Methods: A PubMed database systematic review of the literature has been performed. We screened the intersection between the search terms nominating the different drugs and the different experimental models of persistent nociceptive pain. The drugs searched were duloxetine, venlafaxine, milnacipran and mirtazapine. The experimental pain models used for the search were hot plate test, tail flick test, formalin test, capsaicin test, acetic acid-induced writhing (in mice) and carrageenan-induced inflammation. For the formalin test only the phase 2 was assessed.
Results: The positive and no-effect results are summarized in the table.
Conclusions: Serotonin Noradrenalin Reuptake Inhibitors have been tested in a wide number of animal models. Duloxetine is the most widely tested showing efficacy in 5 out of 6 preclinical models. Preclinical evidence suggest an antinociceptive effect in humans.
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Test	Antinociceptive effect	No antinociceptive effect
Hot plate test	Duloxetine (modest)	Venlafaxine
	Mirtazapine (modest)	Milnacipran
Tail flick test	Venlafaxine	Duloxetine
	Milnacipran	Mirtazapine
Formalin (phase 2)	Duloxetine	
	Venlafaxine	
	Milnacipran	
	Mirtazapine (licking)	
	Mirtazapine (flinching)	
Capsaicin	Duloxetine	
Acetic acid writhing	Duloxetine	
Carrageenan	Duloxetine	

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ANTINOCICEPTIVE EFFECTS OF LACOSAMIDE IN THE STREPTOZOTOCIN RAT MODEL OF DIABETIC NEUROPATHIC PAIN

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Aim of Investigation: Lacosamide (SPM 927, R-2-acetamido-N-benzyl-3-methoxypropionamide) also formerly called harkoseride has shown activity in a wide variety of animal models for pain and epilepsy. Lacosamide is currently being evaluated in phase III clinical development for the treatment of epilepsy and diabetic neuropathic pain. The most commonly used animal model for the study of diabetic neuropathic pain is that of streptozocin (STZ)-induced diabetic neuropathy in rats. Therefore it was of interest to profile lacosamide in comparison to compounds which are used for treatment of patients with neuropathic pain i.e. anticonvulsants and antidepressants using this animal model.
Methods: Diabetic neuropathic pain was induced by acute administration of streptozotocin (55 mg/kg, i.v.) to Sprague Dawley rats. Ten and 21 days following the administration of STZ, tail vein blood of each animal was assayed for glucose. The activity of different anticonvulsants and antidepressants on mechanical and thermal allodynia or hyperalgesia was investigated in neuropathic rats between day 10 and day 21 after treatment with STZ.
Results: Lacosamide dose-dependently inhibited thermal and mechanical allodynia. In comparison to amitriptyline, levetiracetam, pregabalin, lamotrigine and venlafaxine using two different readouts lacosamide seemed to be the compound with the broadest efficacy in inhibiting pain behavior.
Conclusions: Lacosamide has strong antinociceptive activity on thermal and tactile stimuli in the streptozotocin rat model for diabetic neuropathic pain and seemed to be the compound with the broadest efficacy in inhibiting pain behavior.

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ANALGESIC EFFECT OF KETAMINE, MORPHINE AND METHADONE IN A PERIPHERAL NEUROPATHY INDUCED BY PACLITAXEL IN RATS

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Introduction: Paclitaxel is an antineoplastic agent in the treatment of solid tumours that produces a dose-limiting painful peripheral neuropathy in a clinically significant number of cancer patients.
The aim of our study is to compare the analgesic effect of ketamine, a NMDA receptor antagonist, morphine, an opioid agonist, and methadone, an opioid receptor agonist and unselective NMDA receptor antagonist, in an animal model of peripheral neuropathy induced by paclitaxel in rats (Pain 2001; 94:293).
Material and methods: Paclitaxel (1 mg/kg) was administered intraperitoneally (i.p.) on four alternated days (Days 1, 3, 5 and 7). The plantar surface of the hind paw (sciatic nerve territory) was tested (day 21) for thermal-hyperalgesia (Bennett and Hargreaves, 1990) and mechano-allodynia (Tal and Bennett, 1994), using von Frey filaments. Drugs were administered on day 22.
Results: Paclitaxel produced a statistically-significant mechano-allodynia (−70% of pressure threshold) and thermal hyperalgesia (−25% of temperature threshold) in both hind paws. There are no left-right differences.
Ketamine (25, 50 mg/kg i.p.) only reduced allodynia (−38% and +4% of the threshold) whereas hyperalgesia was not affected.
Morphine (2.5, 5 mg/kg i.p.) reduced allodynia (−6.2% and +107% of the threshold) and hyperalgesia (−7% and +23% of the threshold).
Methadone (2.5, 5 mg/kg i.p.) reduced allodynia (−25% and + 22% of the threshold) and hyperalgesia (−10% and +38% of the threshold.
Conclusions: These data can suggest that opioid receptors are more important than NMDA receptors in the modulation of hyperalgesia induced by paclitaxel.
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NEUROPLASTICITY IN RESPONSE PROPERTIES OF ROSTROVENTROMEDIAL MEDULLARY NEURONS IN ANIMALS WITH A SPARED NERVE INJURY MODEL OF NEUROPATHY

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Spared nerve injury (SNI) model of neuropathy produces a robust and long-lasting hypersensitivity. We determined the effect of SNI on response properties of neurons in the rostroventromedial medulla (RVM), a common relay for descending modulatory influence, including that mediated by the amygdala (AMY).
Two months after the nerve injury or sham operation, the response properties of RVM neurons were determined under pentobarbitone anesthesia. The RVM neurons were classified into ON-cells, OFF-cells, and NEUTRAL-cells (being activated, blocked or not responding to noxious stimulation, respectively). We assessed spontaneous activity and responses to mechanical and thermal (heat, cold) noxious mechanical stimulation of the skin, and colorectal distension. Additionally, we determined a centrally evoked response of RVM neurons to microinjection of glutamate or MK-801, an NMDA receptor antagonist, in the amygdala.
Spontaneous activity of ON- and OFF-cells was higher in the SNI than the sham group. The noxious stimulus-evoked excitatory responses in ON-cells and inhibitory ones in OFF-cells were, in general, stronger in the SNI than the sham group. Glutamate in the amygdala increased activity of ON- and OFF-cells in the SNI group only. ON-cell activity in the RVM was decreased in the SNI but not sham group by MK-801 in the amygdala, while it had no marked effect on OFF-cell activity.
SNI induces neuroplastic changes in centrally and peripherally evoked responses of RVM cells. These modulatory changes (increased spon-