Table DS2. Ketamine for pain studies

Study Identification number	Reference	Study design	Number of patients that received ketamine	Diagnosis	Other drugs	Ketamine form	Ketamine regimen	DORED dosage (mg/kg/day)	Number of ketamine days	Duration	Results	Side effects
ORAL ANALGESIC KETAMINE												
48	Nikolajsen et al., 1997 (113)	Single-blind, saline-controlled study	1	Stump pain	Not mentioned	racemate	1) Two test sessions separated by one week with intravenous ketamine 0,42 mg/kg over 50 minutes 2) 50 mg of oral ketamine 4 times per day dissolved in juice	2,9	90	3 months	Effectiveness of oral ketamine in the treatment of postamputation stump pain	No side effects or development of tolerance were observed during a 3-month treatment period
49	Fisher and Hagen, 1999 (114)	open-label trial	1	Neuropathic pain	Haloperidol, baclofen, codeine	racemate	1) Subcutaneous ketamine several times during day 1 (doses between 4 and 10 mg) 2) Intravenous ketamine 3 mg per hour during day 1 3) After day 1, ketamine 10 mg orally every 8 hours during a week of hospitalization 4) After discharge from hospital, 25 mg orally 3 times per day	1,1	150	5 months	The patient's pain was effectively managed without use of any other regularly scheduled analgesic	No side effects
50	Haines and Gaines, 1999 (68)	Randomized, single-blind study	21	Chronic neuropathic pain	buprenorphine, morphine, codeine, meptazinol, dextropropoxyphene, dihydrocodeine, tramadol, ibuprofen, aspirin, paracetamol, mefenamic acid, diclofenac, propranolol, warfarin, nifedipine, isosorbide, amlodipine, thyroxine, enalapril, bendrofluazide, theophylline, ranitidine, HRT, amitriptyline, nitrazepam, hetahistine, carbamazepine	racemate	The dose of 20 mg was increased each day until an analgesic effect was noticed or adverse effects occurred, or until a maximum of 100 mg was reached	1,4	49	7 weeks	Ketamine only gave rise to an extra analgesic response in 14% of subjects	Light headedness, dizziness, tiredness, headache, nervous floating feeling, bad dreams Adverse effects limited the use of ketamine in almost half of the patients
51	Vick and Lamer, 2001 (39)	open-label trial	1	Central post-stroke pain	Morphine, gabapentin, nortriptyline, midazolam, diazepam	racemate	1) One dose of 7 mg (0,1 mg/kg) of intravenous ketamine 2) After 30 minutes, one dose of 14 mg (0,2 mg/kg) of intravenous ketamine 3) After the intravenous trial, oral ketamine 50 mg at night 4) The final dose was 50 mg oral ketamine 3 times per	2,1	270	9 months	Significant improvement in pain, allodynia, and hyperalgesia. Improved mood and sleep and increased activity level	Dysphoria, hallucinations, paranoid feelings
52	Kannan et al., 2002 (67)	open-label trial	9	Neuropathic pain	Morphine, amitriptyline, sodium valproate	racemate	0,5 mg/kg 3 times daily	1,5	60	2 months	Low dose oral ketamine is beneficial and effective in the management of intractable neuropathic pain. However, its utility is limited in some patients by the adverse effects that accompany its use	Nausea, vomiting, loss of appetite, drowsiness, sedation, feeling of unreality
53	Villanueva-Perez et al., 2007 (31)	open-label trial	1	Complex regional pain syndrome type 1	topiramate, clonazepam, tramadol, amitriptyline, ibuprofen, fluoxetine, haloperidol, fentanyl, perphenazine, trimethazidine	racemate	30 mg (3 mL of syrup) of oral ketamine every 8 hours, increasing weekly in 5 mg increments until a maximum dose of 60 mg/6 hours was reached	3,4	900	30 months	Phase 1 (during approximately 17 months): significant improvement was noted. Phase 2 (in the end of the study): severe pain with associated color changes in the affected regions	Phase 1 (during approximately 17 months): nausea and vomiting Phase 2 (in the end of the study): swelling of the face and neck, left exophthalmos
54	Bredlau et al., 2013 (69)	prospective open-label study	12	Chronic pain	Morphine, ibuprofen, naproxen, acetaminophen, ketorolac, meloxicam, lysine, osteo-bi-flex, topamax, verapamil, duloxetine, riboflavin, 6-mercaptopurine, adalimumab, celecoxib, mesalamine, etanercept, methotrexate, sulfasalazine, sulindac, gabapentin, ranitidine	racemate	Oral ketamine 3 times daily, at dosages ranging from 0,25 to 1,5 mg/kg/dose	4,5	14	14 days	Ketamine appears to be safe and tolerable in children and young adults at dosages ranging from 0,25 to 1 mg/kg/dose 3 times daily for a 2-week period	confusion, headache, dizziness, pain, memory impairment, sinus pressure, sore throat, vomiting, anorexia, dysuria, depressed level of consciousness
55	Amin et al., 2014 (115)	open-label trial	1	Cancer-related neuropathic pain	Oxycodone, hydromorphone	racemate	The patient started on doses of intravenous ketamine at 0,2 mg/kg/h and titrated over 2 days to 0,4 mg/kg/h. Then, a 3-day rotation from intravenous to oral ketamine was initiated, and the patient was discharged on ketamine oral solution, 75 mg every 8 hours	3,8	2	Not specified	The use of weight-based dosing of intravenous continuous infusion and transition to oral ketamine was effective and tolerable in the management of opioid-refractory, neuropathic cancer pain	No report of side effects
56	Fitzgibbon et al., 2002 (116)	open-label trial	3	Neuropathic pain syndrome	Patient 1: hydromorphone, lorazepam Patient 2: midazolam, hydromorphone, gabapentin Patient 3: fentanyl, midazolam, hydromorphone, clonazepam	racemate	Patient 1: Started with ketamine 50 mg over 24 hours by continuous subcutaneous infusion. After 7 days, the ketamine infusion was discontinued and ketamine 10 mg orally 3 times daily was started. The final dose of oral ketamine was 20 mg 3 times daily (60 mg per day) Patient 2: Started with ketamine 15 mg subcutaneously. After 4 months, the ketamine infusion was discontinued and oral ketamine 50 mg 3 times daily was started. The final dose of oral ketamine was 75 mg 3 times daily (225 mg per day) Patient 3: Started with ketamine 48 mg over 24 hours by continuous subcutaneous infusion. After 14 days, ketamine was switched to the intravenous route. After 3 months, he started on oral ketamine 54 mg over 24 hours with discontinuation of the parenteral ketamine. Over the next month, ketamine was titrated to 30 mg 3 times daily orally (90 mg per day)	3,2	21	3 weeks	Patient 1: His pain control was good until his death Patient 2: His pain control was good and he reported feeling relaxed Patient 3: His pain was controlled with a reduction in his drowsiness and in the use of breakthrough medications	Side effects were prevented or minimized by a strategy of prophylatic administration of benzodiazepines No deleterious side effects were noted No psychotomimetic side effects were noted
57	Furuhashi-Yonaha et al., 2002 (117)	placebo-controlled trial	8	Chronic neuropathic pain	Loxoprofen, diazepam	racemate	syrup 0,5 mg/kg every 6 hours	2,0	7	1 week	The severity of the pain and allodynia was reduced about 15 minutes after administration, and improvement lasted from 6 to 8 hours	Headache, nightmares, slight dizziness

58	Jennings et al., 2013 (118)	open-label trial	1	Sickle cell crisis pain	Morphine, ibuprofen	racemate	The patient responded well to an intravenous test dose of 5 mg ketamine and was subsequently placed on an oral regimen of 15 mg ketamine every 6 hours. The dose was increased by 10 mg per every 6-hour dose daily. By day 12, the patient was using 50 mg of oral ketamine every 6 hours.	2,9	30	1 month	Improved pain control and less opiate usage	no side effects reported
59	Kaviani et al., 2011 (30)	randomized, double-blind, placebo-controlled clinical trial	18	irreversibly inflamed mandibular molars	lidocaine, epinephrine, ibuprofen	racemate	10 mg of ketamine in cherry juice	0,1	1	1 day	Oral ketamine was effective for enhancing the anesthetic effect of lidocaine and epinephrine. Postoperative pain in the ketamine group was significantly lower as well as the number of analgesic tablets	Not mentioned
INTRAVENOUS ANALGESIC KETAMINE												
60	Mercadante et al., 2000 (70)	randomized, double-blind, crossover, double-dose, placebo-controlled study	10	Cancer pain	Diazepam, morphine	racemate	0,25 mg/kg or 0,5 mg/kg	2,5	3	1 week	Ketamine, but not saline solution, significantly reduced the pain intensity in almost all the patients at both doses Patients who were treated with 0,5 mg/kg had a more relevant analgesic effect than patients who received 0,25 Ketamine improves morphine analgesia in difficult pain syndromes.	Hallucinations, flashes, buzzing feeling in the head, sensation of insobriety, drowsiness, unpleasant sensation
61	Mitchell, 2001 (119)	open-label trial	1	Chronic neuropathic pain	Morphine, hydromorphone	racemate	30 mg of ketamine over 4 hours of infusion fortnightly After 1 month, 50 mg once a week After a week, 60 mg over 3 hours 3 times per week	4,3	24	4 months	The pain intensity experienced by the patient lessened as the frequency of the ketamine infusions increased When the pain did return it was of lesser severity than previously, and was more responsive to hydromorphone 1,3 mg	Not mentioned
62	Klepstad et al., 2001 (32)	open-label trial	1	Neuropathic pain	Morphine, diazepam, midazolam	racemate	7,5 to 10 mg in bolus doses until changed to a continuous intravenous infusion The dose increased steadily until her death Start dose = 30 mg in the first day of ketamine treatment Maximum dose used = 500 mg in one day	62,5	67	67 days	Ketamine treatment may be effective in children with severe neuropathic pain not responsive to other analgesics	Not mentioned
63	McQueen and Baroletti, 2002 (120)	open-label trial	1	cancer pain	gabapentin, amitriptyline, hydromorphone, dexamethasone carboplatin, paclitaxel	racemate	Started with 5 mg, which did not relieve the patient's pain measurably 5 minutes later, 10 mg was administered which reduced the pain score The ketamine infusion was titrated up to a rate of 23	50,2	16	16 days	Ketamine is a viable adjuvant option to relieve cancer pain when other agents either fail or are intolerable	Light headedness, uncomfortable warmth, drowsiness
64	Kvarnström et al., 2003 (121)	Randomized, double-blind, placebo-controlled, cross-over study	12	Peripheral neuropathic pain	Lidocaine, opiates, antiepileptic drugs, tricyclic antidepressants, guanethidine, paracetamol, dextropropoxyphene, tramadol, codeine	racemate	0,4 mg/kg with a constant rate over 40 minutes 3 ketamine sessions separate by a week from each other	2,0	3	1 month	Ketamine showed a significant analgesic effect. The clinical usefulness is, however, limited by disturbing side effects.	Somnolence, out-of-body sensation, changes in hearing, changes in vision, nausea, itching, unpleasant experience, paraesthesia, light-headedness, dizziness
65	Kvarnström et al., 2004 (122)	Randomized, double-blind, placebo-controlled, 3-period, 3-treatment, cross-over study	10	Neuropathic pain	Lidocaine, paracetamol, dextropropoxyphene, tricyclic antidepressants, codeine, tramadol, baclofen, ketobemidone	racemate	0,4 mg/kg with a constant rate over 40 minutes 3 ketamine sessions	2,0	3	1 week	Ketamine but not lidocaine showed a significant analgesic effect in patients with neuropathic pain after spinal cord injury. The pain relief was not associated with altered temperature thresholds or other changes of sensory function.	Somnolence, out-of-body sensation, changes in hearing, changes in vision, nausea, itching, unpleasant experience, paraesthesia, dizziness
66	Cohen et al., 2004 (123)	retrospective chart analysis	25	Neuropathic pain	Dextromethorphan	racemate	0,1 mg/kg over 7 minutes	0,5	1	6 weeks	An intravenous ketamine test may be useful in predicting response to oral dextromethorphan	Confusion, euphoria, nausea
67	Urban et al., 2008 (124)	prospective randomized study	26	Postoperative pain with opioid tolerance	Hydromorphone, midazolam, nitrous oxide, isoflurane, fentanyl, propofol, morphine	racemate	1) 0,2 mg/kg bolus dose 2) 2 mcg/kg/hour for the next 24 hours	1,3	1	1 day	Patients in the ketamine group required less hydromorphone than the control group, but the differences Subanesthetic doses of ketamine reduced postoperative pain in narcotic tolerant patients undergoing posterior	Sedation, nausea, vomiting
68	Cohen et al., 2009 (125)	placebo-controlled, cross-over study	56	Recurrent pain in opioid-exposed patients	Dextromethorphan, opioid, midazolam	racemate	0,1 mg/kg over 7 minutes	0,5	1	1 day	An intravenous ketamine test may be a valuable tool in predictiing subsequent response to dextromethorphan treatment in opioid-exposed patients	Dizziness, anxiety, euphoria
69	Schwartzman et al., 2009 (71)	randomized, double-blind, placebo-controlled trial	9	Complex regional pain syndrome	Clonidine, midazolam	racemate	25 mg/h daily over 4 hours	7,2	10	10 days	Intravenous ketamine administered in an outpatient setting resulted in statistically significant reductions in many pain parameters. Subjects of the placebo group demonstrated no treatment effect in any parameter.	Nausea, headache, tiredness, dysphoria
70	Kang et al., 2010 (126)	open-label, uncontrolled study	103	Neuropathic pain	Midazolam, anticonvulsants, antidepressants, tramadol, acetaminophen, benzodiazepines, opioids, non-steroidal anti-inflammatory drugs, capsaicin, lidocaine	racemate	3 ketamine sessions performed consecutively every other day 0,2 mg/kg over 5 minutes as a loading dose, followed by a continuous infusion of 0,5 mg/kg/h for 2 hours	6,0	7	2 weeks	Reduced severity of neuropathic pain and good tolerance for up to 2 weeks in patients with neuropathic pain refractory to standard treatment.	snoring, involuntary movement, decreased heart rate, decreased blood pressure, increased blood pressure, dizziness, nausea, dry mouth

71	Amr, 2010 (127)	randomized, controlled, double-blind trial	20	Neuropathic pain	Gabapentin, midazolam	racemate	80 mg over a 5-hour period daily	5,7	7	1 week	Multi-day low dose ketamine infusion as adjuvant to gabapentin in post-spinal cord injury-related chronic pain is safe and efficacious in reducing pain, but the effect compared to placebo ceased 2 weeks after infusion	Short-lasting delusions, increase in baseline heart rate, dizziness, tiredness, lack of coordination
72	Elsewaisy et al., 2010 (128)	open-label trial	1	Neuropathic pain	Gabapentin, venlafaxine, methadone	racemate	1) 20 mg/h daily for 5 days 2) After 12 weeks, the ketamine infusion was repeated and this pattern was maintained	34,3	70	3,5 years	Almost complete pain relief was obtained	Mild hallucinations
73	Kapural et al., 2010 (33)	retrospective study	18	Chronic pain	Midazolam, opioids	racemate	Ketamine infusions were initiated at the rate of 10 mg/h. The rate was increased as tolerated until patients reported no pain or until the infusion rate reached 100 mg/h. Once an effective infusion rate was identified, it was continued for 3 hours or as long as tolerated. Weekly ketamine infusions	21,5	6	6 weeks	Outpatient intravenous ketamine infusions did not improve long-term pain scores in patients with high opioid requirements and only a few were able to substantially reduce opioid use.	Supraventricular arrythmia, anxiety, dizziness, unpleasant dreams, sleepiness
74	Loftus et al., 2010 (129)	randomized, prospective, double-blinded, placebo-controlled trial	52	Chronic pain	Morphine, tramadol, midazolam, fentanyl, propofol, isoflurane, sevoflurane, desflurane, ketorolac tromethamine, hydromorphone, dexamethasone, paracetamol, antidepressants, anxiolytics, anticonvulsants, muscle relaxants, synthetic opioid, nalbuphine hydrochloride, acetaminophen	racemate	0,5 mg/kg on induction anesthesia and a continuous infusion at 10 µg/kg/min was begun on induction and terminated at wound closure.	5,5	1	1 day	Total morphine consumption was significantly reduced in the treatment group 48 hours after the procedure. It was also reduced at 24 hours and at 6 weeks	nausea, vomiting, hallucinations, urinary retention, constipation
75	Yazigi et al., 2012 (37)	prospective, randomized, double-blinded, placebo-controlled study	30	Pain after thoracotomy	bupivacaine, paracetamol, ketoprofen, morphine, hydroxyzine, propofol, sevoflurane, fentanyl, vecuronium	racemate	Before skin incision, patients received a bolus dose of ketamine 0,1 mg/kg followed by a continuous infusion of 0,05 mg/kg/h	6,5	3	3 days	Intravenous low-dose ketamine, when combined with continuous intercostal nerve block, did not decrease acute pain scores and supplemental morphine consumption following	Blurred vision, hallucination, nightmares
76	Patil and Anitescu, 2012 (130)	retrospective chart review	49	Refractory chronic pain syndrome	midazolam, ondansetron, memantine	racemate	Mean total ketamine dose per infusion was 0,9 mg/kg over 30-45 minutes The ketamine infusions were scheduled routinely every 3-4 weeks	4,5	60	5 years	Subanesthetic ketamine infusions may improve visual analog scale scores in patients with severe refractory pain of multiple etiologies In half of the studied patients, relief lasted for up to 3 weeks with minimal	agitation, confused state, disorientation, dissociation, feeling cold, hallucination, hypertension, nausea, nystagmus, paresthesia, pharyngolaryngeal pain, restlessness, sedation, somnolence, tachycardia, vertigo, vomiting
77	Joseph et al., 2012 (34)	randomized, double-blind, placebo-controlled study	30	Pain after thoracotomy	Ropivacaine, alprazolam, sufentanil, propofol, remifentanil, cisatracurium, droperidol	racemate	Bolus of 0,5 mg/kg ketamine at anesthesia induction, followed by a 3 µg/kg/min continuous infusion during surgery. 1,5 µg/kg/min the first 48 hours postoperatively	13,3	2	2 days	Adding intravenous ketamine did not potentiate epidural analgesia neither to reduce acute and chronic postoperative pain nor to improve pulmonary dysfunction following thoracic surgery	nausea, urinary retention, hypotension, vomiting, dizziness, pruritus, excessive sedation, hallucinations, nightmares, respiratory depressive episodes
78	Barreveld et al., 2013 (38)	randomized, double-blind, placebo-controlled trial	32	Postoperative pain	Hydromorphone, propofol, remifentanil	racemate	Postoperative continuous ketamine 0,2 mg/kg/h	24,0	1	1 day	The use of a postoperative ketamine infusion at 0,2 mg/kg/h provides limited benefit in improving pain management in patients with chronic	anxiety, hallucination, pruritis, sedation, nausea
79	Tena et al., 2014 (36)	double-blind, randomized-controlled study	33	Pain after thoracotomy	diazepam, lidocaine, midazolam, fentanyl, propofol, cisatracurium, desflurane, remifentanil, ropivacaine, neostigmine, paracetamol, metamizol	racemate	Before surgical incision, a bolus of 0,5 mg/kg Continuous intravenous infusion at a rate of 0,25 mg/kg/h postoperatively	32,5	2	2 days	Adding intravenous ketamine to thoracic epidural analgesia after thoracotomy did not lead to any reduction in persistent postsurgical pain or allodynia.	hypertension, sedation, diplopia, nightmares, hallucinations, nausea, vomiting
80	Hu et al., 2014 (35)	prospective, randomized, double-blind, controlled,	31	Postthoracotomy pain	sulfentanil	racemate	1 mg/kg before incision, followed by 2 µg/kg/min continuous infusion	19,4	3	3 days	The regimen was not beneficial to prevent chronic postthoracotomy pain.	vivid dreams, hallucinations, nausea, vomiting
INTRANASAL ANALGESIC KETAMINE												
81	Carr et al., 2004 (131)	randomized, double-blind, placebo-controlled, multicenter, crossover trial	20	Breakthrough pain	oxycodone, morphine, methadone, fentanyl, hydrocodone, hydromorphone, amitriptyline, gabapentin, nabumetone, methocarbamol, clonazepam, temazepam, celecoxib, rofecoxib, tramadol, Not specified medications for: allergies, hormone replacement therapy, thyroid conditions, insomnia, respiratory disorders, non-insulin dependent diabetes, elevated cholesterol, depression	racemate	Self-administration up to 5 doses of 10 mg at the onset of a spontaneous breakthrough pain episode	1,4	1	3 weeks	Significantly lower breakthrough pain intensity following intranasal ketamine than after placebo, with pain relief within 10 minutes of dosing and lasting for up to 60 minutes. No patient in the ketamine group required his/her usual rescue medication to treat the episode	change in taste, rhinorrea, nasal passage irritation, elevation in blood pressure, fatigue, dizziness, feeling of unreality, changes in vision, nausea, changes in hearing, mood change, generalized discomfort More than half of the reported side effects were mild or moderate in severity, and transient in nature.
82	Reid et al., 2011 (132)	open-label study	1	burn injury	Not mentioned	racemate	0,5 mg/kg was delivered to the nasal mucosa using a mucosal atomisation device in a prehospital emergency setting	1,1	1	1 day	Effective analgesia was achieved. Effective anxiolysis	Drowsiness, desire to sleep
INTRAMUSCULAIR ANALGESIC KETAMINE												
88	Lester et al., 2010 (137)	retrospective review	35	pain	morphine, dilaudid, vicodin, fentanyl, toradol, percocet, roxicet	racemate	Each ketamine dose ranged between 5 to 35 mg, intravenously (30 patients) or intramuscularly (5 patients) The maximum total dose was 60 mg, delivered as 3 separate 20-mg intramuscular doses	4,0	1	not mentioned	Improvement in pain was observed in 54% of cases. The administration of low-dose ketamine in the emergency department may be a safe and effective adjunct for analgesia in some patients	No dangerous adverse events were identified. brief mild dysphoria