# Ketamine pharmacology revisited

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# Chapter 1

# General introduction

## Introduction

Ketamine is by far the most versatile drug available in anesthesia and possibly in all of medicine. Ketamine is a an *N*-methyl-D-aspartate receptor (NMDAR) antagonist and dissociative anesthetic that was designed over 50 years ago by Parke-Davis as a replacement of phencyclidine (PCP).[1-3] In recent years various new indications for ketamine were discovered across multiple clinical settings. While initially exclusively applied as anesthetic in clinical human and veterinarian practice, it is currently also used off-label for the treatment of acute and chronic non-cancer pain, opioid-refractory cancer pain, migraine, epilepsy, post-traumatic stress disorder and major (therapy-resistant) depression.[1-5] Despite its growing popularity, there are various serious concerns with ketamine. These issues relate to its efficacy in pain medicine and depression and its (psychedelic) side effect profile. Both items, efficacy and side effects, led to vivid discussions in the literature and to a division in the fields of anesthesia and psychiatry, between believers who use it on a large scale and non-believers who refuse to use it under any circumstance. Such fierce opposing viewpoints are rarely seen in clinical anesthesia practice.

In this thesis I will discuss the efficacy of ketamine in pain and present a novel route of administration; further, I present a new indication for ketamine, i.e. the prevention of opioid-induced respiratory depression (OIRD). Finally, I will present a new mode of reduction of ketamine psychedelic side effects.

### PHARMACOLOGY

Ketamine (initially known as CI-581) is a non-competitive antagonist of the NMDAR. The NMDAR is an excitatory glutamate receptor present in the dorsal horn of the spinal cord and brain. The receptor has multiple subunits; the NR1 unit in present in all receptors, the NR2 unit has subgroups A-D. The combination of NR1-NR2B subunits is present in spinal cord and brain NMDARs and primarily involved in transmission of nociceptive stimuli.[10] We need to realize that ketamine acts at multiple receptor systems including opioid, cholinergic, monoaminergic, AMPA and innate repair receptors.

Ketamine consists of two enantiomers, the R(-) and S(+) enantiomer, due to the presence of a chiral center. The pharmacokinetics of the two isomers do not differ significantly, but the S(+)-variant has a fourfold higher affinity for the NMDAR compared to the R(-)-variant. Its high lipophilicity leads to rapid brain uptake and redistribution.[11] Ketamine is metabolized in the liver by cytochrome P450 into the active metabolites norketamine and hydroxynorketamine. Norketamine has one third to one fifth of the potency for the NMDA receptor.

The NMDAR receptor plays a crucial role in the development and chronification of (neuropathic) pain. Persistent activation of C-fibers activates the NMDAR in the dorsal horn leading among other things to long lasting depolarization and elevated cytosolic calcium levels causing more intense pain signals and repetitive afferent firing patterns. This in turn facilitates and maintains central sensitization leading to abnormal pain perception (allodynia and hyperalgesia).[6] Ketamine as analgesic acts on the PCP side of the NMDAR and reduce the mean open time and decrease channel opening frequency.[7,8] Besides that, it also enhances the descending inhibiting pathway.[9]

Globally ketamine is available in it racemic form (trademark Ketalar) and in some European countries the S(+)-enantiomer is registered (Ketanest).

**INDICATIONS**

As previous mentioned there are multiple indications for ketamine. In anesthesia it is used for induction and maintenance of anesthesia. Unlike other anesthetics that inhibit synaptic neurotransmission in multiple brain regions, ketamine causes dissociative anesthesia through dissociation between the thalamus and limbic system. Although developed as anesthetic, there is a definite role for ketamine in pain management. For the treatment of acute pain ketamine interacts in a synergetic fashion with opioids. Ketamine reduces opioid consumption and counters opioid induced hyperalgesia.[5] However, despite these findings (often made in experimental models) there are contrary results about the efficacy of ketamine in the treatment of patients with acute and chronic pain (See also Chapter 2).

**SIDE EFFECTS**

Ketamine affects multiple organ systems causing side effects that limits its use or reduced patient and doctor compliance. Ketamine has effects on the vestibular system (causing dizziness, vertigo and nausea), the cardiovascular (tachycardia, palpitations and hypertension), the central nervous system (cognitive impairment, impaired motor function, increased cranial pressure, psychomimetic effects, addiction). Most side effect disappear quickly after termination of infusion. Benzodiazepines or alpha-2-agonist may be administered to suppress symptoms. However also organ damage may occur following long-term misuse such as irreversible ulcerative cystitis, hepatotoxicity and neurotoxicity. The neurotoxicity is only reported in rodent studies were neuronal apoptotic lesions are found following high dose ketamine administration, but these have not been reported in humans.

The psychomimetic side effects (hallucinations, vivid dreams, paranoid, panic attacks) have a major impact on patient and doctor compliance. The exact mechanism of these effects is not clear. One hypothesis assumes hypofunction of the NMDA system as causative factor. Glutamate binding to the NMDAR results (via various steps) in the production of nitric oxide (NO). NO stands at the basis of neuroprotection, neurotrophic actions, neuroplasticity and synaptic plasticity (again via various steps).[12] Loss of NMDAR activity may result in less NO production and consequently deviations from normal neuronal activity and protection, which may be associated with the aforementioned psychomimetic side effects. Several animal studies show that NO donation diminishes ketamine psychosis. Interestingly, schizophrenia patients treated with the NO donor sodium nitroprusside show improvement of psychosis-related symptoms.[13-17]

### OPIOID-INDUCED RESPIRATORY DEPRESSION

In modern medicine, opioids are indicated for the treatment of moderate to severe pain. Although they are very effective, these drugs come with a myriad of adverse effects, including life-threatening respiratory depression (estimated incidence of 1-2% although recent data suggest that this is an underestimation). Currently there is a world-wide opioid epidemic, with only in the Netherlands a sharp increase of opioid prescriptions by more than 100% in the last decade. With more opioid-use, more individuals encounter opioid side effects, including fatal respiratory depression. In the US, for example, there were 54,000 opioid deaths in 2017 from prescription and illicit opioid consumption. Research on the development of a new generation of opioids without or with less respiratory side-effects is ongoing, but none of these novel drugs are available as yet. It may be possible, however, to stimulate breathing through non-opioidergic pathways, for example by stimulating the respiratory centers in the brainstem. Animal and some human studies suggest that ketamine is a respiratory stimulant, possibly through its actions at the NMDAR within the brainstem respiratory networks.[18] We explore such effects of ketamine in Chapter 5.

### THESIS OUTLINE

In this thesis I will investigate the following subjects.

In Chapter 2 we will give an overview of the latest evidence of the efficacy of ketamine in pain management.

In Chapter 3 a novel route of administration, nebulizing, is studied. The pharmacokinetic profile of nebulized ketamine is presented in Chapter 4.

In Chapter 5 we explore the capability of ketamine in reducing opioid-induced respiratory depression and also the effect of solely ketamine on respiration.

Finally, in Chapter 6 we study the effect of a NO donor on reducing the ketamine-induced psychomimetic side-effects including the pharmacokinetics.

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