

The promise and perils of ketamine research

Ketamine began its life as an anaesthetic, but has enjoyed a recent renaissance as a potential treatment for a range of neurological and psychiatric disorders. However, some scientists worry that drug regulations are getting in the way of valuable research. Carrie Arnold investigates.

For Goadsby and colleagues' study of ketamine to treat migraine with aura see *Neurology* 2013; **80**: 642–47

For the study of ketamine's rapid antidepressant action see *Neuropsychopharmacology* 2013; **38**: 729–42

For more on the roles of NMDA receptor modulators see *World J Biol Psychiatry* 2012; **13**: 482–92

For the study into ketamine's effects on complex regional pain syndrome see *CNS Drugs* 2012; **26**: 215–28

For the Australian study of ketamine's antidepressant effects see *Pain Med* 2006; **7**: 92–95

Peter Goadsby's work had hit a major roadblock. He had been trying to set up a study with ketamine to discover the mechanisms that contribute to visual and somatosensory auras in a group of people with migraines, but the Institutional Review Board (a joint ethics committee of the University College London Hospitals NHS Trust and the Institute of Neurology, University College London, UK) had told Goadsby that ketamine was too dangerous to use on such a group of patients.

"Some of these people are debilitated by their migraines and auras—they're not able to get out of their bed for days", Goadsby said. "This problem is much more severe than anything posed by ketamine." Goadsby argued that animal studies had shown that the receptor for ketamine was involved in migraine auras, and that ketamine had been used safely as an anaesthetic for decades. Still, the committee balked. Only after Goadsby added an extra (and costly) safety group to the trial was his study finally allowed to proceed. His persistence paid off. In a paper published earlier this year in *Neurology*, Goadsby and colleagues reported that ketamine could reduce the severity of aura in people with migraines.

Goadsby's experience is being echoed worldwide. Ketamine has shown promise as an antidepressant that acts within minutes to hours, rather than weeks or months, according to a recent study in *Neuropsychopharmacology*. Other studies have shown that ketamine might help in other psychiatric diseases, such as bipolar disorder, obsessive-compulsive disorder, and post-traumatic stress disorder.

Neurologists have shown other benefits of ketamine. The drug can help to relieve post-surgical pain, it has shown potential in reducing complex regional pain syndrome (according to a review in *CNS Drugs*), and it might help to alleviate some symptoms of traumatic brain injury and stroke by preventing further neural injury. However, although the therapeutic potential for ketamine is expanding in both neurological and psychiatric circles, an increase in regulatory and legal difficulties in undertaking ketamine research seems to be hampering these efforts.

Ketamine's popularity in the laboratory has been matched by its popularity on the streets. Its potential for misuse, including addiction and use as a date-rape drug, has led many countries to try to strictly control access to ketamine. Some researchers argue that these drug laws haven't necessarily made it harder for people to get ketamine on a street corner, but have greatly impeded scientists' abilities to research the drug's potential benefits.

"Researchers get frustrated and say they won't bother", says David Nutt, a neuropsychopharmacologist at Imperial College London, UK. "On all levels everywhere, this really impedes the speed of research."

Almost 50 years ago, scientists at Parke-Davis (which was bought by Pfizer in 2000) were experimenting with chemical derivatives of phencyclidine to find those that would have the same anaesthetic effect but with a shorter duration of action and fewer psychotic side-effects. The result of their chemical tinkering was ketamine, which, like phencyclidine, also blocked the actions of the NMDA receptor and was used as a dissociative anaesthetic. The drug's dissociative

properties also led to its misuse and popularity in clubbers.

For several decades, ketamine research stalled, and the drug's main medical use was for anaesthesia. However, trials of low-dose ketamine infusions for complex regional pain syndrome showed an unexpected side-effect: several patients with depression reported that their symptoms lifted almost immediately after their ketamine infusions. In 2006, researchers at MacKay Base Hospital in Queensland, Australia, reported the first formal study of ketamine's immediate antidepressant effects in *Pain Medicine*.

Although this study focused on the potential psychiatric effects of ketamine, the results triggered neurologists to start asking questions about the drug's ability to treat other disorders. Neuroscientist Jed Hartings, at the University of Cincinnati in OH, USA, had been studying a phenomenon called spreading depolarisation. "It's a seizure-like event that we've nicknamed a brain tsunami", Hartings said. It can occur after any type of acute brain injury, but is mainly studied in the context of traumatic brain injury and stroke. The occurrence of a brain tsunami, Hartings said, is consistently associated with worse outcomes. "Spreading depolarisations are both a marker for more severe trauma and brain injury as well as creating more damage in and of itself", he added.

The medical community has tried to target these injuries with therapeutics for the past 15 years, and studies in human beings and animals showed that NMDA receptor antagonists may be the most effective drugs at halting or preventing spreading depolarisation.

Since other NMDA receptor antagonists like dextromethorphan and phencyclidine are toxic, Hartings and collaborators at Heidelberg University Hospital, Heidelberg, Germany have focused on ketamine. In an observational study published in *Brain*, Hartings followed 115 patients with traumatic brain injury, subarachnoid haemorrhage, or malignant hemispheric stroke. Administration of ketamine as both an anaesthetic and a sedative significantly reduced the number of people who experienced spreading depolarisation after one of these three injuries. In those patients in whom spreading depolarisation began, ketamine significantly reduced the spread.

Despite increasing research into the uses of ketamine, scientists have begun to express concern about the difficulties some researchers have reported in obtaining ketamine for scientific studies. Nutt and colleagues Leslie King and David Nichols published a scathing article in *Nature Reviews Neuroscience* earlier this year, arguing that existing drug laws are having a “chilling” effect on research and innovation on controlled substances like cannabis, MDMA (ecstasy), psilocybin, and ketamine.

To obtain a licence from, for example, the UK Home Office or the Drug Enforcement Agency (DEA) in the USA is time consuming and expensive. Nutt said that it can cost an additional £5000–8000 and take an extra year to research schedule 1 drugs (those banned because they have no known medical use), which discourages many scientists from even attempting to do so.

Valerie Curran, a psychopharmacologist at University College London, UK, who studies the effects of ketamine and other controlled substances on cognitive and emotional functioning, says that younger researchers and some universities might be hesitant to start researching these drugs because

of the regulatory difficulties and bureaucratic red tape. In addition to the high cost, researchers need to store the drugs in a locked cabinet, do background checks on laboratory workers, and receive a visit from the police every year or two. “It’s quite complicated”, Curran said.

“Existing drug laws are having a ‘chilling’ effect on research and innovation on controlled substances like cannabis, MDMA (ecstasy), psilocybin, and ketamine.”

“It’s quite difficult to do these studies if you aren’t familiar with the regulations,” said Carlos Zarate, Chief of Experimental Therapeutics and Pathophysiology Branch at the National Institutes of Mental Health, MD, USA. Phil Corlett, a ketamine researcher at Yale University, CT, USA, agrees. He notes that a researcher’s ability to work with ketamine and similar controlled substances has a lot to do with institutional protocols and a history of working with such drugs. Corlett acknowledges the benefits of working with experienced researchers who could guide him through the thorny details of regulatory approval. This know-how has given him the ability to continue working with ketamine. “Often when I go around the USA and give talks about our work, people are surprised that we can do it. I hear from other scientists that this work would be much more difficult to do at other institutions,” Corlett said.

Corlett is studying ketamine’s effects on cognition and the formation of delusional beliefs. To help people with psychosis and other delusional disorders, he says, researchers need to understand how these beliefs form and crystallise. Corlett has been using cognitive neuroscience tests and functional MRI to better understand how the drug can induce a psychotic-like

state and delusional thinking. He is also interested in ketamine’s rapid antidepressant effects. Although the drug remains promising as a new antidepressant, Corlett said that ketamine itself is unlikely to be used in this way because of its known toxicities. “Ketamine is not a compound that should be given repeatedly to people. Prolonged and repeated use can cause damage to your brain and bladder”, he noted.

In December, 2012, the UK Government placed ketamine analogues and structurally similar drugs in schedule 1. “Therein lies the rub: by putting them in schedule 1, the government is saying they have no known medical use, when actually ketamine itself is being known for the first time as a potential antidepressant,” Curran said. A vicious cycle therefore exists: drugs remain in schedule 1 because scientists can’t find a medical use for them, because they are in schedule 1. “Many of these [analogues] have never even been made, let alone tested in humans,” Nutt said. “Banning all of these analogues means that researchers will never be able to find a safer ketamine.”

In the USA, however, ketamine is a schedule 3 drug, meaning that it has an accepted medical use and a low to moderate risk of dependence. This makes it easier to research than in the UK; moreover, the DEA has not yet banned ketamine analogues.

The notion that existing drug laws are slowing ketamine research is probably true, but by how much is unclear. However, ketamine research does not seem to be stopping because of these drug laws. Perhaps the biggest effect will be for researchers in the UK, who will have problems trying to create compounds that have the same beneficial effects as ketamine without the toxic side-effects, since the government has ruled that these compounds have no medical benefits.

Carrie Arnold

For the study of ketamine and spreading brain depolarisations see *Brain* 2013; 135: 2390–98

For Nutt and colleagues’ article about drug laws see *Nat Rev Neurosci* 2013; 14: 577–85