and used tramadol in combination with paracetamol as an analgesic medication.
Conclusion: Intra-articular application of hyaluronic acid is an appropriate therapy in early osteoarthritis. Additionally we recommend the use of dietary supplements (glucosamine, chondroitin) for patients with degenerative changes in large joints.

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ANTI-ALLODYNIC ACTIVITY OF TAPENTADOL IN A RAT MODEL OF NEUROPATHIC PAIN DEPENDS ON OPIOID AND NORADRENERGIC, BUT NOT SEROTONERGIC, MECHANISMS

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Background: While μ-opioid receptor (MOR) agonism and inhibition of noradrenaline (NA) reuptake are well recognized as analgesic principles in neuropathic pain, the efficacy of serotonin (5-HT) reuptake inhibition is less clear. The novel analgesic tapentadol combines MOR agonism and NA reuptake inhibition in a single molecule, but shows only weak 5-HT reuptake inhibition (Tzschentke et al. J Pharmacol Exp Ther. 2007;323[1]:265–276). This study analyzed the contribution of opioid and monoaminergic mechanisms to the activity of tapentadol in experimental neuropathic pain.
Methods: Ipsilateral paw withdrawal thresholds were assessed in the rat spinal nerve ligation model of mononeuropathic pain by means of an electronic von Frey filament to determine neuropathic allodynia. Antagonism studies were performed with the MOR antagonist naloxone (1 mg/kg ip), the noradrenergic antagonist yohimbine (2.15 mg/kg ip), and the serotonergic antagonist ritanserin (0.316 mg/kg ip).
Results: Tapentadol HCl (10 mg/kg iv) showed clear anti-allodynic effects (>75% efficacy). The effect of tapentadol was profoundly blocked by naloxone and yohimbine but not by ritanserin. The suitability of antagonist doses was shown with the MOR agonist morphine HCl (10 mg/kg iv), the mixed NA/5-HT reuptake inhibitor venlafaxine (10 mg/kg iv), and the NA reuptake inhibitor desipramine (10 mg/kg iv).
Conclusions: It is concluded that combined activation of MOR and inhibition of NA reuptake, as obtained with tapentadol, is suitable to induce highly efficient anti-allodynia in a model of neuropathic pain.
TC, JDV, UJ, and TMT are Grünenthal employees.

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BOTULINUM NEUROTOXIN SEROTYPE A AND MORPHINE: A SUCCESSFUL PHARMACOLOGICAL COMBINATION FOR TREATING INFLAMMATORY PAIN

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Background and Aims: In recent years, growing interest in use of Botulinum neurotoxins (BoNTs) for treating pain developed both in humans and animal models. Analgesic effects of the serotype A of BoNTs (BoNT/A) on inflammatory pain were shown. The efficacy of morphine as antinociceptive agent is well known, but side effects and the insurgence of the tolerance phenomen limit its therapeutic use. Aims of the present research were to verify possibile synergistic effects of BoNT/A with morphine and its antagonistic action on tolerance development after the opioid's chronic administration.
Methods: CD1 adult male mice were used. Mice were intraplantarly injected with both BoNT/A (1875–15 pg/paw) and systemically with morphine (1–4 mg/kg) and their single and combinatorial effects on formalin-induced inflammatory pain were tested. Moreover the effects of BoNT/A (15 pg/paw) on the tolerance induced by a chronic administration of morphine (20 mg/kg along 12 days) were evaluated.
Results: Botulinum neurotoxin and morphine exert a synergistic action on licking behavioral response induced by formalin, these effects being evident during both early and late phases characterizing the formalin test. Morphine chronic administration-induced tolerance was inhibited by previous intraplantar injection of BONT/A. The behavioral effects of BoNT/A were correlated with immunofluorescence staining of inflammatory markers at the spinal cord level.
Conclusions: The possibility of decreasing doses of morphine for the treatment of inflammatory pain and of inhibiting the insurgence of morphine tolerance through BoNT/A is a very relevant result with a high therapeutical implication.

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TOLERABILITY OF TAPENTADOL EXTENDED RELEASE (ER) BASED ON DISCONTINUATIONS BECAUSE OF ADVERSE EVENTS IN PATIENTS WITH MODERATE-TO-SEVERE CHRONIC PAIN

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Background and Aims: Tapentadol is a novel, centrally acting analgesic with 2 mechanisms of action, μ-opioid receptor agonism and noradrenaline reuptake inhibition. This study assessed the tolerability of tapentadol ER for treating moderate-to-severe chronic low back or osteoarthritis pain.
Methods: Patients were randomized 4:1 to treatment with tapentadol ER (100–250 mg bid) or oxycodone HCl controlled release (CR; 20–50 mg bid) for 1 year and could make controlled dose adjustments to achieve a self-perceived optimal dose in terms of effectiveness and tolerability. Efficacy was assessed by pain intensity scores (11-point numerical rating scale). Treatment discontinuations were monitored.
Results: Of 1121 patients randomized, 1117 were evaluated for safety, and 1095 were evaluated for efficacy. Mean baseline pain intensity scores were similar for tapentadol ER (7.58) and oxycodone CR (7.61) and decreased to 4.37 and 4.52, respectively, at endpoint. A higher percentage of patients completed the 1-year study with tapentadol ER (46.1%) than oxycodone CR (35.0%). By Week 4, approximately 20% of patients receiving tapentadol ER and 40% receiving oxycodone CR discontinued treatment. The most common reason for treatment discontinuation was adverse events (AEs; tapentadol ER, 22.7%; oxycodone CR, 36.8%). The rate of rise in the percentage of patients who discontinued because of TEAEs was more rapid in the oxycodone CR group than in the tapentadol ER group and continued more slowly from Week 4 throughout the study.
Conclusions: Tapentadol ER (100–250 mg bid) provided long-term relief for patients with moderate-to-severe pain, with fewer treatment discontinuations because of AEs than oxycodone CR (20–50 mg bid).
HW, RL, and AS are Grünenthal employees. BK, BM, AO, ME, and CR are Johnson & Johnson employees and shareholders.

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MELATONIN EFFECTS ON NEUROPATHIC PAIN ARE MEDIATED VIA OPIOID SYSTEM AND BENZODIAZEPINE-GABA$_A$ERGIC MECHANISMS

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Background and Aim: Recent data suggest that MT plays a role in pain modulation. The purpose of this study was to assess the