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Topical Analgesics Gain Momentum in Musculoskeletal Pain

Non-opioid analgesics play an integral role in the management of painful conditions such as chronic pain. These medications are frequently combined with opioid analgesics, such as hydrocodone or oxycodone; however, dose limitations and potentially fatal adverse effects limit their usefulness in select injured-worker populations. The utilization of topical prescription analgesics has been successful for many years in European countries for painful conditions, such as osteoarthritis and other inflammatory conditions. Recent studies demonstrate limited efficacy with the topical administration of NSAID analgesics for non-neuropathic pain conditions. Research conducted by Lin, 2004, Bjordal, 2007, and Mason, 2004 revealed superiority to oral agents for the first two weeks of treatment; however, efficacy appeared to lessen shortly thereafter.

The Work Loss Data Institute, one of the leading information compendiums for workers' compensation injury treatment, suggests that although topical agents may be effective for chronic musculoskeletal pain conditions, long-term studies are still needed regarding long-term safety and effectiveness. Recently, the FDA granted Novartis approval to market the first commercially available topical analgesic, Voltaren® Gel 1%, for the treatment of osteoarthritis-associated pain. Originally approved in 1988, diclofenac sodium is thought to work by blocking the actions of COX-enzymes resulting in a decrease in pain and inflammation. "Voltaren Gel is proven to be effective for osteoarthritis of the hand and knee and has a favorable safety profile. The combination of benefit and safety provides a welcome new treatment approach for osteoarthritis, offering patients an alternative to oral therapies," noted Dr. Roy Altman, medical professor at UCLA's Division of Rheumatology and Immunology. "Voltaren Gel delivers the proven efficacy of diclofenac with significantly less systemic absorption, minimizing the risk of side effects."

features

Methadone 40 mg Distribution Limited to Select Facilities

Manufacturers of methadone 40 mg (dispersible) tablets have agreed to voluntarily limit distribution to hospitals and approved opioid addiction detoxification and maintenance treatment centers after recent reports of methadone associated adverse drug reactions including cardiac rhythm changes and death. This increase in methadone associated complications is suspected as the number of prescriptions for methadone continues to increase. Methadone 40 mg is currently restricted with an FDA approval only for detoxification and maintenance treatment of opioid addiction. Manufacturers indicate that the 5 mg and 10 mg versions will continue to be made available to retail pharmacies and all other Drug Enforcement Administration (DEA) registered facilities for the treatment of pain. This may translate into an increase in the quantity of tablets (5 mg and 10 mg) prescribed to patients previously utilizing the 40 mg strength for chronic pain relief. These new restrictions regarding distribution took effect on January 1, 2008.

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Study Addresses Link Between Sleep Apnea and Opioids

The utilization of opioid analgesics has long been known to cause decreases in respiratory function, especially when administered with other CNS-depressing agents and in those not tolerant to opioid medications. Although this adverse effect is transient in nature, researchers in Utah have discovered a relationship between the use of opioids and the development of disruptive sleep apnea. An observational study in 147 chronic-pain patients utilizing round-the-clock opioid analgesics for at least six months was conducted using overnight polysomnographic assessments. Researchers discovered that 75% of the qualified participants exhibited an abnormal apnea-hypopnea index, a metric used to quantify sleep apnea disruptions. One third of those affected were identified as utilizing methadone therapy with a statistically significant relationship between the occurrence of apnea and methadone utilization. Participants using benzodiazepine therapy were also noted to experience respiratory complications.

FDA Investigating Occurrence of Anxiety and Headaches with Wellbutrin XL Generic

The Food and Drug Administration (FDA) began investigations after receiving several reports of headaches, anxiety, and other adverse effects in patients utilizing Budeprion XL therapy. The popular generic antidepressant was originally tested by ConsumerLab.com after as many as 250 patients complained of the development of nausea, headaches, irritability, and insomnia after switching from the brand name version, Wellbutrin XL®. A large percentage of patients indicated that their symptoms resolved once they returned to the brand name. Although it appears that a significant amount of patients experienced similar side effects when utilizing Budeprion XL therapy, this occurrence should not deter prescribers or patients from taking advantage of cost savings through the utilization of generic prescription formulations. The FDA states that all generic formulations are required to show safety and efficacy and must contain the same active ingredient(s) and work the same way in the body. FDA officials state that they are currently working to investigate the problem.

Genetic Association Suspected Between Antidepressants and Suicidal Thoughts

The National Institute of Mental Health reports a large study conducted by institute researchers may have unlocked a potential genetic predisposition for suicidal thoughts in patients taking commonly prescribed antidepressant medications. Consisting of 1,915 participants, the study indicated that variations in two genes responsible for the development of certain neurotransmitter receptors could be linked to an increased propensity for suicidal tendencies. Researchers discovered that variations in the kainate receptor gene, GRIK2, conferred an eight-fold increase in suicidal ideation while those with AMPA receptor gene alterations exhibited a two-fold increase. Study participants with both genetic variations were found to be 15 times more likely to have similar thoughts, although less than 0.5% of all study participants exhibited both gene variations. Surprisingly, more than 40% of participants who reported thoughts of suicide lacked both gene variations suggesting that other factors may also be involved.

Recent studies have prompted the FDA to require a black box warning on all antidepressants stating the potential for suicidal ideation in young adults up to age 24. Although this increase is alarming, evidence fails to correlate suicidal ideation with actual suicide attempts. However, researchers do note that harmful thoughts can impede patients with depression from overcoming their illness and may possibly sabotage recovery efforts. Results from an earlier trial (STAR*D) showed that 25% of suicidal participants recovered from depression compared to 42% of non-suicidal patients. Dr. Thomas Insel, Director of the National Institute of Mental Health, commented, "These data suggest that genetics may soon help us in our quest to individualize treatments for depression."

clinical literature digest studies

STUDY #1: New Data Shows Reduced Gastrointestinal Complications with Oxycodone/Naloxone Combination

Opioid analgesics are commonly used in the management of severe chronic pain. Although these agents can produce numerous adverse effects, long-term use of opioids leads to tolerance to these adverse effects with the exception of constipation. Opioid-induced constipation can be debilitating and dose-limiting. In order to manage this complication, a prophylactic bowel regimen, commonly consisting of a stool softener and a stimulant laxative, is currently being recommended. The use of opioid receptor antagonists, such as naloxone, for the management of opioid induced bowel dysfunction has been avoided due to the central actions of currently available agents. These central actions can lead to reversal of the analgesic effects and opioid withdrawal.

A Phase III trial looked at the use of prolonged release oxycodone/naloxone combination tablets in order to evaluate the self-reported severity of constipation symptoms associated with this combination medication. The study compared the use of several different dosages of oxycodone/naloxone with OxyContin® and placebo in 463 patients with severe chronic pain who were already stable on oxycodone prior to the study. Results showed that the combination product significantly reduced the occurrence of constipation and the need for laxative therapy when compared to OxyContin alone or placebo. Reportedly, there was no loss in the analgesic efficacy when the combination product was compared to the OxyContin group. This trial suggests that the use of oxycodone/naloxone combination tablets may result in a reduced risk of developing opioid-induced bowel dysfunction.

Mueller-Lissner, S. et al. Oral Prolonged-Release (PR) Oxycodone/Naloxone Combination Reduces Opioid-Induced Bowel Dysfunction (OIBD) in Chronic Pain Patients. *World Institute of Pain*. 2007.

STUDY #2: Combination Intrathecal Morphine/Ziconotide Shown Effective in Severe Chronic Pain

Ziconotide (Prialt®) is a non-opioid analgesic approved for intrathecal administration for the management of severe chronic pain and is derived from the venom of the marine snail, *Conus magus*. Ziconotide is typically used in patients intolerant of or refractory to traditional analgesics. The majority of current trials involving ziconotide therapy have looked at its use as monotherapy in the management of severe pain. This multicenter, open-label trial evaluated the safety and efficacy of the combination of intrathecal morphine and ziconotide therapy. The objectives of the trial included assessment of the safety of the combination at increasing doses of morphine, determining if additional pain relief was provided, and determining if the combination allowed for reduced systemic opioid need. Twenty-three patients who were stabilized on ziconotide therapy and were considered refractory to treatment completed the initial phase, consisting of a four-week titration period in which the dose of morphine was increased on a weekly basis. The extension phase followed and allowed patients to choose to continue combination therapy, convert back to ziconotide monotherapy, or terminate the trial.

The results showed that the combination provided a significant reduction in pain intensity with no new or unexpected adverse effects. A 26.3% reduction in the visual analog scale score (for reporting pain) was seen from the initial visit to the end of the titration period. These reductions in pain intensity were seen during the first week of the trial and increased as the study progressed. Systemic opioid use decreased by 49.1% on average throughout the titration phase. This indicates that the reduction in pain intensity was not due to increased systemic opioid analgesic utilization. The study suggests that the use of this medication combination provides improved pain control in patients previously sub-optimally controlled on ziconotide monotherapy.

Webster LR, Fakata KL, Charapata S, et al. Open-Label, Multicenter Study of Combined Intrathecal Morphine and Ziconotide for Severe Chronic Pain. *Pain Med*. 2007; Online Early Articles.

STUDY #3: Effervescent Morphine Results in Faster Analgesia Than Immediate Release Morphine Tablet

This open-label trial evaluated the safety and efficacy of effervescent morphine, a novel dosage form developed for the management of breakthrough pain, compared to immediate release morphine sulfate (IRMS). The authors of the study hypothesized that the aqueous solution produced by the effervescent tablet would result in increased gastrointestinal transit time, leading to a more rapid onset of analgesia. In total, 76 chronic pain cancer patients were enrolled for a six month study.

The first month of the trial involved a “run-in” period during which all patients used IRMS for breakthrough pain management and were required to document the onset of action, efficacy, and adverse effects. Patients were then started on effervescent morphine at an initial dose of 20 mg (one tablet) and were allowed to increase the dose as needed based on the study protocol. An adequately controlled breakthrough pain episode was defined as a score of 3.0 (out of a scale of 0-10) on the visual analog scale (VAS). During the “run-in” period, the mean VAS score was initially 8.0 and was reduced to a mean of 3.0 by IRMS. In comparison, the mean VAS score was 7.8 when effervescent morphine was initiated, which was reduced to a mean of 3.2, representing a statistically significant decrease ($P < 0.001$). The mean dose of effervescent morphine required was 28 mg and was similar to that required for IRMS, which was 30 mg. Adequate breakthrough pain relief was reported 13 minutes after effervescent morphine administration, while adequate relief with IRMS was reported after 27 minutes. This represents a statistically significant difference in onset of action ($P < 0.001$). Overall, patients rated pain relief and satisfaction significantly higher with effervescent morphine, but its use was still associated with typical opioid-related adverse effects. These findings suggest that this novel breakthrough pain agent may provide adequate pain relief, but larger studies in more diverse patient populations are still necessary.

Freye E, Levy JV, and Braun D. Effervescent Morphine Results in Faster Relief of Breakthrough Pain in Patients Compared to Immediate Release Morphine Sulfate Tablet. *Pain Pract*. 2007; 7: 324-31.

New Drug or Formulation

Voltaren® (diclofenac sodium)

Approved: October 2007

Voltaren, a long available non-steroidal anti-inflammatory analgesic is now available in a topical gel for the treatment of pain associated with arthritis. Voltaren Gel was not assessed for use on the spine, shoulder, or hip. Similar to the oral dosage form, Voltaren Gel works by inhibiting cyclooxygenase enzymes, thereby reducing inflammation.

New Launches

Xyzal® (levocetirizine)

Approved: October 2007

Sanofi-Aventis received approval from the FDA to introduce **Xyzal** into the U.S. market. Xyzal is a selective histamine blocker and is currently indicated for the treatment of allergic rhinitis and urticaria. Xyzal is currently available in a 5 mg dose tablet.

New Approvals

Soma® (carisoprodol)

Approved: September 2007

The FDA granted approval to MedPointe Pharmaceuticals to market **Soma** in a new 250 mg strength formulation after two randomized controlled trials showed this dose to be as effective as the current 350 mg tablet. Researchers note this new dose should decrease the occurrence of common side effects such as drowsiness.

Generic Drug Arrivals

Trileptal® (oxcarbazepine)

Approved: October 2007

Oxcarbazepine tablets are now available as the generic equivalent of **Trileptal**, an oral anticonvulsant used in the treatment of certain seizure disorders. Oxcarbazepine has been shown effective in the non-FDA indicated use of neuropathic pain.

Actonel® (risedronate)

Approved: October 2007

Actonel, a popular bisphosphonate used in the treatment of osteoporosis is now available generically as risedronate. As of August 2006, risedronate has received approval for the treatment of osteoporosis in both men and women.

FDA MedWatch Reports

Inappropriate Use of Fentora®

Posted September 2007—The FDA issued a Public Health Advisory and a Healthcare Professional Sheet to alert healthcare professionals and consumers regarding concerns over the use of Fentora (fentanyl buccal) tablets after recent reports of deaths and other adverse effects. The deaths reported were the result of improper selection of patients, dosing, or improper product substitution. The FDA warned physicians and other healthcare professionals that it is critical to follow product labeling when administering Fentora. The FDA further stated that it is dangerous to use Fentora for any short-term pain such as headaches or migraines.

It is critical that Fentora not be used in patients who are not opioid tolerant. Patients also must be under a doctor's care and close supervision while taking Fentora and the dose should be carefully adjusted to adequately control breakthrough pain. In addition, the FDA is concerned about the improper substitution of Fentora, a quick acting pain medication, for other pain medications. Fentora is not the same as other fentanyl products and cannot be substituted for Actiq, another fentanyl product used to treat breakthrough cancer pain. Because Fentora delivers more fentanyl to the blood than Actiq, substituting Fentora for Actiq using the same dose may result in a fatal overdose.

Provigil® Labeling Changes

Posted October 24, 2007—The FDA and Cephalon notified healthcare professionals regarding updates to the WARNINGS section of the prescribing information for

Provigil (modafinil). Provigil is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder. The revised labeling updates safety information to include warnings regarding serious rash, including Stevens-Johnson syndrome (SJS) and hypersensitivity reactions, as well as psychiatric symptoms. Rare cases of serious or life-threatening rash, including Toxic Epidermal Necrolysis, and Drug Rash with Eosinophilia and Systemic Symptoms have been reported in adults and children in worldwide postmarketing experience. Angioedema and multi-organ hypersensitivity reactions have also been reported in postmarketing experience.

Physicians should instruct patients to immediately discontinue the use of Provigil and contact their doctor if a rash or other hypersensitivity reaction occurs. Healthcare professionals and consumers should also be aware that Provigil is not approved for use in pediatric patients for any indication. In addition, adverse psychiatric effects (including anxiety, mania, hallucinations, and suicidal ideation) have been reported in patients treated with Provigil. Caution should be exercised when Provigil is given to patients with a history of psychosis, depression, or mania.

Haldol® May Cause Cardiovascular Complications

Posted September 17, 2007—Johnson and Johnson and the FDA informed healthcare professionals that the WARNINGS section of the prescribing information for haloperidol has been revised to include a new cardiovascular subsection regarding cases of sudden death, QT prolongation, and Torsades de Pointes (TdP), especially when given intravenously, or at doses higher than recommended. Although injectable Haldol is only approved by the FDA for intramuscular injection, there is considerable evidence that the intravenous administration of haloperidol is a relatively common off-label clinical practice. There are at least 28 case reports of QT prolongation and TdP, some with fatal outcomes in the context of off-label intravenous haloperidol. Healthcare professionals should consider this new risk information when making individual treatment decisions for patients.

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FDA MedWatch Reports

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PPI's and Heart Risk

Posted December 11, 2007—The FDA informed healthcare professionals regarding the Agency's follow-up communication covering safety data for the medications omeprazole and esomeprazole. The communication raises concerns about a potential increased risk of heart problems in patients treated with these medications. The Agency conducted a comprehensive review of the data from two studies which were submitted to the FDA. The FDA continues to state that long-term use of omeprazole or esomeprazole is not likely to be associated with an increased risk of heart problems and they recommend healthcare providers continue to prescribe and patients continue to use these medications in a manner consistent with the medications' labeling.

Genetic Link Between Possibly Fatal Skin Reactions and Carbamazepine

Posted December 12, 2007—The FDA informed healthcare professionals that dangerous or even fatal skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis), that can be caused by carbamazepine therapy, are significantly more common in patients with a particular human leukocyte antigen (HLA) allele, HLA-B*1502. This allele occurs almost exclusively in patients with ancestry across broad areas of Asia and includes South Asian Indians. Patients with ancestry from areas in which HLA-B*1502 is present should be screened for the HLA-B*1502 allele before starting treatment with carbamazepine. If these individuals test positive, carbamazepine should not be started unless the expected benefit clearly outweighs the increased risk of serious skin reactions. Patients who have been taking carbamazepine for more than a few months without developing skin reactions are at low risk for these effects. This is true for patients of any ethnicity or genotype, including patients positive for HLA-B*1502.

Concern Over Usage of Fentanyl Transdermal Patch

Posted December 21, 2007—The FDA issued an update highlighting important information regarding appropriate prescribing, dose selection, and the safe use of the fentanyl transdermal system (patch). The FDA previously issued a Public Health Advisory and Information for Healthcare Professionals in July of 2005 covering the appropriate and safe use of the transdermal system. However, the Agency continues to receive reports of death and life-threatening adverse events related to fentanyl overdose. The adverse events have occurred when the fentanyl patch was used to treat pain in opioid-naïve patients and when opioid-tolerant patients have applied more patches than prescribed, changed the patch too frequently, or exposed the patch to a heat source. The fentanyl patch is only indicated for use in patients with persistent, moderate to severe chronic pain who have been taking a regular, daily, around-the-clock narcotic pain medication for longer than a week and are considered to be opioid tolerant.

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