ADAA Statement on Ketamine

ADAA Scientific Council
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Description of the Issue

Depression is a leading cause of disability world-wide. Fortunately, for many patients specific psychotherapies and antidepressant medicines are effective treatments. However, 15-20% of patients with depression are refractory to most interventions, and have what is termed treatment refractory depression (TRD). This patient group is at very high risk for suicide. A "new" medication treatment, ketamine, is now available for TRD patients. In fact, for many years, intravenous ketamine has been used for the induction and maintenance of general anesthesia. It has been called a "dissociative anesthetic" due to the twilight/dream state of consciousness it can induce; from early on, its potential to produce psychiatric side-effects was apparent. In the 1990s, research studies with ketamine evaluated its ability to briefly trigger psychosis-like symptoms. However, by 2000, there were promising findings that low doses of slowly infused ketamine could rapidly reverse severe depression. Since then, many clinical trials have confirmed these results, establishing ketamine as unique among antidepressants for its rapid effect. In addition to its rapid antidepressant effect, there is emerging evidence of a somewhat independent anti-suicide effect that may persist for weeks, even as the mood improvement effect wanes. In North America, a number of private hospitals and clinics currently offer ketamine infusion for depression, while some academic medical centers offer care via participation in TRD ketamine clinical trials.

> *"This (ketamine) is probably the most interesting and exciting new development that I've seen in my career, and probably going back over the past 50 to 60 years…" Dr. Sanacora of Yale Psychiatry in a March 2017 NPR interview.*

Current Controversies

The mood benefit of ketamine is usually short-lived, typically only lasting several days or a week. Thus, ketamine cannot replace other forms of standard treatment. Ketamine infusion also has a number of short and longer-term risks. For example, during the infusion patients tend to have dissociative/dream-like experiences, and can have brief changes in blood pressure, heart rate, and breathing. As a result, ketamine infusions must be administered in a monitored medical setting making ketamine therapy relatively inconvenient compared to standard pill antidepressants. Longer-term treatment risks include some risk of addiction, cognitive changes and bladder inflammation (cystitis). In addition, since it is not yet an FDA-approved treatment for depression, it is typically not reimbursed by insurance. Out-of-pocket costs for a single infusion vary from $600-$4000; thus, a course of infusions could be very costly if not administered as part of a research trial.

To find out more (websites to visit)
www.nimh.nih.gov
http://jamanetwork.com/journals/jamapsychiatry/fullarticle/2605202
http://www.npr.org/sections/healthshots/2017/03/20/520169959/ketamine-for-severe-depression-how-do-you-not-offer-this-drug-to-people
www.adaa.org

The State of the Science

The short-term effectiveness of ketamine has been well established, and the risk profile is acceptable with close monitoring. It works for different types of severe depression (e.g. major depression and bipolar depression), but should be avoided in psychotic depression. In the TRD patient group, about 50% will have a clinical response to ketamine infusion (a course of 2-3 infusions). Ketamine works on a key activating brain chemical called glutamate by blocking specific glutamate receptors. Thus, it has a different treatment mechanism than standard antidepressants that affect brain chemicals such as serotonin and norepinephrine. In animal studies, a breakdown product of ketamine, esketamine, is primarily responsible for the antidepressant effects. While ketamine is available in a range of preparations (oral, intranasal, intramuscular and intravenous), intravenous administration produces the most robust antidepressant effect.

Recommendations for Future Work: How Ketamine Should be Portrayed in the Media

There is a strong need for standardization of ketamine protocols and care guidelines. The American Psychiatric Association (APA) has a research task force reviewing ketamine, and the task force panel has just published a consensus statement about ketamine use to start to address this need. Other important work remains to be done on topics such as how best to deliver longer-term therapy, biomarkers and predictors of treatment response, and the applicability of ketamine to other treatment-refractory patient populations (e.g. patients with chronic PTSD). Human trials with esketamine promise to offer treatment with an improved side-effect profile and convenience as intranasal formulations of this metabolite are being closely studied. While a very exciting development, ketamine therapy should not currently be viewed or presented as a standard treatment for depression, but rather as somewhat experimental, and a potential option for the TRD patient.