Newsletter of the Mood Disorders Support Group—New York

# MOODS

Serving People with Unipolar and Bi-polar Illness, Their Families and Friends, since 1981 March 2019

## What New Antidepressant Treatments Are On The Horizon?

By Dr. David Hellerstein, M.D.

Interesting question! After a decade-long drought, we finally have some interesting new treatments in the pipeline. For a long time, the pharmaceutical companies have been reluctant to invest in new products, because it was hard to figure out something better than SRI (serotonin reuptake inhibitor) medications, which are reasonably effective, and have largely gone off patent and thus are (or should be) dirt-cheap.

A few SNRI (serotonin-norepinephrine reuptake inhibitors) came out in recent years, like Fetzima, along with tweaked SRIs such as Vilazodone, which claims more antianxiety effects than the regular SRIs, and Vortioxetine, which may have some benefit on cognitive symptoms. But they were at best a minor tweak on the SRI formula.

Interestingly, the new medicines, either on the verge of approval or in the development pipeline, *aren't* SRIs—they work by other mechanisms, which is great since we really have needed alternatives when SRIs don't work.

Here are three new treatments under study that may quickly change the landscape of depression treatment:

### KETAMINE

At this point nearly everyone has heard of ketamine. An anesthetic medicine, often used in veterinary medicine, it was known to have hallucinogenic effects. Back in the day it was a club drug, fondly known as Special K. But is it special? Perhaps so, but not in the way ravers might have thought. Over the past decade, ketamine has been studied for its rapid onset of antidepressant effects—often within hours.

Ketamine works by 'modulating' the glutamate neurotransmitter system. Beyond improving depression, its most striking benefit is that it may rapidly reduce suicidal ideas—and thus could potentially play a significant role in emergency rooms and inpatient psychiatric units. On the other hand, as noted in a recent *NY Times article*, lightly regulated ketamine treatment centers are now springing up through the country, providing intravenous infusions, often with little psychiatric staffing: many are operated by anesthesiologists, not mental health specialists.

An intranasal form of ketamine (esketamine, brand name Spratavo) has just been approved by the FDA. In some ways esketamine is easier to administer than regular ketamine, since it only requires a few sniffs from a small device rather than an intravenous line. Spratavo will only be available in doctors' offices, where it will be administered under supervision. That's good because there may be a high risk of abuse if it's not used properly.

We psychiatrists don't yet know how to best maintain ketamine's benefits after initial improvement. Many ketamine centers are providing monthly maintenance treatments, without data about risks or benefits. Cost is another issue since IV ketamine isn't FDA approved for depression and often isn't covered by insurance (though this is changing). IV ketamine costs in the range of $400 to $800 per infusion plus $300-600 for the initial MD consultation. Spratavo costs $4720 to $6785 for the first month of use and $2360 to $3540 per month after that! Insurance may cover part of that cost.

A number of other glutamate modulating medications are in the process of clinical development, some of which will be taken orally.

*Bottom line:* It's hard to know at this point whether these medicines will be a significant and lasting depression treatment advance or not.

### HORMONES

Another interesting class of medicines under FDA fast-track development is hormonal. Brexanolone and Ganaxolone are two new medicines in clinical trial development for post-partum depression. Both are forms of allopregnanolone, a naturally occurring hormone. Postpartum depression is the first target, since changing hormone levels around childbirth may cause depression in vulnerable women. It seems likely that they will be studied for other forms of depression as well. They also may have a rapid onset

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# New Antidepressant Treatments

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of action—within hours to days rather than weeks to months. Postpartum depression is a devastating condition, not only for the mother herself but also for her child and her extended family, with effects that can last for decades. It has been very much neglected in research in the past, so it's encouraging that there are studies underway of possible treatments.

*Bottom line:* Promising for postpartum if the studies pan out. May benefit other conditions.

## HALLUCINOGENS

Then we have the hallucinogens. In the '70s, research on hallucinogens came to a screeching halt after the Controlled Substances Act of 1970 categorized them as Schedule I, as having 'no currently accepted medical use.' These compounds, including LSD, MMDA, DMT, psilocybin, and ayahuasca. (Unlike ketamine and allopregnanolone, the hallucinogens do work through the serotonin system, but not in the same way as the SSRIs—rather than blocking reuptake inactivation of serotonin, hallucinogens stimulate 5HT2A serotonin receptors, and indirectly affect glutamate).

The most fascinating thing to me about the hallucinogens is that they are being developed as combination pharmacological AND psychotherapy treatments: drug treatment that requires a guided psychotherapy interaction. It's a medical variation on the spiritual guides or shamans who traditionally took part in hallucinogenic rituals.

It's a fascinating thing to see the massive -- and often controversial -- culture change here! In any case, we're in the infancy of understanding the possible risks and benefits of hallucinogens in depression treatment. *Example:* antidepressant treatment with psilocybin as reported by a London researcher involved just *a single pill* of psilocybin, which led to lasting antidepressant benefit. What changes are occurring in the brain? Does psilocybin cause permanent resetting of brain circuitry or activity? If so, how exactly does that occur? And what are its risks and benefits?

*Bottom line:* Paradigm-changing...if they work.

Of these medicines, only esketamine is yet ready for prime time. Off label ketamine use is exciting but somewhat worrisome. We (doctors and patients alike!) are so eager for new treatments that it's possible there will be a rush to adopt the new treatments before we really know their risks and benefits. Who will they work best for? Who should stay away from them at all costs? We don't know that yet.

But practice changes are happening faster than those questions can be answered. Besides ketamine clinics, hallucinogen use (with microdosing and regular dosing) has become mainstream. So the story is only now being told... stay tuned!

*Disclosure:* My research program at Columbia is involved in studies of ganaloxone and psilocybin, and I have collaborated with studies of esketamine. We also have done studies with vortioxtine and other SSRI and SNRI medications.

*Dr. Hellerstein is a medical advisor to and a board member of MDSG.*

# Books of Interest

Grisel, Judith. Never Enough: The Neuroscience and Experience of Addiction. Doubleday, 2019. 256p.

The author is not only a former addict, but also a behavioral neuroscientist.

Miklowitz, David J. The Bipolar Disorder Survival Guide: Third Edition. Guilford Publications, 2019. 420p.

Wilson, Sarah. First We Make the Beast Beautiful: A New Journey Through Anxiety. Dey Street Books, 2018. 320p.

The author takes a deep dive into the science of mental illness and the specific habits that have helped her cope with her own disorder.

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