MIND FOUNDATION

Ketamine – New hope for depression

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Birth of an Anesthetic

In 1962, Calvin Stevens, a chemist at the pharmaceutical company Parke-Davis, synthesized an anesthetic that would have fewer negative side effects than the previously used compound phencyclidine (PCP). He called his creation CI-581.

Shortly thereafter, medical doctor Edward Domino administered CI-581 to human study subjects: inmates at the Michigan Jackson prison. Using sub-anesthetic doses, he hoped to describe its effects on human consciousness. CI-581 turned out to repeatedly cause out-of-body experiences, or states in which the mind seems to dissociate from the body. Domino's wife suggested that the drug be classified as a dissociative anesthetic, and CI-581, later called ketamine, was added to the *materia medica* by the FDA in 1970.

Ketamine's dose-dependent effects—dissociation at low doses and anesthesia at high ones—do not enjoy equal scientific interest. On the one hand, the favorable safety profile for vital functions during anesthesia has boosted ketamine into the medical hall of fame, making it a WHO-declared "essential medicine" since 1985. On the other hand, the shared phenomenology of classical psychedelics and low-dose ketamine, including a tendency towards "loss of the ego", has attracted recreational users. One of the psychedelic scene's most famous figures, John Lilly, was highly addicted to the substance for years. Partly for these reasons, the mind-body dissociation induced by low-dose ketamine has invoked a "dirty drug" image since its psychedelic dawn.

Ketamine has been recently identified as a possibly revolutionary antidepressant, but it is by no means clear how it works. It is possible that the dissociative "side-effect" is the key, bringing an inward journey that can be both blissful or frightening, with some believing that both of these states may be clinically helpful. For instance,

a depressed patient might confront the traumas that led to the development of their disease, following by a stage of regaining meaning in life.

However, many researchers follow a different path and are convinced that ketamine's antidepressant effects are separate from the psychoactive experience that it induces. Instead, they may be hidden deep in the brain's cellular pathways, some of which are yet to be fully described.

To keep up with the pace of newly generated insights, this brief review offers a description of the most important recent papers on ketamine's use in psychiatry and aims to integrate them into the larger picture of psychedelic medicine for depression.

Diagnosing depression

Depression is more than just being sad. Also called major depressive disorder, it is a devastating psychiatric illness and the leading cause of disability worldwide, affecting more than 300 million people.

In the Western world, depression is diagnosed by psychiatrists based on one of two available manuals: The Diagnostic and Statistical Manual of Mental Disorders (DSM) in the United States, or the European International Classification of Disease (ICD). The DSM's clinical criteria for diagnosing depression begin with depressed mood, or a loss of interest or pleasure in daily activities, for more than two weeks. Additional symptoms involve impaired social, occupational, and educational function. The ICD 10's criteria are similar, and split into three main symptoms: depressed mood, loss of interest, and loss of energy. At least two of these must be present for at least two weeks. Other symptoms are also common, including difficulty concentrating, decreased self-esteem, feelings of guilt, and disturbances of sleep and appetite.

Depression can be treated pharmacologically and non-pharmacologically, whereby both approaches aim to help the patient regain a stable sense of cognitive and emotional control. I will focus on pharmacological treatment options and the many pitfalls that must be overcome in order to treat depression successfully.

Clinical blindspots

Although the DSM and ICD have been the gold standard for decades, they have been increasingly criticized for the merely descriptive way they portray the subjective symptoms of a complex disorder. Consider the misfortune of being suddenly dismissed from your job, or even experiencing the death of a loved one. Both events might lead to a mental state which technically fulfills the criteria for clinical depression. But given sufficient time you are likely to recover, and probably without professional assistance or medication.

Because of this blind spot in our diagnostic criteria, some clinicians propose that the (neuro)biological mechanisms underlying depression should supplement the DSM and ICD. Furthermore, diagnostic criteria should be framed in the context of their cultural background, because some symptoms of depression may not be regarded as pathological by all societies. This would lead to a finer distinction between the already existing, but sometimes unclear sub-classes of major depressive disorder.

Promises of the past

A biological assessment of depression would provide valuable information about depression's largely un-explained etiology, as well as new ideas for treatment. In their thoroughly researched publication on anti-depressant drug development1, Vitor Pereira and Vinicius Hiroaki-Sato argue for a rational, evidence-based search for pharmacological interventions against depression. This would seem like a given in a science-driven

field like clinical psychiatry. Nevertheless, the historical application of antidepressants has fallen victim to overemphasis on clinical observations and the failure to acknowledge new theories.

Most antidepressants on today's market increase the active concentration of the neurotransmitters serotonin (5-Hydroxytryptamine, 5-HT) and/or norepinephrine (NE) in the brain, molecules belonging to the chemical class of monoamines. The chance discovery that led to the so-called "monoamine hypothesis of depression" occurred when patients who received reserpine, a drug used to treat high blood pressure, mysteriously developed symptoms of depression. Reserpine had lowered the amount of 5-HT and NE in the synapses by stimulating an enzyme called monoamine oxidase (MAO), which breaks down these neurotransmitters. Conversely, tuberculosis patients that received iproniazid—which inhibits MAO—experienced elevated mood.

Shortly after these discoveries, MAO-inhibitors ("MAOIs") were the first pharmacological agents on the market to treat depression. However, a big problem arose: MAOIs were not sufficiently effective and patients receiving them experienced serious side-effects, such as dangerous changes in blood pressure, excess sweating, sleep disturbances, weight gain, and hypertensive crisis. Consequently, physicians have become reluctant to prescribe MAOIs over the years. Tricyclic antidepressants, the generation following MAOIs, eventually met a similar fate.

Today's well-known and prevalent selective serotonin reuptake inhibitors ("SSRIs") were the first antidepressants that followed a rational drug design, with fluoxetine being the first SSRI to hit the US-American market in 1988. However, SSRI prescriptions also often fail to completely restore patients' psychological homeostasis. Roughly one third of patients do not respond to this treatment at all, and the time lag from first dose to clinical improvement can last up to several weeks, imposing an additional psychological burden on the patient.

Hopes for the future

A possibly groundbreaking discovery emerged at the beginning of this millennium. Robert Berman and colleagues reported that a single subanesthetic dose (0.5 mg/kg) of intravenous ketamine elicited an almost immediate antidepressant response in patients which lasted for several days. Many follow-up studies confirmed and expanded this result. Ketamine treatments appeared especially promising for severely depressed patients with suicidal ideation, and it was also particularly helpful for patients who had been treated unsuccessfully with two rounds of SSRIs, so-called "non-responders".

What did the scientific community do with these results? It was known that Berman's ketamine treatment scheme was accompanied by mild dissociative effects. But scientists attended more to the fact that ketamine does not alter 5-HT or NE levels, but rather affects glutamatergic neurotransmitter systems, suggesting that science might need a paradigm shift in the way it thinks about depression's etiology. Recent research has largely focused on ketamine's interactions with glutamate pathways, attempting to extract a biomarker which could help clinicians explain and treat depression on a larger scale.

Ketamine's dissociative effect, on the other hand, has been widely ignored or viewed as unwanted side-effect. That is to say, just like with the development of the unsatisfactory SSRIs, ketamine research has begun as an investigation into molecular underpinnings. Some scientists, however, are wondering whether this experience is important for ketamine's therapeutic benefits.

A new biology of depression

In March 2018, Panos Zanos and Ted Gould presented a detailed summary2,3 of ketamine's proposed antidepressant mechanisms. Believing that ketamine's dissociative properties are distinct from its antidepressant effects, they argue that the key to understanding ketamine's effectiveness comes from enhanced neuroplas-

ticity: Ketamine strengthens existing neuronal connections and facilitates the growth of new synapses. It does this through its pronounced activity as a non-competitive antagonist of a particular glutamatergic receptor, the NMDA receptor. In the “disinhibition hypothesis”, ketamine’s activity at NMDA receptors stimulates protein production, ultimately giving rise to new synaptic connections.

Apart from the disinhibition hypothesis, there are several other theories of ketamine’s action that result in the same outcome. One revolves around a metabolite of ketamine that is not an NMDA antagonist, but an AMPA agonist (AMPA is another glutamate receptor). This metabolite has antidepressant, but non-dissociative properties in mouse models of depression, further stimulating the authors’ conviction that ketamine’s psychoactive properties are irrelevant for its antidepressant effects. However, the problem of translating results from animal studies to humans, especially when it comes to mental disorders, is an important factor.

From cell to brain

If neuroplasticity plays a crucial role in ketamine’s antidepressant properties, how could establishing new neuronal connections help depressed patients? One speculation is that more neuronal connections allows the brain to gain more cognitive flexibility.

One of depression’s typical symptoms is that patients experience a seemingly inescapable loop of thoughts revolving around their own inferiority, a mental state called *rumination*. Rumination has been associated with the so-called *default mode network* in the brain, defined as the set of structures that are most active when we are not engaged with a specific task.6 The DMN is active, for example, when we think about ourselves. In depressive rumination it is functionally rigid, preserving a tendency towards a negative thinking pattern about oneself. Soon after ketamine enters the depressed brain – so the theory goes – the increase in neuroplasticity allows the DMN to connect with other brain areas.7 The overall brain dynamics become much less rigid, and the cognitive correlate of this may be that patients develop a less negative perspective on themselves.

Let’s go one step further. We’ve just gone from the molecular, single-cellular effect of ketamine to the systems level, the overall brain connectome. Beyond that, the subjective experience induced by ketamine may also play its part in treating depression. Examining molecular pathways with tedious laboratory may not provide the whole picture of ketamine’s antidepressant effects.

From brain to mind

In their manuscript “Ketamine for the Treatment Against Addiction: Evidence and Potential Mechanisms”, Ezquerra-Romano et al. mention Ketamine Psychedelic Therapy (KPT) as a model for using psychedelic experiences to treat depression.4 Mainly developed by the two Russian researchers Krupitsky and Grinenko, the theory behind KPT is that high doses of ketamine make it easier to remodel emotional beliefs related to problematic behavior, such as compulsive drug use. The treatment scheme of KPT entails positive verbal affirmations about creating meaning and a purpose in life, as well as affirmations devaluing the substance of abuse.

Many anecdotal reports of the early studies on KPT emphasize the subjective experience as an important aspect of its therapeutic effects. The motivation to quit may come in particular from mystical-type experiences and inner journeys – states in which patients are given the opportunity to face their individual roots of their depression through self-reflection, contemplation, and navigation through difficult emotions. These experiences can help patients to “undergo a cathartic process, improve relationships with the world and other people, maintain positive psychological changes and enhance self-awareness and personal growth.”4

Ketamine's characteristic dissociative effects may also be important, although scholars still disagree on this. In another study, Marc Niciu and his team found similar results: experiences of both derealization and depersonalization were modest predictors of the antidepressant effects of ketamine infusions. 5

The future of ketamine

In the acclaimed *Good Will Hunting*, Robin Williams' good-hearted psychotherapist gives a thoughtful lecture on the difference between knowledge and experience:

> "If I ask you about art, you'd probably give me the skinny on every art book ever written... But I'll bet you can't tell me what it smells like in the Sistine Chapel. You've never stood there and looked up at that beautiful ceiling... If I ask you about war, you'd probably throw Shakespeare at me: 'Once more into the breach, dear friends!' But you've never been near one. You've never held your best friend's head in your lap and watched him gasp his last breath. If I ask you about love, you'd probably quote me a sonnet. But you've never looked at a woman and been totally vulnerable."

This quote encapsulates the status quo that we are in with regards to research into ketamine as a novel antidepressant. We have a lot of literature on ketamine, but we lack practical and professional wisdom on the experiences that it can bring about. In today's pharmacological interventions against depression, treating symptoms is sometimes mistaken for treating the cause.

Psychotherapy has always been a valid approach to treating depression. Sessions aim to help patients open up so that deeply buried emotional pressure can be released and processed. If combined with ketamine or other psychedelics, this effect can be dramatically potentiated. In the future of depression treatment, we may see that the reductionist view and that of a psychotherapist don't contradict each other – they complement each other.

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