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American Pain Society Troubled by Washington State Chronic Pain Guidelines

The Washington State Agency Medical Directors' Group recently published guidelines on opioid dosing for chronic non-cancer pain. The Group makes the recommendation that in general, the total daily morphine-equivalent dose should not exceed 120 mg, and if it is increased beyond 120 mg a day then this can only be done after consultation by pain management specialists. On July 19, 2007 the American Pain Society issued a letter stating it was "troubled" and "disturbed" by portions of the guidelines set forth by the Washington State Group. "We are troubled that the current guidelines potentially add unnecessary restrictions and additional barriers to patients who experience pain, potentially discriminate against those patients without a cancer diagnosis, and further worsen medical access for those who do not meet the current criteria," wrote Judith Paice, PhD, RN, president of the American Pain Society. Paice also expressed concern regarding the lack of valid study data on which the guidelines were based and with the number of pain management specialists available who could meet the demand of patients identified by the 120 mg criteria.

The guidelines were drafted by a panel of 15 pain specialists in the state of Washington for educational purposes and released to help curb opioid abuse, according to Gary Franklin, MD, Director of the Washington Director's agency. Dr. Franklin stresses that the guidelines were not intended to be interpreted as rules or statutes. In the conclusion of the American Pain Society's letter, Paice offers to collaborate with the Agency Medical Directors' Group "to generate scientifically sound and measurable outcomes related to these guidelines or to provide assistance in future or present development of treatment algorithms for pain."

CHRONIC PAIN PATIENTS: STUDY FINDS LOW RISK OF ABUSE AND ADDICTION

Chronic, non-cancer pain patients being treated by primary care physicians were the focus of a study that examined the prevalence of substance use disorders in that population. A total of 801 patients were recruited and interviewed from the practices of 235 primary care physicians throughout the state of Wisconsin. The most common pain diagnoses were degenerative arthritis, low back pain, migraine headaches, neuropathy, and fibromyalgia. All of the subjects had chronic non-cancer pain and used opioids daily for at least three months. The average age was 49 years and the average duration of chronic pain was 16 years. The most frequently prescribed opioids were oxycodone preparations, which comprised nearly 60% of the prescriptions, followed by hydrocodone and morphine.

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features

Large-Scale Study to Assess Treatment for Prescription Opioid Addiction

The U.S. National Institute on Drug Abuse (NIDA) is launching the nation's first large-scale study to evaluate a treatment for opioid addiction to such prescription medications as OxyContin® and Vicodin®. The study will evaluate the effectiveness of buprenorphine/naloxone (Suboxone®) in conjunction with several types of counseling in 648 patients. Suboxone is currently used in the treatment of opiate dependence. The study will be conducted at New York University Medical Center, as well as at 10 other sites across the country including rural locations with especially high rates of prescription painkiller abuse.

Participants will receive Suboxone for one month; then the dose will be tapered off as part of the detoxification process. Half of the study group will be subjected to intensive individualized drug counseling while the other half will receive a brief drug counseling session from their doctors. "Opioid analgesics were designed to help people in pain, and we want to be sure that those who require them for legitimate reasons can continue to effectively manage their pain," states NIDA director Nora Volkow, MD. "However, we must also recognize the risk of addiction to pain medications and develop treatments for those who become addicted to them. This trial is an important first step in reaching that goal."



Genetic Variation Predicts Success or Failure of the Antidepressant Citalopram

A study conducted by the National Institute of Mental Health (NIMH) has discovered that a variation in a gene called GRIK4 appears to make people suffering from depression more responsive to the antidepressant citalopram (Celexa®). Although the increased response was small, participants were 23% more likely to respond to citalopram when coupled with another small gene variant identified in an earlier study. These findings highlight a key issue in mental health research: People respond differently to antidepressant medications. Understanding the role these genetic variations play are important, especially since patients don't always benefit from the first antidepressant they try. "We're moving steadily closer to being able to personalize treatments based on patients' genetic variations. This is a crucial need for the millions of Americans who suffer from depression," said NIMH Director Thomas R. Insel, MD. "New techniques have led to advances that would have been inconceivable a few years ago and are making individualized treatment an achievable goal."

American Pain Society

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The study found only 30 patients or 3.8% of the subjects met the clinical criteria for opioid abuse or addiction, with 0.6% exhibiting abuse. The study also found that the most significant predictor of abuse was aberrant drug behavior, such as repeated requests for early refills, lost medication, and using opioids for non-pain-related reasons. One of the authors of the study, Michael F. Fleming, MD at the University of Wisconsin in Madison, and his associates warn that those behaviors could also be caused by inadequate levels of medication, untreated psychiatric illness or stressful life situations. Fleming and his colleagues still "support the use of opioids for the treatment of chronic pain by primary care providers." They also state that "considering the potential benefit to improving the lives of patients with chronic pain, a 3.8% rate of opioid addiction is a small risk compared with the alternative of continuous pain and suffering."

"We're moving steadily closer to being able to personalize treatments based on patients' genetic variations..."

**- NIMH Director
Thomas R. Insel, MD**

clinical literature digest studies

STUDY #1: Relationship Between Early Opioid Prescribing for Acute Occupational Low Back Pain and Disability Duration, Medical Costs, Subsequent Surgery and Late Opioid Use

Opioid analgesics have become more accepted for acute pain management; however, treatment guidelines recommend limited opioid use for acute low back pain (LBP) management. Little is known about the long-term impact on outcomes of opioid use for acute LBP. This retrospective cohort study of workers' compensation claims with acute disabling low back pain examined the association between early opioid use for acute LBP and outcomes: disability duration, medical costs, late opioid use (\geq five prescriptions from 30 to 730 days) and surgery in a two-year period following LBP onset. The sample consisted of 8,443 claimants from a large workers' compensation database with new-onset, disabling LBP that occurred between January 1, 2002 and December 31, 2003.

Based on morphine equivalent amount (MEA) in milligrams received in the first 15 days (early opioids), claimants were divided into five groups (0, 1 – 140, 141 – 225, 226 – 450, 450+). The associations between early opioids and outcomes were evaluated using multivariate linear and logistic regression models. Covariates included age, gender, job tenure, and low back injury severity. Injury severity was classified using ICD-9 codes. The study found that 21% of claimants received at least one early opioid prescription. Those who received more than 450 mg MEA were, on average, disabled 69 days longer than those who received no early opioids (95% confidence interval (CI), 49.2 – 88.9). Compared with the lowest MEA group (0 mg opioid), the risk for surgery was three times greater (95% CI, 2.4-4.0) and the risk of receiving late opioids was six times greater (95% CI, 4.9-7.7) in the highest MEA group. Low back injury severity was a strong predictor of all of the outcomes. The researchers concluded that given the negative association between receipt of early opioids for

acute LBP and outcomes, it is suggested that the use of opioids for the management of acute LBP may be counterproductive to recovery.

Webster, Barbara S. BSPT, PA-C, et al. "Relationship Between Early Opioid Prescribing for Acute Occupational Low Back Pain and Disability Duration, Medical Costs, Subsequent Surgery and Late Opioid Use." *Spine*. 2007 September 1; 32(19):2127-2132.

STUDY #2: What Is Different About Workers' Compensation Patients?: Socioeconomic Predictors of Baseline Disability Status Among Patients With Lumbar Radiculopathy

Few studies have compared socioeconomic differences between those receiving or not receiving workers' compensation with the same underlying clinical conditions. This study was a combined analysis of two prospective clinical studies that sought to identify socioeconomic characteristics associated with workers' compensation in patients with an intervertebral disc herniation (IDH) or spinal stenosis (SpS). Patients were identified from the Spine Patient Outcomes Research Trial (SPORT) and the National Spine Network (NSN) practice-based outcomes study.

Patients with IDH and SpS within NSN were identified by satisfying SPORT eligibility criteria. Information on disability and work status at baseline evaluation was used to categorize patients into three groups: workers' compensation, other disability compensation, or work-eligible controls. Enrollment rates of patients with disability in a clinical efficacy trial (SPORT) and practice-based network (NSN) were compared. Independent socioeconomic predictors of baseline workers' compensation status were identified in multivariate logistic regression models controlling for clinical condition, study cohort, and initial treatment designation.

Among 3,759 eligible patients (1,480 in SPORT and 2,279 in NSN), 564 (15%) were receiving workers' compensation, 317 (8%) were receiving other disability compensation, and 2,878 (77%) were controls. Patients receiving workers' compensation were less common in SPORT than NSN (9.2% vs. 18.8%, $P < 0.001$), but patients receiving other disability compensation were similarly represented (8.9% vs. 7.7%, $P = 0.19$). In univariate analyses, many socioeconomic characteristics significantly differed according to baseline workers' compensation status. In multiple logistic regression analyses, gender, educational level, work characteristics, legal action, and expectations about ability to work without surgery were independently associated with receiving workers' compensation.

Clinical trials involving conditions commonly seen in patients with workers' compensation may need special efforts to ensure adequate representation. Socioeconomic characteristics markedly differed between patients receiving and not receiving workers' compensation. Identifying the independent effects of workers' compensation on outcomes will require controlling for these baseline characteristics and other clinical features associated with disability status.

Atlas, Steven J. MD, MPH, et al. "What Is Different About Worker's Compensation Patients?: Socioeconomic Predictors of Baseline Disability Status Among Patients With Lumbar Radiculopathy." *Spine*. 2007 August 15; 32(18):2019-2026.

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STUDY #3: The Impact of Pain and Depression on Assessment of Rehabilitation Need: A Cross-Sectional Study in Long-Term Sick-Listed Patients

The aim of this study was to examine the relationship between pain extent, severity of depressive symptoms and recommended rehabilitation measures in long-term sick-listed patients. In this cross-sectional study, the medical records of 228 long-term sick-listed patients consecutively referred to a multidisciplinary setting were examined retrospectively. Three specialists in psychiatry, orthopedic surgery and rehabilitation medicine had made joint rehabilitation recommendations into the four different groups: (i) back to work without rehabilitation; (ii) vocational rehabilitation or adjusted work; (iii) medical rehabilitation; and (iv) sick pension. Each patient filled in a pain drawing as a measure of pain extent and the self-administered Montgomery-Asberg-Depression-Rating Scale for evaluating the severity of depressive symptoms.

Ninety-five percent of the patients had ongoing pain and 53% had depression. No statistically significant difference was seen between the outcome groups regarding the pain extent. A statistically significant difference was seen between the back to work without any rehabilitation and vocational rehabilitation or adjusted work groups in the Montgomery-Asberg-Depression-Rating Scale score versus the medical-rehabilitation and sick-pension groups [$P < 0.001$ between groups (chi² test); $P < 0.05$ within groups (Tukey-Kramer Honestly Significant Difference test)]. In conclusion, two-thirds of the patients were assessed to need medical rehabilitation. These patient groups could be separated from the ones who were assessed to be able to go back to work

without medical rehabilitation by the severity of the ongoing depression, but not by the pain extent alone. It was found that the combination of severity of depression and pain extent provided more information than the severity of depression alone.

Linder, Jurgen A, et al. "The Impact of Pain and Depression on Assessment of Rehabilitation Need: A Cross-Sectional Study in Long-Term Sick-Listed Patients." *International Journal of Rehabilitation Research*. 2007 September; 30(3):255-260.

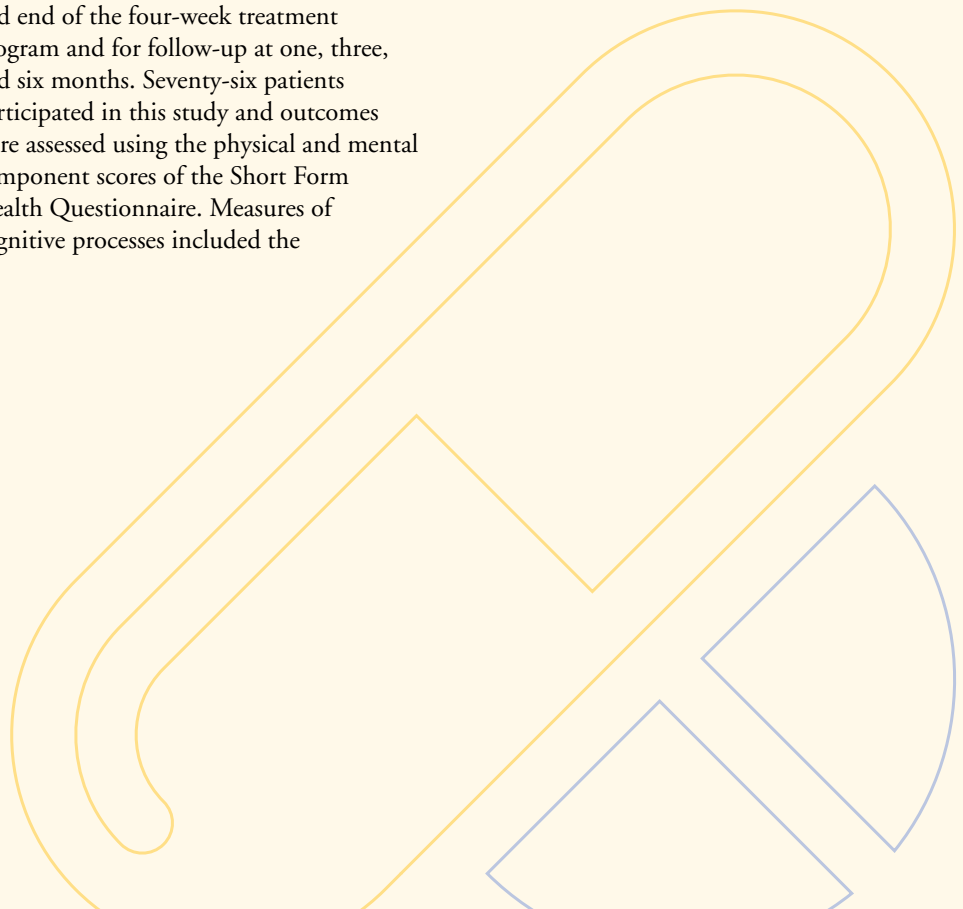
STUDY #4: Patients' Perceptions of Their Pain Condition Across a Multidisciplinary Pain Management Program: Do They Change and if So Does It Matter?

The primary aim of this study was to determine whether changes in cognitive processes are related to improved functional outcomes across a multidisciplinary pain management program. A longitudinal design was employed where patients completed six versions of the same questionnaire at the beginning, middle, and end of the four-week treatment program and for follow-up at one, three, and six months. Seventy-six patients participated in this study and outcomes were assessed using the physical and mental component scores of the Short Form Health Questionnaire. Measures of cognitive processes included the

Illness Perceptions Questionnaire Revised, the Pain Catastrophizing Scale, and the Pain Vigilance and Awareness Questionnaire. Fifty-eight patients (76%) completed all six questionnaires.

This study found reductions in catastrophizing and beliefs about the serious consequences of pain were most strongly associated with improved physical functioning, whereas reductions in pain vigilance, emotional representations of pain, and sense of coherence about pain were the best predictors of improved mental functioning. Overall, change in cognitive processes accounted for 26% of the variance in improved physical functioning and 23% of the variance in mental functioning. These findings suggest that interventions that specifically target cognitive processes may enhance treatment effects for patients with chronic pain.

Moss-Morris, Rona PhD, et al. "Patients' Perceptions of Their Pain Condition Across a Multidisciplinary Pain Management Program: Do They Change and if So Does It Matter?" *Clinical Journal of Pain*. 2007 September; 23(7):558-564.



FDA update

New Drug/Formulation

Selzentry™ (maraviroc)

Approved: August 2007

Accelerated approval was granted to **Selzentry** for use in adults in the treatment of HIV that is resistant to other antiretroviral drugs. The introduction of Selzentry represents a new class of antiretroviral agents, CCR-5 blocking entry inhibitors. Unlike other HIV medications that fight the HIV virus once it has already entered human cells, Selzentry is designed to stop the virus by blocking the entry of the HIV virus into disease-fighting white blood cells.

Zingo™ (lidocaine hydrochloride)

Approved: August 2007

Zingo is an easy-to-administer, single-use, needle-free system that delivers 0.5 mg of sterile lidocaine powder. The medication is used to provide fast, local analgesia allowing intravenous line placement or venipuncture one to three minutes after administration. It is approved for use in children ages three to 18.

New Launches

Magnacet™ (oxycodone/acetaminophen)

Approved: May 2006, Launched: June 2007

Mallinckrodt Pharmaceuticals introduced **Magnacet**, a combination product containing different strengths of oxycodone and 400 mg of acetaminophen. Magnacet is currently indicated for the relief of moderate to severe pain. It is available in 2.5mg/400mg, 5mg/400mg, 7.5mg/400mg, and 10mg/400mg tablets.

New Indication

Reclast® (zoledronic acid)

Approved: August 2007

Novartis has introduced **Reclast**, the first available once-a-year treatment for osteoporosis. Reclast is administered via a

15-minute intravenous infusion and provides a more convenient way to treat the condition. Reclast was initially approved for the treatment of Paget's disease in April 2007.

Generic Drug Arrivals

Fentanyl transdermal system

Approved: August 2007

Two additional companies, Watson Pharmaceuticals and Actavis Group, have been granted approval to manufacture the fentanyl transdermal system, which is the generic equivalent of Duragesic®. The strengths available from Watson and Actavis include the 25, 50, 75, and 100mcg/hour systems. These products are indicated for the management of persistent, moderate to severe chronic pain that requires continuous, around-the-clock opioid administration for an extended period of time and cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids.

Accupril® (quinapril hydrochloride)

Approved: August 2007

Quinapril tablets are now available as a generic equivalent of Accupril, an ACE inhibitor used in the treatment of patients with high blood pressure.

FDA MedWatch Reports

PPIs and Heart Risks

Posted August 9, 2007—FDA issued an early communication about the ongoing review of new safety data for the proton pump inhibitors, Prilosec and Nexium. The new safety data was from two small long-term clinical studies in patients with severe gastroesophageal reflux disease (GERD). In both studies, patients were randomly assigned to receive treatment with a drug (either omeprazole or esomeprazole) or to have surgery to control their GERD. The results from the study of Prilosec and analyses from an ongoing study of Nexium raised concerns that long-term use of Prilosec or Nexium may have increased the risk of heart attacks, heart failure, and heart-

related sudden death in those patients taking either one of the drugs compared to patients who received surgery.

After reviewing this and other data submitted by the company, FDA's preliminary conclusion at this time is that collectively, this data does not suggest an increased risk of heart problems for patients treated with omeprazole or esomeprazole. Healthcare providers should not change their prescribing practices and patients should not change their use of these products at this time. Both drugs are used for the treatment of GERD, esophageal erosions and for maintenance of healing erosions of the esophagus. These drugs are also used for the treatment of ulcers. Prilosec is also sold over the counter for frequent heartburn.

Codeine Products Used By Nursing Mothers

Posted August 17, 2007—FDA issued a Public Health Advisory with important new information about a very rare, but serious, side effect in nursing infants whose mothers are taking codeine and are ultra-rapid metabolizers of codeine. When codeine enters the body and is metabolized, it changes to morphine, which relieves pain. Many factors affect codeine metabolism, including a person's genetic make-up. Some people have a variation in a liver enzyme and may change codeine to morphine more rapidly and completely than other people. Nursing mothers taking codeine may also have higher morphine levels in their breast milk. These higher levels of morphine in breast milk may lead to life-threatening or fatal side effects in nursing babies. In most cases, it is unknown if someone is an ultra-rapid codeine metabolizer.

When prescribing codeine-containing drugs to nursing mothers, physicians should choose the lowest effective dose for the shortest period of time and should closely monitor mother-infant pairs. There is an FDA-cleared test for determining a patient's CYP2D6 genotype. The test is not routinely used in clinical practice but is available through a number of different laboratories. The results of this test predict that a person can convert codeine to morphine at a faster rate than average, resulting in higher morphine levels in the blood. When levels of morphine are too high, patients have an increased risk of adverse events.

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FDA MedWatch Reports

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Thiazolidinediones and Heart Failure

Posted August 14, 2007—After a review of postmarketing adverse event reports, FDA determined that an updated label with a boxed warning on the risks of heart failure was needed for the entire thiazolidinedione class of antidiabetic drugs. These drugs are used in conjunction with diet and exercise to improve blood sugar control in adults with type 2 (non-insulin-dependent) diabetes. Manufacturers of certain drugs have agreed to the upgraded warning. The strengthened warning advises healthcare professionals to observe patients carefully for the signs and symptoms of heart failure, including excessive, rapid weight gain, shortness of breath, and edema after starting drug therapy. Patients with these symptoms who then develop heart failure should receive appropriate management of the heart failure and use of the drug should be reconsidered. People who have questions should contact their healthcare providers to discuss alternative treatments.

Changes to Coumadin Labeling

Posted August 8, 2007—FDA approved updated labeling to include pharmacogenomics information to the CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE AND ADMINISTRATION sections of the prescribing information for the widely used blood-thinning drug, Coumadin. This new information explains that people's genetic makeup may influence how they respond to the drug. Specifically, people with variations in two genes may need lower warfarin doses than people without these genetic variations. The two genes are called CYP2C9 and VKORC1. The CYP2C9 gene is involved in the breakdown (metabolism) of warfarin and the VKORC1 gene helps regulate the ability of warfarin to prevent blood from clotting. The dosage and administration of warfarin must be individualized for each patient according to the particular patient's prothrombin time (PT) / International Normalized Ratio (INR) response to the drug. The specific dose recommendations are described in the warfarin product labeling, along with the new information regarding the impact of genetic information upon the initial dose and the response to warfarin. Ongoing warfarin therapy should be guided by continued INR monitoring.

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