

Meeting Highlights

American Academy of Pain Medicine, 22nd Annual Meeting

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Approximately 1,500 pain specialists and other health care professionals gathered at the 22nd annual meeting of the American Academy of Pain Medicine in San Diego, California, from February 22 to 25, 2006, to hear the latest developments in comprehensive evidenced-based, best-practice approaches to the management of pain.

Studies of particular interest focused on new opioid preparations administered in extended-release formulations for opioid-naïve and opioid-experienced patients with low back pain, a novel



non-opioid analgesic given intrathecally for a wide range of debilitating chronic pain conditions, an intranasal opioid for moderate-to-severe postsurgical pain, a transdermal opioid patch for postoperative pain after knee or hip replacement surgery, a potent opioid analgesic in an effervescent tablet for cancer-related breakthrough pain, optimal dosages for lumbar epidural steroid injections in lumbar radiculopathy and spinal stenosis, and an antidepressant for the long-term management of diabetic peripheral neuropathic pain.

Once-Daily Extended-Release Morphine Sulfate Beneficial for Low Back Pain

Speaker: Richard L. Rauck, MD, Medical Director, The Center for Clinical Research, LLC; Wake Forest University Baptist Medical Center, Winston-Salem, North Carolina

Once-daily extended-release (ER) morphine sulfate (Avinza, Ligand) proved superior to twice-a-day, controlled-release oxycodone HCl (OxyContin, Purdue Pharma) for chronic, moderate-to-severe low back pain in patients naïve to sustained-release opioids.

Researchers enrolled 392 individuals into an open-label, randomized, parallel-group, multicenter study. The patients underwent titration of their opioid dose for three to six weeks; 132 patients were assigned to receive morphine, and 134 received oxycodone. Opioid dose stabilization, as established by a pain score of less than 4 millimeters (mm) for three consecutive days with two or fewer doses of ibuprofen pain rescue medication per day, was achieved in 266 patients. These subjects were then entered into the eight-week evaluation phase of the study.

Patients taking morphine achieved significantly better around-the-clock pain control than those taking oxycodone, as demonstrated by a greater decrease in pain scores from baseline. The patients were evaluated six, nine, and 12 hours after the morning doses of both opioids ($P \leq .02$).

Morphine once daily was also more effective than twice-daily oxycodone in terms of quality of sleep achieved, as measured by the Pittsburgh Sleep Quality Index (PSQI) for the entire evaluation period from weeks one to eight ($P < .04$).

The number of ibuprofen rescue medication doses required for breakthrough pain, adjusted for the number of patient days, was lower in the morphine group than in the oxycodone group. The total daily opioid dose was significantly higher with oxycodone than with morphine when oxycodone was

converted to morphine equivalents (median, oxycodone 84 mg/day vs. morphine 58 mg/day; $P = .0144$).

The two drugs were comparable in safety and tolerability.

Extended-Release Oral Oxymorphone Relieves Low Back Pain in Opioid-Experienced Patients

Speaker: Harry Ahdieh, PhD, Director of Clinical Operations, Endo Pharmaceuticals, Inc., Chadds Ford, Pennsylvania

In an open-label titration study, most opioid-experienced patients with chronic, moderate-to-severe low back pain achieved a well-tolerated and effective dose of extended-release (ER) oxymorphone (Endo) following a program of dose conversion with additional gradual titration, as necessary. Oxymorphone is an active metabolite of oxycodone and a semi-synthetic mu-opioid agonist.

Two hundred fifty patients who had previously received a fixed opioid regimen received oral oxymorphone ER every 12 hours at a daily dosage equivalent to their pre-study opioid requirement. Each dose was titrated in 10-mg increments every 12 hours for three to seven days until a stabilized dose of oxymorphone ER was reached. *Stabilization* was defined as a dose that reduced average pain scores by 40 mm or lower on the 100-mm Visual Analogue Scale (VAS), with an acceptable tolerability for three of five consecutive days and for which no more than two rescue doses of oxymorphone ER were needed per day.

Patients filled out daily diaries to record their pain intensity using the VAS. They also completed a Global Assessment of Pain Medication using a five-point categorical scale. An 11-point Pain Quality Assessment Scale (PQAS) was used to measure the type and quality of pain.

Of the 250 treated patients, 143 were successfully switched to oxymorphone ER and achieved titration to a stable dose. The average pain intensity of patients who successfully completed

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titration decreased from 69.5 mm on the VAS at screening to 23.6 mm at stabilization. After successful titration, PQAS scores also improved significantly; the composite mean \pm the standard deviation (SD) PQAS score decreased by 60.3 ± 34.1 ($P < .0001$).

Only 14.5% of the patients who had achieved dose stabilization at screening rated their prestudy medication as “very good” to “excellent.” By contrast, 74.5% of these patients rated oxycodone ER as “very good” to “excellent” after stabilization.

Adjunctive Intrathecal Ziconotide: An Alternative Approach to Chronic Pain

Speaker: Alexander A. Krakovsky, MD, PhD, DrSc, Pain Management Specialist, Interventional Pain Management, Galileo Medical Center, San Luis Obispo, California

Adjunctive intrathecal therapy with ziconotide (Prialt, Elan) represents the first of a new class of non-opioid analgesics called *N*-type calcium-channel blockers. This novel approach is used to treat a variety of debilitating chronic pain conditions.

To assess the value of this neuroprotective analgesic, investigators evaluated 17 patients with intrathecal delivery systems in place. The patients were enrolled in the study because pain control had been inadequate, dosages were excessive according to the Polyanalgesic Consensus Trial, and adverse drug effects (ADEs) limited therapeutic results.

In this selected group of patients, 70% reported significant efficacy with ziconotide adjunctive intrathecal therapy. Overall, 14 patients (82.3% of the total study group) reported a 10% to 15% decrease in pain scores. Nine patients (53%) increased their general activity level. Two patients (11.8%) were able to decrease their dose of intrathecal opioids, and three patients (17.6%) were able to decrease their adjunctive intrathecal therapy with bupivacaine (Sensorcaine, AstraZeneca) and clonidine (Catapres, Boehringer Ingelheim). Two patients (11.8%) reported a decrease in oral opioid therapy, and three patients (17.6%) were able to stop using ziconotide. Five patients (29.4%) had only limited use of the drug because of possible adverse events that might have been caused by the drug therapy.

Intranasal Morphine Relieves Postsurgical Pain

Speaker: David B. Carr, MD, Chief Executive Officer and Chief Medical Officer, Javelin Pharmaceuticals, Cambridge, Massachusetts

Intranasal morphine (Rylomine, Javelin) provided a non-invasive, dose-dependent alternative to injectable morphine for the relief of moderate-to-severe postoperative pain in a randomized, double-blind, single-dose and multiple-dose, actively controlled and placebo-controlled study.

A total of 187 patients with post-orthopedic surgical pain were selected to receive intranasal morphine 3.75 mg (24 patients), 7.5 mg (24 patients), 15 mg (24 patients), or 30 mg (23 patients), intravenous (IV) morphine 7.5 mg (46 patients), or placebo (46 patients) in a *single-dose phase* and either intranasal morphine 7.5 mg (90 patients) or 15 mg (87 patients) for the rest of the study period.

The primary endpoint was a dose–response relationship, determined by VAS scores for total pain relief over four hours. Secondary endpoints included (1) categorical total pain relief

over four hours; (2) total pain relief over four hours, both VAS and categorized, over other time intervals up to 24 hours; (3) pain intensity; (4) pain relief; (5) the patient global evaluation; and (6) assessment of the frequency, number, and time elapsed until rescue medication following intranasal morphine 7.5 and 15 mg in the multiple-dose phase. Safety assessments included ADEs and a nasal examination.

Intranasal morphine 15 or 30 mg or IV morphine, as measured by total pain relief over four hours, provided statistically superior dose-dependent pain relief compared with placebo ($P < .0001$). Step-down testing demonstrated that the minimum effective dose of intranasal morphine was 7.5 mg. The *multiple-dose phase* of the study showed that dosing intervals of one to two hours for morphine 7.5 mg and two to three hours for morphine 15 mg relieved pain.

Overall, local nasal morphine-related ADEs were transient and mostly mild, including a bad taste, nasal congestion, throat irritation, and sneezing. Systemic ADEs, regardless of the route of administration, were dose-related and were consistent with common ADEs associated with opioids.

Transdermal Hydromorphone Patch for Acute Postoperative Pain

Speaker: Edda Gomez-Panzani, MD, Director of Clinical Research and Development, and Head of Medical Affairs, Altea Therapeutics, Tucker, Georgia

An investigational transdermal hydromorphone patch (Altea Therapeutics) seems to be effective for patients with moderate-to-severe acute pain after knee or hip replacement surgery.

The delivery of hydromorphone through the skin was achieved by Altea’s patented PassPort System, an advanced technique that enhances the permeability of the skin by creating aqueous channels (*micropores*) through the stratum corneum using thermal ablation via an array of metallic filaments. A short pulse of electrical current is generated from a reusable, hand-held applicator.

A randomized, multicenter, parallel-design, three-day study was conducted to evaluate the analgesic effect and safety of two dosages of transdermal hydromorphone in 14 patients. Seven patients were assigned to receive one patch, and seven patients were to receive two patches.

Primary efficacy endpoints were pain relief, defined as a composite of a decrease in VAS pain severity scores of 20 mm or more from baseline, a VAS score of 50 mm or lower at the follow-up visit, and the lack of need for a rescue medication before the follow-up visit. Secondary efficacy endpoints included the time to meaningful pain relief, the amount of rescue medication needed and the time elapsed until its first use, and patients’ assessments of the study drug.

At the end of the first day, the average number of doses of rescue medication needed was significantly higher with one patch (9.5 doses) than with two patches (1.5 doses). This result correlated with the analgesic effect of a serum hydromorphone level of 3 mg/ml, delivered by two patches. Patients rated the patch as “good” in terms of effectiveness (77%); they reported experiencing no sensation from the micropores (69%); they considered the patch comfortable to wear (85%); and they reported a good-to-excellent skin appearance (85%).

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Fentanyl Effervescent Buccal Tablets for Cancer-Related Breakthrough Pain

Speaker: Donald R. Taylor, MD, Medical Director, Comprehensive Pain Care PC, Marietta, Georgia

An effervescent buccal tablet formulation of fentanyl (Actiq, Cephalon) appears to be a superior treatment option for breakthrough pain in cancer patients who can tolerate opioids. Buccal tablets dissolve in the buccal pouch (between the cheek and the gum).

After an open-label titration study established an effective dose for the tablets, 123 patients were randomly assigned to receive one of 18 predefined dose sequences of 10 tablets (seven fentanyl tablets and three placebo tablets). All 10 doses were to be taken within a two-day period. A maximum of four episodes of breakthrough pain were treated each day.

Pain intensity, as measured on an 11-point scale, and pain relief, as measured on a 5-point scale, were recorded at 15, 30, 45, and 60 minutes after the dose was given. The summed pain intensity difference (SPID₃₀) and total pain relief were recorded at 30 minutes after the dose was given. ADEs and supplemental medication were also assessed.

Eighty of the initial patients (65%) identified an effective tablet dose during titration, ranging from 100 to 800 mcg. Of these patients, 77 continued in the double-blind phase of the study; 72 patients were evaluable for efficacy. Overall, significantly greater analgesic effects were recorded at all time points for the tablets, compared with placebo, for the mean difference in pain intensity, pain relief, SPID₃₀, and total pain relief from zero to 60 minutes.

The primary efficacy endpoint, SPID₃₀, was 3.0 ± 0.12 SD for breakthrough pain episodes treated with the tablets and 1.8 ± 0.18 SD for episodes treated with placebo. This highly statistically significant difference favored the tablets ($P < .0001$). Patients who took placebo were twice as likely as patients using the tablets to need supplemental medications for episodes of breakthrough pain.

ADEs were similar to those of opioids. The most common ADEs were nausea, dizziness, and headache. Only two patients stopped therapy because of problems with oral tolerability.

Lower Doses of Epidural Steroids Recommended for Lumbar Radiculopathy and Spinal Stenosis

Speaker: Damon Robinson, MD, Clinical Fellow, Anesthesia, Critical Care, and Pain Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

In a study designed to determine the optimal steroid dose needed for lumbar epidural steroid injections, it was found that lower doses of triamcinolone (Aristocort, Fujisawa) injections for back pain were more effective than higher doses. Injectable triamcinolone 80 mg was the lower optimal dose for lumbosacral radiculopathy and spinal stenosis.

Although steroid injections have been used to treat lumbosacral radical pain and spinal stenosis since the 1960s, the optimal steroid dose has yet to be determined. A prospective, randomized, double-blind clinical trial was performed to evaluate the effects of five different doses of epidural triamcinolone in 160 patients with lumbosacral radiculopathy (60%) or spinal

stenosis (40%), as confirmed by magnetic resonance imaging or electromyography.

The patients were randomly assigned to receive 40, 80, 120, 160, or 200 mg of epidural triamcinolone. The same dose was administered for each subsequent injection. Up to three injections were administered over a six-month period.

At the baseline examination, before injection therapy, the average VAS score was 7 mm, defined as no pain relief. After one week of injections, the average VAS score was below 2 mm, with 77% (123 patients) reporting substantial pain relief. The 80- and 120-mg doses of triamcinolone were optimal for pain relief. Higher doses provided no additional reduction in VAS scores, and the 200-mg dose was associated with an increased number of ADEs.

Duloxetine Safe for Long-Term Management of Diabetic Peripheral Neuropathic Pain

Speaker: Yili L. Pritchett, PhD, Research Scientist, Eli Lilly, Indianapolis, Indiana

Duloxetine HCl (Cymbalta, Eli Lilly), a dual reuptake inhibitor of both serotonin and norepinephrine, was recently approved for the management of diabetic peripheral neuropathic pain (DPNP). Researchers have now found it to be safe and well tolerated, compared with routine care, in the long-term management of patients with DPNP.

Initially, three independent 12-week studies of acute therapy confirmed the safety and efficacy of duloxetine 60 mg once daily and 60 mg twice daily for patients with DPNP. The objectives were to evaluate the safety of duloxetine 60 mg twice daily over a 52-week, open-label extension period; to assess this treatment and progression of diabetic complications for up to 65 weeks; and to compare the effect of duloxetine 60 mg twice daily with routine care in patient-reported health outcomes.

A total of 237 patients who completed a double-blind 13-week period of duloxetine and placebo therapy were randomly reassigned, in a 2:1 ratio, to receive duloxetine 60 mg twice daily (161 patients) or routine care (76 patients) for an additional 52 weeks. Routine care consisted primarily of gabapentin (Neurontin, Pfizer), venlafaxine (Effexor, Wyeth), and amitriptyline (various manufacturers).

The study enrolled men and women 18 years of age or older with a diagnosis of DPNP caused by either type-1 or type-2 diabetes. Overall, a higher percentage of the patients receiving routine care experienced one or more serious ADEs than those taking duloxetine. For the duloxetine patients, changes in laboratory and vital sign values were not considered clinically relevant because of the small magnitude of the changes.

Duloxetine did not appear to have an adverse effect on nerve function, to change the progression of retinopathy, or to have a negative effect on the course of DPNP. Neither therapy group showed any statistically significant differences in the 36-item Short-Form Health Survey (SF-36) subscales or in the EuroQd 5-Dimension Questionnaire (EQ-5D).

The lack of significant cardiovascular changes with duloxetine suggests that patients with diabetes mellitus do not need more intensive assessment of their cardiovascular status with duloxetine than they require for their underlying diabetes. ■