The Emerging Role of Ketamine-Assisted Therapy for Major Depressive Disorder and Treatment-Resistant Depression

What Employers Need to Know to Enable Safe, Effective & Affordable Access

Depression: Current State of Affairs

Tens of millions of individuals are affected by depression each year. One of the most common mental health conditions, depression is a major cause of morbidity and mortality in the United States. In 2020, almost 1 in 5 adults reported having been diagnosed with depression at some point in their life.

In one survey:
- 23% of a panel of US workers and managers indicated they have received a diagnosis of depression at some time in their life.
- 40% of those respondents reported taking time off from work—an average of 10 days a year—as a result of their diagnosis.
- People experiencing depression also have a higher rate of visits to the emergency room and develop other comorbidities and functional limitations that can affect their productivity.

Clinical depression is a more severe form of depression. It is also known as major depressive disorder (MDD) and is defined as a mental health condition characterized by a persistently low or depressed mood, decreased interest in pleasurable activities, feelings of guilt or worthlessness, lack of energy, poor concentration, appetite changes, psychomotor retardation or agitation, sleep disturbances or suicidal thoughts.

In 2021, the National Institutes of Health (NIH) estimated that 61% of US adults with MDD received treatment in the previous year. However, only 30% of these patients achieved remission with traditional mental health therapies such as medication and psychotherapy, including cognitive-behavioral therapy.

For some people, taking an antidepressant medication or engaging in psychotherapy eases symptoms of depression. For others, symptoms do not improve despite treatment. These individuals may have a condition known as treatment-resistant depression (TRD).

Depression is one of the most common mental health conditions. According to the National Alliance on Mental Illness (NAMI), depression is a serious condition that requires understanding and medical care. Left untreated, depression can be devastating for those who experience it and for their families.
Treatment-Resistant Depression

Approximately 30% of adults who suffer from depression have TRD, often defined as MDD that has not responded to conventional antidepressant medications of adequate dose and duration. These individuals have the same signs and symptoms as others with MDD but are likely to have:

- More severe symptoms
- Depressive episodes that last longer
- Reduced ability to experience pleasure
- Higher number of lifetime depressive episodes
- Anxiety
- Thoughts of suicide or self-harm

Cost to Employers

Employers and health care payers spend $29 to $48 billion annually on treatment-resistant depression in their workforce; this is an average of $50,000 per employee and 36 lost workdays per year. Employees with TRD have a higher turnover rate, leading to additional employer costs.

Consequences of Treatment-Resistant Depression

In February 2023, over 30% of adults in the US reported symptoms of anxiety and/or depression. Individuals often suffer for an average of 10 years before seeking treatment.
Psychedelics are psychoactive substances that produce changes in perception, mood and cognitive processes. A recent study found that 65% of Americans with a mental health condition want access to psychedelic treatments. There is increasing interest in exploring the therapeutic potential of psychedelics as a way to support individuals with TRD. Several recent studies of ketamine, psilocybin and MDMA show promising results.

In 1970, ketamine was approved as a general anesthetic. Today, in its intranasal form, it is the first psychedelic approved by the FDA for the treatment of depression. Intravenous (IV) ketamine is often used off-label to treat depression and other mental health conditions. Once a drug becomes FDA-approved, health care providers may generally prescribe it for off-label use when they judge that such use is medically appropriate for their patient. Ketamine is included on the World Health Organization’s Essential Medicines.

Psilocybin was highly researched in the 1950’s and ’60’s but was reclassified as a schedule 1 drug as a result of the 1970 Controlled Substance Act, which was enacted as a response to the counterculture movement that emerged during the Vietnam War era. In 2018 the FDA designated psilocybin a breakthrough therapy for treating drug-resistant depression and MDD.

MDMA has been designated as a schedule 1 drug since 1985 but is currently in phase 3 FDA trials for potential treatment of post-traumatic stress disorder. MDMA and psilocybin may become FDA-approved in 2024 or soon thereafter.

**Efficacy of Ketamine**

Ketamine is often referred to as a psychedelic drug because it is a dissociative anesthetic that can produce hallucinogenic effects, but it has a different mechanism of action and is not technically a psychedelic substance. However, it is often grouped together with psychedelic substances such as psilocybin and MDMA.

In clinical trials, IV ketamine has been shown to have a significant effect in treatment of depression. Research shows that up to 89% of patients with TRD respond positively to ketamine. In one study of over 1200 participants, depression response rates were significantly higher than those seen in studies of traditional treatments such as antidepressants and psychotherapy.

Ketamine is also used as a pain management tool and as a treatment for anxiety, PTSD, and substance abuse disorder. As a dissociative anesthetic, ketamine makes users feel separated from their body and from the environment. It can induce feelings of calm, relaxation, and euphoria. It is also used as a pain management tool and as a treatment for anxiety, PTSD, and substance abuse disorder. Like any drug, it can be dangerous when used without appropriate clinical supervision.
Ketamine-Assisted Therapy

In the past two decades ketamine has emerged as a promising legal alternative to traditional medication and has been used in low doses to safely and effectively treat TRD.

The psychotherapy component of ketamine treatment is known as integration therapy; this therapy maximizes long-term benefit in alleviating depression. Although ketamine alone can improve symptoms of depression, ketamine plus integration therapy increases the response rate of the treatment.

Multiple research studies have demonstrated that integration therapy can facilitate rapid and clinically significant reductions of depression. It has been estimated that providing ketamine-assisted therapy (KAT) as a covered benefit can save over $18,000 per employee treated. Covering this treatment may improve access and affordability and reduces employer medical costs that are related to TRD, including comorbidities such as cardiovascular and metabolic diseases.

Plan members who experience TRD are among the most high-risk, vulnerable populations in the workforce. KAT has the potential to help fill treatment gaps for these members through safe and effective treatment.

The American Psychiatric Association published a consensus statement about the off-label use of IV ketamine to treat depression; in it they state, to date the strongest data supporting ketamine’s clinical benefit in benefiting psychiatric disorders are in the treatment of major depressive episodes. The statement recommends additional clinical trials and the development of a coordinated system of data collection for all patients receiving ketamine for the treatment of mood disorders.

Patient Experience in Ketamine-Assisted Therapy

1. Preparation
   Individual meets with KAT therapist to discuss concerns and set expectations prior to treatment.

2. Treatment
   Individual goes to clinic where they undergo treatment in clinically monitored, supportive environment.

3. Integration
   Therapist meets with client to help them extract insights from experience to inform behavioral change.

4. Monitoring
   Individual’s progress is monitored closely to ensure safety and optimize treatment course and outcomes.

Evidence-based personalized treatment and monitoring is critical for success.
Guidelines for Treatment Protocols

Currently, there are no official standards of care that must be followed when administering ketamine treatments other than the standards for any IV treatment. However, to be considered a safe medical treatment for depression, ketamine must be administered by a licensed medical professional in a medical setting. The patient must be monitored during and after treatment and must not drive or operate machinery after treatment.

Most clinical treatment protocols include six ketamine infusions, given twice a week over the course of three weeks. Ketamine is delivered in low doses and because it is a short-acting, the acute effects such as a feeling of detachment, elevated blood pressure and loss of muscle coordination resolve within 2-3 hours.

The patient starts treatment by scheduling an intake session with a licensed mental health professional and with the physician or nurse anesthetist who will administer the ketamine. The patient is monitored and supported throughout the ketamine infusion. An additional therapy session is provided within a day or two of each infusion.

Follow-up sessions may be recommended by the clinician, typically once a month or as needed. Ongoing monitoring and treatment may be necessary to assess the long-term impact.

I am a strong believer. I think the most important thing is to give this treatment to the people who need it.

Benefits Leader

Ketamine and the Workplace

Employers who offer ketamine to their eligible employees must be aware of work requirements that may be affected by the treatment. For example:

1. Driving an automobile, operating machinery, or engaging in physical activities that are potentially hazardous should not be undertaken on the day of the KAT session.

2. The short-term effects of ketamine typically wear off within a few hours, but some more sensitive individuals may need to wait until the following day to return to work. Employers must decide whether to grant mental health time off, require employees to use PTO for treatments, or allow on-the-clock treatment sessions.

3. Ketamine is not included in standard workplace drug screenings. However, a separate test specifically for ketamine can be ordered. This is usually only requested if ketamine abuse is suspected, which means ketamine testing is not standard practice for employers, schools or government agencies. It is important to note that ketamine may be detectable in the blood for up to three days after treatment. Urine tests can detect ketamine for up to 14 days after use. Employers who conduct random drug screens of their employees should review the drug panels used to determine whether ketamine is included. If it is, the employer will need to implement a HIPAA-compliant policy that allows for a positive ketamine test for employees undergoing KAT.

Addressing the Elephant in the Room

Due to the increasing popularity of ketamine and its legal status as an FDA-approved drug, it is important to address recent celebrity and other high-profile deaths attributed to illegal and unsupervised ketamine use. These unfortunate deaths have highlighted the dangers of using ketamine without adequate clinical supervision.

Ketamine is used recreationally and illegally as a party drug to induce hallucinations and out-of-body experiences, often in conjunction with alcohol or other drugs. This can increase the likelihood of adverse effects, including seizures, respiratory depression and cardiac arrest.

It will take a concerted effort on the part of KAT providers to reassure employers that, when prescribed and monitored appropriately, ketamine can be a safe and cost-effective treatment for TRD.
Benefit Plan Design & Costs

- The initial treatment regimen costs an estimated $6000 per member and includes both the medication and therapy sessions. Per-infusion costs can range from $400-$1300.
- Therapy sessions may be covered by a benefit plan as a mental health benefit.
- Therapy sessions may or may not be included in the per-infusion cost and are a critical component of treatment.
- Overall costs to employers will vary depending on plan design and member cost-sharing.
- Due to financial constraints, KAT is out of reach for most adults who would benefit from the treatment.

Closing the Therapeutic, Benefits Design, and Affordability Gap

Is ketamine addictive?

Medical evidence regarding drug abuse and dependence suggests that ketamine does not cause tolerance and withdrawal symptoms. However, cravings have been reported by individuals with a history of heavy use of psychedelic drugs. In addition, ketamine can have pleasurable effects on mood, cognition and perception, leading some individuals to want to use it repeatedly.

Therefore, ketamine should only be used under the direct supervision of a licensed provider.

I felt I was well aware of mental health treatments, but I had never heard of ketamine treatment or the potential success rate.

Benefits Leader
KAT is a fast-growing segment of the health care services sector and as a covered benefit has the potential to eliminate existing therapeutic, accessibility, and affordability barriers for individuals struggling with TRD. To ensure patient safety and optimize outcomes, employers must know how to evaluate and differentiate between a growing list of emerging vendor offerings.

When assessing a potential partnership, employers should consider evaluating the following:

### Ensuring appropriate treatment

- Do the providers in the network include integration therapy by licensed providers as a part of ketamine treatment? **Be cautious of programs that offer ketamine-only treatment without therapeutic support from licensed providers.**
- Do the providers in the network administer ketamine in a controlled clinical setting and monitor the patient during and after treatment? **Be cautious of programs that offer at-home treatment; unmonitored use of ketamine can pose risks to the individual.**
- How is patient clinical eligibility determined? **Be cautious of programs that have not defined specific clinical eligibility criteria.**
- Does the vendor ensure personalized treatment and monitoring for every patient? **Be cautious of vendors that have a one-size-fits-all approach.**
- What systems are in place to monitor and differentiate patient response to treatment (e.g. remission and non-responders)? **Be cautious of vendors that do not track patient response.**
- Do the providers in the network use FDA-approved ketamine? **Be cautious about programs that utilize compounded ketamine, which is not FDA-approved.**

### Delivery model

- What is the vendor’s payment structure? PPEM, per treated patient (episodic fee), hybrid model, etc.
- Does the vendor support a collaborative care delivery model that enables the sharing of patient diagnostic and symptom response across the clinical care team?
- Does the vendor support continuous improvement of personalized clinical pathways across its provider network? **Be cautious of vendors that do not continually reassess for best practice.**

### Education and outreach

- What is the strategy to engage the most at-risk population? These individuals are least likely to have a relationship with a primary care provider or other medical professional.
- Education and awareness is key to successful engagement. What is the strategy for educating providers and plan members about the availability of KAT?

### Reporting

- Does the vendor track utilization and outcomes and provide de-identified data for treatment response, cost and cost avoidance, and ROI? **Be cautious of vendors that do not track patient outcomes and ROI.**
- Are patient outcomes reported across all co-morbidities included within the diagnostic assessment?
- How are outcomes reported? Does this include functional outcome measures?

### Plan design and implementation

- How does the vendor recommend adapting the benefits plan design to accommodate coverage?
- How does the vendor work with the employer’s carrier to facilitate claim payment?
- Can the vendor’s platform be integrated with existing electronic health record databases?
- Will the vendor meet with your employer’s representatives for review, and how often?
Benefits leaders have expressed cautious optimism about the potential for KAT to support employees who suffer from TRD. Education about the potential value is key, along with helping benefits professionals understand the efficacy and cost-effectiveness of KAT.

These action steps can help you educate yourself, your team and your leadership and build a business case for coverage.

• Review your data for:
  ▪ Prescription use for anti-depressant medications, especially claims for multiple medications for depression as this can indicate TRD.
  ▪ Claims from your EAP and medical plan for depression.
• Create a financial model that includes: cost per individual, estimated number of people eligible, the cost to your organization, member cost-share and the potential ROI.
• Help your partners (EAP, carrier, TPA, etc.) understand the value of referring members to KAT when they are eligible.
• Work with your leadership team to ensure that their questions and concerns are addressed.
• If your organization has a medical director or onsite clinic, engage them in this process.
• Be aware that your current vendors (EAP, carrier, TPA, consultants, brokers) may not be well-educated about TRD and the potential role of KAT.
• Ask your partners to work with any KAT providers you may contract with to map out referral pathways for individuals.
• Ensure your vendor partners can assist you in communicating the value of KAT to your members.

Before 2016, I was on up to 10 anti-depressants and I was still not getting better. In 2016, I was introduced to psychedelics, and within a week I was back to my old self.

Patient

After so many failed treatments, I felt that I had nothing left to lose at that point. But when my treatment was a complete success, I knew we had to pay this forward...

Patient
If an employee or family member is experiencing symptoms of depression, make them aware of resources such as the 988 Suicide & Crisis Lifeline.