Selective NMDA Receptor Modulation: The Superior Efficacy of Ketamir-2 in Neuropathic Pain Treatment

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Background

Neuropathic pain, a debilitating condition caused by nerve damage, is often inadequately managed due to the limitations in the efficacy and safety of existing therapies. Ketamir-2, a novel oral ketamine analog, has been developed to address these issues by selectively targeting NMDA receptors, aiming to reduce side effects like sedation and cognitive impairment while delivering consistent pain relief. This study evaluates the effectiveness of Ketamir-2 in treating neuropathic pain compared to standard treatments such as ketamine, pregabalin, and gabapentin in preclinical models.

Objective

To evaluate the effectiveness of Ketamir-2 in alleviating neuropathic pain across two models: the Chung model of nerve injury in rats and chemotherapy-induced neuropathy in mice, with comparisons to standard treatments such as ketamine, pregabalin, and gabapentin.

Methods

Neuropathic pain was induced in rats using the Chung model. Following anesthesia with a ketamine/xylazine mixture, a dorsal midline incision was made at the lumbar-sacral region. The left paraspinal muscles were separated from L4 to S2, and the L6 transverse process was removed to expose the L5-L6 spinal nerves, which were then isolated, ligated, and severed. Post-operative care included daily disinfection of the incision site for six days. Tactile allodynia was assessed on days 15 and 22 post-surgery using the Von Frey Filament (VFF) test, with filament forces ranging from 0.6 g to 15 g. The withdrawal threshold was measured in grams. In the PTX model, mice received paclitaxel (PTX) administration every other day for a total of four doses, and peripheral neuropathy was subsequently assessed by evaluating the withdrawal response using the VFF test.

Comparative effects of several oral doses of Ketamir-2 to Ketamine, Pregabalin and Gabapentin in the Chung model of Neuropathic pain in rats

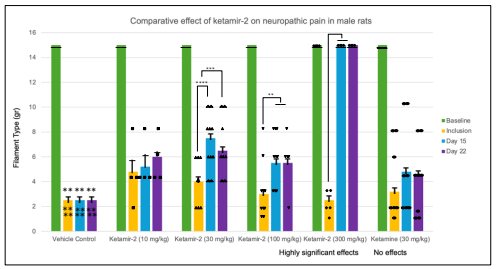

Figure 1. Comparative effects in male rats

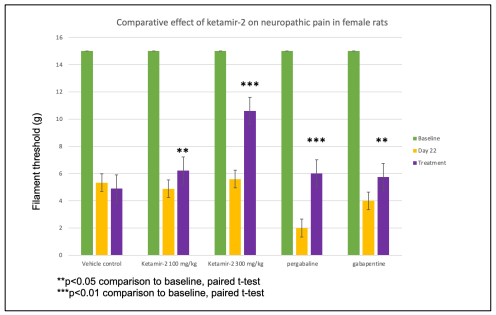

Figure 2. Comparative effects in female rats

Comparative effects of several oral doses of Ketamir-2 to Gabapentin in the PTX model of Neuropathic pain in mice

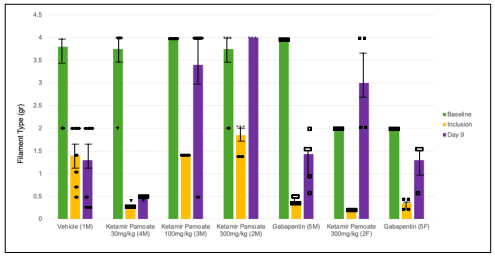

Figure 3. Comparative effects in male and female mice

Results

- Nerve Injury Model: Ketamir-2 achieved significant pain reduction at doses of 30, 100, and 300 mg/kg, with the highest dose producing a 100% normalization of pain thresholds—a complete reversal of pain symptoms. Ketamir-2 significantly outperformed oral ketamine, which showed no efficacy, and surpassed pregabalin and gabapentin by 112% and 70%, respectively, by Day 22.

- Chemotherapy Model: Ketamir-2 led to a full reversal of pain sensitivity in both male and female mice, outperforming gabapentin, which showed only moderate relief.

Conclusion

Ketamir-2 demonstrated exceptional efficacy in reversing neuropathic pain across multiple models, achieving complete pain normalization at higher doses where other treatments fell short. These findings underscore Ketamir-2's potential to not only surpass existing therapies but to set a new standard for neuropathic pain management. Its superior efficacy, oral bioavailability, and safer profile position it as a transformative treatment option poised to redefine care for patients suffering from this challenging condition.

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