followed by vehicle treatment postoperatively. Ralfinamide, administered only postoperatively, also significantly delayed the autotomy in a dose-dependent manner, compared to rats treated with the vehicle postoperatively. The analgesia outlasted the treatment period since in rats treated with the higher Ralfinamide dose, autotomy remained significantly suppressed till the end of the experiment on day d63, even though the treatment was administered for 42 days. Significantly suppressed autotomy levels were also seen in the group receiving the combined pre- and postoperative Ralfinamide treatment.
Conclusions: These results show that Ralfinamide can provide both "preemptive analgesia" and "palliative analgesia" against spontaneous neuropathic pain.

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LACOSAMIDE IN PAINFUL DISTAL DIABETIC NEUROPATHY: RESULTS OF A MULTI-CENTER, PLACEBO-CONTROLLED US TRIAL

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Background and Aims: Lacosamide is being investigated as an anticonvulsant with potential for reducing diabetic neuropathic pain.
Methods: Four hundred sixty-nine (469) patients were randomized (1:2:2:2) to placebo (n = 66), 200 (n = 141), 400 (n = 125), or 600 mg/day (n = 137) lacosamide treatment arms. Subjects titrated to their assigned dose then entered a 12-week maintenance phase. No dose adjustments were allowed. Subjects rated their pain twice daily using an 11-point Likert scale. Adverse events were assessed throughout the trial.
Results: Mean reduction in pain scores from baseline to the last 4 weeks of maintenance were −1.8, −2.2, −2.5, and −2.4 in the placebo, 200, 400, and 600 mg/day lacosamide arms, respectively, and approached significance (p = 0.0507) for the 400 mg/day lacosamide arm. A statistically significant separation between 400, and 600 mg/day lacosamide treatment and placebo arms was achieved early during titration and also observed for the entire titration and maintenance period. Most AEs were mild or moderate in intensity and had their onset during the titration phase. The incidence rates of AEs were similar across all treatment arms. The rate of early discontinuations was 31.8%, 32.6%, 43.2%, and 66.4% in the placebo, 200, 400, and 600 mg/day lacosamide arms, respectively. The most frequently reported AEs were dizziness, nausea, balance disorder, tremor, and headache.
Conclusions: Lacosamide at doses of 400 mg/day and 600 mg/day significantly reduced pain scores in subjects with diabetic neuropathy during titration and the entire 12 week maintenance period of this trial. The 200 mg/day and 400 mg/day lacosamide doses were better tolerated than the 600 mg/day dose in this trial.

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LACOSAMIDE IN PATIENTS WITH PAINFUL DIABETIC NEUROPATHY: 1 YEAR INTERIM RESULTS FROM A LONG-TERM, MULTI-CENTER, OPEN-LABEL TRIAL

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Background and Aims: Lacosamide is an anticonvulsant drug with the potential to reduce diabetic neuropathic pain. This trial assessed the long-term safety and efficacy of lacosamide in patients with painful diabetic neuropathy.
Methods: Patients were titrated to their optimal lacosamide dose (up to 600 mg/day) in weekly increments of 100 mg/day. They then entered a long-term maintenance period with dose adjustments as necessary. Morning and evening pain, interference with sleep and activity were assessed by daily diary entries (11-point Likert scales). Scores for each visit were summarized as observed. Adverse events (AEs) were recorded throughout the trial.
Results: Three hundred seventeen (317) patients (51% male, 49% female) were enrolled in the trial and received lacosamide; 71% were <65 and 29% were ⩾65 years of age. The most commonly prescribed lacosamide maintenance dose was 400 mg/day. The maximum duration of lacosamide exposure was 385 days. Clinically relevant reductions in pain scores were achieved during titration and were sustained over the whole treatment period. The mean (SD) change of average daily pain score from baseline to the first 24 weeks of the maintenance phase across all dose groups was −3.29 (±2.02). 10% discontinued the trial for AEs and 4% for lack of efficacy. The most common AEs were dizziness, vertigo, and headache.
Conclusions: In this long-term trial, lacosamide was generally well tolerated and led to early and sustained reductions in pain scores. These interim results indicate that patients might benefit from long-term treatment with lacosamide.

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TAPENTADOL, A NOVEL CENTRALLY ACTING ANALGESIC WITH A DUAL MODE OF ACTION: EFFICACY AND SAFETY IN CLINICAL ACUTE PAIN MODELS

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Background and Aims: Tapentadol is a new centrally acting analgesic with a dual mode of action: μ-receptor agonism and noradrenaline reuptake inhibition. The efficacy and tolerability of tapentadol was investigated in two validated acute pain models, third molar surgical extraction (TMSE) and bunionectomy.
Methods: Single oral doses of tapentadol HCl (25, 50, 75, 100, or 200 mg), morphine sulfate (60 mg), ibuprofen (400 mg), and placebo were evaluated in double-blind, randomized, phase II clinical trials in patients with moderate-to-severe pain following TMSE (N = 400) or bunionectomy (N = 517). Total pain relief over 8 hours (TOTPAR-8), measured using a 5-point pain relief scale (0 = none to 4 = complete), was the primary endpoint of both trials.
Results: TOTPAR-8 scores in each model were significantly greater (indicating better pain relief) for tapentadol HCl (doses ⩾75 mg, TMSE; doses ⩾50 mg, bunionectomy) compared with placebo (P ⩽ 0.05). Mean TOTPAR-8 scores for tapentadol HCl 200 mg and morphine sulfate 60 mg were 15.3 and 13.8, respectively, in TMSE and 8.1 vs 6.7, respectively, in bunionectomy. Overall, tapentadol was associated with lower nausea, vomiting, and dizziness incidences and similar somnolence incidences compared to morphine.
Conclusions: Single oral doses of tapentadol HCl from 75 to 200 mg showed efficacy in 2 validated pain models with the highest doses being comparable to or better than 60 mg morphine sulfate. This study demonstrates that tapentadol has improved GI tolerability compared with oral morphine at doses showing similar efficacy.

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LOW POTENTIAL FOR DRUG-DRUG-INTERACTION OF LACOSAMIDE

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Background: Lacosamide is a new drug being developed for the treatment of epilepsy and neuropathic pain. Preclinical and clinical data have been established in a series of trials. Information about the pharmacokinetic drug-drug-interaction (DDI) potential of lacosamide is an important part of its safety profile.
Methods: Regarding the DDI potential the results of several preclinical studies as well as of 9 Phase 1 trials (n = 184 subjects) and a Phase 2 trial (n = 91 patients) are presented.