The following information is provided for use by qualified bioinformatics professionals to understand the role of ketamine and biosimilar neuromodulators in their near certain role relative to psychological and physiological health.

An inadvertent discovery in 2005 lead to the discovery of the fact that brain chemistry (neurohormones) have interactions and, when imbalances occur, the results can be behavioral health abnormalities.

As the discipline of epigenetics emerged, it became apparent that interactions and imbalances between cellular signaling that were configured in 3s were the primary cause of chronic diseases.

By 2007, another inadvertent discovery led to the fact that activities at the level of subatomic particles also existed in 3s (trefoils). Intrigued by the correlation, nearly 40,000 hours were dedicated to quantum mechanics and various iterations of physical science that included physical chemistry (inorganics) that reflect the agonistic, antagonistic and transitional activities of elements and minerals. It was at this point that MCFIP, Inc. discovered the ability to use bioinformatics to mine the data from research to identify the fact that minerals and elements were hidden in plain sight. In conjunction with MCFIP's discovery for the mechanism by which cell surface signaling molecules are formed[1], modeling tools were created to enable the identification of near certain causes of chronic diseases based on a verifiable and replicable model using physical science.

In addition to the discovery of an explicit model for endocytosis that transfers cell surface molecules into the cytoplasm[2], several other factors relative to cellular physiology have been added to MCFIP's portfolio for

[1] http://www.mcfip.net/upload/Cell%20Surface%20Signaling%20Molecule%20Formation%207-2017.pdf

[2] https://www.mcfip.net/upload/Endocytosis%20Modeling%204-30-17.pd

DNA repair mechanisms. However, to date, the most significant one has addressed the interactions between the neuropeptides in search of the cause of chronic pain that had been verified as being caused by mutation of neuropeptide Y (NPY) in glial cells in the hippocampus. In keeping with empirical evidence for interactions and imbalances that involve cellular signaling in threes, more than two thousand hours were dedicated to create an explicit and replicable model based on physical science that explained the interactions between the neuropeptides.

The Ketamine Role

When the activities of pancreatic polypeptide (PP or PPY) were identified, the mechanisms for brain derived neurotropic factor (BDNF) and nerve growth factor (NGF) both because obvious. The neuromodular serotonin was the primary factor for activation of BDNF. Many studies establish ketamine and other substances as biosimilars for serotonin. In addition to factors associated with brain chemistry, these finding and those associated with "downstream" imbalances between the three neuropeptides can be verified as primary cause of chronic physiological and physiological diseases.

Summary

An understanding of the cellular roles of neuromodulation can provide guidance to identify the benefits and hazards associated with the use of ketamine or its biosimilars.

https://www.theguardian.com/science/2019/mar/23/ketamine-can-it-really-be-antidepressant

Ketamine: can it really be an antidepressant?

A version of the club drug licensed in the US could usher in a wave of fast-acting treatments, but experts are worried

David Cox

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‘It was like a spring breeze had blown through my head’: for some patients with depression, the benefits of ketamine can last for weeks.

Claudia Kieffer remembers the first time she encountered the drug she describes as having “saved my life”. Eight years ago, Kieffer, who had suffered from treatment-resistant depression for decades, was given ketamine as a routine anaesthetic, as part of a post-mastectomy breast reconstruction procedure.

But as well as alleviating the pain, Kieffer noticed an instantaneous change in her state of mind.

“My head suddenly felt different to any previous time in my entire life,” she says. “I wasn’t high. It wasn’t like I had smoked a joint or had morphine. It was like a spring breeze had blown through my head and just cleaned out all the detritus that had built up over years and years. And when you’ve suffered from depression for as long as I had, it feels like you’re drowning. So when something comes along that makes you feel so very different and healthy, you want to know what that drug is.”

At the time, Kieffer had tried almost every depression-related treatment available, without success. “I’d had three nervous breakdowns and been hospitalised three times,” she remembers. “I’d had 13 rounds of electric-shock therapy and it didn’t help. When I was in my 20s and 30s, I would self-medicate, just because that’s what you do when you don’t know what else to do. I was thinking about taking my life every single day. I just wanted to fall asleep and not wake up.”

But unbeknown to her at the time, a growing number of clinical trials was already investigating the potential benefits of ketamine infusions as a treatment for depression. Two years after her operation, Kieffer enrolled on one such study, run by the US National Institutes for Health.

Traditional antidepressants take several weeks before patients feel any relief, but ketamine works in a matter of hours

“The researchers were astounded at how well it worked for me,” she says. “There were other patients for whom the effects lasted for maybe a day, but for me it was two weeks. So after that I began going to a treatment centre once a month for an infusion and now that’s how I live. If I go too long without it, things can quickly slip back. But I have hope now.”

Kieffer is far from alone. There are thousands of similar stories, both in the US and the UK, where psychiatrists sometimes prescribe ketamine off-label as a last-ditch treatment for the estimated 12-20% of depression patients for whom every other medication has failed. For while ketamine is best known in modern culture as either a powerful anaesthetic – when applied in large doses – or "Special K", the club drug with mind-bending psychedelic effects, its new use is rapidly gaining momentum.

In the US, the Food and Drug Administration(FDA) recently made the landmark decision to officially license a ketamine-related drug called Spravato as a medication for depression. As the first novel regulatory-approved treatment for the condition in more than 30 years, it comes with vast expectations. But experts warn that it isn't necessarily a "miracle cure" – it can come with side-effects and nothing is known about the risks of using it long term.

The main reason why ketamine has attracted so much attention is the rapid effect it can have on patients who have exhausted all other treatment options. While traditional antidepressants take several weeks before patients feel any relief, ketamine works in a matter of hours and the benefits of a single dose can last for up to a week. Because of the speed with which it works, doctors in the US will often administer ketamine infusions to emergency room patients who have attempted to kill themselves.

One of the complexities of depression is how diverse it is. There can be a spectrum of symptoms and, unlike other antidepressants, ketamine appears to have wide-ranging benefits across many of them. Studies have shown positive effects in patients with anxious bipolar depression, PTSD, anhedonia or loss of pleasure and suicidal thoughts. All this led Thomas Insel, the former director of the US National Institutes of Mental Health, to describe ketamine as potentially "the most important breakthrough in antidepressant treatment in decades". MCFIP - In our opinion, ketamine is classified as an antidepressant because the mental health research community has been unable to identify the role of neuromodulation as part of the interactions between the three neuropeptides and the role of BDNF as part of pancreatic polypeptide to provide homeostasis with neuropeptide Y.

"What's particularly interesting about ketamine is that it has multiple effects throughout different brain biologies," says Dr Carlos Zarate, head of experimental therapeutics and pathophysiology at the US National Institute of Mental Health, who conducted the first clinical trial of ketamine for depression in 2006. "This makes it much more unique than other treatments. Many of the symptom domains seen in depression, but not all, seem to respond to it."

The reason scientists were driven to try ketamine in the first place is because of long-standing theories that it blocks receptors in the brain that interact with the neurotransmitter glutamate, a key brain chemical long implicated in mental illnesses. But they are still trying to tease apart exactly how it works.

Research is also ongoing into MDMA, or ecstasy, which is being trialled for use in treating PTSD.

Intriguingly, ketamine's antidepressant effects appear to take place after it leaves the body, which is something scientists don't understand. One idea is that it triggers the brain to regrow connections between cells that are involved in mood, but no one really knows for sure.

At the same time, ketamine does not always work. There have been other studies where few patients benefited, while the cost of infusions at private clinics in the US – estimated from $350 to nearly $1,000 – has proved prohibitive for many patients. Concerns have also been repeatedly raised about its known side-effect profile, which can include hallucinations and out-of-body experiences following treatment, as well as fluctuations in blood pressure.

Part of the reason that Spravato has been developed, and now approved by the FDA, is to try to make ketamine more accessible. The $900 cost per treatment will be covered partly by health insurance and its being administered as a nasal spray reduces the risk of side-effects compared with an infusion. The only snag is that it's not technically ketamine.

Ketamine is made up of two mirror-image molecules, so in order to turn it into a potential cash cow, pharma company Janssen patented the left one – esketamine – and turned it into a drug and named it Spravato. The problem is that there's not a huge amount of evidence that it's as effective as ketamine infusions. For a start, Spravato has only been studied in four fairly small phase III trials, three of which lasted only four weeks. The results were decidedly mixed and some scientists have pointed out that the FDA relaxed its usual rules for accepting drugs, in order to let it through.

"I didn't find the evidence persuasive," says Julie Zito, professor of pharmacy and psychiatry at the University of Maryland. "They evaluated the efficacy using symptom score change and there was only a three- to four-point improvement on a 60-point scale, which you have to say is very modest. And that is what the whole thing hangs on. And the FDA created this new innovative study category, which means they only required one randomised, double-blind placebo-controlled trial, not two, which is usually the criterion for a new drug."

Cannabis plants at a medical plantation in Israel. The drug is used to treat anxiety-related disorders.

Scientists in favour of the drug argue that there should be some leniency, given the lack of existing treatments for patients with severe depression, but Zito says the clinical trials also raised some serious safety concerns.

"I'm concerned about the hallucinations that were prominent in some individuals," she says. "You're going to have people coming to a clinic, receiving a dose, waiting for two hours… and we don't know what's going to happen after that. There were three suicides that all occurred in the Spravato-exposed group, and a fourth death that, for me, was suspicious: a motorcycle accident in which a man drove into a tree soon after the dosing.

The manufacturer claims that all those events are unrelated to use of the drug, but nothing like that happened in the placebo group."

With depression being a chronic condition, there is also the possibility that patients may need to continue treatment over a period of years or even decades. Little is known about the long-term effects on the body of either Spravato or ketamine infusions.

But as Zarate points out, given the lack of options for patients, the benefits that could come from treatment may well outweigh any potential risks.

"Depression causes cognitive problems, heart and lung problems, bone problems, as well as the risk of death from suicide, so when it comes to treating patients with ketamine for long periods of time, it's a risk-benefit judgment," he says. "To leave the body in that ongoing state is not good either. But nobody's saying we're not continuing to study ketamine. If there are complications and side-effects that we don't know about, we will find them."

Such is the expectancy around Spravato that analysts have already predicted the drug will generate more than $600m in sales by 2022, despite the relative paucity of studies demonstrating its benefits.

Its effects may also be wide-reaching, potentially paving the way for a new class of rapid-acting antidepressants. In recent years, researchers have begun to re-examine other psychoactive substances which were first touted as potential antidepressants in the 1950s, such as psilocybin, the active ingredient in magic mushrooms, and MDMA. Some clinical trials have already suggested it could have beneficial effects on patients.

Psilocybin, as found in magic mushrooms, is being tested for use on patients with clinical depression resistant to other treatments.

But there is a dark side to the rise of ketamine – and, in future, potentially psilocybin – about which scientists have long been concerned. Such is the hype around the possible benefits of these treatments that the potential for their abuse among patients looking to self-medicate is very high. Dr Rupert McShane, who leads the UK's only ketamine treatment centre, says there's a need to set up a register that monitors exactly what patients are taking, in order to get accurate information about long-term harms within the population.

"It is possible that people will end up treating themselves with ketamine obtained illegally," McShane says. "One of the things that happens with ketamine is [that]because

it makes you feel better so quickly, when you relapse you want to take it again. And when the dosage and frequency get too high, that's when it becomes toxic. So it's important to track treatments, because one of the issues in the opiate addiction epidemic was the difficulty of getting any data that showed the extent of the problem."

Zito also fears that the hype around ketamine could lead to patients seeking treatment when they aren't sufficiently ill enough to require it. "There's been a huge expansion in what constitutes depression," she says. "There are low-moderate depressives who are going through a divorce or struggling with a new job… what they might really need is counselling. But in the US, we love our pills and simple solutions to very complex problems."

Kieffer's main hope is that the FDA's approval of Spravato will reduce the stigma and negative associations around ketamine treatment.

"People kept referring to it as the club drug and I would love it if we could just erase that from the vocabulary and say the 'depression drug,'" she says. "It's frustrating as a patient to have to constantly defend myself for taking it, because people also use it to get high. I don't know anything about that. All I know is that it's given me my life back. "