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Ketamine applications beyond anesthesia – A literature review

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ABSTRACT

Ketamine's clinical use began in the 1970s. Physicians benefited from its safety and ability to induce short-term anesthesia and analgesia. The psychodysleptic effects caused by the drug called its further clinical use into question. Despite these unpleasant effects, ketamine is still applied in veterinary medicine, field medicine, and specialist anesthesia. Recent intensive research brought into light new possible applications of this drug. It began to be used in acute, chronic and cancer pain management. Most interesting reports come from research on the antidepressive and antisuicidal properties of ketamine giving hope for the creation of an effective treatment for major depressive disorder. Other reports highlight the possible use of ketamine in treating addiction, asthma and preventing cancer growth. Besides clinical use, the drug is also applied to in animal model of schizophrenia. It seems that nowadays, with numerous possible applications, the use of ketamine has returned; to its former glory. Nevertheless, the drug must be used with caution because still the mechanisms by which it executes its functions and long-term effects of its use are not fully known. This review aims to discuss the well-known and new promising applications of ketamine.

1. Introduction

After the discovery of anesthesia, in the 19th century, a quest for safe, efficient and short-acting anesthetics commenced (Baillie, 1965). One of the achievements on this path was a novel chemical organic Grignard reaction which led to the synthesis of phencyclidine (PCP) in 1956 (Maddox, 1965). PCP was a very safe anesthetic in humans but it also produced a state of prolonged delirium and sensory deprivation (Greifenstein, 1958). Thus, PCP began to be used as a drug model of schizophrenia (Luby et al., 1962) and the search for a short-acting derivative continued. The quest ended with the synthesis of CI-581, commonly known as ketamine, which also produced anesthesia but its effects where shorter (McCarthy et al., 1965; Domino, 2010). Ketamine was first used in humans in 1964 when it was administrated to 20 volunteer prisoners of the State Prison of Southern Michigan at Jackson, USA (Domino et al., 1965). Depending on the dose, the drug produced both full anesthesia and profound analgesia and an increase in blood pressure with no clinically significant respiratory depression. It had no effect on liver or kidney function and blood count (Domino et al., 1965). Due to ketamine's fast onset of action and the fact that it did not produce respiratory depression making it relatively safe (Corssen et al., 1965), it was used as a field anesthetic during the Vietnam War (Domino, 2010).

The most significant undesirable effect of ketamine is its psychological effects. Drug administration can cause very realistic hallucinations, dream-like experiences or mood changes. Usually, these effects would wear off within 1–2 h (Domino et al., 1965). Since ketamine synthesis, effects caused by these types of drugs were termed "dissociative anesthesia". Due to its fast onset, a short period of action and hallucinogenic properties, ketamine has become a recreational drug of abuse. In subanesthetic doses, the drug produces hallucinations, distortion of time and space and mild dissociative effects. Recreational users describe it as a "melting into the surrounding" or an "out of body experience". At higher doses, the drug can cause severe dissociative effects where people experience a complete detachment from reality (Curran and Morgan, 2000). First reports of ketamine recreational use appeared in the 1960s (Siegel, 1978) and the drug reached its peak in popularity in the 1990s when it was a common component of ecstasy tablets in Europe (Dalgarno and Shewan, 1996). To this day ketamine remains a popular drug of choice among young people of Hong-Kong (Joe-Laidler and Hunt, 2008).

Nowadays ketamine's most common clinical application is veterinary medicine. Due to its easy intramuscular administration route and because it does not depress respiratory function, ketamine has been used as a sedative and anesthetic in non-human primates, many zoological and exotic animals, birds and reptiles since the early seventies (Green et al., 1981). It is often applied in a combination with Xylazine, an adrenergic receptor agonist and can be used to aid anesthesia with

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inhalatory agents and to treat postoperative pain in non-human animals (Green et al., 1981; Wagner et al., 2002; Pöppel et al., 2015). In humans, its use as a general anesthetic has been minimized because of its psychological effects. However, Ketamine remains an anesthetic in special cases: in hemodynamically compromised emergency patients, such as patients in septic shock (Morris et al., 2009) and in adult and pediatric burn victims (Bayat et al., 2010; Zor et al., 2010; Reid et al., 2011; Norambuena et al., 2013; Kurdi et al., 2014). Ketamine is also applied in pain management (Curran and Morgan, 2000). The drug can be utilized as a model to study memory impairments and psychosis (Newcomer et al., 1999). In recent years the application of ketamine in treating depression (Serafini et al., 2014; Grady et al., 2017) as well as heroin and alcohol addiction (Krupitsky et al., 2002; 2007; Jovaisa et al., 2006; Wong et al., 2015) has been extensively studied. Ketamine's application in the management of acute, chronic and cancer pain is also being intensively researched (Kurdi et al., 2014). This review article aims to describe the wide range of ketamine applications.

2. Ketamine properties

2.1. Chemistry

Ketamine is a derivative of phencyclidine. It is a water-soluble aryl-cyclo-alkylamine with a molecular mass of 238 g/mol (Mion and Villevieille, 2013). Ketamine occurs in two enantiomers (S)-(+) and (R)-(-)-2-(2-chlorophenyl)-2-(methylamino) cyclohexanone (Morgan and Curran, 2012). Ketamine drugs such as Ketalar® are racemic mixtures of both enantiomers. The S(+) enantiomer is more potent and available as Ketanesth® in Europe (Mion and Villevieille, 2013). In 2019 the FDA has approved a nasal spray containing S(+)-ketamine Spravato® for the treatment of treatment-resistant depression (Traynor, 2019).

2.2. Mechanism of action

Most of the anesthetic, analgesic and psychodysleptic effects are mediated through its action on NMDA receptors of which ketamine is a non-competitive antagonist (Anis et al., 1983; Zorumski et al., 2016) (Fig. 1). Ketamine is an open-channel blocker (MacDonald et al., 1987) which means that it can bind to the NMDA receptor only in its open state, preventing ion flow (Dilmore and Johnson, 1998). Ketamine can occupy two sites in the NMDA receptor: inside the Ca^{2+} channel pore (the PCP binding site), which decreases the channels opening time or a site located within the hydrophobic domain of NMDA receptors which decreases the frequency of channel opening (Mion and Villevieille, 2013). The S(+)-enantiomer is around four-fold more potent towards binding to NMDA receptors (Iadarola et al., 2015)

Apart from the NMDA receptor, ketamine interacts with opioid (μ, δ, and κ) monoaminergic, cholinergic, muscarinic and nicotinic receptors (Mion and Villevieille, 2013). The S(+)-enantiomer has a 2 to 3- fold bigger affinity towards opioid receptors compared to the racemic form of ketamine. This interaction is not responsible for the analgesic effects of ketamine but might contribute to the psychosomatic effects (Hustveit et al., 1995). Ketamine can potentiate γ-aminobutyric acid type A (GABAA) receptors increasing GABA inhibitory properties. This effect occurs only at very high concentrations of the drug so it is not clinically significant (Flood and Krasowski, 2000). Ketamine can inhibit nicotinic receptors by interacting with the open and closed state of the receptor and it affects muscles via this pathway (Maleque et al., 1981; Scheller et al., 1996). However, with the administration of additional muscle relaxants, its effects on skeletal muscles are clinically insignificant (Kress, 1994). Ketamine is also a muscarinic receptor antagonist and it interacts with the monoaminergic system functions (Kohrs and Durieux, 1998). It can inhibit norepinephrine, dopamine and serotonin uptake, the later because of its interaction with a serotonin transporter (Kohrs and Durieux, 1998). Moreover, the drug inhibits non-NMDA glutamate

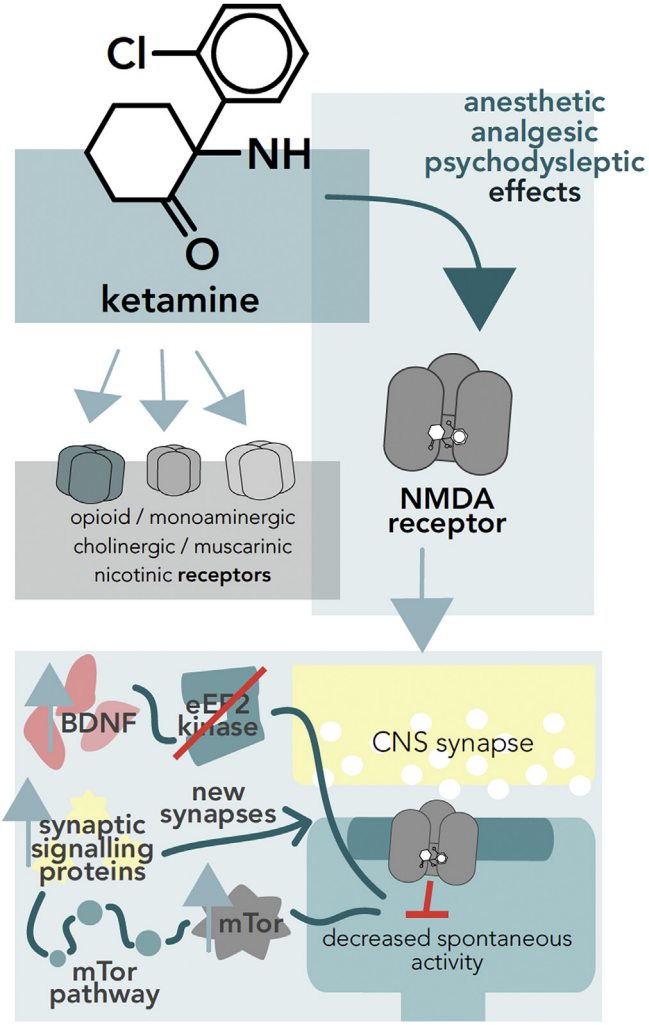

Fig. 1. Ketamine acts mainly on NMDA glutamate receptors. (upper panel) Ketamine exerts its properties mainly through NMDA receptors, but it also acts on other receptor types as described in the figure. (lower panel) Ketamine application leads to decreased synaptic activity, and new synapse formation via BDNF and mTor signaling.

receptors such as AMPA or kainate receptors (Gonzales et al., 1995). This effect is executed by ketamine-induced NO-synthase inhibition. NO can play a role in neurotransmission and pain perception so this role of ketamine may also contribute to its analgesic effects (Gordh et al., 1995).

2.3. Pharmacokinetics

Ketamine can be administered intravenously and it reaches NMDA receptors within 1 min of injection rapidly crossing the blood-brain barrier (Peltoniemi et al., 2016). The intramuscular injection also provides high bioavailability and plasma peak concentration occurs after 5 min of injection (Mion and Villevieille, 2013). Around 10–30% of ketamine is bound to plasma proteins (Dayton et al., 1983; Hijazi et al., 2003). For analgesic purposes, ketamine can be administered orally, intranasally, transdermally, rectally and subcutaneously (Kronenberg, 2002). Oral bioavailability is generally poor but the intranasal administration route has been extensively researched and seems potent (Grant et al., 1981; Yanagihara et al., 2003; Weber et al., 2004; Chong et al., 2009; Riediger et al., 2015). Ketamine is highly liposoluble so it undergoes a quick distribution to peripheral tissues (Kurdi et al., 2014). 80 percent of ketamine is metabolized in the liver

by a microsomal enzyme system (N-methylation) to norketamine (Mion and Villevieille, 2013). Norketamine is an active metabolite that has one-third to one-fifth of ketamines anesthetic potency (Dinis-Oliveira, 2017). In humans and other animals, like horses, ketamine is excreted from the organism in urine and feces as norketamine and other hydroxylated derivatives (Wieber et al., 1975; Dugdale and Dugdale, 2010). Cats do not metabolize ketamine and they excrete the unchanged compound with urine. In rats, it has been found to be excreted via the bile duct (Ireland and Livingston, 1980; Dugdale and Dugdale, 2010). The half-life of ketamine elimination is 2–3 h (Domino et al., 1984), depends on blood flow rate through the liver (Schüttler et al., 1987) and maybe 20% quicker in women than in men (Sigtermans et al., 2009). Ketamine can be also directly metabolized to hydroxyketamine (5%) (Noppers et al., 2011) with the participation of the liver, kidneys, the intestine and lungs (Edwards and Mather, 2001). Pharmacokinetics of S(+)-ketamine is better than that of the racemic mixture thus it may be administered in smaller doses and has been reported to cause less adverse effects (Kharasch and Labroo, 1992; Adams and Werner, 2002). Intravenous administration of 50mg/min of both racemic and S(+)-ketamine produces narcosis in 3 ± 1 min that lasts 6 ± 2 min (White et al., 1985) but the S(+)-enantiomer has a shorter emergence phase (White et al., 2006).

2.4. Pharmacodynamics

Ketamine provides the state of dissociative anesthesia (Domino et al., 1965) which is a term for profound anesthesia with a state of altered consciousness (Corssen et al., 1965) in which the eyes stay open with nystagmus and the basic reflexes such as laryngeal, corneal and papillary are preserved (White et al., 1982). The anesthetic effect is dose-dependent (Kurdi et al., 2014). Ketamine also provides profound analgesia (Domino et al., 1965). As shown by functional magnetic resonance ketamine decreases the activity of the insular cortex and thalamus which are usually activated by painful stimulation (Rogers et al., 2004). In healthy volunteers given painful heat stimuli, subanesthetic doses of ketamine have been shown to decrease pain perception and dose-dependent cerebral activity of secondary somatosensory cortex, insula and anterior cingulate cortex (Sprenger et al., 2006). Ketamine administration produces episodic memory deficits. Functional magnetic resonance imaging (fMRI) studies show that ketamine administration alters normal frontal and hippocampal activity during memory encoding and retrieval (Honey et al., 2005). Ketamine causes an increase in heart rate and blood pressure and a non-clinically significant respiratory depression (Domino et al., 1965). Actually, it relaxes the airways by acting on receptors and pathways that produce bronchospasms. This action may be utilized in patients with status asthmaticus improving ventilation and gas exchange (Goyal and Agrawal, 2013). The drug doesn't affect liver or kidney function, blood count or electrolyte levels (Domino et al., 1965) however there have been reports of kidney injury (Selby et al., 2008) and multiorgan dysfunction (Pappachan et al., 2014) caused by chronic ketamine abuse. Ketamine produces psychodysleptic effects such as visual and auditory hallucinations, conscious dreams, floating, disturbance of mood, body image, and time perception. These symptoms produce a general state of unreality and depersonalization (Mion and Villevieille, 2013). The intensity of psychodysleptic effects is dose-dependent (Bowdle et al., 1998) with anxiety and paranoid feelings appearing at high doses (Hartvig et al., 1995). Ketamine can also produce psychopathological symptoms. In a counter-balanced, placebo-controlled, double-blind study, subjects where administered an initial 8 mg bolus of ketamine intravenously followed by a 5 min equilibration period and then received an approximately 1 h-long infusion of 0.01 mg/kg/min of ketamine during which they performed an overt word generation task while being scanned with fMRI to test for cortical activity (Nagels et al., 2012). Subjects given ketamine had difficulties in abstract thinking, thought disorder lack of spontaneity and flow of conversation. Thought disorder correlated with activation measures encompassing the left superior temporal gyrus, the right middle, and inferior frontal gyrus and the precuneus. Lack of abstract thinking correlated with pronounced activations in prefrontal as well as in anterior cingulate regions, whereas hyperactivations in the left superior temporal gyrus were found in association with a lack of spontaneity and flow of conversation. Such psychopathological symptoms and patterns of brain region activation are also found in patients with schizophrenia (Nagels et al., 2012). Interestingly, ketamine has neuroprotective properties. It inhibits NMDA receptor activation and excitotoxic signaling, reduces neuronal apoptosis, attenuates the systemic inflammatory response to tissue injury, and also maintains cerebral perfusion pressure as a result of sympathetic nervous system activation (Hudetz and Pagel, 2010). Ketamine can also limit the development of inflammation by interacting with inflammatory cell recruitment, cytokine production, and inflammatory mediators regulation as described in section 4.3 (Loix et al., 2011).

3. Ketamine applications

In the following sections, various applications of ketamine are described (summarized in Fig. 2). A summary of example trials on ketamine's non-canonical functions is presented in Table 1.

3.1. The role of ketamine in anesthesia

Despite its psychodysleptic effects, ketamine is still being applied as an anesthetic in veterinary, pediatrics, specialist anesthesia and field medicine (Curran and Morgan, 2000). One of the first clinical uses of ketamine was as an anesthetic for soldiers injured during the Vietnam War. Ketamine serves as a good field anesthetic because it provides quick effects and doesn't cause hypotension or respiratory depression (Domino, 2010). To this day ketamine is the drug of choice for inducing anesthesia in field conditions when no anesthesiologist and monitoring equipment is available (Guldner et al., 2006). Because of its safety, ketamine plays an important role in procedural sedation in the emergency department (ED), also during pediatric emergencies. Its use in disaster situations, where resources are limited, are also well documented (Bredmose et al., 2009). Thanks to its excitatory effects on the cardiovascular system, ketamine is the drug of choice when rapid

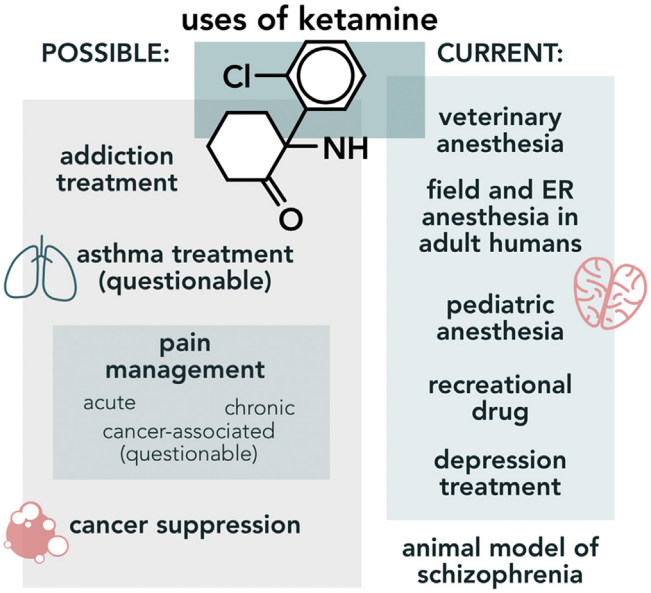

Fig. 2. Canonical and non-canonical uses of ketamine. This figure summarized known and possible uses of ketamine. Some of the possible uses are already widely recognized, such as the pain management area.

Table 1
Summary of example clinical trials regarding various possible action of ketamine described in this review.

Type of study	No of patients	Type of patients	Age	Dose of ketamine	Treatment time	Effect	Was ketamine effective?	Reference
Acute pain								
Double-blind, randomized, placebo-controlled crossover study	14	Healthy volunteers	no data	50 or 100 ng/ml plasma concentration	One-time infusion until plasma concentra-tion was reached	Administered with remifentanil prevented respiratory depression and hyperalgesia	Yes	Luginbuhl et al., 2003
Double-blind, randomized, placebo-controlled study	75	Patients undergoing major abdominal surgery	no data	0,5 mg/kg b.m. followed by intraoperative infusion of 5 μg/kg b.m. and 2 μg/kg b.m.	48h	Remifentanil induced hyperalgesia was prevented by small-dose ketamine	Yes	Joly et al., 2005
Double-blind randomized, placebo-controlled clinical trial	190	Opioid abusers undergoing moderate sedation	18–60 years	0.1 mg/kg b.m.	Single dose	Ketamine had opioid-sparing effects in opioid abusers undergoing moderate sedation	Yes	Gharaei et a., 2013
Triple-blind, randomized, active- and placebo-controlled clinical trial	56	Patients undergoing elective major abdominal surgery	> 18 years	Low-dose S(+)-ketamine: a 0.25 mg/kg b.m. bolus and 0.125 mg/kg/h infusion or minimal-dose S(+)-ketamine: 0.015 mg/kg/h infusion following a saline bolus	48h	Minimal-dose S(+)-ketamine reduced postoperative opioid consumption and hyperalgesia	Yes	Bornemann-Cimenti et al., 2016
Nonblinded, nonrandomized, observational, prospective study	30	Emmer-gency department (ED) patients with severe pain	Adult	15 mg injection	Single dose	Produced rapid, profound pain relief without significant side effects	Yes	Ahern et al., 2013
Double-blind, randomized, prospective trial	45	ED patients with moderate to severe acute abdominal, flank, or musculo-skeletal pain	18–55 years	0.3 mg/kg b.m.	3–5 min	Provided analgesic effects and safety compara-ble to morphine	Yes	Motov et al., 2015
Chronic pain								
Open, prospective study	5	Patients with post-herpetic pain	63–76 years	0,05-0,15mg/kg b.m./h	4 weeks	Conti-nuous infusion of ketamine reduced, pain but is associated with intolerable side effects	Yes/No	Eide et al., 1995
Open-label trial	20	Patients suffering from refractory complex regional pain syndrome	16–48 years	3–7 mg/kg b.m./h	5 days	Reduced pain and improved the quality of life, associated movement disorder and the ability to work	Yes	Kiefer et al., 2008
Double-blind, randomized, placebo-controlled, crossover study	29	Patients with fibromy-algia syndrome	31–64 years	0,3 mg/kg b.m.	30 min	Inhibited pain at rest, temporal summation, referred pain and muscular hyper-algesia	Yes	Graven-Nielsen et al., 2000
Double-blind, randomized, placebo-controlled, crossover study	20	Patients with phantom limb pain	18–85 years	0,4 mg/kg b.m.	1h	Reduced intensity of pain	Yes	Eichenberger et al., 2008
N of 1 randomized control trial	21	Patients with chronic neuropathic pain	no data	20–100 mg per day	6 weeks	High frequency of adverse effects and no analgesic effect in most of the subjects	No	Haines & Gaines (1999)
Retrospective chart review	21	Patients with chronic neuropathic pain	29–81 years	100–500 mg per day	> 1 year	High frequency of adverse effects and no analgesic effect in most of the subjects	No	Enarson et al., 1999
Cancer pain								
Case series	11	Patients with cancer and cancer pain	3–17 years	0,1-0,5 mg/kg b.m./h	1–75 days	Improved pain control and opioid-sparing effect	Yes	Finkel et al., 2007
Double-blind, randomized, placebo-controlled, crossover study	10	Patients with cancer and opioid-refractory cancer pain	21–69 years	0,25 or 0,5 mg/kg b.m.	180 min	Reduced pain intensity at both doses	Yes	Mercadante et al., 2000
Retrospective case review	14	Patients with cancer, terminal prognosis and opioid-refractory neuropathic pain	1 month-23 years	0.014–0.308 mg/kg b.m./h	7 days	Pain relief and no dose escalation of opioids	Yes	Taylor et al., 2015
Double-blind randomized, placebo-controlled clinical trial	214	Patients with cancer, chronic, chemo-therapy induced, neuropathic cancer pain	51–66 years	40–400 mg per dose	1 month	No difference between ketamine and placebo groups in relieving cancer pain	No	Fallon et al., 2018

(*continued on next page*)

Table 1 (*continued*)

Type of study	No of patients	Type of patients	Age	Dose of ketamine	Treatment time	Effect	Was ketamine effective?	Reference
Double-blind, randomized, placebo-controlled clinical trial	185	Patients with opioid-refractory cancer pain	> 18 years	100, 300 or 500 mg per dose	5 days	No observed pain reliving benefits	No	Hardy et al., 2012
Treatment of depression disorders								
Double-blind, randomized, placebo-controlled trial	7	Patients with major depression	23–56 years	0,5 mg/kg b.m.	3 days	Improvement in depressive symptoms within 72 h after ketamine infusion	Yes	Berman et al., 2000
Double- blind, randomized, placebo-controlled, crossover study	18	Patients with treatment-resistant major depressive disorder	18–65 years	0,5 mg/kg b.m.	7 days	Single dose of ketamine produced robust and rapid antidepre-ssant effects	Yes	Zarate et al., 2013
Double-blind, randomized, placebo-controlled trial	24	Patients with mood and anxiety spectrum disorders, with suicidal ideations	18–80 years	0,045 mg/kg b.m.	7 days	Suicidal ideation score was lower in subjects treated with ketamine	Yes	Murrough et al., 2015
Noncontrolled, longitudinal study	10	Patients with treatment-resistant major depressive disorder	25–65 years	0,5 mg/kg b.m.	4 weeks	Rapid reduction of depression symptoms and suicidal thoughts lasting up to 15 days from administration	Yes	Vidal et al., 2018
Addiction treatment								
Controlled clinical trial	111	Alcoholics undergoing treatment with ketamine psychedelic therapy (KPT)	no data	2,5 mg/kg b.m.	10 years	Higher abstinence rate in KPT patients	Yes	Krupitsky & Grinenko (1997)
Double- blind, randomized, active-placebo controlled clinical trial	70	Detoxified heroin addicts undergoing KPT	17–26 years	2 mg/kg b.m.	2 years	KPT produced a higher rate of abstinence in heroin addicts, a greater and longer-lasting reduction in craving for heroin, greater positive change in nonverbal uncon-scious emotional attitudes	Yes	Krupitsky et al., 2002
Double-bling, crossover trial	8	Cocaine addicts	21–52 years	0,41 or 0,71 mg/kg b.m.	1 month	Enhanced motivation to quit cocaine addiction and reduced cue-induced craving	Yes	Dawkar et al., 2014
Asthma treatment								
Case report	2	Severe asthma exacerbation	9,4 years	2–3 mg/kg b.m. per h	Acute therapy	Improvement of respiretory status and preventing the need for mechanical ventilation	Yes	Denmark et al., 2006
Double-blind, randomized, placebo-controlled trial	68	Acute asthma exacerbation	2–18 years	0,2-0,5 mg/kg b.m. per h	120 min	No respiretory benefit as compared to standard therapy	No	Allen and MacIas, 2005

emergency anesthesia is required in patients in shock or hypotensive (Morris et al., 2009). Ketamine can also be administered as a safe anesthetic during endotracheal intubation of critically ill patients (Jabre et al., 2009). Traditionally the use of ketamine has been contraindicated for patients with brain injuries because it has been reported to increase cerebrospinal fluid pressure, however, with the accumulation of more studies, it seems not to be the case (Gardner et al., 1971; 1972; Zeiler et al., 2014; Green et al., 2015). Some reports even show that ketamine, in a controlled ventilation setting, can be used as a sedative and anesthetic in patients with brain injuries thanks to its neuroprotective effects, resulting in reduced cell death and neuronal degeneration (Mayberg et al., 1995; Chang et al., 2013). The drug serves as an anesthetic for pericardial window surgeries in patients with pericardial tamponade (Aye and Milne, 2002; Webster and Self, 2003). It enables the maintenance of spontaneous ventilation, bronchodilation and relative preservation of the CO_2 curve (Aye and Milne, 2002). Ketamine can be utilized to anesthetize patients, especially children, with congenital heart disease (White and Peyton, 2012) due to its beneficial cardiovascular effects and the fact that it improves blood oxygenation (Tavakollian and Allahyary, 2011). It is also often applied for anesthesia and analgesia in burn victims that undergo repeated dressing changes or grafting procedures. It preserves the airway patency, hypoxic and hypercapnic responses and decreases airway resistance so it is especially useful in cases where no airway manipulations due to severe burns are possible (Griggs et al., 2017). In combination with other anesthetics, ketamine serves in the induction and maintenance of local and regional anesthesia during surgeries (Kurdi et al., 2014). Ketamine is one of the few drugs that can be administered to induce anesthesia during caesarian section procedures (Gao et al., 2016). Including ketamine to induce anesthesia in patients undergoing cardiac surgery in cardiopulmonary bypass attenuates postoperative delirium (Hudetz et al., 2009). Ketamine is also a useful drug for pediatrics anesthesia (Lois and De Kock, 2008). A quantitative systematic review has shown that caudally administered ketamine, accompanying a local anesthetic prolongs postoperative analgesia with few adverse effects (Schnabel et al., 2011). In children undergoing surgeries 0.5 mg/kg b.m. ketamine with 5% sevoflurane and alfentanil 10 mg/kg b.m. improved intubating conditions, while preserving spontaneous breathing and hemodynamic stability (Kim et al., 2011). Ketamine is recommended for the induction of general anesthesia in children with cyanogenic cardiopathy (Tuğrul et al., 2000) and mandatory for children presenting with neuromuscular diseases associated with malignant hyperthermia triggered by volatile agents or neuromuscular blocking drugs (Ramachandra et al., 1990; Rosenberg et al., 2015). Its frequently used for anesthesia in high-risk children patients (Lois and De Kock, 2008).

3.2. Analgesic use of ketamine

Concerns about psychodysleptic effects induced by ketamine limited its use. At first, it was applied mainly for anesthesia purposes. Only in 1970, after FDA approval, ketamine became available and began to be applied for analgesic purposes (Vadivelu et al., 2016).

3.2.1. Ketamine in acute pain management

A usual approach towards the therapy of acute post-operative pain is the use of opioids (Gao et al., 2016). However, opioids, apart from other side effects such as respiratory depression, nausea, and vomiting, (Schug et al., 1992) cause hyperalgesia that results in increased analgesic requirements (Gao et al., 2016). A study in rats has shown that repeated administration of ketamine can reduce the hyperalgesic effects of opioid treatment (Laulin et al., 2002). Studies in humans have shown that adding ketamine to opioid treatment for acute pain prevents respiratory depression induced by opioids and hyperalgesia (Luginbuhl et al., 2003; Nesher et al., 2009). Adding a small dose of ketamine to opioids administered during and after surgery completely prevented the increase in postoperative pain sensitivity (Luginbuhl et al., 2003). Patients that receive opioids with ketamine during surgery have lower postoperative morphine requirements (Joly et al., 2005). A large systematic review on the efficacy and safety of perioperative intravenous ketamine in adult patients during different surgical procedures concluded that perioperative intravenous ketamine reduces postoperative analgesic consumption and pain intensity without causing CNS adverse effects (Brinck et al., 2018). A preemptive bolus dose of ketamine has opioid-sparing effects in opioid abusers undergoing moderate sedation (Gharaei et al., 2013). In a triple-blind, randomized, active- and placebo-controlled clinical trial Bornemann-Cimenti et al. showed that using minimal doses of S-ketamine, smaller than normal low doses of racemic ketamine, during perioperative anesthesia reduce postoperative opioid consumption and hyperalgesia and decreased the frequency of postoperative delirium (Bornemann-Cimenti et al., 2016). Allen and Ivester in their review conclude that ketamine's potential for decreasing postoperative opioid requirements and reducing opioid-induced hyperalgesia coupled with its ability in supporting hemodynamic function and respiratory drive makes it appealing for use as an analgesic agent (Allen and Ivester, 2018). However, the application of ketamine alone as prevention for chronic postoperative pain seems not to be effective (Chaparro et al., 2013; Dualé et al., 2009; Ryu et al., 2011). Ketamine is becoming increasingly popular as an analgesic in the emergency department and pediatric patients (Gao et al., 2016). Low-dose ketamine combined with a reduced dose hydromorphone protocol produced rapid, profound pain relief without significant side effects in a diverse cohort of emergency department patients with acute pain (Ahern et al., 2013). Sub-dissociative intravenous ketamine administered at 0.3 mg/kg b.m. provides analgesic effectiveness and safety comparable to that of intravenous morphine for short-term treatment of acute pain in the ED (Motov et al., 2015). In a prospective observational study Andolfatto et al. analyzed the effectiveness of intranasal ketamine administration as an analgesic in the ED. Intranasal ketamine decreased pain scores in 88% of patients and adverse effects were minor and transient (Andolfatto et al., 2013).

3.2.2. Ketamine in chronic pain

Treating chronic pain is challenging in numerous ways. Finding the right treatment for each individual typically involves the use of antidepressants, anti-epileptics, and opioids and requires multiple adjustments of the treatment regime (drugs, dosage, etc) (Niesters et al., 2014). Regardless of the treatment, its efficacy is limited to 30–40% of patients showing pain relief with the rest of the patients responding poorly to treatment (Dworkin et al., 2010). Anesthesiologists have been using ketamine in treating chronic pain, especially one with a neuropathic component. The increasing popularity of ketamine as a treatment of chronic pain is due to its positive effects observed on suffering patients and the fact that benzodiazepines or α_2-adrenoceptor agonists are now added to the treatment to prevent the psychodysleptic effects of ketamine (Niesters et al., 2014).

Neuropathic pain is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system (Treede et al., 2008). There are several neurochemical processes that lead to the transition of pain caused by nerve/neuronal damage to chronic neuropathic pain that persists through the original etiological cause has disappeared. Those processes usually include maladaptive plasticity of the nervous system (Costigan et al., 2009): phosphorylation and upregulation of NMDA receptors (Petrenko et al., 2003), loss of descending inhibition (Costigan et al., 2009), axonal sprouting in the spinal cord (Woolf et al., 1992) and the activation of immune cells in the spinal cord that release pro-inflammatory cytokines (Marchand et al., 2005). Ketamine produces strong analgesia in neuropathic pain syndromes due to its inhibition of NMDA receptors (Niesters et al., 2014). There is also evidence that ketamine can influence descending pain pathways. Descending pathways modulate the spinal transmission of nociceptive input and they involve inhibitory neurotransmitters. In patients with neuropathic pain, this inhibitory control system shifts so that the

inhibition is suspended or changed to facilitation (Costigan et al., 2009). A placebo-controlled fMRI study showed that low dose ketamine activates brain regions (anterior cingulate cortex, the orbital frontal cortex, the insula, and brainstem) involved in descending inhibition of pain (Niesters et al., 2012). In a randomized placebo-controlled study patients with peripheral neuropathy administration of low dose S (+)-ketamine enhanced or reactivated descending inhibition (Niesters et al., 2013).

Unfortunately, chronic administration of ketamine can produce undesired side effects. The most frequent adverse effects are sedation, sleepiness, dizziness, sensory illusions, hallucinations, nightmares, dissociative feeling and blurred vision (Blonk et al., 2010). These lead to high patient withdrawal rates during studies on ketamine use in chronic pain treatment. In one study in 21 patients with neuropathic pain 10 withdrew from the study (Haines and Gaines, 1999). The same study states that the administration of ketamine in patients with chronic neuropathic pain increased analgesia only in three out of 21 patients concluding that it probably has no true therapeutic effect. A similar withdrawal rate was observed in a study where nine out of 21 patients dropped out because of the adverse effects of the drug (Enarson et al., 1999). A problem that has been described numerous times is the effect of prolonged ketamine use on the urinary tract. Ketamine abuse can lead to ketamine ulcerative cystitis, a syndrome consisting of a small volume, scarred and painful bladder with resulting severe lower urinary tract symptoms, incontinence and haematuria (Gray and Dass, 2012). The presence of urinary tract disease can lead to renal failure (Chu et al., 2008). However, ketamine-associated ulcerative cystis is common mostly among recreational ketamine abusers (Shahani et al., 2007; Chu et al., 2008; Gray and Dass, 2012). Ketamine has the potential to cause addiction. Rats administered ketamine once a week for 5 weeks developed locomotor sensitization (Trujillo et al., 2008). Also in humans repeated administration of ketamine over a prolonged period of time can produce tolerance to the drug and psychological dependence, however, it does not produce any physical withdrawal symptoms (Jansen and Darracot-Cankovic, 2001). A study in 21 ketamine addicts from 0,5–12 years using MRI techniques showed possible brain damage in many areas of the brain caused by ketamine abuse (Wang et al., 2013).

Administration of ketamine has been reported to reduce pain in patients with different types of chronic pain syndromes, mostly neuropathic, including postherpetic neuralgia (Eide et al., 1995), complex regional pain syndrome (Kiefer et al., 2008), cancer pain (Mercadante et al., 2000), fibromyalgia (Graven-Nielsen et al., 2000) and phantom limb pain (Eichenberger et al., 2008). The results of these studies are summarized in Table 1 in the 'chronic pain' section. Although many of the outcomes look promising, critical reviews and meta-analyses of clinical studies indicate that the evidence of efficacy of ketamine in chronic pain is of moderate to low quality and that, the variety of drugs' infusion protocols and dosage regimens make it difficult to draw unequivocal conclusions (Hocking and Cousins, 2003Hijazi et al., 2003; Maher et al., 2017; Bell and Kalso, 2018; Michelet et al., 2018). Some authors state that ketamine as an analgesic has proven to be of effect in patients with severe pain who have failed to respond to routine pharmacotherapy, yet still its efficacy and long-term adverse effects are insufficiently studied to promote the routine use of oral ketamine in chronic pain management (Blonk et al., 2010).

3.2.3. The role of ketamine in cancer pain management

Recently ketamine has been used to treat cancer pain (Gao et al., 2016). In cancer pain therapy ketamine is usually prescribed as an adjuvant to opioids in patients who suffer from opioid-refractory cancer pain (when they no longer respond to opioids) or when neuropathic pain symptoms become dominant (Jonkman et al., 2017). In these cases, ketamine is beneficial since it reduces opioid tolerance, hypersensitivity to pain (Kissin et al., 2000) and enhances endogenous pain inhibition (Niesters et al., 2013).

The literature on ketamine use in cancer pain therapy is inconclusive. In studies with a smaller number of participants, ketamine has been shown to be effective in reducing cancer pain (Jonkman et al., 2017). In a study on 11 children and adolescent patients who were administered high doses of opioids and still suffered from severe pain, ketamine infusions used as an adjuvant to opioid analgesia was associated with opioid-sparing effects and apparent improvement in pain control in 8 of 11 patients (Finkel et al., 2007). In a study on 10 patients suffering from opioid-refractory cancer pain, ketamine was given as an adjuvant to morphine. Patients after ketamine but not saline administration had reduced pain intensity (Mercadante et al., 2000). A retrospective case review of 14 pediatric patients with terminal prognoses and opioid-refractory neuropathic pain showed that ketamine, administered along with benzodiazepines that limited ketamines psychodysleptic effects, relieved pain (Taylor et al., 2015). For more information about studies on the effects of ketamine therapy on cancer pain the reader is referred to extensive reviews (Bell et al., 2003; Bredlau et al., 2013; Zgaia et al., 2015). However when it comes to big, prospective, fully blinded, active- or a placebo-controlled clinical trials, the effects of ketamine on relieving cancer pain are not that definitive (Jonkman et al., 2017). The most recent multicenter, double-blind randomized clinical trial of oral ketamine vs placebo in the treatment of cancer pain in 214 patients was conducted by Fallon et al. The subjects represented a variety of cancer types however 74,7% were in remission and had chronic, chemotherapy-induced, neuropathic pain. The subjects were given ketamine as an adjuvant to cancer pain therapy. The authors conclude that the effects of ketamine were equivalent to placebo for cancer-related neuropathic pain (Fallon et al., 2018). In a study on 185 subjects, a 5-day subcutaneous ketamine treatment as an adjuvant to opioid therapy also didn't reduce pain significantly as compared to the placebo group (Hardy et al., 2012). Jonkman et al. in their review of literature on ketamine use in cancer pain conclude that the retrieved randomized controlled trials contain insufficient evidence of a clinical relevant beneficial effect of ketamine as an adjuvant for the relief of moderate to severe cancer pain (Jonkman et al., 2017).

3.3. The role of ketamine in depression treatment

For over 10 years ketamine has been in the center of research concerning the treatment of the major depressive disorder (Aan Het Rot et al., 2012). It all started from a randomized controlled trial in 2000 that proved that a single, sub-anesthetic dose of ketamine relieves depressive symptoms (Berman et al., 2000). Most approved anti-depressant medications effects are focused on the monoamine system, so targeting NMDA receptors is a completely new approach (Mathew et al., 2008). Some patients do not show any response to standard anti-depressant drugs, this group is termed to suffer from treatment-resistant depression (TRD) group (Sackeim, 2001). The second randomized-controlled trial studied the effects of ketamine on these patients only. Again, a single ketamine administration had robust anti-depressive effects that were rapid but transient since they passed after a week (Zarate et al., 2013). From that time a significant amount of trials have been done to determine the effects of ketamine on major depression disorder, bipolar disorder, treatment-resistant depression, and others. An extensive review of those trials has been presented in Aan Het Rot et al., 2012 and Serafini et al., (2014). Moreover, ketamine has also been shown to rapidly reduce suicidal thoughts in patients with suicidal ideation (Murrough et al., 2015; Wilkinson et al., 2018). These studies, apart from indicating a potential drug for depression, brought to the fore a lot of questions. How ketamine executes its antidepressive properties? How can a single dose reduce depressive symptoms for a week? Do all patients respond to ketamine?

One of the possible mechanisms in which ketamine executes its antidepressive properties is related to brain-derived neurotrophic factor (BDNF). Ketamine has been shown to rapidly induce antidepressant-like behavioral effects in mice through the inhibition of spontaneous

miniature NMDA receptor-mediated currents leading to decreased eEF2 kinase activity and allowing an increased BDNF translation (Autry et al., 2011) (Fig. 1). Anti-depressant actions of ketamine were blocked in BDNF-knockout mice (Autry et al., 2011) and in mice with a knock-in of the BDNF Val66Met allele, which blocks the processing and activity-dependent release of BDNF (Liu et al., 2012). Further evidence comes from a study where a neutralizing BDNF antibody was infused into the medial prefrontal cortex and this blocked the behavioral effects of ketamine in rats (Lepack et al., 2015). Some patients that do not respond to ketamine treatment are carriers of a single-nucleotide polymorphism (SNP) that is associated with attenuation of BDNF functioning (Laje et al., 2012). However, some studies that undermine the role of BDNF in ketamine anti-depressive effects. A study on 23 patients showed that a single infusion of ketamine reduces depressive symptoms but did not affect BDNF levels (Machado-Vieira et al., 2009). In a forced swim test, ketamine produced similar antidepressive effects in wildtype and heterozygous bdnf $^{\pm}$ mice and the levels of BDNF were not altered by ketamine administration (Lindholm et al., 2012).

Another possible mechanism of ketamine's action might be through the mTOR pathway. Ketamine rapidly activates the mammalian target of rapamycin (mTOR) pathway, leading to increased synaptic signaling proteins expression and increased number and function of new spine synapses in the prefrontal cortex. The blockade of mTOR signaling with rapamycin blocked ketamine induction of synaptogenesis and behavioral responses in models of depression (Li et al., 2010) (Fig. 1). Ketamine administration in rats has been shown to increase both hippocampal mTOR and BDNF levels during the forced swim test (Yang et al., 2013) but ketamine-dependent stimulation of mTOR has been shown also in many other studies (Dwyer et al., 2012; Yang et al., 2012; Zhou., 2014; Paul, 2015; Harraz et al., 2016; Yang et al., 2018). Apart from BDNF and mTOR, ketamine administration is also related to an increase in hippocampal Synapsin levels (Akinfiresoye and Tizabi, 2013). Since these are markers of neurogenesis and synaptogenesis and that ketamine induces synaptogenesis and spine formation in the prefrontal cortex (Duman and Li, 2012), ketamine might execute its antidepressive functions through neurotrophic mechanisms. Ketamine could also work through affecting the opioid system since administrating opioid receptor antagonists to 30 human subjects attenuated the antidepressive effects (Williams et al., 2018). Surprisingly, studies on antidepressive actions of other non-selective NMDA receptor antagonists such as memantine and lanicemine have been negative (Sanacora et al., 2017; Zarate et al., 2006). To exhibit its antidepressive properties ketamine should be administered intravenously which comes as an inconvenience, however nasal application of the S(+)-ketamine stereoisomer seems to be efficient and has recently been released into the market by Janssen (Duman, 2018; Traynor, 2019). The recommended dosing procedure is 56 mg twice a week for 1–4 weeks and then 56 or 84 mg once a week for weeks 5–8, and then bi-weekly of weekly administration of 56 or 84 mg depending on the patients response (Medscape, 2016).

The vast amount of clinical trials and other studies show that ketamine is efficient in treating TRD (Serafini et al., 2014) and other depressive disorders (Aan Het Rot et al., 2012). It also is an effective treatment for suicidal ideation (Reinstatler and Youssef, 2015). However, still the exact mechanisms of how ketamine executes its antidepressive and antisuicidal properties seem to not be fully understood and it is not clear if these properties are elicited via the same or separate mechanisms (Wilkinson et al., 2018). The drug formulation, the delivery device and technique, and individual patient factors seem to play a role efficacy of Ketamine treatment, and more long-term safety studies need to be performed, particularly with repeated dosing (Loo, 2018). Nevertheless, the use of ketamine for depression treatment is growing and in March 2019 the first intranasal spray with S-Ketamine has been approved by FDA for use in adults with depression that have not responded to at least 2 other therapies (Singh et al., 2017; Traynor, 2019).

3.4. The role of ketamine in addiction treatment

The discovery of ketamine's antidepressive properties urged further psychiatric research. It appears that ketamine can also help in treating various drug addictions (Ezquerra-Romano et al., 2018). Ketamine reduces ethanol drinking in alcohol-preferring rats and this effect was dose-dependent. These effects were blocked by the mTOR pathway inhibitor rapamycin (Sabino et al., 2013). In studies on morphine-induced place preference, rats administered with ketamine had reduced preference for morphine (Zhai et al., 2008). In 1997 Krupitsky and Grinenko published a study summarizing 10 years of research on ketamine psychedelic therapy (KPT). In this therapy detoxified alcoholics were administered ketamine and experienced its psychedelic effects. During the psychedelic phase, the therapist would verbally guide the patient to find a new purpose in their life and present the smell of ethanol to create negative emotions related to alcohol. KPT is meant to help the patients realize the negative effects of their addiction. Compared to a group receiving conventional therapy, significantly less KPT patients relapsed (Krupitsky and Grinenko, 1997). KPT resulted in a greater rate of abstinence in heroin addicts (Krupitsky et al., 2002). Ketamine also enhanced motivation to quit cocaine addiction and reduced cue-induced craving in cocaine addicts (Dawkar et al., 2014). In their systematic review of ketamine efficacy in the treatment of substance use disorder Jones et al. conclude that ketamine may facilitate abstinence across multiple substances of abuse and warrants broader investigation in addiction treatment (Jones et al., 2018).

3.5. Ketamine as a model for studying schizophrenia and memory impairment

Schizophrenia has been traditionally linked to the malfunction of the dopaminergic system, manifesting in increased dopamine release and D_2 receptor hyperactivation (Drożak and Bryła, 2005). An alternative hypothesis emerged along with the observation that ketamine administration produces schizophrenia-like symptoms including psychosis, negative symptoms, and cognitive impairment (Coyle et al., 2012). These syndromes can be indistinguishable from acute schizophrenia symptoms (Newcomer et al., 1999). Interestingly ketamine produces hallucinations in children less frequently than in adults (Reich and Silvay, 1989), which is consistent with schizophrenia symptoms appearing usually after 16 years of age (Coyle et al., 2012). Ketamine has been demonstrated to increase positive and negative symptoms in schizophrenia patients (Lahti et al., 1995; 2001). Acute doses of ketamine in healthy volunteers induce schizophrenic-like positive and negative symptoms (Krystal et al., 1994; Lahti et al., 2001). Chronic ketamine users have upregulated D_1 receptor expression similar to schizophrenics (Narendran et al., 2005). Brain imaging studies have shown that changes in brain morphology after repeated ketamine administration are consistent with these appearing in patients with established schizophrenia (Liao et al., 2011; Stone et al., 2014). These observations brought the idea of using ketamine as a laboratory model of schizophrenia (Becker and Grecksch, 2004). Ketamine is now used as a model of drug-induced schizophrenia in both rodents and humans (Winship et al., 2018). Research using these models aim to explain schizophrenia pathophysiology and find accurate treatment (Bubeníková-Valešová et al., 2008).

Ketamine can also be used as a pharmacological model of memory impairment (Newcomer et al., 1999). Ketamine's administration affects episodic, working and semantic memory, attention, executive functioning and procedural learning (Morgan and Curran, 2006). These deficits most probably arise through the same mechanism as schizophrenia symptoms and are not due to neurodegeneration mechanisms like in Alzheimer's disease. Ketamine leads to errors in associative learning resulting in disrupted encoding of predictions. Thus, it may not be the episodic memory itself that is blocked by the drug, but rather ketamine may prevent the association of a given memory with its

meaning augmenting the possibility of delusions (Corlett et al., 2007).

4. Other applications of ketamine

4.1. Ketamine in asthma treatment

Ketamine works also as an airway relaxant and bronchodilator (White and Elig, 2013). Thanks to these properties, attempts were made to use ketamine for the treatment of asthma exacerbations (Sarma, 1992; Denmark et al., 2006; Shlamovitz and Hawthorne, 2011; Hendaus et al., 2016). It has been shown that IV administration of ketamine to children and adults suffering from an acute attack of asthma can prevent the need for intubation (Sarma, 1992; Denmark et al., 2006). The literature reports are however conflicting. In a double-blinded, randomized, placebo-controlled trial on 68 children patients presenting with an acute asthma exacerbation showed no significant improvement after treatment with IV ketamine as compared to standard therapy (Allen and MacIas, 2005).

4.2. Ketamine in suppressing cancer

It appears that ketamine can play an important role not only in cancer pain therapy but also in the treatment of cancer itself. In a study from 2015 Malsy et al. showed that treatment with ketamine or S (+)-ketamine can decrease proliferation rate, apoptosis and increase necrosis in human adenocarcinoma pancreatic cells. This effect is related to the fact that pancreatic cancer cells express NR2A subunit of the NMDA receptor (Malsy et al., 2015). In fact NMDA receptor subunits are known to be expressed on various types of cancer cell lines (Aronica et al., 2001; Choi et al., 2004; Abdul and Hoosein, 2005; Liu et al., 2007) and glutamate antagonists can inhibit proliferation of human cancer cell lines including colon adenocarcinoma, astrocytoma, and breast and lung carcinoma (Rzeski et al., 2001). Moreover, another NMDA open channel blocker MK-801 has been shown to suppress hepatocellular carcinoma growth (Yamaguchi et al., 2013). A recent study shows that ketamine can induce apoptosis of lung adenocarcinoma cells by upregulating CD69 expression. CD69 is a leukocyte and natural killer (NK) cell activation marker and it is downregulated in patients suffering from lung adenocarcinoma (Zhou et al., 2018).

4.3. Anti-inflammatory and immunomodulatory properties of ketamine

Ketamine has been shown to have a positive effect on the regulation of inflammation without affecting healing processes (Beilin et al., 2007; Dale et al., 2012). In vitro studies on cultured macrophages have shown that ketamine inhibits the production of IL-6 (interleukin 6), TNF-α (tumor growth factor α) and nitric oxide (Shimaoka et al., 1996; Li et al., 1997; Chang et al., 2005; Lankveld et al., 2005) and inhibits their oxidative function (Yang et al., 2005). In vitro studies on animal isolated neutrophils have shown that ketamine inhibits the production of free radicals (Pekoe et al., 1983) and cytokines (Tekenaka et al., 1994). Similar effects were observed in human isolated neutrophils (Zilberstein et al., 2002). In several studies in human ketamine has been shown to decrease the production of pro-inflammatory cytokines (Roytblat et al., 1998; Kawasaki et al., 2001; Zeyneloglu et al., 2005; Bartoc et al., 2006). Low dose administration of ketamine before anesthesia induction in human patients resulted in a decrease in IL-6 and TNF-α secretion during the early postoperative period. At the same time, it preserved the pre-operative levels of IL-2 (interleukin 2) which is important for regulating cellular and humoral inflammatory responses (Beilin et al., 2007). Due to its anti-inflammatory properties, ketamine administration has lowered mortality in a study on septic mice (Takahashi et al., 2010) and rats (Shaked et al., 2004). In a systematic review evaluating 14 studies done on 684 patients Dale et al. conclude that intraoperative administration of ketamine inhibits the early post-operative inflammatory response (Dale et al., 2012). These results indicate that ketamine application might be a successful strategy to attenuate perioperative cytokine responses and thus possibly improve surgical outcomes.

4.4. Ketamine as a recreational drug

The story of ketamine's recreational use began around the same time as its first applications in anesthesia, thus around 1965 (Siegel, 1978). Ketamine is a potent recreational drug due to its rapid onset, short duration of action and unique psychedelic properties termed as „K-hole" characterized as a state of extreme dissociation with visual and auditory hallucinations and a sense of near-death experience (Corazza et al., 2013). In 1978 an American physician, psychoanalyst and philosopher John Lilly in his book "The Scientist" enthusiastically described his experiences with ketamine (Lilly, 1978). The drug's use increased with the rising popularity of rave parties during the 1990s and remained a part of the club dance culture (Riley et al., 2008). Ketamine has also been sold as a component of ecstasy tablets (Copeland and Dillon, 2005). During the last 20 years ketamine's use as a recreational drug have become more and more popular. This is due to its price being half lower than that of cocaine and its opinion of a safe drug (The Independent, 2009). Interestingly, as compared with other cities, ketamine has been widely used in Hong Kong, when it became a drug of choice within 3 years of its introduction in the 1990s and it remains so to this day (Joe-Laidler and Hunt, 2008). The first report of ten cases that connected recreational ketamine abuse with the occurrence of ulcerative cystitis came from Hong Kong (Chu et al., 2007). Recently a ketamine derivative methoxetamine has emerged as a ketamine alternative that does not cause bladder toxicity (Corazza et al., 2013).

5. Conclusions and discussion

Ketamine has a wide range of applications. Its anesthetic properties are well established and continue to be used in some clinical settings. The use of ketamine in burn victims and in patients that are hemodynamically unstable remains of importance. Recent years, however, have brought the substance under the spotlight again due to its non-canonical uses. These fall on two interesting paths – one related to its psychological effects and another one independent of them.

In the areas related to ketamine's psychological effects, pain management and treatment of depression seem most promising. After a thorough review of the literature it appears that, in pain management, ketamine is best used in combination with opioids. In such treatment, it can have an opioid-sparing effect and perhaps limit the possibility of development of opioid addiction. In chronic pain, the application of ketamine alone remains controversial and a need for more clinical studies in this area exists. Among new applications of ketamine, its antidepressive and antisuicidal properties seem to be particularly promising and create hope for developing effective treatments. The recent approval of intranasal S-ketamine to treat treatment-resistant depression marks a large development in the field, as novel TRD therapies are lacking. Next years will undoubtedly bring new information about the effectivess of ketamine in psychiatric disorders and confirm or disprove the reservations about ketamine's use due to possible abuse of the substance by patients.

Another interesting and completely new application of ketamine could emerge from preliminary research showing ketamine's cancer-suppressing and immunomodulatory properties. Although this research is in its early phase, cancer patients could both benefit from the antidepressive, opioid-sparing and cancer-suppressing properties of the substance. However, caution must be applied to such ideas as at this point of time the anti-cancer properties of ketamine are weakly researched.

Despite so many applications, how ketamine executes its clinical effects is often not fully understood. A major problem in the field is that the treatment regimens and dosage vary so greatly between the trials

that it is often difficult to draw conclusions by comparing different reports. It is still unknown which properties of the substance are exhibited through independent mechanisms. That's why further research on mechanisms of action and long-term effects of ketamine use are still required.

Conflicts of interest

Authors declare no conflicts of interest.

Authors contributions

AN wrote most of the manuscript and prepared the table, MB provided essential revisions, wrote sections of the manuscript and prepared the figures.

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