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.

Results: In vitro, lacosamide is not substantially metabolized and shows no or low potential to inhibit or to induce CYP isoforms. Since lacosamide has low binding to plasma-proteins (<15%), drug displacement interactions are unlikely.
A phase 1 trial performed in CYP2C19 extensive and poor metabolizers demonstrated the minor relevance of CYP2C19 for the clearance of lacosamide.
Further DDI trials have been performed with carbamazepine (CYP450 inducer) and valproic acid (CYP450 inhibitor) under steady-state conditions. In these trials, lacosamide had no influence on rate or extent of absorption of carbamazepine or valproic acid and vice versa. DDI trials with digoxin and metformin showed no relevant influence of these drugs on lacosamide and vice versa. Lacosamide did not modify the pharmacokinetics and pharmacodynamics of the oral contraceptive Microgynon®. Coadministration of food did not alter the absorption of lacosamide.
In epileptic patients, lacosamide showed no influence on plasma levels of common antiepileptic drugs.
Conclusions: No DDI have been observed in these studies. Therefore the data suggest that lacosamide has low potential for DDI in clinical use.

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LACOSAMIDE HAS NO POTENTIAL FOR INTERACTION WITH METFORMIN

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Background: Lacosamide is a new drug under development for epilepsy and neuropathic pain. As patients with diabetic neuropathy represent a target population for the treatment with lacosamide, an interaction trial with the frequently prescribed oral anti-diabetic metformin was performed.
Methods: In an open-label trial 16 healthy male subjects received 200 mg lacosamide bid and 500 mg metformin tid to dermine a possible influence of lacosamide on metformin and vice versa. Lacosamide and metformin plasma concentrations were detected by a LC-MS/MS method.
Pharmacokinetic (PK) parameters $C_{max,ss}$, $AUC_{0-tz,ss}$, $t_{max,ss}$, and Ae of lacosamide and metformin were evaluated under single-dose and steady state conditions. Log transformed data of $C_{max,ss}$ and $AUC_{0-tz,ss}$ were analyzed using analysis of variance and point estimates and 90% confidence intervals (CI) for the ratios of $C_{max,ss}$ and $AUC_{0-tz,ss}$ (combined vs sole treatment) were calculated.
Results: The PK parameters for lacosamide were similar when lacosamide was given with or without metformin. The PK parameters for metformin were also similar when metformin was given with or without lacosamide. The 90% CI for $AUC_{0-z,ss}$ and $C_{max,ss}$ were within the generally accepted bioequivalence ranges of 80–125% for lacosamide and metformin.
Lacosamide and metformin were well tolerated when given alone or in combination. No clinically relevant changes of vital signs, ECG- or laboratory parameters were detected.
Conclusions: Thus, it was demonstrated that lacosamide has no influence on the steady state pharmacokinetics of metformin and vice versa. In this trial, there was no drug-drug interaction seen between lacosamide and metformin.

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THE EFFECT OF LORNOXICAM FOR PAIN RELIEF DURING EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY

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Background and Aims: In this randomised, controlled, double blinded study we evaluated the efficacy of two different doses intravenous-lornoxicam for pain relief during extracorporeal shock wave lithotripsy (ESWL).
Methods: Sixty ASAI-II patients undergoing ESWL were randomyl divided into three groups to receive two different doses of iv-lornoxicam (Group I: saline, Group II: 8 mg, Group III: 16 mg lornoxicam), 15 min before ESWL. All patients received intravenous 1 mcg/kg fentany l 3 minutes before ESWL. Pain scores, blood pressure, heart rate, respiratory rate and oxygen saturation were noted before ESWL, at the first minute, and every five minutes during the procedure. Pain was evaluated using a 10 cm visual analoque scale (VAS). During ESWL, additional doses of 20 mcg intravenous fentanyl were provided when the VAS > 3 and oxygen support was provided when the SpO2 < 95. Additional fentanyl consumption, oxygen support requirement, time for recovery room discharge, adverse effects and patient satisfaction were recorded.
Results: VAS scores were higher in Group I at all time points except before ESWL ($p < 0.001$). In GroupI, the decrease of blood pressure, heart rate and oxygen saturation were significant at the 5 and 10 min of the ESWL ($p < 0.01$). Fentanyl consumption, requirements of oxygen support and time for recovery room discharge were higher in Group I compared with the other groups ($p < 0.001$). Patient satisfaction scores were lower in Group I than in other groups ($p < 0.001$), and were similar in Group II and III. Nause, vomiting, and sedation insidence were higher in GroupI than in Group II and III ($p < 0.05$).
Conclusions: 8 mg iv-lornoxicam administered 15 min before procedure provides similar pain relief in those 16 mg iv-lornoxicam during ESWL, reducing intra and postoperative opioid requirements as well as decreasing the incidence of side effects.

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DYLOJECT™, A NOVEL INJECTABLE DICLOFENAC: EFFICACY OF UNEXPECTEDLY LOW DOSES AND FASTER ONSET THAN KETOROLAC

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Background and Aims: Dyloject™, a novel diclofenac formulation, employs the solubilizer hydroxypropyl-â-cyclodextrin to permit IV bolus administration. This study compared the efficacy and safety of Dyloject™ (5 dose levels), IV ketorolac and placebo following molar extraction.
Methods: 353 adults with moderate-to-severe pain received placebo; ketorolac 30 mg; or Dyloject™ 3.75, 9.4, 18.75, 37.5, or 75 mg (N = 51 for all groups except N = 47 for ketorolac). The primary endpoint was superiority of Dyloject™ to placebo assessed over 0–6 hr (TOTPAR6). Secondary endpoints included multiple measures of pain intensity and relief; patient global evaluation; and times to pain relief and rescue medication. Dropouts and adverse effects (AEs) were monitored.
Results: Dyloject™ at all doses, except 3.75 mg, was superior to placebo according to TOTPAR6 ($p < 0.0001$). Dyloject™ 3.75 mg was statistically superior to placebo for TOTPAR2 and TOTPAR4. Dyloject™ was superior to placebo ($p < 0.0001$) at the earliest (5 min) assessments of pain intensity (37.5 and 75 mg) and pain relief (18.75, 37.5 and 75 mg) while ketorolac was not. Secondary endpoints confirmed the primary findings. Treatment-related AEs were generally mild to moderate and typical for NSAIDs.
Conclusions: The minimum effective dose of Dyloject™ in this study was one-twentieth of the standard injectable diclofenac dose. Moreover, the more rapid onset of action of Dyloject™ than the reference injectable NSAID, ketorolac suggests additional clinical benefit. If confirmed in larger series, these findings may improve the safety and efficacy of postoperative NSAID analgesia.