Ketamine pharmacometrics

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Pharmacokinetic and pharmacodynamic considerations for NMDA-receptor antagonist ketamine in the treatment of chronic neuropathic pain: an update of the most recent literature.

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NEUROPATHIC PAIN

On their website, the International Association for the Study of Pain (IASP) defines neuropathic pain (NP) as "pain caused by a lesion of the somatosensory nervous system".[1,2] The IASP further states that NP is a description rather than a diagnosis that requires a detectable lesion or a disease according to recognized neurologic criteria. NP may be central or peripheral depending on the location of the lesion in the peripheral or central somatosensory nervous system. It is evident from these statements that NP is associated with multiple diseases or syndromes (Table 1).[3] Additionally, in many patients no cause for their NP is found.

Table 1. Examples of diseases and syndromes associated with neuropathic pain.

Trauma to the peripheral or central nervous system	Surgical trauma, spinal cord injury, traumatic peripheral nerve damage, amputation with phantom limb pain, complex regional pain syndrome, complex regional pain syndrome
Nerve or spinal cord compression	Disc herniation, canal stenosis
Vascular disease	Stroke, ischemia of the lower extremities
Degenerative neurological disease	Multiple sclerosis, amyotrophic lateral sclerosis, syringomyelia, Parkinson's disease, Huntington's disease, Alzheimer's disease
Infectious disease	HIV/AIDS, leprosy, shingles, neuritis
Hereditary neuropathic syndromes	Erythromelalgia, Fabry's disease, sodium channelopathy
Metabolic syndromes	Diabetes mellitus, sarcoidosis, alcoholism, amyloidosis, malnutrition, obesity
Drugs and toxins	Chemotherapeutics, thalidomide, arsenic
Cancer	Paraneoplastic, dysglobulinemia, nerve damage (in cancer pain often both neuropathic and nociceptive components are present)
Other	Idiopathic, fibromyalgia

Patients with NP often display similar characteristic symptoms irrespective of the underlying disease, such as spontaneous pain often described as burning (hot), electric or shooting, an increase in pain sensitivity (hyperalgesia) with reduced pain thresholds (allodynia).[3] In case of hyperalgesia and allodynia there is often central sensitization or a heightened responsiveness of nociceptive neurons to normal and subthreshold inputs.[4] The presence of central sensitization can be examined by so called experimental proxies such as conditioned pain modulation or temporal summation in humans and windup in animals.[4] It is important to realize that, particularly in case of central sensitization, there is a discrepancy between the amount of tissue damage and the intensity of pain experienced by the patient, due to the fact that aberrant pain processing within the central nervous system is now the main cause of the pain.[4]

Many chronic pain syndromes, including and possibly even especially NP, are associated with comorbidities such as depression, anxiety, difficulty sleeping, fatigue, cognitive decline, and other often poorly diagnosed vague symptoms such as diffuse bodily pain or general malaise.[5] In conclusion, NP is a debilitating condition associated with an often difficult-to-treat underlying (or idiopathic) disease that has a major impact on the well-being of the patient and may have serious socioeconomic consequences to the affected individual and his or her family.

TREATMENT OF NEUROPATHIC PAIN

NP is difficult to manage with just a limited treatment effect in 30-60% of patients. Most, if not all, treatments are aimed at symptom reduction. In 2015, Finnerup et al. published a systematic review and meta-analysis of randomized controlled trials of oral and topical pharmacotherapy *versus* placebo to treat NP.[6] They used the number-needed-to-treat (NNT) as primary end-point, where an effective treatment was defined by a reduction in pain score by at least 50%. There was no evidence of efficacy for any drug in in any disease. Hence, irrespective of underlying disease, they observed an average NNT of 3.6 for tricyclic antidepressants and number-needed-to-harm (NNH) of 13.4; NNT of 6.4 for SNRI-(selective serotonin-noradrenaline reuptake inhibitors; mainly duloxetine)-type antidepressants (NNH = 11.8); 7.2 for gabapentin (NNH = 29) and 7.7 for pregabalin (NNH 13.9), both anticonvulsants. NNT and NNH values for strong and weak (tramadol) opioids were 4.3 and 4.7, respectively, with NNH values of 11.7 and 12.6. Based on the quality of evidence and efficacy, the authors give a strong recommendation for use of antidepressants (tricyclics and SNRIs) and GABAergic anticonvulsants, and a weak recommendation for use of opioids and the lidocaine (5%) and capsaicin (8%) patches. The recommendation regarding the use of oral or topical N-methyl-D-aspartate receptor (NMDAR) antagonists was inconclusive. Finnerup et al. did not include intravenous NMDAR antagonists, such as ketamine, in their analyses.[6]

Since the NMDAR plays a crucial role in the development and chronification of pain, especially NP, and given the fact that the current array of treatment options still lacks adequate efficacy in the majority of patients, many physicians in second and third line attempt treatment of refractory NP with NMDAR antagonists, particularly ketamine.[7-9] In chronic NP, there is an enhanced release of the excitatory amino acids (glutamate) in the dorsal spinal horn of the spinal cord, with consequently persistent activation of post-synaptic excitatory NMDARs that maintain afferent neurotransmission to sensory brain sites.[7] Prolonged stimulation will cause upregulation of the NMDAR and consequently establishes a state of central sensitization with pain, allodynia and hyperalgesia, often spreading across multiple dermatomes. Note that sensitization is not restricted to NP but

may also occur in nociceptive pain.[4] Given the above, blockade of sensitized NMDARs seems an opportunistic method of pain relief in NP by curtailing central sensitization. There are several drugs available in clinical practice with (variable) antagonistic activity at the NMDAR including xenon, nitrous oxide, magnesium, methadone, amantadine, riluzole, memantine, phenytoin, carbamazepine, valproic acid and ketamine.[10,11] Just a restricted number of these drugs are used to specifically treat NP. The largest number of positive trials in the treatment of NP is observed with ketamine.[11] Of all mentioned NMDAR antagonists, ketamine is possibly most efficacious in reducing windup and temporal summation.[12] In a recent study in patients with refractory NP, temporal summation measured just before treatment was a predictor of the efficacy of ketamine. [13]

In this review, we discuss recent data on the pharmacokinetics and pharmacodynamics of ketamine in the treatment of NP. This is an update of our previous review on this same topic published in 2012.[7] Since then, the interest in ketamine and other NMDAR antagonists has increased significantly, primarily due to the positive results of studies on the treatment of therapy-resistant depression with ketamine. Moreover, the use of ketamine in the management of several refractory (neuropathic) pain conditions persists. Alongside the increased clinical interest in ketamine, new data have emerged on the pharmacokinetics of ketamine and its metabolites, and on the complex and comprehensive modes of action of ketamine in its intended and adverse effects. Finally, additional studies were published that scrutinized ketamine efficacy, particularly in NP conditions.

KETAMINE

Ketamine is a rather complex drug; it is a racemic mixture containing an *S*- and *R*-isomer.[7,8] Since 2000, both the racemic mixture (Ketalar® or *RS*-ketamine) and the *S*-ketamine enantiomer (Ketanest®, Spravato® or esketamine) are commercially available. Additionally, ketamine has several active metabolites. Major metabolites include norketamine (NK) and hydroxynorketamine (HNK), of which multiple enantiomers are produced in the liver.[14] (2*R*,6*R*)-HNK is the most studied ketamine metabolite due to its specific pharmacodynamic properties. Both enantiomers and metabolites differ in their pharmacokinetics and pharmacodynamics (such as molecular site of action), although detailed information on these differences is still not fully available.[14] Therapeutically, ketamine is used as anesthetic, analgesic for acute and chronic (cancer and non-cancer) pain, and since a few years as antidepressant. Additionally, ketamine is occasionally used as anti-inflammatory agent in perioperative care, in the treatment of post-traumatic stress disorder, and finally to induce bronchodilation in refractory asthma. [15-17]

MECHANISM OF ACTION

Ketamine is a promiscuous drug that interacts with multiple receptor systems within the central nervous system (*e.g.* opioid receptors, sigma receptor, dopamine D_2 receptors, muscarinic acetylcholine receptor, innate repair receptor, HCN1 cation channels).[7,8] In NP, however, its main mechanism of action is blockade of sensitized NMDARs.[7,8] As discussed previously, this will interrupt the continuing and excessive barrage of afferent input from damaged peripheral sites (such as a peripheral nerve injured by surgery).[7] Secondary mechanisms include the reset or desensitization of spinal and supra-spinal glutamatergic nociceptive pathways, the inhibition of reuptake of monoaminergic compounds (*e.g.* dopamine, serotonin and norepinephrine) and the restoration of descending pain inhibition.[8] An interesting recent observation is that ketamine does not produce relief of NP in mice lacking the β-common receptor (CD131).[18] The erythropoietin receptor-β-common receptor complex (also named the innate repair receptor) is a tissue protective receptor that is upregulated in tissue injury (including various diseases associated with NP) and activated by the local release of erythropoietin. Ketamine acts at the innate repair receptor causing effective relief of allodynia in wild type mice and rats. NP persists in knockout mice that lack the β-common receptor. Interestingly, acute pain relief was still observed in these β-common receptor knockout mice. It was argued that ketamine acts *via* a yet unknown link between the NMDAR and this specific repair pathway. An interesting secondary observation was that ketamine reduced inflammatory markers in the spinal cord of rats with NP from peripheral nerve damage.

PHARMACOKINETICS

Ketamine inhalation

Ketamine is administered by several routes of administration including intranasal, sublingual, subcutaneous, rectal, transcutaneous and intravenous routes. However, in clinical practice, the intravenous route is the most frequently applied mode of ketamine delivery with consequently the need for a venipuncture or intravenous cannula. Recent studies addressed the safety and feasibility of ketamine inhalation following nebulization or aerosolization of preservative free *RS*- and *S*-ketamine.[19,20] The main rationale for this route is the ability to administer ketamine for longer periods of time without the need for intravenous access. Additionally, inhalation results in a rapid absorption into the systemic circulation, which is only surpassed by intravenous administration. Inhaled ketamine could be an alternative mode of delivery outside of the hospital setting (for example at home in palliative care).

The safety of preservative free *S*-ketamine inhalation was addressed by Jonkman et al.[20] They showed rapid *S*-ketamine uptake with C_{MAX} values > 100 ng/mL attained within 15-30 min, following inhalation of 0.35-0.70 mg/kg *S*-ketamine for 20-40 min. All adverse effects that were observed were related to the drug itself and not to the mode of administration and were perceived as mild. Side effects included nausea, vomiting, drug high, schizotypal effects and mild hypertension. None of these side effects interfered with the operation of the inhalation device. During and following inhalation, there were no signs of oropharyngeal irritation, hypersalivation, stridor, laryngospasm, bronchospasm, dyspnea, aspiration or desaturation.

In a second publication, Jonkman et al. addressed the pharmacokinetics and bioavailability of inhaled ketamine.[19] The pharmacokinetic data were analyzed with a multicompartmental model that consisted of three *S*-ketamine, two *S*-norketamine disposition and three metabolism compartments. Uptake into the systemic circulation was modelled through a rapid (immediate) and a slow pathway with rate constant 0.05 min^{-1}, probably related to pulmonary uptake. Bioavailability ranged from 40 to 70%. Thirty percent of the *S*-ketamine was lost due a dose-independent mechanism (ketamine swallowed, exhaled or stuck to the inhalation device) while the remainder was lost in a dose-dependent fashion, probably due inefficient inhalation. No safety issues became apparent in bystanders (research personnel).

Intranasal ketamine

Similar to ketamine inhalation, the delivery of ketamine via a nasal spray is possible without intravenous access, and thus facilitates ketamine use in outpatient settings. In a study by Nielsen et al., fifty children received a combination of intranasal sufentanil (0.5 µg/kg) and racemic ketamine (0.5 mg/kg) preceding painful procedures.[21] Ketamine bioavailability was 36%, with C_{MAX} values > 100 ng/mL reached after 8.5 min. The authors reported few adverse effects (vomiting in three patients). Recently, the FDA approved an intranasal *S*-ketamine preparation (Spravato®; Johnson & Johnson) for management of treatment-resistant depression (*i.e.,* for patients who experienced previous treatment failure with two other antidepressants without success).[22] Spravato® should be used in conjunction with an oral antidepressant. The intranasal device delivers 28 mg of *S*-ketamine in two sprays and is available as a 56-mg kit (two 28-mg devices) or an 84-mg kit (three devices). Dosing is 56 or 84 mg once weekly but eventually (after 8 weeks) aimed at an individualized dosing frequency to the least frequent dose that maintains remission or treatment response.

Ketamine pharmacokinetic model parameters

We recently performed a meta-regression analysis to synthesize ketamine PK parameter values, volume of distribution and terminal clearance, and determined a possible

effect of age, disease state, administration form (*S*- or *RS*-ketamine), analyte (*S*-, *R*- or *RS*-ketamine), sampling site (arterial or venous) and population size.[23] Data from 30 ketamine PK modeling studies were retrieved from the literature. Interestingly, despite sometimes large inter-study heterogeneities, the values for volume of distribution and elimination clearance were similar among studies with values for volume of distribution 200-270 L/70 kg (95% confidence interval) and for elimination clearance 70-85 L/h at 70 kg. Additionally, no influence of any of the covariates on PK parameters was observed. This indicates that one set of ketamine model parameters may be used to determine dosing in a variety of conditions. However, dosing in the pediatric population remains preferable by titration to effect rather than dosing by body weight as these analyses were scaled to a standardized 70 kg patient. Due to a paucity of studies, assessment of the effect of metabolic enzyme variants or sex on model parameters was not possible. Similarly, just a minority of studies included ketamine's metabolites into their PK models and hence it remains unclear whether inclusion of these metabolites would improve the performance of ketamine PK (and PD) models.

Metabolites

Ketamine is extensively metabolized via cytochrome P450 (CYP) enzymes, mainly by CYP2B6 and CYP3A4. The main metabolic pathway involved in ketamine metabolism is N-demethylation to NK. Subsequently, NK can be either hydroxylated to HNK or dehydroxylated to dehydronorketamine (DHNK). In addition, several minor metabolic pathways have been described, most of them involving the conversion of ketamine to hydroxyketamine with or without a subsequent conversion to HNK.[24] Approximately 80% of the ketamine dose is metabolized to NK, 5% to hydroxyketamine and 15% to HNK. [25-27] The relative importance of CYP enzymes 2B6 and 3A4 in the metabolic pathways of ketamine remains a matter of debate. A recent *in vitro* study showed a higher ketamine affinity for CYP2B6 than CYP3A4 for ketamine N-demethylation to NK in human liver microsomes.[25] However, since CYP3A4 is more abundant than CYP2B6, CYP3A4 is considered to be the main CYP subtype in this metabolic pathway. Ashraf et al. report that CYP2B6 is the main enzyme responsible for ketamine metabolism.[28]

It is well known that CYP polymorphisms can substantially influence ketamine clearance and thus plasma concentrations. In a study evaluating the effects of CYP2B6 polymorphisms and age on ketamine clearance, the presence of the CYP2B6*6 allele explained 40% of the variation in ketamine steady state concentrations.[29]

One recent study in patients with treatment resistant bipolar disorder allowed extraction of relevant PK parameter values for HNK and DHNK.[30] Assuming that central volumes of distribution for HNK and DHNK are equal to that of ketamine, clearances were 4.7 L/h at 70 kg, 15.2 L/h at 70 kg and 8.34 L/h at 70 kg for HNK, *R*-DHNK and *S*-DHNK. Total plasma exposure (area under the curve, AUC) was shown to be higher for

the HNK metabolite than for ketamine, which is likely to be caused by rapid and efficient metabolic generation of HNK combined with a relatively slow HNK clearance.

Enantiomers

In agreement with earlier observations, Henthorn et al. report a 15% lower *R*- than *S*-ketamine clearance following the separate administration of the two ketamine enantiomers in healthy volunteers.[31] A part of the stereoselective metabolism may be explained by the higher affinity of CYP3A4 for *S*- than *R*-ketamine, which results in a higher metabolic rate for *S*-ketamine. In contrast, demethylation by CYP2B6 occurs with near similar efficiency for both enantiomers.[24] Rat studies indicate the importance stereoselective metabolism of ketamine into HNK.[32] Moaddel et al. showed that the *S*-ketamine enantiomer is a more efficient source of (2,6)-HNK than the *R*-enantiomer.[32] However, HNK brain uptake and the clearance from plasma were not enantioselective. These results point towards similar enantioselectivity in the metabolism of ketamine into NK and HNK in humans and rats.

PHARMACODYNAMICS

Systematic reviews and randomized trials

A large number of studies on the efficacy of ketamine in pain management has been conducted and numerous clinical trials and case series have been published since 1990. In 2012 we stated that with respect to the ability of NMDAR antagonists in general and ketamine in particular to relief neuropathic pain "... *good-quality RCTs are sparse and point to just one NMDAR antagonist, ketamine, as a possible tool in the treatment of neuropathic pain. Still also for ketamine the proof is limited* ....".[7] To determine whether this picture on ketamine persists, we searched for systematic reviews published since 2012 that evaluated randomized controlled trials on the efficacy of ketamine (irrespective of administration route) in chronic pain conditions with a neuropathic pain component. We also included cancer pain, since cancer pain is often a mixed form of nociceptive and neuropathic pain. We retrieved seven relevant meta-analyses, systematic or literature reviews (Table 2). Five reviews focus on chronic neuropathic pain,[11,33-36] of which two predominantly on complex regional pain syndrome (CRPS) patients,[35,36] and two reviews on cancer pain.[37,38] Although there is some overlap in studies included in the various reviews, the approach of the different reviews is sufficiently distinguishing to be included in our analysis. The overall picture that emerges from these reviews is that (1) the heterogeneity among studies is large and synthesis of data is often not possible; (2) irrespective of the underlying disease, intravenous administration of ketamine seems to have a higher efficacy than other administration forms (oral, subcutaneous,

intranasal or topical); (3) the efficacy of intravenous ketamine is often rather small and does not last longer than 1-2 days following end of administration; (4) longer infusion times are associated with longer effect durations; (5) none of the studies phenotyped their patients or restricted treatment to patients with central sensitization; and (6) most studies were effectively not blinded due to the occurrence of ketamine side effects. One randomized controlled trial on the effect of oral ketamine *versus* placebo in cancer-related neuropathic pain was not included in any of the reviews and deserves mentioning. Fallon et al. randomized 214 patients with chemotherapy-induced neuropathic pain.[39] A ketamine or placebo titration phase was followed by a pain control maintenance phase. Just 24 and 26 patients in the respective ketamine and placebo arms completed the study. The others were excluded in the titration or maintenance phase due to treatment failure. Overall, ketamine was equivalent to placebo with 31.8% (ketamine) and 36.4% (placebo) of patients displayed maintained analgesic benefit at day 4 of treatment and 22.4% (ketamine) and 25.2% (placebo) at day 16. The authors further mention that there still may be subgroups of patients, such as those with central sensitization, that may be sensitive to the analgesic effects of ketamine. However, they did not phenotype patients in their study.

Finally, one important therapeutic indication for ketamine is its ability to provide long-term pain relief in opioid-dependent chronic low-back pain patients following low-back surgery.[40,41] The pathology causing low-back pain and the trauma from surgery will have neuropathic pain components and ketamine might have beneficial effects in subduing central sensitization and chronification. Additionally, the long-term use of opioids may have worsened central sensitization and consequently may have amplified hyperalgesia and allodynia. A recent randomized placebo-controlled trial studied patients undergoing spinal fusion surgery for chronic low-back pain.[41] Patients who had moderate to severe low-back pain (average pain score 50 mm, on a 0 to 100 mm scale) for at least 3 months and consumed an opioid for at least 6 weeks, were treated with either ketamine or placebo (bolus 0.5 mg/kg, followed by an infusion of 0.25 mg/kg per h) during the surgical procedure. Compared to placebo, ketamine-treated patients that preoperatively consumed more than 0.5 mg/kg intravenous morphine equivalents per day, used less morphine in the first 24 and 48 h following surgery; patients using less daily morphine equivalents preoperatively did not benefit from morphine in the first 24 and 48 postoperative hours. Most importantly and irrespective of prior opioid dose, patients treated with ketamine displayed significantly more improvement of their back pain after 6 months compared to placebo-treated patients and had less disability. At that time 44% of patients in the ketamine group and 62% of patients in the placebo group still had a daily consumption of opioids. Moreover, after 1 year these patients had less pain at rest and during mobilization (mean difference 13-17 mm) and used fewer opioid analgesics (ketamine group 0-20 mg/day *versus* placebo 0-62 mg/day, $p = 0.02$).[42]

Table 2. Meta-analyses, systematic and literature reviews on the efficacy of ketamine in the treatment of chronic (neuropathic) pain.

Authors/ type of analysis	Disease	Number of RCTs included	Number of patients	Ketamine efficacy	Comments
Orhurhu et al. 2019/ meta-analysis [34]	Chronic (neuropathic) pain	7	211	Small positive effect of intravenous ketamine.	Effect lasting for 2 weeks after ketamine infusion with a pain reduction of 1.83 points with 95% ci -2.35 to -1.31.
Aiyer et al. 2018/ literature review [11]	Chronic neuropathic pain	21	548	15/21 trials showed some (non-specified) benefit, of which 13/13 i.v. ketamine studies showed some benefit.	Oral (n = 3), topical (n = 5) and intravenous ketamine studies (n = 13) were included.
Zhao et al. 2018/ meta-analysis [36]	Complex Regional Pain Syndrome	15	258	A small meaningful reduction in pain scores was observed immediately following treatment and after 1-3 months.	The number of patients with at least 30% pain relief was 69% with 95% ci 53 to 84%, immediately after treatment and 58% (41 to 75%) 1-3 months after treatment.
Michelet et al. 2017/ meta-analysis [33]	Chronic neuropathic pain	6	195	No effect at 4 weeks after the beginning of ketamine treatment was observed although analyzing just the studies with no high-risk bias did find a moderate effect.	Leaving the one study with high-risk bias out of the analysis leads to a pain reduction of -1.73 points with 95% ci -2.39 to -1.07.
Bell et al. 2017/ systematic review [37]	Cancer pain	3	215	Two small studies (total n = 30) reported small reductions in pain intensity and morphine requirements. The larger trial (n = 185) showed no difference in pain scores between subcutaneous ketamine and placebo.	Various administration routes: intravenous, intrathecal and subcutaneous.
Jonkman et al. 2017/ literature review [38]	Cancer pain	4	245	3 of 4 trials had a negative effect; the remaining trial had an effect lasting no longer than 3 hours following the end of treatment.	Two additional trials are discussed on epidural (n = 12) or intrathecal (n = 20) ketamine + morphine *vs.* just morphine. Pain scores did not differ between treatments.
Connolly et al. 2015/ literature review [35]	Complex Regional Pain Syndrome, breakthrough pain, and postherpetic neuralgia	5	107	4 of 5 trials with intravenous (n = 3) and intranasal (n = 1) ketamine showed some efficacy; topical ketamine was without effect in Complex Regional Pain Syndrome patients.	

These reports contrast outcome of several other trials that show just limited effects of ketamine treatment during a range of surgeries for prevention of persistent postoperative pain.[9] However, none of the included patients in these earlier trials were opioid-dependent. It may well be that in opioid-dependent patients, ketamine interacts with brain circuits involved in opioid rewarding, causing a neuronal reset and consequently fewer opioid requirements (without withdrawal symptoms), re-engagement of descending pain inhibition and reversal of opioid-related paradoxical effects (opioid-induced hyperalgesia). A recent case report confirms such mechanisms.[43] A patient with CRPS and severe pain (score 9 out of 10) consuming daily more than 300 mg of morphine equivalents was successfully and rapidly opioid tapered with two 5-day ketamine treatments and cognitive behavioral therapy and remained opioid free for up to 1 year.

(2*R*,6*R*)-hydroxynorketamine

While it is generally accepted that ketamine is most important in producing the analgesic effects, it may well be that, in parallel to ketamine treatment in depression, the active metabolites play an important role in ketamine analgesia. In three mouse models of pain (nerve-injury neuropathic pain, tibia fracture complex regional pain syndrome pain, and plantar incision postoperative pain), Kroin et al. compared the analgesic effects of (2*R*,6*R*)-HNK and ketamine.[44] In all three models, (2*R*,6*R*)-HNK was superior to ketamine in producing long-lasting (> 24 h) relief of allodynia. Since the half-life of (2*R*,6*R*)-HNK is less than 1-h in the mouse brain, these effects are not pharmacokinetically driven but are possibly related to neuroplastic and neurotrophic changes causing reduction of central sensitization. Importantly, unlike ketamine, (2*R*,6*R*)-HNK is not associated with motor incoordination and has a lower potential for abuse or addiction. Further, this metabolite is associated with profound antidepressant effects. These observations make (2*R*,6*R*)-HNK an attractive new candidate analgesic. Zanos et al. showed that (2*R*,6*R*)-HNK antidepressant actions are independent of the NMDAR but are related to agonistic activity at the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor.[14] Whether a similar mechanism plays a role in the analgesic effects of (2*R*,6*R*)-HNK is still unknown.

ADVERSE EFFECTS

In humans, ketamine produces undesirable adverse effects that limit treatment compliance. Similar observations are made in animal studies. For example, in rodents, ketamine causes hyperlocomotion, ataxia and stereotypical behavior such as continuous running, head weaving, shaking or twitching.[45] In humans, symptoms include drug high, dissociative or psychedelic effects with psychosis-like behavior (paranoia,

hallucinations, changes in internal and external perception) and severe anxiety with panic attacks.[46] Treatment is aimed at symptom reduction with benzodiazepines and α_2-adrenergic receptor agonists (*e.g.* clonidine). One possible explanation for the occurrence of psychedelic effects during ketamine exposure is related to hypofunction of the NMDAR.[47-50] Upon glutamatergic NMDAR activation, calcium-ions flow into the cell and bind to calmodulin that stimulates nitric oxide (NO) synthase to produce the gaseous neuromodulator NO from L-arginine. Nitric oxide subsequently activates a cascade that in the end has neuroplastic, neurotrophic and neuroprotective effects. Blockade of the NMDAR by ketamine reduces the intracellular NO production causing the loss neuronal stability with consequently generation of negative behavioral symptoms. In animals, increasing intracellular NO content using NO donors blocks both phencyclidine and ketamine behavioral responses, attenuates ketamine-induced memory deficits, and reduces social withdrawal and anxiety.[47-51] Interestingly, there are data that show improvement of schizophrenia symptoms with the NO donor sodium nitroprusside (SNP).[51]

In one recent experimental study performed in healthy volunteers, the influence of the NO donor SNP was studied on drug high and changes in internal and external perception during infusion of racemic ketamine and *S*-ketamine.[52] Relative to placebo, SNP significantly reduced symptoms during and following racemic ketamine but not during and following *S*-ketamine infusion, suggesting that the symptoms induced by R-ketamine are alleviated by NO. Since the affinity of *S*-ketamine for the NMDAR is fourfold higher than that of *R*-ketamine, possibly higher SNP doses (causing more NO release) may be required to counteract *S*-ketamine-induced symptoms. However, it may equally be that the two ketamine isomers activate divergent intracellular transduction pathways, one of which is NO sensitive and the other is not. At present, adding a NO donor during racemic ketamine treatment for chronic pain seems premature and unsubstantiated. Possibly part of ketamine's intended effect is mediated by its dissociative pathway. For example, in the treatment of depression with ketamine, dissociative effects may play a modulatory role.[53] Hence, further (animal) studies are needed to assess whether modulation of the NMDAR-calmodulin-NO pathway negatively affects engagement of antidepressant and analgesic pathways.

CONCLUSIONS

The interest in ketamine has increased over the last decade. This is predominantly related to the development of ketamine for treatment of patients with therapy-resistant depression. This resulted recently in the approval by the FDA of the intranasal *S*-ketamine application Spravato® for this treatment indication.[22] The consequence of these developments is that knowledge on ketamine metabolomics has increased

significantly. While an important role for hydroxynorketamine has been detected in treatment of depression, just one experimental study studied the anti-allodynic effects of this ketamine metabolite in neuropathic and postoperative pain.[44] The results are promising, not only because of long-lasting analgesic efficacy, but also because this specific metabolite has fewer side effects than ketamine. Interestingly, the long-lasting analgesic effect is not driven by HNK pharmacokinetics. It is therefore likely that the metabolite has neuroplastic and/or neurotrophic effects at spinal and supraspinal sites that effectively counteracts central sensitization. Similar modes of action have been proposed for ketamine and are thought to be related to prolonged NMDAR desensitization.[54,55] Further studies are needed to fully understand the mechanism of action of HNK in pain relief. In the meantime, we encourage further development of HNK in humans for the treatment of pain.

Akin the recent development of esketamine intranasal application, inhalation as route of administration opens the possibility of long-term ketamine treatment outside the conventional hospital setting, for example in palliative care at home or in a hospice.[19,20] Since long-term treatment rather than short high-dose infusions seems to be crucial in effective management of chronic NP, this application form has an evident advantage over the intranasal form. The inhalation of esketamine is safe, but a practical inhaler has not been developed yet.

The following conclusions may be drawn from the seven systematic reviews and meta-analyses that were published since 2012[11,33-38] : irrespective of underlying disease, intravenous administration of ketamine seems to have the highest analgesic efficacy compared to other administration forms; the efficacy of intravenous ketamine is often rather small and does not last longer than 1-2 days following end of administration; longer administration times are associated with longer effect durations; none of the studies phenotyped their patients or restricted treatment to patients with central sensitization; most studies were effectively not blinded due to the occurrence of ketamine adverse effects.

EXPERT OPINION

The most important conclusion from the current update is that our current findings on the efficacy of ketamine to treat chronic neuropathic pain are in agreements with our conclusions from 2012 that *definitive proof of the efficacy of ketamine in management of neuropathic pain is limited*, with just small analgesic effects lasting no longer than a few days or (in some studies employing long-term infusion paradigms) a few weeks.[7] In 2012, we stated that additional randomized studies were urgently needed. We currently doubt whether additional randomized trials in often ill-defined groups of chronic

pain patient groups are useful and suggest to restrict future studies to patients with neuropathic pain and signs of central sensitization or to patients with opioid refractory severe neuropathic pain.

It is important to realize that the results of these systematic reviews on randomized controlled trials sharply contrast the findings from observational studies and case series. As discussed earlier, most open studies show unequivocally that ketamine has benefit in the management of chronic pain with positive patient-related outcome measures.[7,55] Additionally, experimental human and animal studies show analgesic efficacy of ketamine in neuropathic pain. We recently gave several explanations for the gap between controlled trials and open-label or case studies. In short, randomized controlled ketamine trials may fail for the following reasons[9,38] :

(1) Short-term infusions of ketamine will cause effects no longer than the treatment period or for just hours to a few days after treatment. Most trials on long-term intravenous treatment show greater signals of efficacy lasting days to weeks;
(2) Often the ketamine dose is restricted because of fear of adverse effects. Co-administration of benzodiazepines and/or α_2-agonists may be helpful. Especially, α_2-agonists may be useful as they are analgesic by themselves and temper the hemodynamic effects of ketamine;
(3) Rigid dosing titration regimens will have a negative effect on personal analgesic needs of the patient. In real life rapid and loose up-and-down titrations are allowed, aiming at optimizing effect with as few as possible side effects and often combined with co-medication;
(4) Pain intensity scores are often not well understood by patients and additionally may not capture the beneficial effects of ketamine on mood, cognition and quality of life. Linear metric scores on a 100 mm scale or numerical ratings poorly represent the actual perceived pain, particularly under conditions of chronic pain and cognitive impairment[56,57]. Moreover, ketamine may affect cognition and consequently more qualitative than quantitative scoring systems are likely required;
(5) Placebo controls may cause a bias in study outcome either due to an inflated placebo effect or due to the fact that well-informed clinical-trial participants that experience absence of side effects may decide to terminate their participation in the study[58]; and finally,
(6) In real life, patients with severe and progressive neuropathic pain often have other symptoms or complaints that restrict their ability to be included in the trial.

The debate on the efficacy of ketamine in the treatment of chronic neuropathic pain is certainly not closed. But more inventive ketamine studies than rigid randomized controlled trials are required before we can come to definite conclusions.[59] Possibly, restricting treatment to patients with specific neuropathic phenotypes and/or using

standard practice as control may result in a synthesis of randomized and open trials. Trials in which patients with central sensitization, irrespective of the cause of the underlying NP syndrome, *versus* those without central sensitization are needed to assess whether this subpopulation of patients is best served with long-term ketamine treatment. Other subpopulations that may benefit from ketamine are those chronic pain patients with confirmed small fiber neuropathy, larger nerve damage, central pain or patients with opioid-induced hyperalgesia. In other words, future ketamine trials should include patients with specific NP manifestations rather than patients suffering from general NP with a certain level of pain intensity. Additionally, apart from pain-related biomarkers, other study endpoints are needed. For example, mood-related indices and other patient-related outcome measures related to quality-of-life, daily activity and sleep quality/duration may better reflect the effect of ketamine on the patient's overall condition.

Finally, the use of ketamine for chronic NP should be viewed in light of the current opioid epidemic. Opioids are currently prescribed for a myriad of pain conditions including NP. The surge in opioid consumption has devastating consequences of which addiction, abuse and often fatal respiratory depression are common.[60,61] Two questions come to mind: (1) is ketamine a viable replacement of opioids for treatment of NP? and (2) is the treatment of ketamine safe when administered in combination with opioid therapy? The response to the first question is that ketamine should be used exclusively in therapy-resistant NP with clear signs of central sensitization or in opioid-tolerant patients. Treatment should always be offered under the supervision of health care providers in a healthcare setting. Additionally, one needs to realize that ketamine produces a drug high and, in high dose, a dissociative state. It can be addictive and may be abused (worldwide, ketamine is a popular party drug). Ketamine abuse is associated with a variety of adverse effects including liver failure and hemorrhagic cystitis.[8,62] These factors should be considered when considering ketamine treatment. The second question has recently been addressed by Jonkman et al. They showed that ketamine effectively counteracts opioid-induced respiratory depression, possibly through its (indirect) actions at the AMPA receptor.[63,64] This is an important observation that is relevant in perioperative care as well in NP patients treated with (high dose) opioids.

REFERENCES

1. International Association for the Study of Pain (IASP). IASP terminonoly: neuropathic pain., 2019
2. Scholz J, Finnerup NB, Attal N, Aziz Q, Baron R, Bennett MI, Benoliel R, Cohen M, Cruccu G, Davis KD, Evers S, First M, Giamberardino MA, Hansson P, Kaasa S, Korwisi B, Kosek E, Lavand'homme P, Nicholas M, Nurmikko T, Perrot S, Raja SN, Rice ASC, Rowbotham MC, Schug S, Simpson DM, Smith BH, Svensson P, Vlaeyen JWS, Wang SJ, Barke A, Rief W, Treede RD, Classification Committee of the Neuropathic Pain Special Interest G: The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. Pain 2019; 160: 53-59
3. Jensen TS, Finnerup NB: Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms. Lancet Neurol 2014; 13: 924-35
4. Arendt-Nielsen L, Morlion B, Perrot S, Dahan A, Dickenson A, Kress HG, Wells C, Bouhassira D, Mohr Drewes A: Assessment and manifestation of central sensitisation across different chronic pain conditions. Eur J Pain 2018; 22: 216-241
5. Dahan A, van Velzen M, Niesters M: Comorbidities and the complexities of chronic pain. Anesthesiology 2014; 121: 675-7
6. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpää M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice ASC, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M: Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet Neurology 2015; 14: 162-173
7. Niesters M, Dahan A: Pharmacokinetic and pharmacodynamic considerations for NMDA receptor antagonists in the treatment of chronic neuropathic pain. Expert Opin Drug Metab Toxicol 2012; 8: 1409-17
8. Niesters M, Martini C, Dahan A: Ketamine for chronic pain: risks and benefits. Br J Clin Pharmacol 2014; 77: 357-67
9. Jonkman K, Dahan A, van de Donk T, Aarts L, Niesters M, van Velzen M: Ketamine for pain. F1000Res 2017; 6
10. Collins S, Sigtermans MJ, Dahan A, Zuurmond WW, Perez RS: NMDA receptor antagonists for the treatment of neuropathic pain. Pain Med 2010; 11: 1726-42
11. Aiyer R, Mehta N, Gungor S, Gulati A: A Systematic Review of NMDA Receptor Antagonists for Treatment of Neuropathic Pain in Clinical Practice. Clin J Pain 2018; 34: 450-467
12. Arendt-Nielsen L, Nielsen J, Petersen-Felix S, Schnider TW, Zbinden AM: Effect of racemic mixture and the (S+)-isomer of ketamine on temporal and spatial summation of pain. Br J Anaesth 1996; 77: 625-31
13. Bosma RL, Cheng JC, Rogachov A, Kim JA, Hemington KS, Osborne NR, Venkat Raghavan L, Bhatia A, Davis KD: Brain Dynamics and Temporal Summation of Pain Predicts Neuropathic Pain Relief from Ketamine Infusion. Anesthesiology 2018; 129: 1015-1024
14. Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, Elmer GI, Alkondon M, Yuan P, Pribut HJ, Singh NS, Dossou KS, Fang Y, Huang XP, Mayo CL, Wainer IW, Albuquerque EX, Thompson SM, Thomas CJ, Zarate CA, Jr., Gould TD: NMDAR

inhibition-independent antidepressant actions of ketamine metabolites. Nature 2016; 533: 481-6

15. Liriano F, Hatten C, Schwartz TL: Ketamine as treatment for post-traumatic stress disorder: a review. Drugs Context 2019; 8

16. Rehder KJ: Adjunct Therapies for Refractory Status Asthmaticus in Children. Respir Care 2017; 62: 849-865

17. Dale O, Somogyi AA, Li Y, Sullivan T, Shavit Y: Does intraoperative ketamine attenuate inflammatory reactivity following surgery? A systematic review and meta-analysis. Anesth Analg 2012; 115: 934-43

18. Swartjes M, Niesters M, Heij L, Dunne A, Aarts L, Hand CC, Kim HS, Brines M, Cerami A, Dahan A: Ketamine does not produce relief of neuropathic pain in mice lacking the beta-common receptor (CD131). PLoS One 2013; 8: e71326

19. Jonkman K, Duma A, Olofsen E, Henthorn T, van Velzen M, Mooren R, Siebers L, van den Beukel J, Aarts L, Niesters M, Dahan A: Pharmacokinetics and Bioavailability of Inhaled Esketamine in Healthy Volunteers. Anesthesiology 2017; 127: 675-683

20. Jonkman K, Duma A, Velzen M, Dahan A: Ketamine inhalation. Br J Anaesth 2017; 118: 268-269

21. Nielsen BN, Friis SM, Romsing J, Schmiegelow K, Anderson BJ, Ferreiros N, Labocha S, Henneberg SW: Intranasal sufentanil/ketamine analgesia in children. Paediatr Anaesth 2014; 24: 170-80

22. Kaufman MB: Pharmaceutical Approval Update. Pharm Ther 2019; 44: 251-254

23. Kamp J, Olofsen E, Henthorn TK, Van Velzen M, Niesters M, Dahan A: Ketamine Pharmacokinetics. Anesthesiology 2020; 133: 1192-1213

24. Zanos P, Moaddel R, Morris PJ, Riggs LM, Highland JN, Georgiou P, Pereira EFR, Albuquerque EX, Thomas CJ, Zarate CA, Gould TD: Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. Pharmacological Reviews 2018; 70: 621-660

25. Hijazi Y, Boulieu R: Contribution of CYP3A4, CYP2B6, and CYP2C9 Isoforms to N-Demethylation of Ketamine in Human Liver Microsomes. Drug Metab Dispos 2002; 30: 853-858

26. Yanagihara Y, Kariya S, Ohtani M, Uchino K, Aoyama T, Yamamura Y, T I: Involvement of CYP2B6 in n-demethylation of ketamine in human liver microsomes. Drug Metab Dispos 2001; 29: 887-890

27. Noppers I, Olofsen E, Niesters M, Aarts L, Mooren R, Dahan A, Kharasch E, Sarton E: Effect of rifampicin on S-ketamine and S-norketamine plasma concentrations in healthy volunteers after intravenous S-ketamine administration. Anesthesiology 2011; 114: 1435-1445

28. Ashraf MW, Peltoniemi MA, Olkkola KT, Neuvonen PJ, Saari TI: Semi-mechanistic population pharmacokinetic model to predict the drug-drug interaction between S-ketamine and ticlopidine in healthy human volunteers. CPT Pharmacomet Syst Pharmacol 2018; 7: 687–697

29. Li Y, Jackson KA, Slon B, Hardy JR, Franco M, William L, Poon P, Coller JK, Hutchinson MR, Currow DC, Somogyi AA: CYP2B6*6 allele and age substantially reduce steady-state ketamine clearance in chronic pain patients: impact on adverse effects. Br J Clin Pharmacol 2015; 80: 276-84

30. Zhao X, Venkata SL, Moaddel R, Luckenbaugh DA, Brutsche NE, Ibrahim L, Zarate CA, Jr., Mager DE, Wainer IW: Simultaneous population pharmacokinetic modelling of ketamine and three major metabolites in patients with treatment-resistant bipolar depression. Br J Clin Pharmacol 2012; 74: 304-14

31. Henthorn TK, Avram MJ, Dahan A, Gustafsson LL, Persson J, Krejcie TC, Olofsen E: Combined Recirculatory-compartmental Population Pharmacokinetic Modeling of Arterial and Venous Plasma S(+) and R(-) Ketamine Concentrations. Anesthesiology 2018; 129: 260-270

32. Moaddel R, Sanghvi M, Dossou KSS, Ramamoorthy A, Green C, Bupp J, Swezey R, O'Loughlin K, Wainer IW: The distribution and clearance of (2S,6S)-hydroxynorketamine, an active ketamine metabolite, in Wistar rats. Pharm Res Per 2015; 3: 1-10

33. Michelet D, Brasher C, Horlin AL, Bellon M, Julien-Marsollier F, Vacher T, Pontone S, Dahmani S: Ketamine for chronic non-cancer pain: A meta-analysis and trial sequential analysis of randomized controlled trials. Eur J Pain 2018; 22: 632-646

34. Orhurhu V, Orhurhu MS, Bhatia A, Cohen SP: Ketamine Infusions for Chronic Pain: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Anesth Analg 2019; 129: 241-254

35. Connolly SB, Prager JP, Harden RN: A systematic review of ketamine for complex regional pain syndrome. Pain Med 2015; 16: 943-69

36. Zhao J, Wang Y, Wang D: The Effect of Ketamine Infusion in the Treatment of Complex Regional Pain Syndrome: a Systemic Review and Meta-analysis. Curr Pain Headache Rep 2018; 22: 12

37. Bell RF, Eccleston C, Kalso EA: Ketamine as an adjuvant to opioids for cancer pain. Cochrane Database Syst Rev 2017; 6: CD003351

38. Jonkman K, van de Donk T, Dahan A: Ketamine for cancer pain: what is the evidence? Curr Opin Support Palliat Care 2017; 11: 88-92

39. Fallon MT, Wilcock A, Kelly CA, Paul J, Lewsley LA, Norrie J, Laird BJA: Oral Ketamine vs Placebo in Patients With Cancer-Related Neuropathic Pain: A Randomized Clinical Trial. JAMA Oncol 2018; 4: 870-872

40. Nielsen RV, Fomsgaard JS, Siegel H, Martusevicius R, Nikolajsen L, Dahl JB, Mathiesen O: Intraoperative ketamine reduces immediate postoperative opioid consumption after spinal fusion surgery in chronic pain patients with opioid dependency: a randomized, blinded trial. Pain 2017; 158: 463-470

41. Loftus RW, Yeager MP, Clark JA, Brown JR, Abdu WA, Sengupta DK, Beach ML: Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. Anesthesiology 2010; 113: 639-46

42. Nielsen RV, Fomsgaard JS, Nikolajsen L, Dahl JB, Mathiesen O: Intraoperative S-ketamine for the reduction of opioid consumption and pain one year after spine surgery: A randomized clinical trial of opioid-dependent patients. Eur J Pain 2019; 23: 455-460

43. Ocker AC, Shah NB, Schwenk ES, Witkowski TA, Cohen MJ, Viscusi ER: Ketamine and Cognitive Behavioral Therapy for Rapid Opioid Tapering With Sustained Opioid Abstinence: A Case Report and 1-Year Follow-up. Pain Pract 2020; 20: 95-100

44. Kroin JS, Das V, Moric M, Buvanendran A: Efficacy of the ketamine metabolite (2R,6R)-hydroxynorketamine in mice models of pain. Reg Anesth Pain Med 2019; 44: 111-117

45. Swartjes M, Morariu A, Niesters M, Aarts L, Dahan A: Nonselective and NR2B-selective N-methyl-D-aspartic acid receptor antagonists produce antinociception and long-term relief of allodynia in acute and neuropathic pain. Anesthesiology 2011; 115: 165-74

46. Khalili-Mahani N, Martini CH, Olofsen E, Dahan A, Niesters M: Effect of subanaesthetic ketamine on plasma and saliva cortisol secretion. Br J Anaesth 2015; 115: 68-75

47. Maia-de-Oliveira JP, Lobao-Soares B, Ramalho T, Gavioli EC, Soares VP, Teixeira L, Baker GB, Dursun SM, Hallak JE: Nitroprusside single-dose prevents the psychosis-like behavior induced by ketamine in rats for up to one week. Schizophr Res 2015; 162: 211-5

48. Bujas-Bobanovic M, Bird DC, Robertson HA, Dursun SM: Blockade of phencyclidine-induced effects by a nitric oxide donor. Br J Pharmacol 2000; 130: 1005-12

49. Trevlopoulou A, Touzlatzi N, Pitsikas N: The nitric oxide donor sodium nitroprusside attenuates recognition memory deficits and social withdrawal produced by the NMDA receptor antagonist ketamine and induces anxiolytic-like behaviour in rats. Psychopharmacology (Berl) 2016; 233: 1045-54

50. Bird DC, Bujas-Bobanovic M, Robertson HA, Dursun SM: Lack of phencyclidine-induced effects in mice with reduced neuronal nitric oxide synthase. Psychopharmacology (Berl) 2001; 155: 299-309

51. Hallak JE, Maia-de-Oliveira JP, Abrao J, Evora PR, Zuardi AW, Crippa JA, Belmonte-de-Abreu P, Baker GB, Dursun SM: Rapid improvement of acute schizophrenia symptoms after intravenous sodium nitroprusside: a randomized, double-blind, placebo-controlled trial. JAMA Psychiatry 2013; 70: 668-76

52. Jonkman K, van der Schrier R, van Velzen M, Aarts L, Olofsen E, Sarton E, Niesters M, Dahan A: Differential role of nitric oxide in the psychedelic symptoms induced by racemic ketamine and esketamine in human volunteers. Br J Anaesth 2018; 120: 1009-1018

53. Luckenbaugh DA, Niciu MJ, Ionescu DF, Nolan NM, Richards EM, Brutsche NE, Guevara S, Zarate CA: Do the dissociative side effects of ketamine mediate its antidepressant effects? J Affect Disord 2014; 159: 56-61

54. Sigtermans MJ, van Hilten JJ, Bauer MC, Arbous MS, Marinus J, Sarton EY, Dahan A: Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. Pain 2009; 145: 304-11

55. Borsook D: Ketamine and chronic pain--going the distance. Pain 2009; 145: 271-2

56. Oudejans L, van Velzen M, Olofsen E, Beun R, Dahan A, Niesters M: Translation of random painful stimuli into numerical responses in fibromyalgia and perioperative patients. Pain 2016; 157: 128-36

57. Torensma B, Oudejans L, van Velzen M, Swank D, Niesters M, Dahan A: Pain sensitivity and pain scoring in patients with morbid obesity. Surg Obes Relat Dis 2017; 13: 788-795

58. Tuttle AH, Tohyama S, Ramsay T, Kimmelman J, Schweinhardt P, Bennett GJ, Mogil

JS: Increasing placebo responses over time in U.S. clinical trials of neuropathic pain. Pain 2015; 156: 2616-26

59. Woodcock J, LaVange LM: Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. N Engl J Med 2017; 377: 62-70

60. Okie S: A flood of opioids, a rising tide of deaths. N Engl J Med 2010; 363: 1981-5

61. Bedene A, Lijfering WM, Niesters M, van Velzen M, Rosendaal FR, Bouvy ML, Dahan A, van Dorp ELA: Opioid Prescription Patterns and Risk Factors Associated With Opioid Use in the Netherlands. JAMA Netw Open 2019; 2: e1910223

62. Niesters M, Khalili-Mahani N, Martini C, Aarts L, van Gerven J, van Buchem MA, Dahan A, Rombouts S: Effect of subanesthetic ketamine on intrinsic functional brain connectivity: a placebo-controlled functional magnetic resonance imaging study in healthy male volunteers. Anesthesiology 2012; 117: 868-77

63. Jonkman K, van Rijnsoever E, Olofsen E, Aarts L, Sarton E, van Velzen M, Niesters M, Dahan A: Esketamine counters opioid-induced respiratory depression. Br J Anaesth 2018; 120: 1117-1127

64. Dahan A, van der Schrier R, Smith T, Aarts L, van Velzen M, Niesters M: Averting Opioid-induced Respiratory Depression without Affecting Analgesia. Anesthesiology 2018; 128: 1027-1037