more apparent in those with psychotic depression, while HF-rTMS was as effective as ECT when used for non-psychotic depression. This review noted the lack of good quality trials comparing the long-term outcome and cognitive effects of rTMS compared to ECT.[39]

Conclusion

There is currently an interest in psychiatry to find treatments for severe TRD that are less invasive than ECT using TMS or medications that inhibit NMDA receptors or activate GABA or 5-HT2A receptors.

- Ketamine seems promising and does have some literature support. An intranasal form of esketamine has been approved for TRD treatment.
- Propofol also seems promising, but more trials are needed to assess its value for TRD treatment.
- Nitrous oxide had positive effects in two small studies, and would be easier to administer than some of the other treatments discussed, but larger trials are needed to confirm its effectiveness.
- Microdosed psychedelics have some literature support for treating TRD, but a recent trial found no improvement over using an oral antidepressant alone.
- TMS is currently an FDA approved procedure to treat TRD. Trials have had very mixed results, some positive, and others negative, with some authorities questioning its value. Differences in TMS machines or how the TMS is administered may be responsible for some of the differences. ECT was found superior to TMS in some comparative trials, but TMS also had some positive effects on depression in those trials. Different protocols for TMS treatments, such as adding theta waves, changing the frequency used, accelerating the doses to complete the therapy faster, trying bilateral treatments instead of unilateral, and deeper brain stimulation are being tested to see if outcomes can be improved. Larger randomized controlled trials are needed to confirm the effectiveness of the procedure.
- The medical practice of treating TRD using methods other than ECT is in its infancy, and while these treatments offer these patients some hope, more randomized controlled trials with larger numbers of subjects are needed to determine how effective they truly are.

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