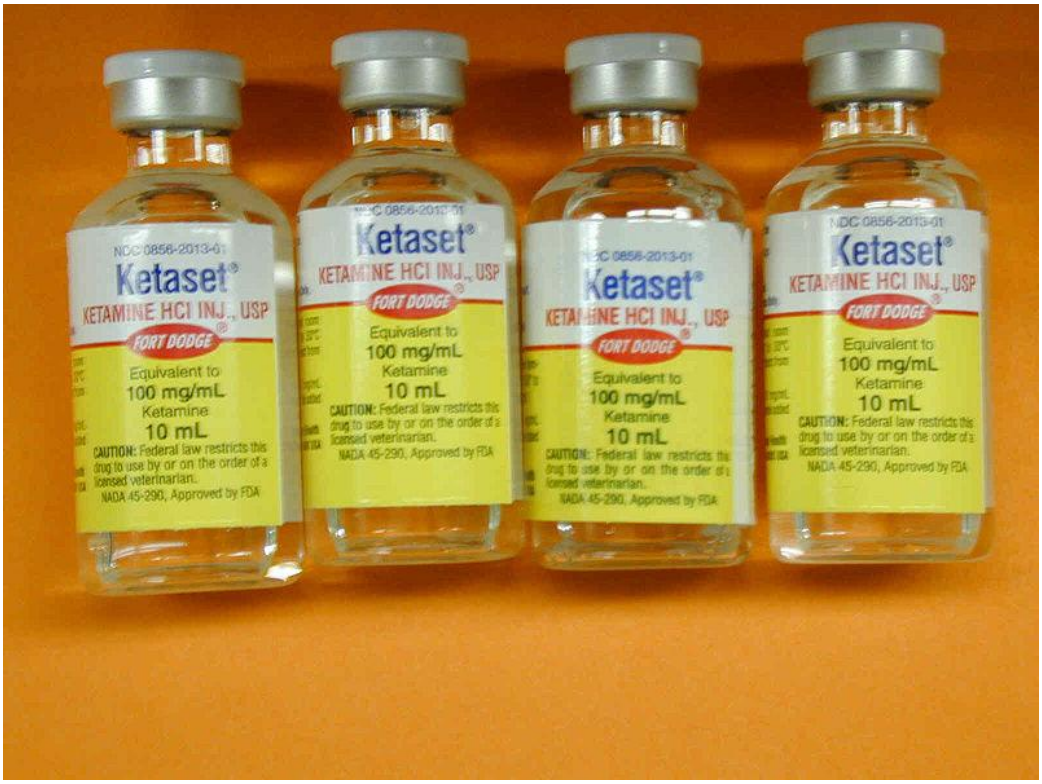
Special K and the Special Ways It Affects Society

By: Tiffany Homewood



Bottles of ketamine. Reprinted from Wikimedia Commons (2006). Copyright Wikimedia Commons 2006[1].

Introduction

For years, medical professionals used phencyclidine as an anesthetic. However, they noticed many patients waking up from the anesthesia would experience a psychosis eerily similar to schizophrenia and began research into a suitable alternative. In 1962 ketamine, a derivative of phencyclidine, was first synthesized by Calvin Stevens[2]. After several trial tests on live prisoners, ketamine was found to have much milder side effects than phencyclidine and was approved for use as a battlefield anesthetic[2]. It soon after replaced phencyclidine as the go-to anesthetic for medical procedures[2].

However, this replacement would not last. Because ketamine is still able to induce psychosis and because abuse of the drug became more prevalent, ketamine was discontinued as an anesthetic for most procedures[2]. Typically, it is relegated to use in veterinary medicine as a sedative and a calming agent for agitated animals. Though its importance faded for some time, ketamine has seen a resurgence in popularity. In

[1] File:Ketamine 10ml bottle.jpg https://commons.wikimedia.org/wiki/File:Ketamine_10ml_bottle.jpg (accessed Jun 4, 2021).

[2] Restorative health - history of Ketamine https://www.restorativehealthprimarycare.com/about/published-articles/history-of-ketamine (accessed Apr 16, 2021).

recent years, ketamine has seen many uses. Aside from being used recreationally and nefariously, ketamine is also a chemical restraint utilized by police and a potential tool in the treatment of depression.

Illicit uses

Given its anesthetic properties, ketamine is ripe for abuse. As an illicit substance, it is typically used recreationally due to the euphoric feelings and out of body experiences associated with it. Not surprising considering people like to feel good. But there is a much more horrific use for ketamine. Sometimes the drug is used to facilitate sexual assault. At anesthetic doses, ketamine can render the victim physically helpless. The dissociative effect and possible amnesia can also make identifying the perpetrator extremely difficult. Sexual assault cases are often difficult to prosecute to begin with. Date rape drugs provide a much bigger hurdle to overcome. So how do we prove they were drugged? How do we know ketamine was used? To answer this, we must first understand the metabolic pathway of ketamine.

Ketamine's metabolic pathway begins in the liver where the process is facilitated by various cytochrome P450 enzymes[3,4]. Most commonly, ketamine undergoes N-demethylation[3,4]. This means the nitrogen atom loses a methyl group which is then replaced with a hydrogen. The process turns ketamine into its primary metabolite, norketamine, which is still biologically active[3,4]. From there, norketamine can then be hydroxylated on one of several locations on the cyclohexane ring by CYP2B6 and CYP2A6 to form hydroxynorketamine[4]. Hydroxynorketamine can further metabolize by shedding a water molecule non-enzymatically, creating dehydronorketamine[3]. Other metabolic pathways are facilitated by various enzymes as shown in **Figure 1**. Metabolism of ketamine occurs quite quickly with the elimination half life being around 2 to 4 hours[4]. About 90% of ketamine leaves the body through urine as either norketamine or dehydronorketamine while 2-4% leaves unchanged[4]. Some of the drug becomes attached to hair as it passes through the bloodstream, allowing for some interesting analytical techniques.

[3] Yartsev, A. Ketamine https://derangedphysiology.com/main/cicm-primary-exam/required-reading/nervous-system/Chapter%20802/ketamine (accessed Apr 14, 2021).
[4] Das, J. Repurposing of Drugs-the Ketamine Story. J. Med. Chem. 2020, 63 (22), 13514–13525.

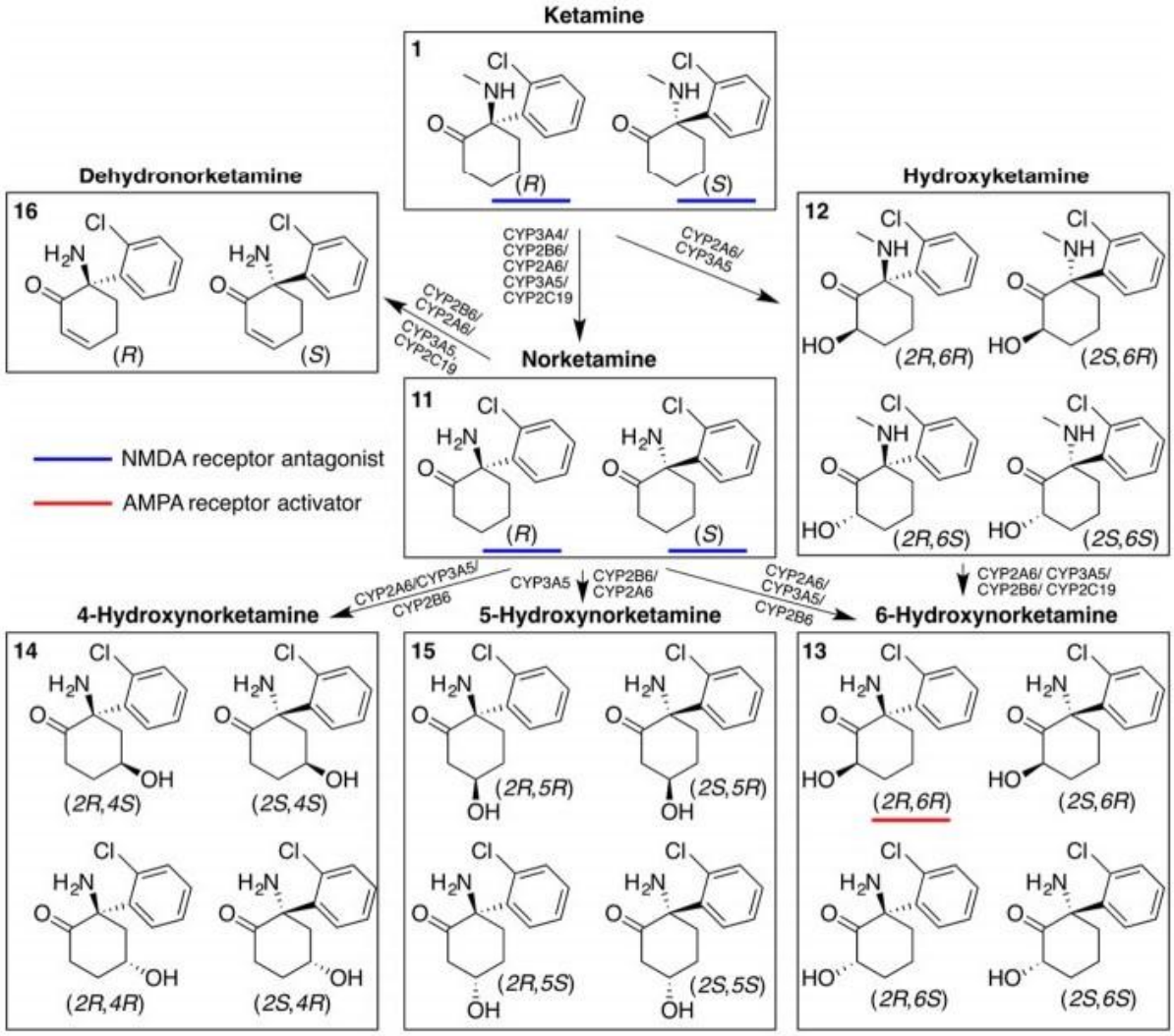


Figure 1. The metabolic pathways of ketamine. Reprinted from Yartsev. (2020). Copyright 2020 Alex Yartsev[3].

Currently, possession and use of ketamine outside of a medical environment is illegal. Obviously when police come across ketamine, there is no way to tell what it is just by looking. Luckily, there are chemical presumptive tests that can be used to distinguish ketamine from other substances. Reagents like gold (III) bromide and Mandelin's reagent will change color upon contact with ketamine[5,6]. Mandelin's reagent is the more commonly used between the two and will change to a reddish color upon reacting with ketamine as shown in **Figure 2**. Unfortunately, these reagents can react with other chemicals, potentially giving a false positive. One recently developed chemical test, a modified Scott's test, has so far shown to be relatively specific to

[5] Dubey, P.; Shukla, S. K.; Gupta, K. C. Modified Scott's Test for Ketamine Hydrochloride. Aust. J. Forensic Sci. 2013, 45 (2), 165–171.
[6] Agro, H. Test it before you ingest it https://cssdp.org/test-it-before-you-ingest-it/ (accessed Jun 2, 2021).

ketamine[5]. A typical Scott's test uses cobalt (II) thiocyanate to test for cocaine and gives a blue color upon a positive result. A modified test converts the reagent to cobalt (II) tetrathiocyanate and adds potassium hydroxide to prevent reactions with cocaine as shown in **Figure 3**. When reacted with ketamine, the test gives a pinkish-purple precipitate[5]. A negative test will result in either no color change, or a blue solution[5]. Though the test is highly specific to ketamine, there is always a chance for false positives. For this reason, presumptive tests are not admissible in court. This is where confirmatory tests play a role.

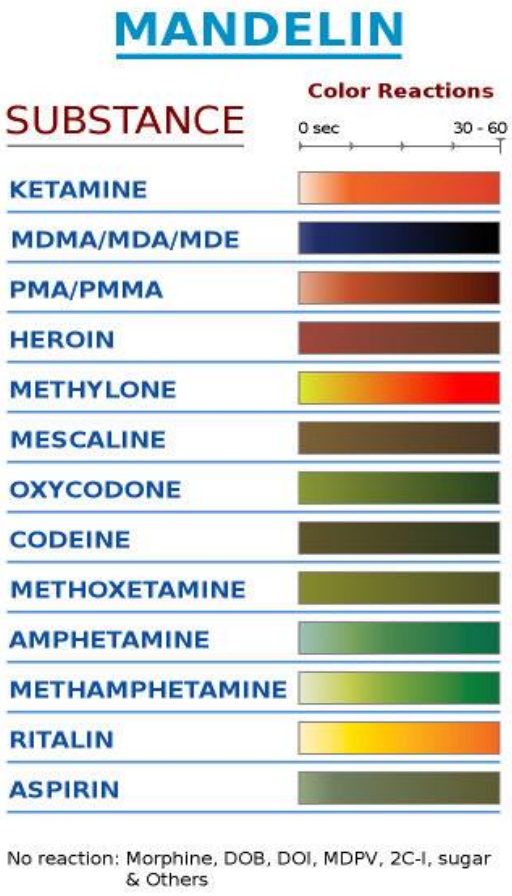


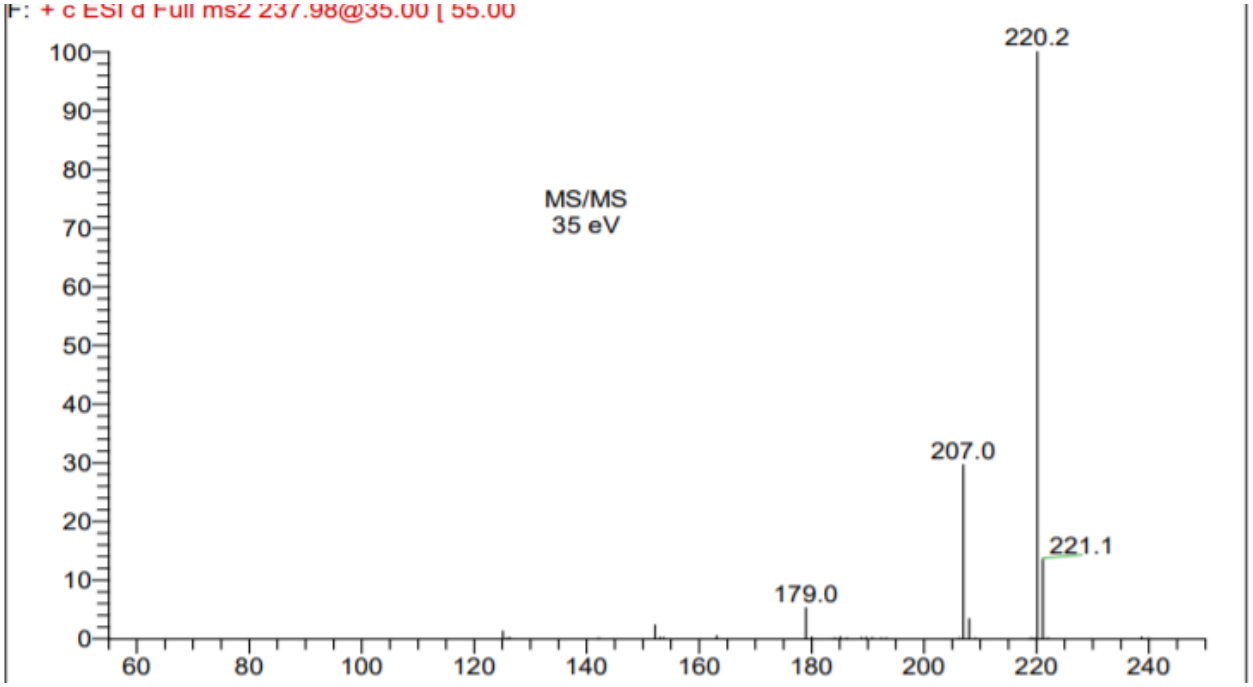
Figure 2. Chart of Mandelin reagent with various drugs. Reprinted from Agro (2015). Copyright CSSDP 2015[6].

$$Co(SCN)(H_2O)_5]^+(aq) + 3SCN^-(aq) \leftrightarrow [Co(SCN)_4]^{2-}(aq) + 5H_2O \qquad (1)$$

$$\underset{\text{(Ketamine)}}{[Co(SCN)_4]^{2-}(aq)} + 2R_3NH^+ + KOH \leftrightarrow \underset{\text{(Complex)}}{(R_3NH)_2Co(SCN)_4}$$

Figure 3. The chemical equation of tetrathiocyanate synthesis and a modified Scott's test reaction. Reprinted from Dubey et al. (2013). Copyright 2013 Taylor & Francis Group[5].

Confirmatory tests are conducted through instrumentation such as gas chromatography, liquid chromatography, and infrared spectroscopy. By analyzing a drug or biological sample, these instruments can determine the composition of a mixture and identify illicit substances. Liquid and gas chromatography work by separating complex samples into their components so they can be analyzed by a mass spectrometer which measures the mass to charge ratio of molecules as shown in **Figure 4**. In gas chromatography, the mobile phase is a gas and separation is based on the boiling points of the solute[7]. In liquid chromatography , a liquid mobile phase is used and separation is based on the interactions of the solute with the medium[8]. Another instrument that's commonly used is infrared spectroscopy. This technique works by shining beams of light with different combinations of frequencies at a sample. Once the raw data is collected, it is put through an algorithm called a Fourier Transform to create a spectrum like in **Figure 5** that can be used to determine what functional groups are present.



[7] Matey, J. M.; Moreno de Simon, M. D.; García-Ruiz, C.; Montalvo, G. A Validated GC-MS Method for Ketamine and Norketamine in Hair and Its Use in Authentic Cases. Forensic Sci. Int. 2019, 301, 447–454.
[8] Harun, N.; Anderson, R. A.; Cormack, P. A. G. Analysis of Ketamine and Norketamine in Hair Samples Using Molecularly Imprinted Solid-Phase Extraction (MISPE) and Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS). Anal. Bioanal. Chem. 2010, 396 (7), 2449–2459.

Figure 4. A mass spectrum of ketamine. Reprinted from Scientific Working Group (2005). Copyright Scientific Working Group 2005[9].

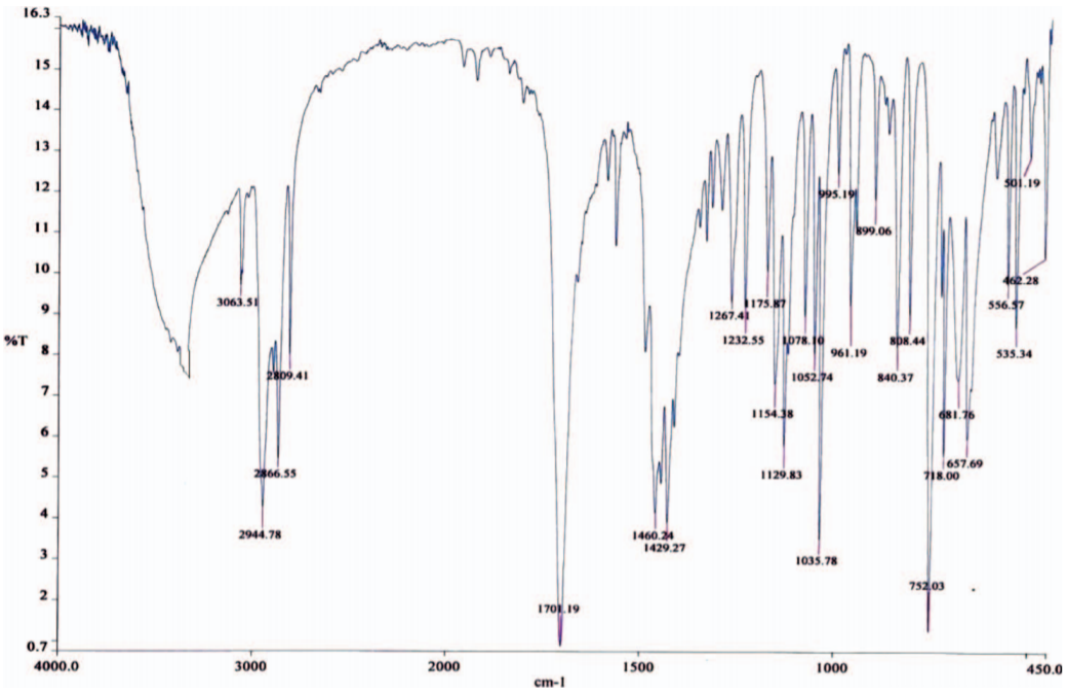


Figure 5. Ketamine FTIR spectra. Reprinted from Dubey et al. (2013). Copyright 2013 Taylor & Francis Group[5].

A more recent and fascinating instrumentation technique involves using molecular imprinting to separate ketamine from hair samples before it is analyzed through liquid chromatography. Molecular imprinting works by building a template polymer[8]. This polymer is totally synthetic and is designed to bind to molecules with certain structures and constituents[8]. Once the polymer is imprinted to the specific shape, it is able to bind to target molecules and others that share similar structures[8]. For example, an experiment was able to use molecular imprinting to pull ketamine and its metabolite, norketamine from hair[8]. **Figure 6** shows a generic example of the process. This technique can also be refined so it is highly specific to the target molecule.

[9] Scientific Working Group. Ketamine, 2005.

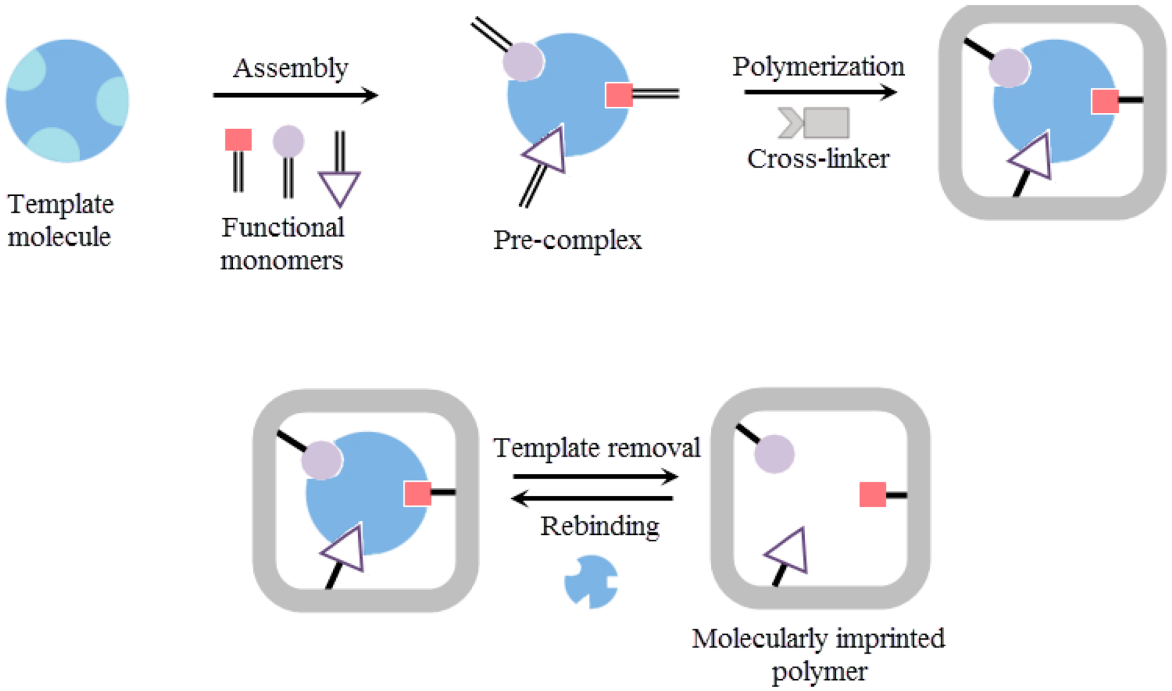


Figure 6. The process of molecular imprinting. Reprinted from Saylan et al. (2019). Copyright MDPI 2019[10].

Uses in law enforcement

As ironic as it sounds, ketamine is sometimes used by law enforcement. In certain states, a law enforcement officer can mandate an EMT to administer ketamine to chemically restrain a suspect when they are declared to be in a "state of excited delirium". What is worrisome is that the definition of this condition is about as vague as the name. To this day, there is no universal definition of Excited Delirium nor is there a standard list of symptoms required to diagnose someone with the syndrome[11]. The general consensus is that the patient must be in a state of agitation and aggression coupled with unexpected strength and they must pose a danger to themselves or others[11]. Typically this syndrome is considered to be a result of drug abuse or a mental health crisis. As it stands, Excited Delirium is a bit of a controversial topic. At least half of well-known medical organizations, including the World Health Organization, do not consider Excited Delirium to be real[11]. Another point of contention is the potential for law enforcement to abuse the diagnosis to justify excessive force. The story of Elijah McClain justifies this concern.

Elijah McClain (**Figure 7**) was just 23 years old on the fateful night of his death. McClain was returning home from a convenience store on August 24, 2019 when police

[10] Saylan, Y.; Akgönüllü, S.; Yavuz, H.; Ünal, S.; Denizli, A. Molecularly Imprinted Polymer Based Sensors for Medical Applications. Sensors (Basel) 2019, 19 (6), 1279.
[11] Gonin, P.; Beysard, N.; Yersin, B.; Carron, P.-N. Excited Delirium: A Systematic Review. Acad. Emerg. Med. 2018, 25 (5), 552–565.

confronted him after receiving a report of someone who looked suspicious[12,13]. After a brief altercation where he was rendered unconscious through a carotid chokehold, McClain was injected with ketamine by EMS while physically restrained[12]. McClain went into cardiac arrest soon after and had to be intubated. He was ultimately declared brain dead and unfortunately died a few days later[12]. Follow up medical examiner reports declared they could not determine whether the ketamine injection caused McClain's death, but they could also not rule out the possibility[12]. This tragic incident, and others like it, raised a vital question about ketamine sedation and chemical restraints in general: Are they truly that safe?

Figure 7. A photograph of Elijah McClain. Reprinted from Tompkins, L. (2019). Copyright New York Times 2019[14].

[12] Ortiz, E. Elijah McClain was injected with ketamine while handcuffed. Some medical experts worry about its use during police calls https://www.nbcnews.com/news/us-news/elijah-mcclain-was-injected-ketamine-while-handcuffed-some-medical-experts-n1232697 (accessed Apr 14, 2021).

[13] Young, R.; McMahon, S. Some states allow authorities to use ketamine to subdue suspects in the field. But is it safe? https://www.wbur.org/hereandnow/2020/09/08/ketamine-police-safety-elijah-mcclain (accessed Apr 14, 2021).

[14] Tompkins, L. Here's What You Need to Know about Elijah McClain's Death. The New York times. The New York Times February 23, 2021.

Though ketamine sedation is considered relatively safe in a hospital setting, there are inherent risks involved during police encounters. Some of the more immediate effects of ketamine include increased heart rate and laryngospasms[15]. A study conducted in Minneapolis found that 49% of patients given ketamine in a prehospital setting experienced severe side effects that required immediate attention[16]. Naturally, this is extremely dangerous in cases where a patient has pre existing medical conditions involving the heart or lungs. It has also been noted that fatal ketamine toxicity overwhelmingly occurs when other drugs, particularly depressants, are present[17]. Because of these factors, ketamine sedation poses a dangerous threat in situations that involve police when medical histories are typically unknown and the presence of other drugs is likely. It should also be mentioned that the FDA has not approved the use of ketamine as a chemical restraint[16]. Not surprisingly, the risks of ketamine toxicity increase greatly when given at higher doses and when given rapidly. Now how much is a safe dose?

Studies have recommended a sedation dose of 4 mg/kg[15]. Others have noted that any dose beyond that greatly increases the risk of complications with the likelihood of intubation increasing by 20%[15]. Respiratory depression appears to be common at high doses. In the United States, in the states where it is legal, the standard dose of ketamine is 5 mg/kg[15]. There does not appear to be an official reason for the higher dose. One possible reason is to get the sedative effect much quicker. Now looking back at the Elijah McClain case, it seems very unlikely that ketamine sedation had no role in his death. For reasons unknown, McClain was estimated to be around 90 kg while in reality, he weighed about 63 kg at the time of his death[12]. Because of this estimation, he was given 500 mg of ketamine. After doing the math, this means he was given a dose of 7.95 mg/kg, almost twice the amount of the scientifically determined safe dose. Given that McClain had several pre existing conditions like asthma and anemia, and combined with how roughly he was handled by police, it is unlikely he would have ever left that situation unscathed.

Medicinal uses

Despite some questionable uses, ketamine can actually be quite helpful. While it is no longer administered during most procedures, ketamine is still used in veterinary

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[15] Bernard, S.; Roggenkamp, R.; Delorenzo, A.; Stephenson, M.; Smith, K.; Ketamine in Severely Agitated Patients Study Investigators. Use of Intramuscular Ketamine by Paramedics in the Management of Severely Agitated Patients. Emerg. Med. Australas. 2021, No. 1742-6723.13755. https://doi.org/10.1111/1742-6723.13755.

[16] Zaret, A.; Obasogie, O. Medical Professionals, Excessive Force, and the Fourth Amendment. California Law Review 2021. https://doi.org/10.15779/Z38NK3658H.

[17] Darke, S.; Duflou, J.; Farrell, M.; Peacock, A.; Lappin, J. Characteristics and Circumstances of Death Related to the Self-Administration of Ketamine. Addiction 2021, 116 (2), 339–345.

and occasionally pediatric medicine[18]. As has been mentioned plenty of times, ketamine functions primarily as an anesthetic due to its dissociative properties[18]. Ketamine also makes a good analgesic, or painkiller, even at subanesthetic levels[19]. When given ketamine, a patient essentially is dissociated physically and mentally from the pain. Obviously these two functions are extremely important when performing any kind of surgery. Any good doctor would not want his patients to feel pain during an operation. But there are more properties that make ketamine a bit more ideal for surgical procedures. Ketamine has anti-inflammatory properties[18]. This is ideal for surgeries because it reduces over exaggerated inflammatory responses[18]. Oftentimes, these responses can cause hyperalgesia or send the patient into shock[18]. Another advantage is that, unlike other anesthetics, ketamine renders the patient unconscious while allowing them to breathe autonomously[18]. The patient's airway is still able to respond to outside stimuli. This means that surgeons don't have to be as concerned about airway collapses during the surgery. There is a tradeoff, however. Ketamine maintains the airway by inducing muscle tone[18]. This makes surgeries that require muscle relaxation extremely difficult without the use of benzodiazepines[18].

Ketamine's primary mechanism of function is through its action on NMDA receptors[18]. It can non-competitively bind to a channel blocker site within the ion channel such as in **Figure 8**. During normal functions, cations like sodium and calcium flow through the channel to allow for the activation of cell signalling pathways[4,18]. Ketamine blocks the flow of these cations which prevents depolarization of the neuronal membrane and stops the activation of different pathways[4,18]. One of these pathways is neuronal activation which is needed to remain conscious. This antagonism of the NMDA receptors is also heavily linked to ketamine's psychomimetic effects[18].

[18] Zanos, P.; Moaddel, R.; Morris, P. J.; Riggs, L. M.; Highland, J. N.; Georgiou, P.; Pereira, E. F. R.; Albuquerque, E. X.; Thomas, C. J.; Zarate, C. A., Jr; Gould, T. D. Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. Pharmacol. Rev. 2018, 70 (3), 621–660.
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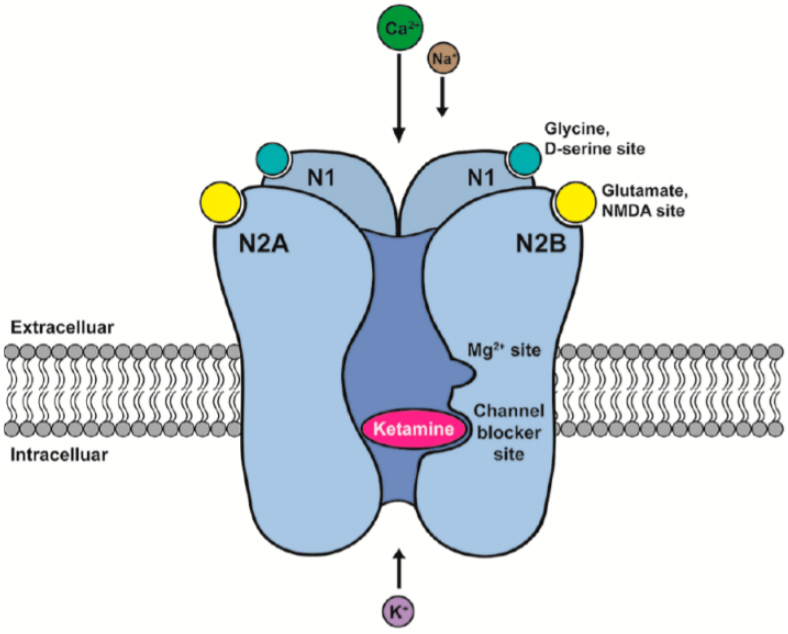

Figure 8. Ketamine blocking an NMDA receptor. Reprinted from Das (2020). Copyright 2020 ACS Publications[4].

There are a variety of other receptors that ketamine can bind to. Some of these, like the opioid receptors and non-opioid sigma receptors, are believed to be the cause of ketamine's analgesic effect[19]. Though it can bind to opioid receptors, ketamine's mechanism of action on them is still a bit of a mystery since naloxone, a known opioid receptor antagonist, has so far shown no effect on ketamine[19]. To reduce inflammation, ketamine reduces the excess of proinflammatory cytokines[18]. This is done by inhibiting the protein nuclear kappa B, the protein responsible for producing the cytokines[18].

Now by far the most fascinating use for ketamine is its potential as an antidepressant. Right now, there are many issues with current antidepressants. Mainly, traditional antidepressants can take weeks to months for effects to be felt[4]. Depending on the patient, the effects may not even be felt at all. Additionally, side effects from these antidepressants can vary greatly from person to person. Sometimes these side effects actually worsen the depression symptoms[18]. During clinical trials for ketamine, patients were able to start feeling the antidepressant effects in about 2 hours after the first treatment was finished[4]. This effect often lasted up to about a week per dose[4].

Unfortunately, the mechanism of action behind the antidepressant effects of ketamine is still mostly a mystery. What we do know is that ketamine primarily inhibits NMDA receptors, but it can also bind to several other receptors with less selectivity. A few possible mechanisms that have been proposed based on NMDA receptor inhibition are

shown in **Figure 9**. The first one hypothesizes that ketamine inhibits NMDA receptors on GABAergic interneurons[4]. From there, the presynaptic glutamate nerve terminal is activated, releasing glutamate so it can bind to AMPA receptors on the postsynaptic nerve terminal[4]. Binding of AMPA receptors would then trigger TrkB and the rapamycin complex 1 to synthesize proteins that restore synaptic connectivity[4]. Another proposed mechanism is that ketamine causes direct intracellular changes on postsynaptic nerve terminals that activate AKT and ERK/MAPK pathways that suppress eukaryotic elongation factor 2[4]. This would then increase the release of brain-derived neurotrophic factors. These neurotrophic factors produce proteins that are able to repair the degenerated synapses associated with depression[4]. If this mechanism is correct, it may be possible to actually reverse the neuro degeneracy that causes depression.

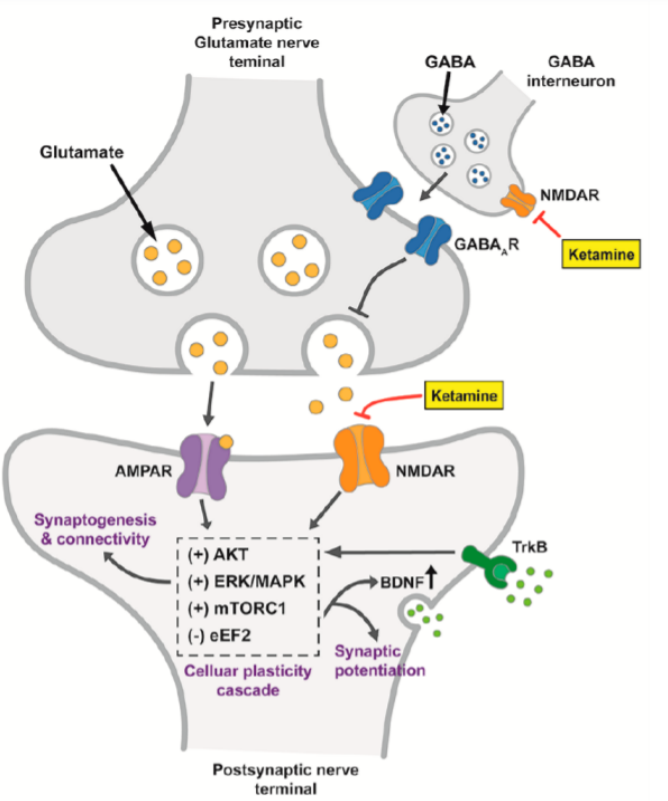

Figure 9. Proposed mechanisms of ketamine antidepressant effects. Reprinted from Das (2020). Copyright 2020 ACS Publications[4].

It also turns out that the configuration of ketamine determines what functions it is more potent for. **Figure 10** shows the two enantiomers of ketamine. Studies found that R ketamine is 4 times more potent as an antidepressant while S ketamine is three times more potent as an analgesic in rat models[18]. S ketamine was also found to be the enantiomer that causes more of the unwanted side effects[18]. As with other chiral drugs, this difference in effects happens because biological systems are also chiral making

them more favorable to certain configurations[18]. This could be extremely useful in getting more potent antidepressant effects and studying biosystems responsible for causing depression.

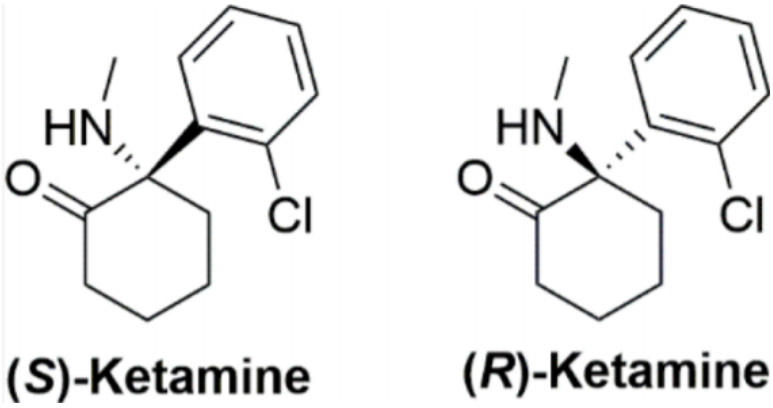

Figure 10. Ketamine's enantiomers. Reprinted from Das (2020). Copyright 2020 ACS Publications[4].

When comparing ketamine to traditional antidepressants, you can really see the potential. From what researchers can tell, ketamine works by binding certain receptors rather than trying to increase the amount of monoamine neurotransmitters through blocking their reuptake transporters[4]. Ketamine also works significantly quicker than traditional medicine and has more predictable side effects that can resolve on their own[4]. Another advantage that ketamine has is that patients experience a much lower rate of suicidal thoughts than they do with other antidepressants[4]. This is because conventional antidepressants can induce mood swings[20]. They can also marginally elevate the mood of someone who is severely depressed to the point where they have no motivation[21]. This margin is often just enough that the patient regains their motivation, but not enough to stop the hopeless feeling. Because they are no longer immobilized by feeling helpless, suicidal thoughts and actions may actually increase[21]. With ketamine, the antidepressant effect is significantly stronger and is usually enough to decrease both the helpless and hopeless feeling[4]. Right now, ketamine is available as a treatment in humans though it is not covered by any insurance. There also isn't any information on whether these lower doses of ketamine will have any significant long term effects or not. But with more research into ketamine, we may have safer and more effective treatments for depression.

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Conclusion

Regardless of why it's used, there are many reasons to care about how ketamine affects us and there are just as many concerns we should have. In terms of illegal uses, our focus should not be on whether recreational use is moral. The main concern in this case is the potential for abuse as a date rape drug. Currently, ketamine is illegal to possess outside of a medical setting and therapeutic use is restricted to medical facilities. Because it's a common date rape drug, ketamine should only be legal to possess as a medicine, similar to other prescription drugs.

In terms of law enforcement, to call ketamine sedation concerning would be an understatement. As we saw in the Elijah McClain incident, not everyone who's forcefully given ketamine needs it. Currently, Colorado, Minnesota, and New York allow paramedics to assist officers through ketamine injections. Ketamine injections in these situations are dangerous enough on their own, but the potential for abuse and excessive force is way too high. An internal affairs report in Minneapolis reviewed body cam footage of incidents involving ketamine and the results were horrific. In many cases, suspects were compliant and officers pressured paramedics into administering ketamine[16]. With today's political climate and the frequency of the blatant police brutality we're seeing, we should be asking ourselves if this is the standard we want to set.

In terms of medicine, the possibilities extend beyond just how ketamine can be directly used. While it has been shown to be a powerful antidepressant, there are side effects. These side effects can be dangerous enough to prevent people with certain pre-existing conditions from getting the treatment they need. But if we use ketamine to help research and map out the mechanisms of depression, we could theoretically build a safer molecule. This could lead to significantly safer and effective treatments than what we currently have. And these treatments could be available even to people with high risk health conditions. We could even extend the research and treatments to other mental illnesses. NMDA receptor antagonism is linked to psychosis and memory loss. Ketamine could be used to model these conditions so we can research medicine to treat diseases such as Huntington's and schizophrenia. There is so much untapped potential that can come from exploring the possibilities of ketamine in the medical field. Ultimately, ketamine on its own isn't super scary. Depending on who's using it, it can be a helpful medicine or a nightmarish tool. With that being said, hopefully you learned something from this. And hopefully now you too can teach others about Special K and the special ways it affects society.

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