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'Party drug' turned antidepressant approaches approval

Johnson & Johnson has submitted its esketamine for regulatory approval, but researchers still don't understand how the fast-acting antidepressant lifts moods.

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When researchers showed in 2006 that the anaesthetic ketamine — also known as the club drug Special K — was a rapid and potent antidepressant, big pharmaceutical companies quickly jumped into the game. Extensive efforts to improve on decades-old antidepressants had floundered, but ketamine finally promised a novel mechanism of action and the potential to help treatment-resistant patients.

Because ketamine is an old drug and difficult to commercialize for a new indication, early entrants into this space set out to build ketamine mimetics that could replicate the anaesthetic's effect, ideally without its hallucinatory side effects. A few of these ketamine-inspired drugs are now nearing the finish line (TABLE 1). In September, Johnson & Johnson (J&J) filed for FDA approval of a nasal spray containing esketamine — an isomer of ketamine that the company has patented. Despite some lingering questions about its efficacy compared with ketamine, experts in the field expect the drug will be approved, providing the first antidepressant breakthrough in decades.

"What's exciting is not that there's going to be a new drug approved, but that we're going to have a whole new class of drug approved," says psychiatrist James Murrough at Mount Sinai Hospital. "Everyone's waiting with bated breath."

This is fostering high hopes that psychiatric drug development — which has seen an exodus of major pharma companies owing to continuing failures — could be poised for a renaissance. The number of ketamine trials has skyrocketed, not only in depression but also for obsessive–compulsive disorder, post-traumatic stress disorder and even chronic pain. "If ketamine works and we understand the effects of ketamine on these different disorders, it could really open the way for drug discovery," says Lisa Monteggia, a neuroscientist at Vanderbilt University.

Yet it is far from clear how this work will play out. Whereas early evidence suggested that ketamine acted through the NMDA receptor, many of the first-generation ketamine mimetics that were designed to act on this target failed in clinical trials (TABLE 1). Accumulating evidence now suggests that ketamine's antidepressant activity may be more complicated.

As a result, some companies are quietly going back to the drawing board. "My sense is that NMDA-receptor blocking studies are diminishing quite quickly and people are looking at other mechanisms," says psychiatrist Carlos Zarate at the National Institute of Mental Health (NIMH). While NMDA blockers haven't been abandoned, he says, "companies are just giving a second thought to whether they want to continue pursuing these programmes." Until a clearer picture of the mechanism is worked out, the field may be doomed to a trial and error hunt for better-than-ketamine mimetics.

Novel antidepressant activity

The most commonly used antidepressants target signalling by the monoamine neurotransmitters serotonin, dopamine and noradrenaline. But starting in the 1950s, researchers using the antibiotic D-cycloserine to treat tuberculosis found that the drug alleviated patient melancholy. Researchers later learned that the antibiotic, at low doses, blocks the NMDA receptor, a glutamate receptor. Then in the late 1990s, when psychiatrist John Krystal of Yale University was curious about whether the neurotransmitter glutamate contributed to schizophrenia, he decided to test the known NMDA receptor antagonist ketamine in nine depressed patients.

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At the time, glutamate had mostly been studied for its role in learning and memory. But Krystal's group found that ketamine induced a rapid improvement in mood in patients.

Zarate and Husseini Manji, who is now head neuroscience researcher at J&J, set out to replicate the surprising findings at the NIMH in a larger trial, enrolling 18 subjects with major depression. The results from this small study suggested that ketamine was a miracle drug — lifting a person's mood almost immediately. Reporting in the *Archives of General Psychiatry*, they showed that 70% of depressed patients responded to ketamine within 24 hours. By contrast, in one of the largest studies of people with depression, only one-third of patients responded to selective serotonin reuptake inhibitors (SSRIs) after 8 weeks.

Ketamine also appears to reduce suicidal thoughts — something that no other drug is known to do — and its effects last for weeks to months.

"Ketamine works so well it would be hard to do better," says neuroscientist Todd Gould of the University of Maryland. Some clinics have taken this conclusion to heart, and are already offering ketamine to depressed patients on an off-label basis (BOX 1). Drug developers have meanwhile been working hard to make next-generation alternatives, armed with a preliminary hypothesis for how the drug lifts moods.

When ketamine is used as an anaesthetic or a hallucinogen, it blocks the NMDA receptor. This in turn stimulates the release of a glutamate burst, which is believed to be responsible for the drug's hallucinatory

Table 1 | **Select list of ketamine mimetics as antidepressants**

Drug	Company	Mechanism	Status
Esketamine	Janssen/J&J	NMDAR antagonist	NDA
Rapastinel (formerly GLYX-13)	Allergan	NMDAR partial agonist	Phase III
AV-101	VistaGen Therapeutics	NMDAR antagonist	Phase II
NRX-101 (D-cycloserine plus lurasidone)	NeuroRx Pharma	NMDAR modulator plus 5-HT_{2A} receptor antagonist	Phase II
AGN-241751	Allergan	NMDAR modulator or partial agonist	Phase II
AXS-05 (dextromethorphan plus bupropion)	Axsome Therapeutics	NMDAR antagonist plus norepinephrine and dopamine reuptake inhibitor	Phase I
Traxoprodil	Pfizer	NMDAR antagonist	Discontinued
Lanicemine	AstraZeneca	NMDAR antagonist	Discontinued
Decoglurant and basimglurant	Roche	mGlu modulators	Discontinued
Rislenemdaz	Cerecor/Merck & Co.	NMDAR antagonist	Discontinued

5-HT_{2A}, 5-hydroxytryptamine receptor 2A; J&J, Johnson & Johnson, mGlu, metabotropic glutamate receptor; NDA, new drug application; NMDAR, *N*-methyl-D-aspartate receptor.

effects. The neurotransmitter then stimulates other receptors that control gene transcription to enable rapid rewiring of brain circuits. This rewiring, or plasticity, is thought to cause the antidepressant effect.

When developing a pharmaceutical version of ketamine, companies have generally decided to target the start of this pathway. J&J, for instance, chose to develop the *S*-enantiomer of ketamine because it is four times as potent at blocking the NMDA receptor as regular ketamine, which is a mix of *R* and *S*-enantiomers. J&J's Manji says that the company has no plans to compare its product directly with ketamine in a clinical trial. But overall, esketamine's side effects — including hallucinations — seem similar to the original drug.

The company recently published results from two phase III studies on depression, and will conclude a suicidal ideation trial next year. Clinical trial results were mixed, however. In one study of 223 participants, esketamine significantly reduced depression at 28 days. But the results were not as strong as the company had anticipated, and esketamine took longer to take effect than ketamine and missed its secondary end point of lifting mood within 24 hours. In the second study in 138 people over 65 years old, the drug missed its primary end point.

Nevertheless, these results have buoyed hopes for glutamate-based antidepressants. Whereas Pfizer, AstraZeneca, Roche and others terminated development of NMDA receptor modulators for mood disorder in recent years owing to failed trials or severe side effects, researchers hope that success for J&J will lift all boats.

"I think once esketamine is approved, and it becomes likely a multibillion-dollar drug, you'll see big pharma coming back," says drug researcher Ronald Duman at Yale University.

Upping the AMPA?

Basic research on ketamine's mechanism of action complicates future ketamine-mimetic discovery plans, however. In 2016, Gould and Zarate published a startling paper in *Nature*, proposing that a metabolic byproduct of ketamine — not the drug itself — was responsible for the mood altering activity in mice. The metabolite (2R,6R)-hydroxynorketamine, or HNK, didn't seem to interact with the NMDA receptor at all. Nor did it appear to cause the hallucinatory side effects of esketamine, even at doses nearly 40 times greater than the normal dose of ketamine.

The result suggested that drug developers may have been going after the wrong target all along. "It definitely created a stir," says Murrough. "It contributed to a realization that we don't really know how ketamine is working, and whatever the mechanism is, it's not simple."

> "Ketamine works so well it would be hard to do better"

Others aren't ready to give up on NMDA inhibition just yet. Monteggia reported earlier this year in *Neuropsychopharmacology* that when she repeated a similar experiment, she found that very high levels of HNK could indirectly block the NMDA receptor through an as-yet-unknown mechanism.

J&J's Manji is also skeptical about reading too much into the effect of HNK in mice. If the NMDA receptor is uninvolved, the company's esketamine nasal spray should not work as well as it has, Manji says. He suspects that previous NMDA antagonist failures can largely be chalked up to dosing problems and side effect profiles, rather than a problem with the target itself.

Researchers are trying to reconcile these various results. For instance, ketamine might quickly reverse depression by blocking the NMDA receptor, but perhaps HNK is responsible for maintaining the effect over time, says Monteggia. Zarate and Gould are planning to file for FDA permission later this year to start clinical trials with HNK in 2019, which they say should be able to answer some of these questions.

Other studies add further complications. In August, a twelve-patient study led by Alan Schatzberg of Stanford University suggested that ketamine might be acting through the opioid system and not the glutamatergic system at all. The researchers gave depressed patients naltrexone to block the opioid receptor before administering ketamine, and found that this eliminated ketamine's antidepressant effects but not its hallucinatory side effects.

Box 1 | **Ketamine clinics**

Although the FDA has not approved ketamine for depression and most insurance companies do not cover it, an estimated 300 clinics are already providing off-label ketamine to depression patients.

Some researchers consequently question the need for next-generation drugs such as esketamine. "It's not going to do anything ketamine doesn't do, but it will cost 10 to 100 times as much as ketamine," says Scott Thompson, a neurobiologist at the University of Maryland. "If esketamine is safe enough to release into the general population, then ketamine is safe enough. It's a backwards way to get a drug approved."

But ketamine is not a perfect drug, either. In 2017, researchers published a consensus paper for the American Psychiatric Association that included guidelines for physicians prescribing ketamine for depression. Among other recommendations, the paper said that ketamine should only be used in the clinic and not sent home with patients because of the potential for abuse. It also warned about the lack of long-term data and the acute risks for people with heart conditions.

Esketamine faces similar limitations, and if approved will also be administered in the clinic.

Promising data from Allergan's lead antidepressant rapastinel, an intravenous drug in phase III trials for depression and suicidality, adds another wrinkle. Whereas ketamine and esketamine block the NMDA receptor, rapastinel is a partial agonist of the NMDA receptor. Phase II data suggest that the drug relieves depression quickly and that its effects last for several weeks. Phase III trials are currently underway, with first pivotal results expected next year.

And Allergan is doubling down on the mechanism. In May, the company bought rights to an experimental oral drug AGN-241751, which targets the NMDA receptor and is currently in phase II trials for depression.

"It's really hard to reconcile all those different studies into a unified model," says Gerard Sanacora, a psychiatrist at Yale University.

But he, Gould and others believe that studies are beginning to home in on one convergent mechanism: a glutamate receptor known as AMPA, which is activated when glutamate levels increase and that stimulates brain rewiring. Ketamine, HNK and rapastinel all activate AMPA receptors, and animal studies have shown that directly blocking AMPA receptors eliminates the antidepressant effects of these drugs. Yet targeting AMPA receptors directly tends to raise the risk of seizures, Sanacora cautions, making it unlikely that AMPA receptor agonists could be turned into therapeutics.

Allergan's chief R&D officer David Nicholson, meanwhile, remains unfazed by the lingering uncertainty about the mechanism of action of ketamine-inspired drugs — as long as the drugs work. "We didn't know really how tricyclic [antidepressants] were working, or how SSRIs were working," he says. "You can debate if we really know that today, to be frank."

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