

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.



LOOK FOR THIS ICON



This Action Brief provides information for employers about understanding ketamine-assisted therapy as a new treatment option for treatment-resistant depression.

As you review the Action Brief look for this icon, which highlights quotes from health benefits professionals.

ACTION BRIEF ACRONYMS

MDD

Major depressive disorder

TRD

Treatment-resistant depression

KAT

Ketamine-assisted therapy

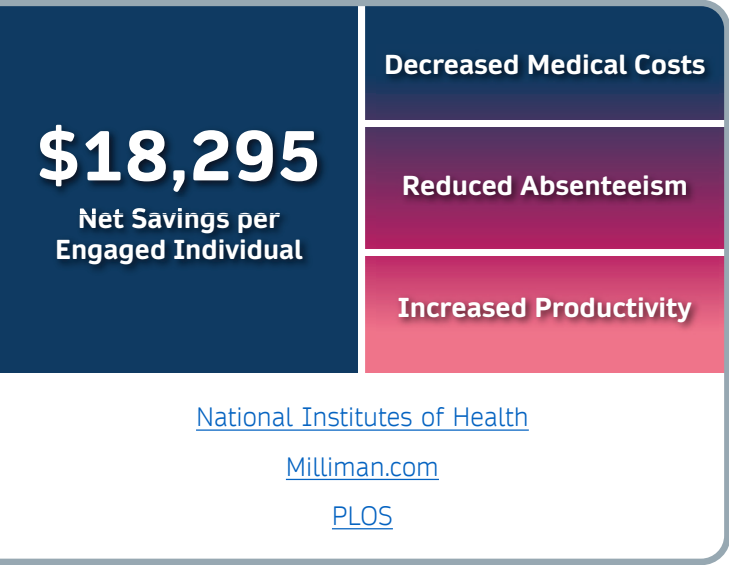
Treatment-Resistant Depression

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




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.



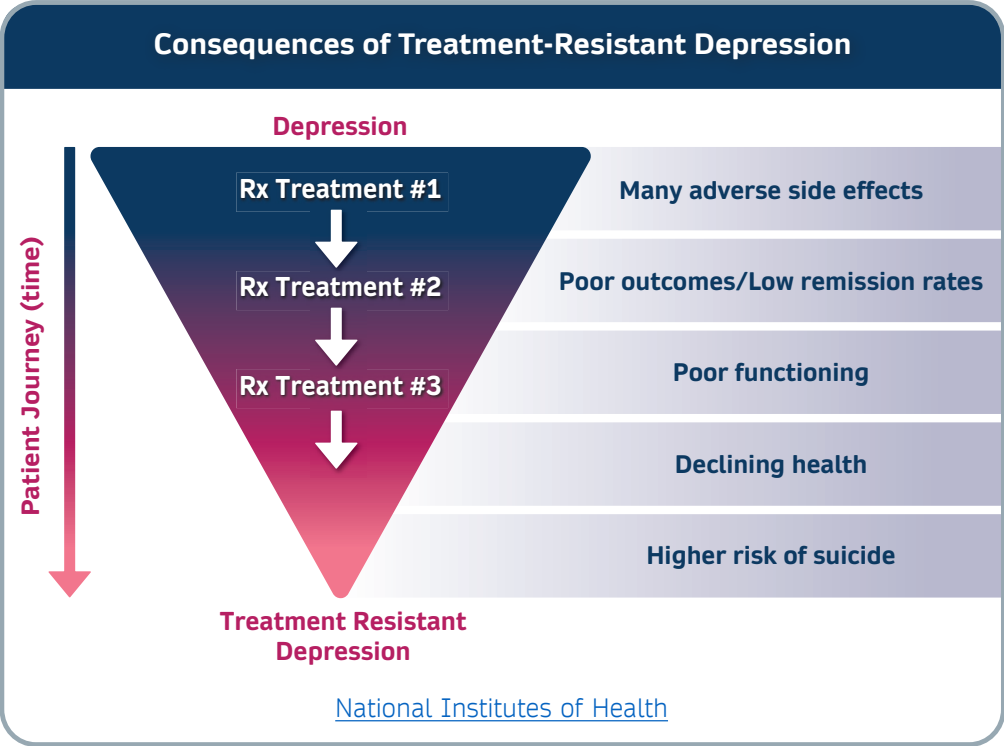
Cost to Employers

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.

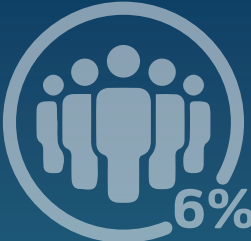


Every time someone comes into my office and closes my door and cries, it is over mental health. I think 'This treatment could save lives'.

Benefits Leader



Clinically Eligible Treatment Population



6%

An estimated 6% of working adults will develop TRD, making them clinically eligible for ketamine-assisted therapy.

Current Employer Strategies

Most employers currently focus on disease management programs, EAPs, and managed behavioral health organizations to provide covered treatment for members with depression. Although these programs may be adequate for treatment-responsive patients, they do not provide adequate support for members suffering from TRD.



This is an intriguing treatment option. We will need to do a significant amount of education to our population before we consider implementing.

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I'm looking forward to seeing this treatment option develop further and gain traction in the employer market.

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New Therapies for Treatment-Resistant Depression

[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](#).

Below is an overview of an [FDA-approved](#) therapy and other treatments that are expected to receive [FDA approval soon](#).

- 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 counter-culture 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.

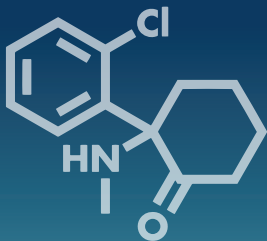
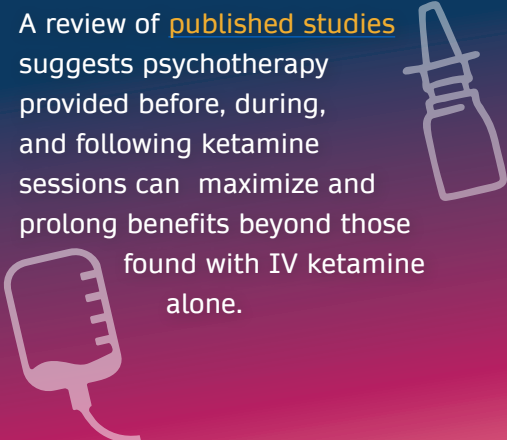
It has been estimated that providing ketamine-assisted therapy (KAT) as a covered benefit can save over \$18,000 per employee treated. Covering this treatment may improve access and



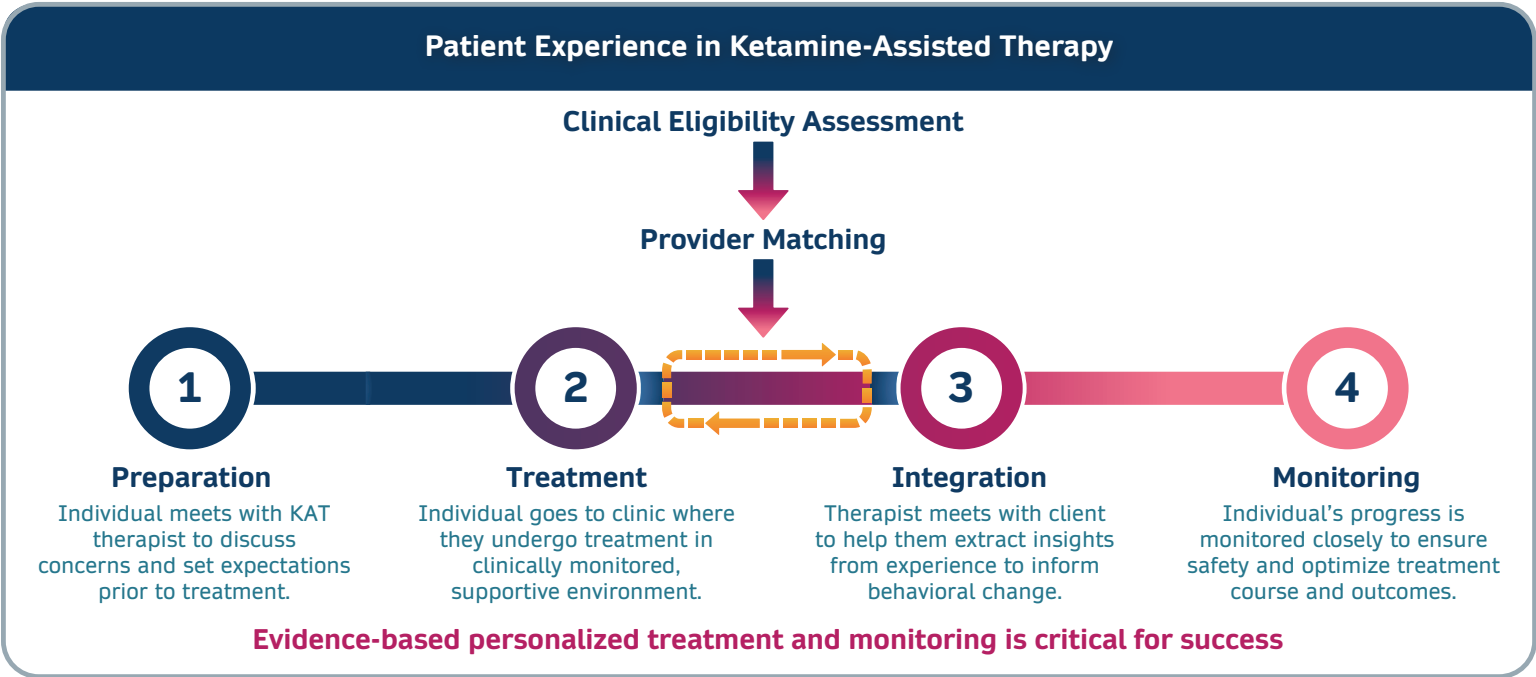
affordability and reduces employer medical costs that are related to TRD, including comorbidities such as [cardiovascular and metabolic diseases](#).

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.

A review of [published studies](#) suggests psychotherapy provided before, during, and following ketamine sessions can maximize and prolong benefits beyond those found with IV ketamine alone.



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.



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.

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.

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.



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

Benefits Leader



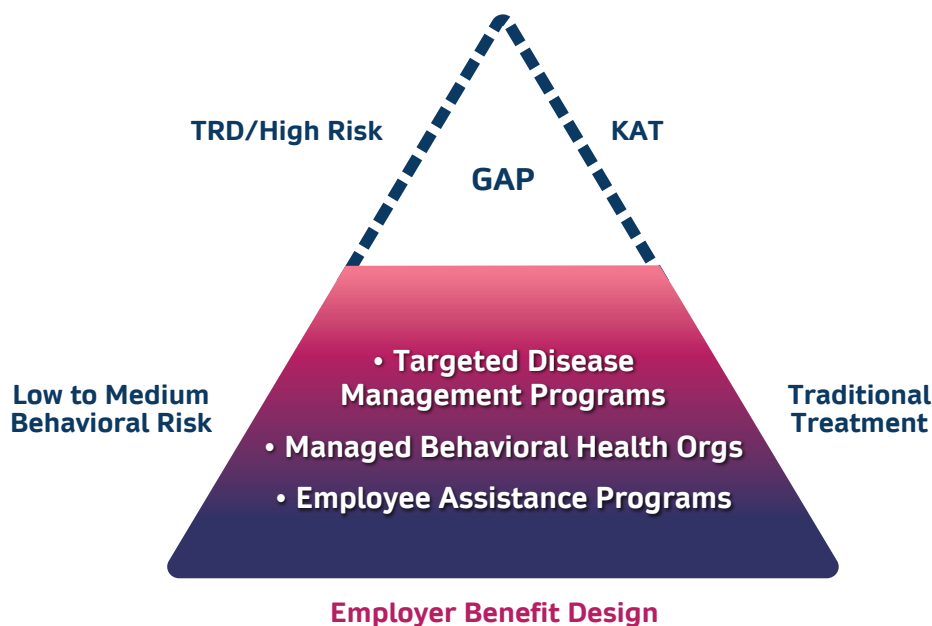
Recent Research Supports the Use of IV Ketamine to Treat TRD

- A landmark 2023 [study](#) favorably compared IV ketamine to electroconvulsive therapy (ECT), the previous “gold standard” for TRD.
- The National Network of Depression Centers released a [statement](#) in February 2024 advocating for coverage of IV ketamine for TRD by both commercial insurers and government programs.
- A 2024 [meta-analysis](#) indicated that IV Ketamine is three times more effective than intranasal esketamine.

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

Important Questions for Vendors

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? PEPM, 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.*

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?

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?

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?

Employer Action Steps

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 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.



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

- 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.



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

About MBGH

Midwest Business Group on Health (MBGH) is a 501c3 non-profit supporting employers seeking solutions to better manage the high cost of health care and the health and productivity of their covered populations. Founded in 1980, MBGH offers members leading educational programs, employer-directed research projects, purchasing opportunities and community-based activities that increase the value of health care services and the health benefits they offer to members. MBGH serves over 150 companies who provide benefits to over 4 million lives, with employer members spending more than \$15 billion on health care each year.

mbgh.org

Authors

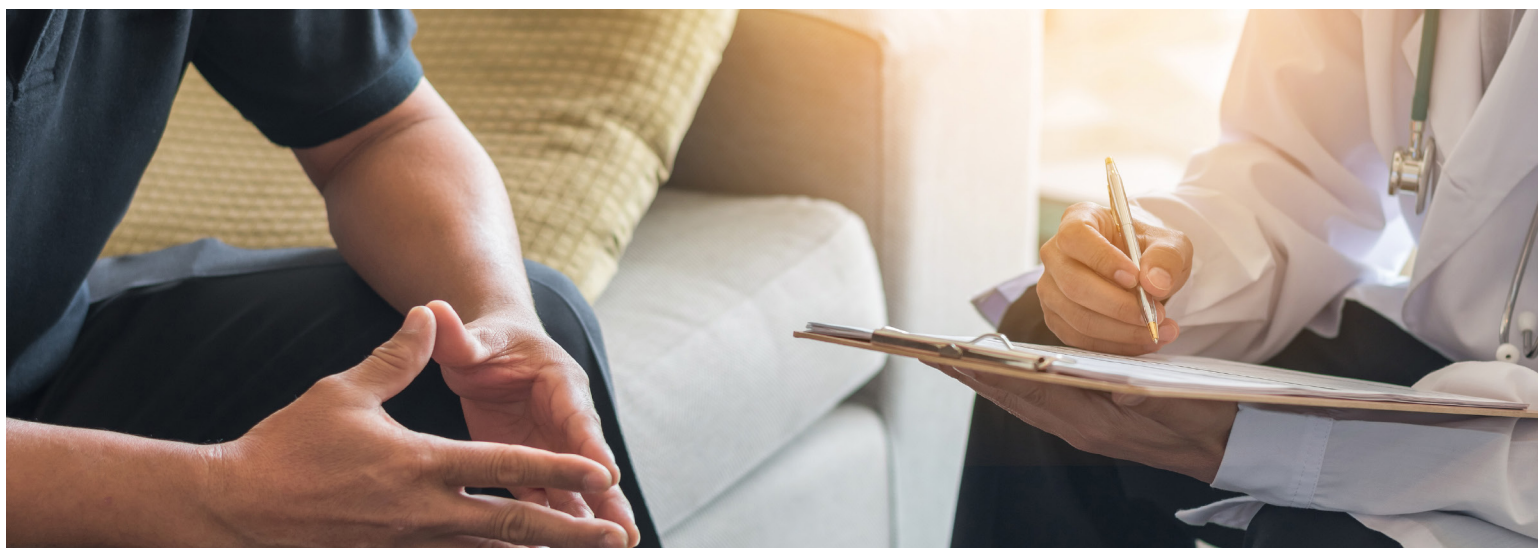


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The information provided in this resource is based on the authors' and contributors' experiences working in the health benefits and health care industry. For more information on any aspect of this report, please contact info@mbgh.org.



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

988 SUICIDE & CRISIS
LIFELINE