BRAIN HEALTH

PRECISION THERAPEUTICS

Ray of Hope

A New, Take-At-Home Ketamine Pill is a Gamechanger for Treatment-Resistant Depression

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KETABON.HEALTH

For half a century, ketamine has been numbing and soothing people who are in pain. American chemist Calvin Lee Stevens,[1] while working as a consultant at drug maker Parke-Davis, synthesized the compound in 1962, the same year that The Beatles released *Love Me Do*. It didn't take long for the drug to earn a reputation as a fast, safe, and well-tolerated dissociative anesthetic, and the FDA approved ketamine in 1970.[2]

Ketamine did not receive its baptism of fire in an emergency room, but on the battlefield. The U.S. military used the drug to provide pain relief to severely wounded soldiers in the Vietnam War.[3] It proved its mettle, and within a few years, clinicians worldwide were using the drug to induce anesthesia, and to treat trauma.

Ketamine's uses have multiplied over the decades: The drug is now a trusty sedative for children needing short emergency procedures and for several eye, ear, nose, and throat operations. Some patients undergoing wisdom teeth removals will also receive ketamine as an analgesic during and after extractions. Of course, society found another use for ketamine in the trippy 1970s, which was recreational. 'Special K', the street name for the drug, and the infamous 'K-hole', a state of dissociation with visual and auditory hallucinations, are now part of West Coast countercultural lore.

ANTI-DEPRESSIVE POTENTIAL

Although ketamine rapidly became one of the most versatile drugs in a hospital's medicine cabinet, nearly 20 years passed before medical researchers cottoned onto the drug's robust anti-depressive action. In 1981, Nabil Anis and David Lodge discovered that ketamine works as an N-methyl-D-aspartate (NMDA) receptor antagonist. (The initial response from academia was muted, with Nature editors deeming the finding as 'not of sufficient general interest'.) [4]

Major depressive disorder (MDD) is a leading contributor to disability globally.

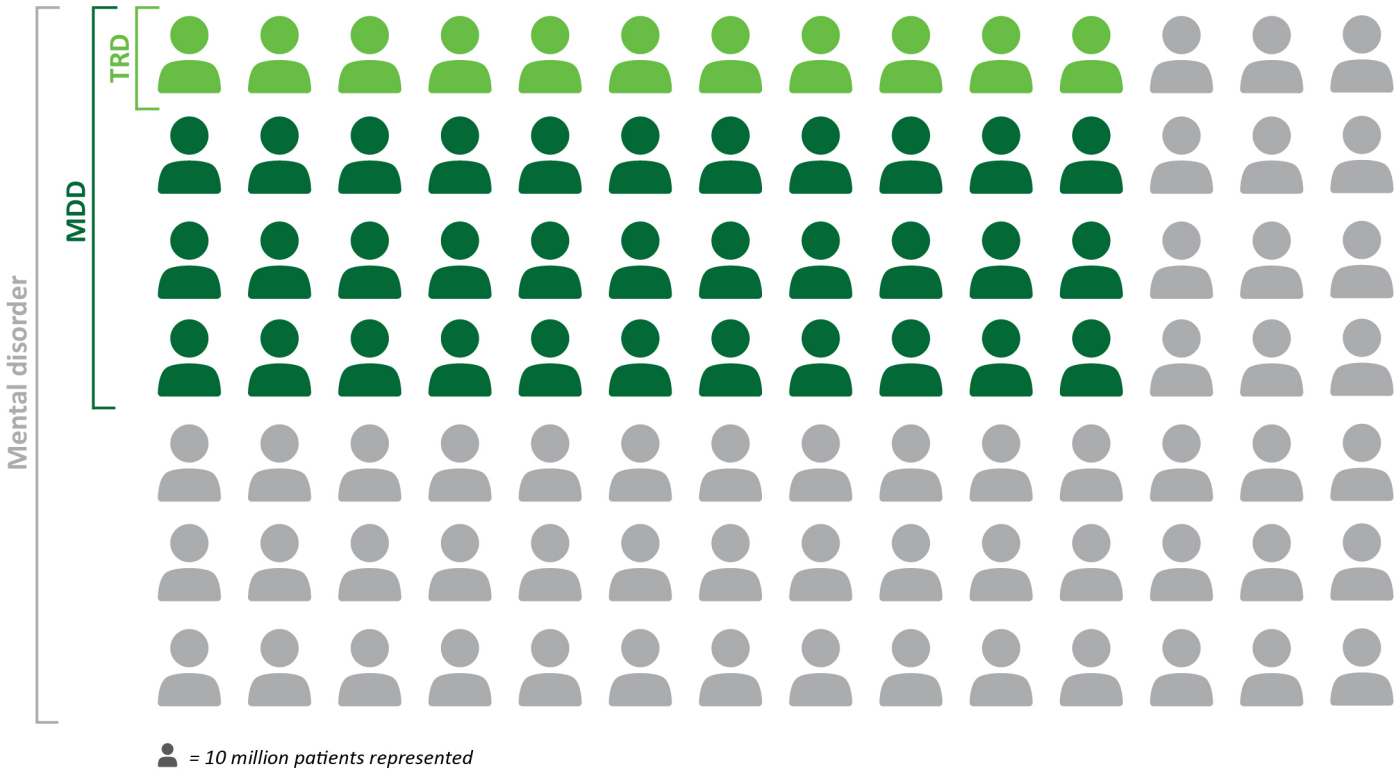
But when medical researchers discovered in 2000 that ketamine rapidly reduces suicidal ideations at the more severe end of the depressive spectrum, the scientific community sat up and took notice. Distinguished medical journals and psychiatrists have hailed the discovery as one of the greatest advancements[5] in mood disorder research in the past 60 years.

Despite ketamine's considerable anti-depressive potential, uptake of the drug has snagged on tolerability, convenience, and accessibility issues. These are related to the pharmacokinetic profile of intravenous and intranasal formulations, which deliver a relatively high concentration of the drug to a patient's system very quickly. This increases the risk of some negative side effects, such as increased heart rate and increased blood pressure, and unwanted dissociative events. Patients usually require medical supervision in a clinic for several hours after treatment, and are unable to medicate at home.

1. https://pubs.asahq.org/anesthesiology/article/113/3/678/10426/Taming-the-Ketamine-Tiger
2. https://www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified
3. https://pubmed.ncbi.nlm.nih.gov/20180434/
4. https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bph.13222
5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6851782/

94 million patients suffer from treatment-resistant depression worldwide

Around one-third of the 970 million people currently living with a mental health condition suffer from Major Depressive Disorder (MDD), and approximately one-third of this MDD cohort fail to remit after multiple lines of treatment, meeting the criteria for Treatment-Resistant Depression (TRD).



A SUPERIOR FORMULATION

But Ketabon,[6] a joint venture between HMNC Brain Health and Develco Pharma, is in the final stages of development for an oral prolonged-release derivative of ketamine (ketamine hydrochloride) called KET01[7] that addresses these problems. The formulation releases ketamine slowly into a patient's bloodstream, maintaining a relatively low concentration of the drug in their system, while building up a relatively high concentration of the active metabolite 2R,6R-Hydroxynorketamine, that has shown antidepressant efficacy in animal models, but does not cause dissociation.

This raises the potential of minimizing ketamine's potential cardiovascular and dissociative downsides, with no likely impact on the drug's antidepressive upside.

A tolerable, convenient, and accessible formulation of ketamine offers a new platform for further development of the drug into a potential treatment for the most acute forms of depression. In the longer-term, KET01 could be the go-to take-at-home treatment option for the 94 million patients suffering from Treatment-Resistant Depression (TRD) worldwide.

6. https://www.hmnc-brainhealth.com/research-and-programs/ketabon
7. https://www.ketabon.health/

TRD TREATMENT STILL ELUSIVE

The depression landscape is growing larger but becoming increasingly fragmented. The number of people suffering from neuropsychiatric disorders globally continues to increase, with depression now the most prevalent mental health disease. For decades, research into depression and treatment of the disease have focused on modulating the serotonin and norepinephrine levels of patients. Economic, efficacious, and relatively well-tolerated selective serotonin reuptake inhibitors (SSRIs) are the treatment paradigm for treating most forms of depression, often in conjunction with a talking therapy such as cognitive behavioral therapy (CBT).

But the combination of SSRIs and CBT often don't cut it for the most severe forms of depression. Around one-third of the 970 million people currently living with a mental health condition suffer from Major Depressive Disorder (MDD). And one-third of this MDD cohort fail to remit after multiple lines of treatment, meeting the criteria for TRD.[8] The outlook for patients with TRD is bleak, since the illness comes with more comorbidities, poorer health-related quality of life, and a greater risk of suicide. The hard-to-treat disease also imposes huge economic costs on society. The world sorely needs a rapidly efficacious, safe, and well-tolerated treatment for TRD.

Medicine is starting to tackle the problem. Today, patients suffering from TRD in the United States can follow two routes of ketamine-based step therapy. They can use an intranasal formulation of esketamine that has regulatory approval, or opt for 'off-label' treatment plans, which rely on intravenous formulations. But neither of these formulations are the magic bullet for TRD, because they result in patients receiving a relatively high concentration of the medication in their bloodstream very quickly. In fact, the intranasal formulation currently available on the market reaches peak systemic concentration in 40 minutes or less.

How KET01 is different than 'traditional' ketamine treatments

Limited acute side effects vs. sizeable acute side effects

Prolonged release formulation leads to a later and lower concentration peak of ketamine, reducing the effects on cardiovascular function, psychologically harmful dissociative effects, and potentially, of the drug's abuse.

Take-at-home pill vs. doctor-office monitoring

Potential to take a dose safely at home, eliminating the need for two hours of medical supervision, following a dose.

More accessibility vs. limited accessibility

Less time spent on driving to the doctor's office, and supervision after dosing makes the take-at-home pill a more convenient treatment alternative.

Cost savings up to 70% vs. high costs

Potential for full reimbursement and broad availability for TRD patients contrasts with limited access and high costs associated with the need for medical supervision with current medications.

8. https://www.mayoclinic.org/diseases-conditions/depression/in-depth/treatment-resistant-depression/art-20044324

Treatment-resistant depression patients have limited treatment options currently available, with only one FDA approved drug for TRD in the last 10 years.

That hefty shot of ketamine straight into the system presents two major tolerability issues. The drug causes an increase in the patient's blood pressure and heart rate, which raises cardiovascular risk. This is obviously undesirable for individuals suffering from lower cardiovascular function, which is more prevalent among TRD patients. It also increases the probability of psychologically harmful dissociative effects.

Of course, ketamine is classed as a dissociative anesthetic, which means that some discontinuity between thoughts, actions, and surroundings is inevitable, and even necessary to treatment. But clinicians are wary of patients experiencing 'out of body'-style psychological experiences, which can be distressing. Many patients just don't want 'the trip' if they can avoid it. Other patients with personal or family history of schizophrenia, who generally avoid psychedelics such as LSD and psilocybin, will want to avoid such dissociative experiences at all costs. The risk of these undesirable side effects makes 'traditional' ketamine formulations very inconvenient. The label on the intranasal formulation in the U.S. state that at least two hours of medical supervision is necessary following a dose. The typical severely depressed patient will need to attend a physician's office on at least eight occasions in the first month of treatment, and then once every fortnight subsequently.

In fact, the demands that ketamine treatment makes on patient and clinician time have severely impeded uptake of the drug. The limited number of practitioners offering ketamine treatment reduces the accessibility of a drug with vast antidepressant potential.

KET01: SAME UPSIDE, LESS DOWNSIDE

But KET01 has a more favorable pharmacokinetic profile, which promises to be a game-changer when it comes to TRD. The breakthrough is no accident: Ketamine and prolonged release oral formulations are among the academic interests of one of HMNC's founders, Professor Florian Holsboer, a renowned psychiatrist who specializes in depression.

Ketamine has a relatively high 'first pass metabolism' in the liver, a phenomenon of drug metabolism that results in a reduced concentration of the pharmaceutical entering and circulating in a patient's system. An oral formulation, which consists of a pill ingested by the patient, harnesses this effect. The patient's liver metabolizes much of the ketamine, which significantly reduces the concentration of the drug in systemic circulation. The prolonged-release formulation, reaches a lower peak concentration of ketamine, occurring in 7 hours. This significantly reduces the risks of lower cardiovascular function and psychologically harmful dissociative effects, and abuse potential of the drug.

The vast improvement in the tolerability of the formulation also makes treatment much more convenient. In theory, the lower risks of undesirable side effects would reduce or remove the need for time-consuming medical supervision and ease the logistical headache of visits to the physician's office. Patients can medicate in the comfort of their homes, simply by swallowing a pill, which improves the compliance outlook for KET01.

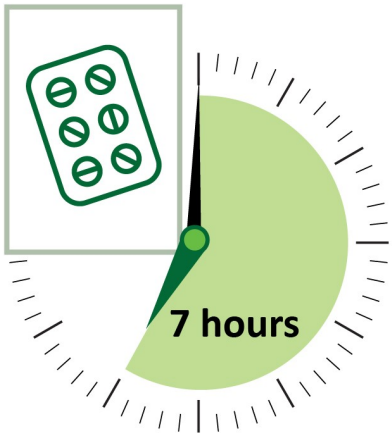
The KET01 formulation also minimizes the downsides with no impact on the drug's considerable antidepressive upside. Due to the slow release of ketamine from the formulation and the rapid and comprehensive metabolization, patients will receive a relatively high concentration of the drug's downstream metabolite, which is called 2R,6R-Hydroxynorketamine[9] in their system. This metabolite is thought to reduce depressive symptoms without blocking the body's NMDA receptors. KET01 thus has the potential to be better tolerated than other ketamine-based treatments, and to overcome depressive symptoms faster than standard antidepressants, which theoretically reduces the risk of great suffering and suicide.

The clinical data to date suggest KET01 as a potential first-line treatment option for TRD. The early read-out from a recent Proof-of-Concept investigator-initiated clinical trial in 27 TRD patients has reaffirmed KET01's efficacy and tolerability potential. After two weeks of daily treatment with 240 mg of KET01, patients saw a lessening in the severity of their depressive symptoms on the MADRs score, a ten-item assessment tool commonly used by psychiatrists.

Based on the promising results from the Proof-of-Concept trial, Ketabon has initiated a multicenter, double-blind, randomized, placebo-controlled Phase 2 trial in Germany, the Czech Republic and Poland. The study investigates the efficacy, safety, and tolerability of add-on treatment with KET01 in 122 patients suffering from TRD.

Ketamine formulations available today, next versions better

Intranasal formulation for ketamine-based therapy currently available on the market reaches peak systemic concentration in **40 minutes or less**.



An **oral prolonged-release formulation**, which consists of a pill ingested by the patient, reaches a lower peak concentration of ketamine, occurring in **just under 7 hours**.

9. https://ncats.nih.gov/chemtech/projects/active/ketamine

Finally, since a long-time I am feeling some emotions again. A lot of positive and some negative emotions, but the negative ones enable me to interact more with my psychotherapy. Overall, it gives me a much better outlook on my future and depressive symptoms.

— TESTIMONIAL OF TRD PATIENT IN KET01 PHASE 2 STUDY

They were split into three treatment arms: One cohort received a daily 240 mg dose of KET01, a second received a daily 120 mg dose of KET01, and a third received placebo, all given as an adjunctive treatment to a standard antidepressant over three weeks.

Phase 2 results will be available in Q3 2023, with a view to entering Phase 3 in early 2024. This will put Ketabon in pole position among companies developing orally administered formulations. Phase 3 trials should also establish the optimum frequency of KET01 treatment. The commercial landscape looks promising, with Ketabon's IP protection providing exclusivity in the U.S. and Europe until 2035.

BLUE SKY VISION

It is worth reaffirming Ketabon's main aims. KET01 will not replace SSRIs as the first-line treatment for depression, but there are grounds for confidence that the novel formulation will be an additional option in the physician's toolbox for treatment-resistant forms of the disease. In fact, Ketabon's primary objective is to demonstrate that its formulation can be safely used at home by patients who are suffering from severe depression.

KET01 has significant therapeutic and commercial potential beyond severe depression. For example, several traditional ketamine-based formulations have shown promise for other psychiatric conditions, such as generalised anxiety disorder, obsessive compulsive disorder, and traumatic stress disorder. There is also potential lying outside of the psychiatric field, such as treatment of chronic pain conditions.

Forbes reported in 2021 that the "blue sky" vision for ketamine was an effective antidepressant formulation with minimal hallucinogenic properties that could be accessible to broader populations. Those blue skies are beckoning.

KETABON

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