Supplemental Table 1: Comprehensive Compendium of Preclinical Studies Evaluating the Antinociceptive Effects of Ketamine.

Study (First Author, Year)	Pain Model	Animal(s) Studied	Generalizable Pain Category	Generalizable Medical Conditions	Findings
M'Dahoma et al 2014 [S1]	Spinal cord transection	Rat	Neuropathic	Central neuropathic pain, spinal cord injury	Acute treatment with ketamine (50 mg/kg IP) increased pressure threshold to trigger a nocifensive response. Effect lasted 90 minutes.
Rodrigues-Filho et al 2004 [S2]	Brachial plexus avulsion	Rat	Neuropathic	Plexopathy, traumatic nerve injury, neuropathic pain	Ketamine (25 mg/kg IP) reduced mechanical and cold allodynia 20 days after brachial plexus avulsion.
Mei et al 2011[88]	SNL	Rat	Neuropathic	Plexopathy, traumatic nerve injury, neuropathic pain	Ketamine (IT 100, 300 μg/kg) attenuated mechanical allodynia in a dose-dependent manner, as measured on POD 0 to 3. No effect on paw withdrawal threshold at 30 a dose of μg/kg
Mei et al 2011[89]	SNL	Rat	Neuropathic		Ketamine (IT 100, 300 μg/kg) administered daily from POD 8 to POD 10 after SNL produced a reduction in mechanical allodynia as measured 30 minutes after injection
Suzuki et al 2001 [S3]	SNL	Rat	Neuropathic		Ketamine (IV 1, 5, and 10 mg/kg) given 2 weeks after SNL and sham operated rats inhibited post-discharge, thermal, and mechanical evoked responses, with greater effect in nerve ligated rats.
Qian et al 1996 [S4]	SNL	Rat	Neuropathic		Ketamine (IP 0.01 mg/kg) attenuated mechanical hyperalgesia, cold allodynia, and other nociceptive behaviors for 15-30 minutes. Ketamine (IP 1 mg/kg) attenuated all nociceptive behaviors for 45-75 minutes.
Xie et al 2017 [S5]	Spared nerve injury (SNI)	Rat	Neuropathic	Peripheral neuropathy	Ketamine (IP 20 mg/kg) given on POD 16 decreased levels of inflammatory cytokines (IL-1β, IL-6) in rats with depression-like phenotype subjected to SNI.
Vega-Avelaira et al 2012[90]	SNI	Rat	Neuropathic		In rats undergoing SNI on P10, Ketamine (SC 1, 10, 20 mg/kg) produced dose-dependent reversal of mechanical allodynia on POD 21.
Truin et al 2011 [S6]	Partial sciatic nerve ligation	Rat	Neuropathic	Peripheral neuropathy, traumatic neuropathy	Low dose ketamine (IT, either 50 or 100μg) followed by 30 minutes of SCS in rats who were non-responders to SCS led to a significant increase in paw withdrawal threshold, thereby converting them into SCS responders.
Doncheva et al 2019 [S7]	Chronic constriction injury (CCI)	Rat	Neuropathic	Radicular pain (disc herniation, nerve entrapment)	In a neuropathic pain model, Ketamine (IP, 50 mg/kg doses over 14 days) provided antinociceptive effect to thermal nociception for 180 minutes and to mechanical nociception for 60 minutes after administration.
M'Dahoma et al 2015 [S8]	CCI	Rat	Neuropathic		Ketamine (IP 50 mg/kg) given 15 days after CCI reduced mechanical hyperalgesia and allodynia, though effects were less pronounced than with pregabalin.
Chen et al 2014 [S9]	CCI	Rat	Neuropathic		Inhaled butorphanol (100μg) + ketamine (1mg, either inhaled or SC) increased mechanical pain threshold for 4 hours after administration in rats subjected to CCI.
Pelissier et al 2003 [S10]	CCI	Rat	Neuropathic		Ketamine (SC 12.5, 25, 50, 100 mg/kg) showed a synergistic response when used with opioids in CCI rats.
Yamamoto et al 1993 [S11]	CCI	Rat	Neuropathic		Ketamine (IT 24 to 240 μg) temporarily eliminated hyperalgesia at doses which did not alter normal motor function.

Lim et al 2013 [S12]	CCI	Mouse	Neuropathic		7 days after CCI, IT ketamine (3 or 10 μg) plus pregabalin (30 μg) suppressed response to mechanical allodynia and thermal hyperalgesia. Ketamine and pregabalin alone at these doses were ineffective.
Castel et al 2013 [S13]	Induced intrathalamic hemorrhage	Rat	Neuropathic	Central neuropathic pain, post-stroke pain	Ketamine (IP 25 mg/kg) given on days 28, 30, 32 post-injury alleviated mechanical allodynia in rats with induced intracerebral thalamic hemorrhage.
Pelissier et al 2008 [S14]	Intraarticular CFA injection	Rat	Inflammatory	Monoarticular osteoarthritis	IT ketamine (1, 10, and 30 μg) induced dose-dependent increases in vocalization threshold to pressure on hind paw and reduced capsaicin-induced nociceptive behavior in normal and monoarthritic rats
Boettger et al 2010 [S15]	Antigen-induced arthritis	Rat	Inflammatory	Rheumatoid arthritis, other inflammatory arthritis	Spinal ketamine (single IT dose at 50 μg) decreased arthritis severity and hyperalgesia in the acute stage after induced arthritis. Ketamine IT infusion at 50 μg/hr for 21 days after induction produced similar results in the chronic stage. Reduced inflammatory cell infiltration was observed on histopathology in both phases in animals treated with ketamine.
Zhang et al 2016 [S16]	CFA injection (hindpaw)	Rat	Inflammatory	Tissue injury or inflammation (arthritis, tumor growth, etc)	Single-dose ketamine (IP 20 mg/kg) injected 14 days after CFA relieved mechanical allodynia and associated depression-like behaviors.
Edwards et al 2007 [S17]	CFA injection	Rat	Inflammatory		Ketamine (SC 5, 10 mg/kg) produced anti-nociceptive but not antihyperalgesic effects.
Romero et al 2011 [S18]	PGE_2 injection	Rat	Inflammatory		Ketamine (10-80 μg in paw) produced local antinociceptive response against PGE_2 induced hyperalgesia.
Nishihara et al 1995 [S19]	PGE_2 injection	Rat	Inflammatory		Ketamine (IT 1 to 1000ng) attenuated PGE2-induced hyperalgesia.
Rivat et al 2002 [S20]	Carrageenan injection	Rat	Inflammatory		Ketamine (SC 10 mg/kg, 3 doses in 5-hour intervals) prevented enhancement of inflammation-induced hyperalgesia caused by repeat carrageenan administration or fentanyl administration.
Klimscha et al 1998 [S21]	Carrageenan injection	Rat	Inflammatory		Racemic and S(+)-ketamine (IT 10, 50, 100 μg) attenuated hyperalgesia from carrageenan-induced hindpaw inflammation.
Lebrun et al 2000 [S22]	Formalin injection	Rat	Inflammatory		Pretreatment with ketamine (IP 5 mg/kg) 10 minutes before SC formalin injection attenuated the increase in amplitude of cortical SSEPs.
Gilron et al 1999 [S23]	Formalin injection	Rat	Inflammatory		Pretreatment with ketamine (IV 10 mg/kg) produced lower nociceptive scores in the formalin test compared to post-treatment after formalin administration.
Shimoyama et al 1999 [S24]	Formalin injection	Rat	Inflammatory		Pretreatment with oral ketamine (30 to 180 mg/kg) reduced formalin-induced flinching behavior.
Das et al 2017 [S25]	Closed distal tibia fracture/casting	Mouse	Neuropathic	CRPS, orthopedic trauma	Ketamine (IP 2.5mg/kg) given 6 weeks after injury reduced mechanical allodynia on the fracture side and improved burrowing activity.
Minville et al 2010 [S26]	Closed distal tibia fracture/casting	Mouse	Neuropathic		Ketamine (SC 1, 10, and 50 mg/kg) given before injury/surgery prevented sufentanil-induced hyperalgesia to mechanical and thermal nociception.
Sher and Mitchell 1990 [S27]	Ischemia of femoral artery	Rat	Ischemic		Ketamine (5.94 and 594 μg IT) significantly reduced hyperalgesia to noxious pinching after induced femoral artery ischemia.
Andoh et al 2008 [S28]	Inoculation with melanoma cells	Mouse	Nociceptive/neuropathic	Mixed cancer pain	Oral ketamine (50 mg/kg) produced no effect on thermal hyperalgesia.
Kuraishi et al 2003 [S29]	Inoculation with melanoma cells	Mouse	Nociceptive/neuropathic		Ketamine (IP 30 mg/kg) given 2 weeks after tumor inoculation partially inhibited allodynia.

Saito et al 2006 [S30]	Induced bone sarcoma	Mouse	Nociceptive/neuropathic	Bone cancer	Ketamine (IP 5 to 40 mg/kg) given 14 days after tumor cell implantation inhibited pain-related behaviors in a dose dependent manner, with 40 mg/kg producing similar efficacy to morphine 80 mg/kg
Pascual et al 2010 [S31]	Intraperitoneal paclitaxel injection	Rat	Nociceptive/neuropathic	Visceral pain, chemotherapy agents	High-dose ketamine (IP 50 mg/kg) increased mechanical and thermal pain thresholds when given 2 weeks after paclitaxel injection. Lower doses of ketamine (IP 12.5 mg/kg) showed additive analgesic effect when combined with morphine 1 mg/kg.
Sun et al 2016 [S32]	Nociceptive testing after inducing opioid-induced hyperalgesia (OIH)	Rat	Nociceptive	Opioid-induced hyperalgesia	Ketamine (IT 10 µg) attenuated development of mechanical and thermal hyperalgesia after remifentanil administration and surgical incision.
Rozisky et al 2011 [S33]	OIH	Rat	Nociceptive	Opioid-induced hyperalgesia	Ketamine (IP 30 mg/kg) given 30 minutes before formalin testing at postnatal day 30 and 60 (P30, P60) reversed the increased nociceptive response caused by daily morphine exposure during P8-14.
Gu et al 2010 [S34]	OIH	Rat	Nociceptive	Opioid-induced hyperalgesia	Pretreatment with ketamine (SC 10 mg/kg) attenuated the increase in allodynia/hyperalgesia from intraoperative remifentanil infusion.
Van Elstraete et al 2005 [S35]	OIH	Rat	Nociceptive	Opioid-induced hyperalgesia	Pretreatment with ketamine (SC 10 mg/kg) produced near complete attenuation of the delayed hyperalgesia produced by IT morphine, without modification of morphine's initial analgesic effects.
Holtman et al 2005 [S36]	OIH	Rat	Nociceptive	Opioid-induced hyperalgesia	Pretreatment with ketamine (IP 0.75 and 1.5 mg/kg) attenuated morphine-induced hyperalgesia in a dose-dependent manner.
Richebé et al 2005 [S37]	OIH	Rat	Nociceptive	Opioid-induced hyperalgesia	Ketamine pretreatment (SC, 3 - 10 mg/kg doses) attenuated fentanyl-induced hyperalgesia in the postoperative phase.
Laulin et al 2002 [S38]	OIH	Rat	Nociceptive	Opioid-induced hyperalgesia	Ketamine (SC 10 mg/kg) prevented fentanyl-induced hyperalgesia and acute tolerance to morphine.
Kissin et al 2000 [S39]	OIH	Rat	Nociceptive	Opioid-induced hyperalgesia	Ketamine (IP 10 mg/kg) attenuated acute tolerance to anesthesia during alfentanil infusion and suppressed rebound hyperalgesia 1 day after infusion.
Célèrier et al 2000 [S40]	OIH	Rat	Nociceptive	Opioid-induced hyperalgesia	Ketamine pretreatment (SC 10 mg/kg) enhanced the initial analgesic effect and prevented development of hyperalgesia with fentanyl bolus administration
Galeotti et al 2006 [S41]	OIH	Mouse	Nociceptive	Opioid-induced hyperalgesia	Ketamine pretreatment (SC 0.05 to 0.5 µg/mouse) produced a dose-dependent inhibition of morphine induced hyperalgesia as measured by the hot plate test. Ketamine 0.5 µg/mouse sustained reversion of the hyperalgesia for 30 minutes after administration.
Shimoyama et al 1996 [S42]	Opioid tolerance	Rat/Mouse	Nociceptive	Opioid tolerance	Systemic ketamine in mice (SC 0.3, 3, 10 mg/kg) attenuated and reversed systemically induced morphine tolerance. IT ketamine in rats (12 µg) attenuated morphine tolerance produced by IT morphine.
Lilius et al 2015 [S43]	Opioid tolerance	Rat	Nociceptive	Opioid tolerance	In morphine-tolerant rats, ketamine (SC 10 mg/kg) produced an antinociceptive effect and led to increased brain concentrations of morphine. Authors noted that no opioid-induced hyperalgesia was seen in study animals.
Trujullo and Akil 1994 [S44]	Opioid tolerance	Rat	Nociceptive	Opioid tolerance	Ketamine (SC 10 mg/kg/day) inhibited but did not reverse morphine tolerance.
Shen et al 2016 [S45]	Skin/muscle incision and retraction (SMIR)	Rat	Nociceptive pain	Surgical pain	Ketamine (IP 10 mg/kg) during surgery alleviated postoperative pain behaviors and prevented upregulation of phosphorylated and total NMDA receptors.

Pacheco et al 2014 [S46]	Thermal/tail flick	Mouse	Nociceptive	Thermal injury	Naloxone and other μ/δ opioid receptor antagonists antagonized antinociception from ketamine (2, 4, 8 μg intracerebroventricular).
Shikanai et al 2014 [S47]	Hot plate test	Rat	Nociceptive	Thermal injury	Subanalgesic doses of ketamine (IP 1mg/kg) enhanced morphine-induced analgesia to thermal pain
Lizarraga et al 2008 [S48]	Mechanical stimulation	Sheep	Nociceptive	Acute pain, drug synergism	Ketamine (IT 0.594 to 9.51 μg) did not produce hypoalgesia but did prevent NMDA-induced mechanical hypersensitivity. IT ketamine and NSAID produced no added benefit.
Petrenko et al 2006 [S49]	Formalin injection, thermal/mechanical/electrical stimulus	Mouse	Nociceptive	Inflammation, thermal injury	Ketamine (IP 25, 50, 100 mg/kg) had no antinociceptive effects in response to thermal/mechanical/electrical stimuli but reduced phase 2 nociceptive behavior after formalin injection
Koizuka et al 2005 [S50]	Hindpaw incision	Rat	Nociceptive	Surgical pain	Either pre- or post-operative ketamine administration (IP 3 to 30 mg/kg) produced antihypersensitivity effects in a dose-dependent manner. IT ketamine had no effect.
Nielsen et al 2004 [S51]	Acidic saline injection into hindpaw	Rat	Nociceptive	Inflammation, chemical injury	Ketamine (IP 15 mg/kg) transiently increased paw withdrawal threshold to tactile stimulation after acidic saline injection, with effect lasting 30 minutes.
Alvarez et al 2003 [S52]	Capsaicin application	Rat	Nociceptive	Inflammation, chemical injury	Ketamine alone (SC 0.4 to 12.5 mg/kg) reduced facial rubbing/scratching in the orofacial capsaicin test in a dose-dependent manner and showed a synergistic effect when used with morphine.
Butelman et al 2003 [S53]	Capsaicin application	Monkey	Nociceptive	Inflammation, chemical injury	Ketamine (SC 0.32 to 1.8 mg/kg) produced a varying degree of capsaicin-induced thermal allodynia
Nadeson et al 2002 [S54]	Tail flick and response to electric current	Rat	Nociceptive	Opioid potentiation for acute pain	Subanalgesic doses of ketamine (IP, up to 3.75 mg/kg; IT, 25μg) potentiated the antinociceptive effects of IT fentanyl to noxious heat.
Arendt-Nielsen et al 2011 [S55]	Repetitive electrical stimulation	Rat	Nociplastic	Central sensitization	Highest ketamine dose (IV 0.2 mg/kg/min for 15 minutes) inhibited wind-up response of WDR neurons. Lower doses did not have a statistically significant effect.
Quintero et al 2011 [S56]	Formalin injection/induced stress with forced swimming	Rat	Nociceptive	Inflammation, chemical injury	Forced-swim rats post-treated with subanalgesic doses of ketamine (IP 5 mg/kg) displayed significantly lower pain scores after formalin injection

*: dosing data unavailable
μg: microgram
BID: bis in die (twice a day)
CCI: chronic constriction Injury
CFA: complete Freund's adjuvant
CPA: conditioned place aversion
CRPS: complex regional pain syndrome
HSV: herpes simplex virus
IL2: interleukin 2
IP: intraperitoneal
IT: intrathecal
IV: intravenous
kg: kilogram
mg: milligram
NMDA N-methyl-D-aspartate
NRS: numerical rating scale
NSAID: nonsteroidal anti-inflammatory drug
PD: pharmacodynamics.
PK: pharmacokinetic
POD: postoperative day
SC: subcutaneous
SNI: spared nerve injury
SNL: spinal nerve ligation
TNFα: tumor necrosis factor alpha
WDR: wide dynamic range

Abbreviations used in figures:

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