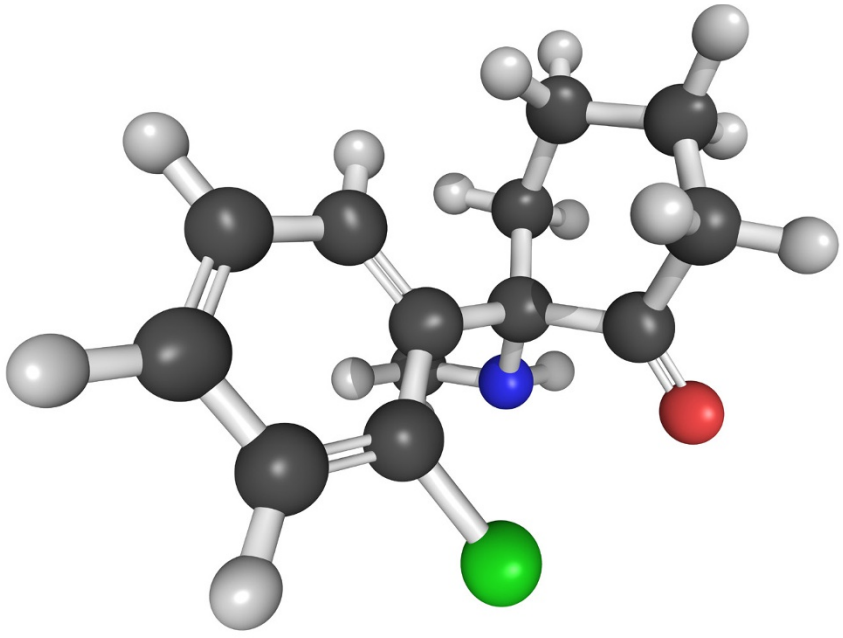

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Ketamine therapy: Scientists are tapping into ketamine's benefits while overcoming its side effects.

time of memantine. The company completed a multiple-ascending-dose trial a year ago, which identified a dosage range for the medication and determined that the drug was safe for healthy individuals.

The demand for fast-acting antidepressants, however, has caused some companies to re-evaluate their research on NMDA-receptor antagonists. Relmada told *Nature Medicine* that it has identified a greater market demand for drugs that can treat depression—another area in which researchers see a role for NMDA receptor antagonists. Last year, the company switched its focus from exploring d-methadone's use for chronic pain to its use for major depression. Relmada intends to return to the pain trials after it has completed its depression studies, according to Mangano.

> "It was the classic Goldilocks dilemma. We needed something that was just right."

In a departure from Relmada's strategy of blocking the ion channel in the NMDA receptor, VistaGen Therapeutics, a small biopharmaceutical company in San Francisco, has developed a drug called AV-101 that prevents glycine from binding to the NMDA receptor and so prevents the ion channel from opening. Unlike ketamine, AV-101 does not cause hallucinations or agitation, and it can be given in pill form. A phase 1 safety trial in healthy individuals, conducted in 2012, showed that the drug is safe. Participants also reported improved mood, which led VistaGen to begin investigating the drug as a potential antidepressant and to temporarily halt its exploration of the drug as a chronic-pain treatment.

VistaGen is not the first company to develop a compound that blocks glycine from attaching to the NMDA receptor. GlaxoSmithKline, for instance, had success with a similar therapeutic in rat models, but human trials for neuropathic pain failed to show any benefit from the drug. In one study, of 63 patients enrolled in the trial, neither the placebo group nor the group receiving the experimental drug GV196771 reported any difference in pain levels[7].

Similarly to Relmada, VistaGen has shifted its NMDA research away from chronic pain, says Mark Smith, chief medical officer at VistaGen. "We're all definitely still interested," he adds, but the potential payouts from the development of a rapid antidepressant have caused the company to put the development of drugs for pain on the back burner for now.

Spinning off

Not everyone has been lured away from the chronic-pain field, however. Northwestern University neurobiologist Joe Moskal founded Naurex, a company that developed an NMDA receptor modifier known as GLYX-13 for the treatment of depression. Naurex was bought in July 2015 by Allergan for $560 million to further develop the product, now called rapastinel, but Moskal is continuing to work on the drug. After founding another company called Aptinyx, Moskal is using GLYX-13 as a scaffold "to build fully synthetic molecules that are orally deliverable for use in chronic pain," he says. The GLYX-13-based molecules that Aptinyx is building are currently under exploration in animal studies.

Jamie Sleigh, an anesthesiologist at the University of Auckland in New Zealand, says that although NMDA-receptor antagonists hold promise, pharma still has a long road ahead. Even though the drugs seem safe and show efficacy in animal models, the field is littered with similar drugs that ultimately failed in phase 2 and 3 trials. He also notes that chronic pain is a complex process, and so targeting the NMDA receptor alone might not be sufficient. "Chronic pain essentially rewires the brain and changes gene expression. It's still not clear how to reverse that process, with ketamine or any other drug," Sleigh says.

Cosgrove has been receiving ketamine infusions off and on for five years now, and is anxiously watching the field. "They're coming out with new things all the time. Maybe the next drug will work even better than ketamine," she says.

Carrie Arnold is a freelance science writer based in Richmond, Virginia.

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Correction

In the October 2016 issue, the piece "Reservoirs of resistance: To understand why antibiotics fail, geneticists chase the 'resistome'" (*Nat. Med.* **22**, 1069–1071, 2016) incorrectly stated that PCR sequencing is a form of short-read sequencing. The article also incorrectly attributed a quote to Justin O'Grady instead of to Gautam Dantas. These errors have been corrected in the HTML and PDF versions of this article.

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