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EXPLORING

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INTEGRATIVE PAIN MANAGEMENT
FOR OPTIMAL PATIENT CARE

POSTER ABSTRACTS

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Poster Abstracts

Wednesday, September 21

Opioids

1. Is the Opioid REMS an Emerging Solution in Pain?

Presenter: Joan Meyer, RN, MHA

Authors: Bronwyn Boyes; Joan Meyer, RN, MHA

Background: Chronic pain affects many Americans, yet treatment of pain remains inadequate due in part to clinician beliefs and knowledge regarding the best ways to manage pain and concern for misuse.¹ In April 2011 the FDA announced, in concert with the White House ONDCP, a new risk reduction program, Approved Risk Evaluation and Mitigation Strategies (REMS), for all extended-release and long-acting opioid medications.²

Objective: To investigate clinician beliefs and knowledge of the new FDA's REMS key elements.

Methods: Emerging Solutions in Pain (ESP) conducted a survey via email in June 2011 to almost 30,000 loyal pain clinician members to assess their beliefs and knowledge of REMS on opioid prescribing. These clinicians were asked to respond to questions about their current opioid prescribing and on various components of the REMS.

Results: A total of 627 surveys was completed. Most respondents were either hospital (28.2%) or office-based (24.1%). Prescribing practices showed that 34% currently prescribed opioids for acute pain, 26% for cancer pain, and 41% for chronic noncancer pain. Of those prescribing opioids, 26.5% prescribe short-acting opioids, 25.1% long-acting opioids, 24.7% extended-release opioids and 23.6% methadone. Only 20% reported that they are currently not confident in fulfilling their regulatory responsibilities to demonstrate compliance with federal and state requirements for prescribing opioids. More than a quarter (25.9%) used opioid treatment agreements, but 13% reported that they do not routinely use any risk assessment tools. Thirty-five percent had not yet heard of or read about the FDA REMS elements, while 72% said that there is currently not enough information available to health care professionals about REMS. Interestingly, 43.5% felt that the REMS will have the most impact on prescribers.

Conclusions: Will the Opioid REMS program become an Emerging Solution in Pain? Will it improve the undertreatment of pain and reduce the rates of misuse? It is currently unknown what sort of opioid-education program will be developed for prescribers or when federal agencies will mandate additional education as a part of DEA licensure to prescribe long-acting and extended-release opioids. However, the results of this survey suggest that over 86% of the responding clinicians would complete a pain education certification process to retain DEA registration if mandated. Therefore, a REMS program may have a positive impact on pain medicine.

References:

1. IOM Report. Relieving Pain in America. A Blueprint for Transforming Prevention, Care, Education and Research. Released June 20, 2011.
2. US Food and Drug Administration. Opioid Drugs and Risk Evaluation and Mitigation Strategies (REMS). <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugclass/ucm163647.htm>. Accessed July 11, 2011.

2. Safety of Oxymorphone Extended Release with Selective Serotonin Reuptake Inhibitors and Serotonin-Norepinephrine Reuptake Inhibitors

Presenter: Bobbie-Sue Brown, MS

Authors: John H. Peniston, DO; Susan Potts, MS; Xiaojun Hu, PhD; Matthew S. Wieman, MD

Background: The safety and efficacy of oxymorphone extended release (ER) for chronic low back pain (CLBP) were established in 2 multicenter, randomized-withdrawal trials.^{1,2} Concomitant use of opioids and selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) may occur in patients with comorbid depression or patients prescribed SSRIs or SNRIs as adjunctive pain medication. There is no known potential for adverse interaction of oxymorphone with SSRIs or SNRIs as exists with some other opioids (eg, oxycodone and tramadol).

Objective: To explore the safety of oxymorphone ER with concomitant use of SSRIs or SNRIs in patients with CLBP.

Methods: A post hoc subanalysis of pooled data from 2 12-week trials examined the safety of oxymorphone ER with concomitant use of SSRIs or SNRIs in patients with CLBP. The study protocols were approved by institutional review boards; patients provided informed consent.

Results: During 4 weeks of open-label titration of oxymorphone ER, 348 of 575 patients achieved an effective tolerated dose. In patients taking SSRIs or SNRIs (n=89) compared with patients not taking SSRIs or SNRIs (n=486) the incidence of ≥ 1 adverse event (AE) was similar (75.3% vs 68.1%; not statistically significant). During 12 weeks of double-blind treatment, in patients taking oxymorphone ER concomitantly with SSRIs or SNRIs (n=29) and patients taking oxymorphone ER without concomitant use of SSRIs or SNRIs (n=146), incidence of ≥ 1 AE was similar (62.1% vs 50.7%; not statistically significant). Treatment-related AEs included nausea, constipation, somnolence, headache, and diarrhea, which occurred with similar frequency in patients taking concurrent SSRIs or SNRIs vs those not taking them.

Conclusions: Oxymorphone-CRF 40 mg is bioequivalent to oxymorphone ER 40 mg under fasted conditions.

References:

1. Katz N, et al. *Curr Med Res Opin*. 2007;23(1):117-128.
2. Hale ME, et al. *J Pain*. 2007;8(2):175-184.

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3. Oxymorphone Extended Release in Patients with Depression

Presenter: Bobbie-Sue Brown, MS

Authors: John H. Peniston, DO; Susan Potts, MS; Xiaojun Hu, PhD; Matthew S. Wieman, MD

Background: Depression is common in patients with chronic pain^{1,2} and is known to increase health care costs in this patient population.³

Objective: To compare the safety of oxymorphone extended release (ER) treatment for chronic low back pain (CLBP) in patients with and without a history of depression.

Methods: Data from 2 multicenter, 12-week trials.^{4,5} of oxymorphone ER for CLBP were pooled in an exploratory, post hoc analysis. The study protocols were approved by institutional review boards, and patients provided written informed consent before participating.

Results: Of 575 patients in the pooled analysis, 132 (23.0%) had a medical history of depression. After 4 weeks of open-label titration of oxymorphone ER, 56.8% (n=75/132) of patients with a history of depression and 61.6% (n=273/443) patients without a history of depression achieved an effective tolerated dose of oxymorphone ER. During titration, the percentage of patients who experienced ≥ 1 adverse event (AE) was similar in those with a history of depression (75.0%; n=99) compared with those without a history of depression (67.5%; n=299). During 12 weeks of subsequent double-blind treatment, the percentage of patients taking oxymorphone ER who experienced ≥ 1 AE was similar in those with a history of depression (64.1%; n=25/39) compared with those without a history of depression (49.3%; n=67/136).

Conclusions: Oxymorphone ER was generally well tolerated for CLBP in patients with a history of depression. Depression did not appear to present an obstacle to successful titration of patients to an effective tolerated dose of oxymorphone ER.

References:

1. Currie SR, et al. *Pain*. 2004;107:54-60.
2. Sullivan MD, et al. *Phys Med Rehabil Clin N Am*. 2006;17:381-400, vi-vii.
3. Arnow BA, et al. *Psychiatr Serv*. 2009;60:344-350.
4. Hale ME, et al. *J Pain*. 2007;8:175-184.
5. Katz N, et al. *Curr Med Res Opin*. 2007;23:117-128.

4. Bioequivalence of IRO-A, IRO-A/Niacin, and a Branded Oxycodone

Presenter: Mark T. Leibowitz, MD

Authors: Mark T. Leibowitz, MD; Cynthia A. Zamora, MD, FCCP; Albert W. Brzeczko, PhD; Jeffrey G. Stark, PhD

Background: Snorting and intravenous use are common routes of administration for advanced opioid abusers.¹⁻³ A tablet form of immediate-release oxycodone developed using Aversion® Technology (Acura Pharmaceuticals) combines oxycodone HCl with inactive functional excipients to create potential barriers to intranasal and intravenous abuse (IRO-A; Acura Pharmaceuticals).

Objective: To evaluate bioequivalence by comparing the pharmacokinetic characteristics of IRO-A with those of a branded, commercially available immediate-release oxycodone HCl (IRO) (Roxicodone®, Xanodyne Pharmaceuticals, Inc.) that was the reference-listed drug, and IRO-A with niacin, a similar product containing niacin as an aversive agent.

Methods: A phase 1 single-dose, open-label, randomized, 3-period, 3-treatment crossover study involving 40 healthy adult subjects who received single 15-mg doses of IRO-A, IRO, or IRO-A with niacin after fasting overnight. Subjects were male (n=26) or female (n=14) and aged 18 to 55 years with a body mass index 18 to 30 kg/m² and a minimum weight of 110 lb. Naltrexone was administered to diminish opioid effects. Plasma samples were analyzed using liquid chromatography with tandem mass spectrometry.

Results: For the log-transformed exposure parameters C_{max} , AUC_{last} , and AUC_{∞} , the 90% confidence intervals were within the accepted 80% to 125% range for establishing bioequivalence of oxycodone in IRO-A to IRO, the reference-listed drug. The geometric mean ratios of IRO-A to IRO were 92%, 104%, and 104% for C_{max} , AUC_{last} , and AUC_{∞} , respectively. IRO-A was also bioequivalent to IRO-A with niacin. Adverse events were mild to moderate in intensity and typical of opioid therapy.

Conclusions: IRO-A was bioequivalent to IRO, as well as IRO-A with niacin. Because of its unique Aversion Technology, IRO-A provides an alternative approach to conventional immediate-release oxycodone therapy that may reduce potential intranasal and intravenous abuse.

References:

1. Young AM, Havens JR, Leukefeld CG. Route of administration for illicit prescription opioids: a comparison of rural and urban drug users. *Harm Reduct J*. 2010;7:24.
2. Hays L, Kirsh KL, Passik SD. Seeking drug treatment for OxyContin abuse: a chart review of consecutive admissions to a substance abuse treatment facility in Kentucky. *J Natl Compr Canc Netw*. 2003;1(3):423-428.
3. Hays LR. A profile of OxyContin addiction. *J Addict Dis*. 2004;23(4):1-9

5. Hysterectomy and Predictors for Opioid Prescription in a Chronic Pain Clinic Sample

Presenter: Beth D. Darnall, PhD

Authors: Beth D. Darnall, PhD; Hong Li, MD, MSPH

Background: Hysterectomy is the most common nonobstetric medical procedure performed on American women younger than 45 years of age¹, and nearly 1 in 5 women of reproductive age have had the surgery.² Although pain is a commonly reported symptom prior to³ and following hysterectomy,⁴ little is known about the experience and impact of chronic pain in the posthysterectomy years or pain treatment patterns such as opioid prescription. It is important to understand the pathways by which women may arrive at opioid prescription. For instance, hysterectomy may confer risk for opioids that could be driven by patient characteristics, medical complexity, hormonal factors, or a combination of these factors. In addition to the possibility that women who have had hysterectomy may have distinct pathways to opioid prescription, they may also experience unique consequences from chronic opioid use.

Objective: To describe the prevalence of hysterectomy for women aged 18 to 45 seeking treatment at a chronic pain clinic, to describe patient characteristics (pain intensity, age, smoking status, hormone replacement status, and psychosocial factors) based on opioid and hysterectomy status, and to determine whether hysterectomy status predicted receipt of opioid prescription.

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Methods: Retrospective cross-sectional chart review of 323 new female patients aged 18 to 45 who completed the Brief Pain Inventory-Short Form at initial evaluation at a chronic pain clinic during a 12-month period (July 2008 through June 2009). Data were collected from the Brief Pain Inventory and medical charts. Variables included opioid prescription, average pain intensity, pain type, age, hysterectomy status, smoking status, and pain-related dysfunction across domains measured by the Brief Pain Inventory. The association of opioid prescription with hysterectomy and other factors was determined by logistic regression.

Results: Of 323 women, prevalence of hysterectomy was 28.8%. Almost 2 out of 3 women had a current opioid prescription at initial evaluation. Average pain intensity was not associated with either hysterectomy or opioid prescription status. However, hysterectomy and high levels of pain-related dysfunction were significantly and independently associated with opioid prescription after adjusting for age and pain intensity. More than 85% of women with hysterectomy and high pain-related dysfunction had opioid prescription.

Conclusions: Hysterectomy may confer risk for pain-related dysfunction and opioid prescription in women 45 and younger. More research is needed to understand (1) how patient characteristics influence prescribing patterns and (2) the specific medical risks and consequences of chronic opioid therapy in this population.

References:

1. Centers for Disease Control and Prevention. Department of Health and Human Services, Division of Productive Health. Women's reproductive health: Hysterectomy fact sheet. Available at: http://www.cdc.gov/reproductivehealth/WomensRH/00-04-FS_Hysterectomy.htm. Retrieved March 10, 2010.
2. Merrill RM. Hysterectomy surveillance in the United States, 1997 through 2005. *Med Sci Monit.* 2008;14(1):CR24-31.
3. Merrill RM, Layman AB, Oderda G, Asche C. Risk estimates of hysterectomy and selected conditions commonly treated with hysterectomy. *Ann Epidemiol.* 2008;18(3):253-60.
4. Brandsborg B, Nikolajsen L, Hansen CT, Kehlet H, Jensen TS. Risk factors for chronic pain after hysterectomy: A nationwide questionnaire and database study. *Anesthesiology.* 2007;106(5):1003-12.

6. Intranasal Abuse Potential of an IR Oxycodone Formulation

Presenter: Robert L. Rolleri, PharmD

Authors: Robert L. Rolleri, PharmD; Janice Y. Faulknor, BSc, MD, CCFP; Kerri A. Schoedel, PhD; Glenn C. Pixton, MS; Nancy Chen, PhD; Almasa Bass, PharmD; Edward M. Sellers, MD, PhD, FRCPC, FACP

Background: The abuse of controlled prescription pain relievers is a significant health problem in the United States. An immediate-release (IR) oxycodone HCl tablet has been formulated with functional excipients (IRO-A) to create potential barriers to intranasal and intravenous abuse.

Objective: To compare the relative abuse potential of crushed IRO-A tablets with crushed IR oxycodone HCl tablets (IRO)¹ when administered intranasally to nondependent recreational opioid users.

Methods: A single-center, single-dose, randomized, double-blind, active-controlled, 2-way crossover study was conducted in

nondependent recreational opioid users, as confirmed by naloxone challenge, who were experienced with intranasal opioid administration. Subjects who were able to discriminate between intranasally administered crushed IRO tablets and placebo were randomized to a treatment phase and received crushed IRO-A (2 x 7.5-mg tablets) or crushed IRO (3 x 5-mg tablets) in crossover fashion, separated by 48 hours. Primary endpoints were maximum effect (E_{max}) for Drug Liking, and effect at 8 hours (E_{8h}) postdose for Take Drug Again and Overall Drug Liking (all assessed using 100-point visual analog scales [VAS]). Primary endpoints were analyzed using a linear mixed model with appropriate multiple comparison adjustments. Secondary endpoints included pupillometry, Subject Rated Scale for Nasal Effects, and safety assessments.

Results: Forty subjects received at least 1 dose of study drug in the treatment phase (safety population); 39 were evaluable, 1 subject was excluded because of postdose vomiting. Subjects were predominantly men (80%) and white (75%) with a mean (\pm SD) age of 35.7 (\pm 10.2) years. For all 3 primary endpoints, crushed IRO-A was associated with significantly reduced least squares mean VAS scores vs crushed IRO for Drug Liking E_{max} (70.8 vs 93.5), Take Drug Again E_{8h} (45.9 vs 91.3), and Overall Drug Liking E_{8h} (47.8 vs 87.4) (all $P=0.0001$). Assessment parameters for pupillary response showed no meaningful differences between treatments. Opioid-related adverse events were observed with IRO-A and IRO. The incidences of rhinorrhea, nasal congestion, nasal discomfort, throat irritation, increased lacrimation, and facial pain were greater with IRO-A vs IRO.

Conclusions: In nondependent recreational opioid users, results of the study suggest that crushed IRO-A tablets may have a lower intranasal abuse potential than IRO tablets because of the functional excipients in IRO-A.

References:

1. Roxycodone [package insert]. Newport, KY: Xanodyne Pharmaceuticals, Inc; March 2009.

Encore Presentation: Presented at the 73rd Annual Meeting of The College on Problems of Drug Dependence; Hollywood, Florida, June 18-23, 2011.

7. A Retrospective Review of Outcomes After Opioid Reduction

Presenter: Kristen Zak, PharmD; Raj Kalra, MD

Authors: Kristen Zak, PharmD; Raj Kalra, MD; Tania Chopra, PharmD

Background: There is little evidence in the literature to support the use of high-dose opioids for patients with chronic pain. Unfortunately, there are limited definitive clinical guidelines at this time to assist pain management practitioners with the difficult process of opioid dose reduction.

Objective: The primary objective of this study was to assess pain, depression, and quality of life (QOL) outcomes after opioid dose reduction in patients with chronic pain who are taking high-dose opioids. A second objective for this research was to develop an opioid dose reduction guideline to be used in future patients who are candidates for opioid reduction.

Methods: This retrospective chart review is a one-group, pre-post study design to compare pain and QOL outcomes before and after

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opioid dose reduction. The review was conducted of patients enrolled in the Kaiser Permanente Union City Chronic Pain Program from December 2009 to May 2011. Patients aged 18 to 75 with a diagnosis of chronic pain, taking opioid medications greater than or equal to 300 mg per day of oral morphine equivalent, with a pain score of 6 or above, were included in the chart review. Patients with a diagnosis of opioid addiction, malignant pain, pregnancy, or opioid therapy of less than 6 months' duration were excluded.

Results: Sixteen patients met the inclusion criteria, and outcomes were assessed both before and after opioid dose reduction. The average pain score was decreased from approximately 7.2 to 4.9 ($P < 0.001$) based on the Brief Pain Inventory. Depression was also improved from an average of 13.5 to 9.5 ($P < 0.01$) based on the Patient Health Questionnaire. The daily morphine equivalent was significantly reduced from an average of 945 mg to 275 mg over about 17 weeks ($P < 0.001$). Opioid dose reduction improved QOL outcomes. Pain interference in activity was significantly improved ($P < 0.05$). An opioid reduction guideline was then created which provides dosing recommendations for opioid tapering. The guideline will be presented.

Conclusions: An opioid dose reduction of approximately 70% was achieved in this patient population. Moreover, both pain and depression scores improved significantly after opioid reduction. This research provides opioid dose reduction guidelines that demonstrate an improvement in pain, depression, and QOL outcomes. Overall, this study illustrates the benefits of opioid reduction for patients with uncontrolled pain and highlights the need for awareness of alternative treatment options for patients with chronic pain.

8. PK of an IR Oxycodone Tablet Designed to Deter Tampering

Presenter: Almasa Bass, PharmD

Authors: Almasa Bass, PharmD; Robert L. Rolleri, PharmD; Glenn C. Pixton, MS; Kenneth Sommerville, MD; Jeffrey G. Stark, PhD; Cynthia A. Zamora, MD; Mark Leibowitz, MD

Background: Misuse and abuse of controlled prescription pain relievers are significant public health issues in the United States.¹ Tamper-resistant and abuse-deterrent opioid formulations are being developed to address this problem.² An immediate-release oxycodone hydrochloride product (IRO-A, OXECTA™)³ for management of moderate to severe pain was designed to discourage common forms of tampering and deter intranasal and intravenous abuse.

Objective: This study evaluated dose-proportionality (primary) and food effects (secondary) on pharmacokinetics of oxycodone in IRO-A and relative bioavailability vs an immediate-release, commercially available oxycodone hydrochloride tablet (IRO). The safety of single doses of IRO-A was also a secondary objective.

Methods: An open-label, single-dose, randomized 5-way crossover study with a ≥ 7 -day washout period between consecutive treatments was conducted in healthy subjects aged 18–55 years. Subjects received single oral doses of 1x5-mg, 2x5-mg, and 2x7.5-mg IRO-A after an overnight fast, and 2x7.5-mg IRO-A and 1x15-mg IRO following a high-calorie, high-fat breakfast. Subjects received 50-mg naltrexone hydrochloride ~ 12 h and ~ 1 h before dosing to minimize opioid-associated adverse events. Peak plasma concentration (C_{max}), time to C_{max} (T_{max}), and area under the concentration-time curve (AUC) from time zero to the last quantifiable concentration

(AUC_{last}) were determined. Dose-proportionality of oxycodone was assessed, with results dose-normalized to 5 mg, using a 90% confidence interval (CI) criterion of 80%–125%. Dose proportionality was also assessed by linear regression and a power model. The 90% CI also was used to assess food effects.

Results: Of 35 subjects (mean [\pm SD] age 32.6 [\pm 11.1] years) enrolled, 33 were included in the pharmacokinetics analysis. Oxycodone exposure (C_{max} , AUC_{last}) increased in proportion to dose between 5-mg and 15-mg IRO-A in the fasted state by all three methods of analysis. Concomitant food intake with IRO-A resulted in a 14% reduction in oxycodone C_{max} (90% CI: 79%–94%), a 21% increase in AUC_{last} (90% CI: 113%–129%), and a delay in T_{max} from 1.25h to 3.00h compared with the fasted state. IRO-A in the fed state had bioavailability comparable to IRO based on AUC_{last} (90% CI: 94%–104%) but slightly reduced C_{max} (90% CI: 77%–91%). Common adverse events were nausea, headache, abdominal pain, dizziness, and abdominal distention, with similar incidence for IRO-A and IRO.

Conclusions: Oxycodone pharmacokinetics were dose-proportional between 5-mg and 15-mg IRO-A in the fasted state. Administration of IRO-A with food resulted in small changes in oxycodone pharmacokinetics that are not expected to be clinically significant. Oxycodone AUC_{last} was equivalent and C_{max} was lower for IRO-A compared with IRO following administration in the fed state. Tolerability of IRO-A and IRO was similar.

References:

1. Kuehn. *JAMA*. 2007;297(3):249.
2. Hamed. *Curr Drug Abuse Rev*. 2010;3:139.
3. OXECTA [package insert]. King Pharmaceuticals®, Inc; 6/2011.

9. Education Documentation for Patient Controlled Analgesia

Presenter: Natalia Marcum, CPNP-AC

Authors: Natalia Marcum, CPNP-AC; John Jones, MD; Emily Parke, DO; Richard Cotugno, MHSM

Background: The Department of Pain Management (DPM) at Phoenix Children's Hospital (PCH) began a systematic review of patient hospital records in spring 2010 to assess the documentation of patient-controlled analgesia educational material distribution to both patients and family members. Data from this chart review demonstrated a 58% deficiency in patient-controlled analgesia (PCA) patient education forms. The educational program is mandatory for any patient treated with a PCA pump, and it is mandated in our PCA policy. An educational process was implemented in October 2010 using electronic learning modules for nursing. A review of patient hospital records performed 1 month later demonstrated a 20% increase in nursing compliance.

Objective: To evaluate the effectiveness of nursing education for the improvement of patient education.

Methods: The DPM worked with clinical educators to disseminate the results of the review and create an educational process to promote Good Clinical Practice (GCP) in patient education. The educational process was implemented using electronic learning modules required by nursing in October 2010. For follow-up, a secondary review of patient hospital records was completed 8 months later to assess sustainability of the educational program that was implemented.

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Results: Our initial study in October 2010 demonstrated a successful evidence-based process improvement for patient education. Our subsequent review 8 months later showed the 20% increase remained consistent.

Conclusions: There was a significant and sustainable increase in nursing compliance documentation of patient-controlled analgesia educational material distribution. Although this demonstrates a successful evidence based process improvement, a 38% deficiency rate still remains. One might have expected that a further improvement 8 months later might have occurred, but the deficiency rate remained the same. Our CQI initiative significantly increased the number of patients who received the materials. There is no way to know if meaningful patient education has been provided unless the hospital staff educational process has been evaluated critically. Although our CQI initiative achieved this measurement, there is still a need for continued improvement. Effective PCA patient education is not only about ensuring that the mandated educational materials are provided, but also that the materials have educated patients and families.

References:

Nelson KL, Yaster M, Kost-Byerly S, Monitto CL. A national survey of American pediatric anesthesiologists: patient-controlled analgesia and other intravenous opioid therapies in pediatric acute pain management. *Anesth Analg.* 2010;110:754-760.

10. Effects of CT-guided Selective Nerve Root Blocks for the Treatment of Postherpetic neuralgia

Presenter: Junmo Park, MD

Authors: Junmo Park, MD; Sang-Ho Lee, MD, PhD

Background: Postherpetic neuralgia (PHN), defined as a pain persisting more than 3 months after the rash has healed, is a challenging neuropathic pain syndrome. PHN continues to be a significant clinical problem, with an average 25% of patients developing persistent neuropathic pain after acute herpes zoster (HZ). Like other types of neuropathic pain, PHN can be resistant to many types of pharmacologic and interventional therapies. Anticonvulsants, tricyclic antidepressants, opioids, and topical treatment modalities such as lidocaine- or fentanyl-containing patches and capsaicin cream offer moderate pain relief to some patients with PHN, but these agents may be associated with adverse events that limit their use. Interventional therapies for PHN are sympathetic nerve blocks, neuraxial blocks, peripheral nerve blocks, spinal cord stimulation and so on.

Objective: In this retrospective study, we assessed the effectiveness of CT-guided selective spinal nerve root blocks using nerve stimulator with local anesthetics and steroids for the treatment of PHN patients.

Methods: We treated 20 PHN patients by CT-guided selective spinal nerve root blocks using a nerve stimulator. After CT scanning, we selected the target spinal nerve corresponding to the dermatome of PHZ patients using the nerve stimulator. We injected local anesthetics and steroids to the selected spinal nerve roots under CT guidance.

Results: Among 20 patients, one had a block performed 3 times, two had blocks performed 2 times, and the others, 1 time. All patients

improved their symptoms and their Visual Analog Scale (VAS) decreased. Initially the VAS was more than 7 in eight patients and 5 or 6 in the others. After all procedures were completed, the VAS scores were decreased less than 3 in all patients. In one female patient, BUN and Cr were increased due to NSAID prescribed after the block; the patient discontinued the NSAID. No other patients showed abnormal findings.

Conclusions: Selective spinal nerve root blocks using nerve stimulator can be an effective treatment for PHN patients.

11. NSAID Treatment Patterns and Adverse Health Outcomes

Presenter: Rebecca L. Robinson, MS

Authors: Rebecca L. Robinson, MS; Trong Kim Le, MPH, MS

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce many types of pain by blocking cyclo-oxygenases (COX) enzymes via COX-1 or COX-2 inhibitors. In light of safety concerns,^{1,2} greater understanding is needed of the clinical characteristics and treatment patterns of patients prescribed NSAIDs.

Objective: To characterize treatment patterns, cardiovascular (CV), and gastrointestinal (GI) events after initiating NSAID therapy.

Methods: Employing a retrospective study design on a large US national health care claims database (MarketScan), patients aged 18+ with a prescription for an NSAID between 1/1/07 and 12/31/07 were identified. Using the first prescription as the index date, patients were required to have continuous pharmaceutical and medical benefit enrollment for 1 year before and 2 years after the index date. CV, GI, and index diagnoses were categorized using International Classification of Diseases, 9th edition codes. Chi-square and t-test were used to compare patients initiating on COX-1 vs COX-2 inhibitors with and without gastroprotective agents (GPA).

Results: Patients (n=255,618) had a mean age of 53 years and 63% were female, with 91% initiating on COX-1, 32% using GPAs, and 89% using other pain medications in addition to NSAIDs. Mean length of therapy on NSAIDs was 3.0 months (5.1 months when GPAs included), and rates of GI and CV conditions were 7% and 12%, respectively. Index diagnoses included neuropathic pain (28%), musculoskeletal pain (86%), migraine (11%), inflammatory arthritis (9%), and visceral pain (6%). Patients initiating on COX-1 vs COX-2 had higher rates of osteoarthritis and rheumatoid arthritis (66% vs 46%; 6.1% vs 4%), lower rates of migraine (7% vs 11%), more GI and CV events (9% vs 6%, 20% vs 12%) (all $P<0.0001$). Groups had similar rates of other pain medication use; however COX-1 initiators used fewer GPAs (31% vs 45%) and remained on other pain therapies and GPAs longer than COX-2 patients (12 vs 9 months, 14 vs 11 months) (all $P<0.0001$).

Conclusions: In this study, type of NSAID initiated was associated with differences in clinical characteristics and rates of cardiovascular and gastrointestinal conditions. Duration of NSAID use was consistent with the recommended care. Findings may further elucidate patient heterogeneity for patients with pain.

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References:

- Chen YF, Jobanputra P, Barton P, et al. Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation. *Health Technol Assess.* 2008;12(11):1-278.
- Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ.* 2011;342c7086

12. Evaluation of Withdrawal During Conversion of Patients from Vicodin® to Buprenorphine Transdermal System

Presenter: Shau Yu Lynch, PhD

Authors: Warren Wen, PhD; Shau Yu Lynch, PhD; Catherine Munera, PhD; Ruth Swanton, MPH; Steven R. Ripa MD

Background: Buprenorphine transdermal system (BTDS) is a recently approved opioid analgesic dosed once weekly. Buprenorphine is a partial mu opioid receptor agonist and is said to have a potential to precipitate withdrawals in patients receiving full mu agonists.

Objective: To evaluate whether withdrawal symptoms developed in patients during conversion from Vicodin® (hydrocodone/APAP) to BTDS.

Methods: Adult patients with osteoarthritis pain receiving a stable dosage of hydrocodone 15 to 30 mg/day with ≤ 2 doses/day of supplemental analgesia (either opioids other than hydrocodone/APAP or nonopioid medication) were switched to a near equivalent dosage of open-label Vicodin® for 7 days. Patients were stratified based on their hydrocodone dosage (stratum 1:15 to ≤ 22.5 mg/d, stratum 2: > 22.5 to 30 mg/day) and randomized to receive either BTDS 10 mcg/h (with an option to titrate up to BTDS 20 mcg/h for additional analgesia as required) or fixed dose BTDS 20 mcg/h for 14 days. Vicodin® was allowed as rescue during the first 3 days.

Results: No patient experienced withdrawal (based on the reported AEs) according to the DSM-IV criteria (development of withdrawal symptoms in ≥3 of 9 symptom categories). The incidences of withdrawal-type AEs are shown in the table below. Majority of the AEs were nausea and vomiting. Higher doses of BTDS (20 mcg/h) and higher dose stratum of the incoming hydrocodone (22.5 to 30 mg/d) were not associated with higher incidence of these AEs.

DSM-IV Withdrawal Symptoms [MedDRA term]	Titratable BTDS 10-20 (N=101) n (%)	Fixed Dose BTDS 20 (N=103) n (%)
(1) dysphoric mood	0	0
(2) nausea or vomiting	12 (11.9)	11 (10.7)
(3) muscle aches [myalgia]	1 (1.0)	0
(4) lacrimation [increased lacrimation] or rhinorrhea	0	0
(5) pupillary dilation [mydriasis], piloerection, or sweating [hyperhidrosis]	0	0
(6) diarrhea	3 (3.0)	2 (1.9)
(7) yawning	0	0
(8) fever [pyrexia]	0	0
(9) insomnia	0	0

Conclusions: Based on AEs reported in the study, converting patients from Vicodin® to BTDS produced little sign of withdrawal with 14 days of treatment.

13. Application Site Adverse Events of Buprenorphine Transdermal System

Presenter: Shau Yu Lynch, PhD

Authors: Warren Wen, PhD; Shau Yu Lynch, PhD; Catherine Munera, PhD; Steven R. Ripa, MD; Howard Maibach, MD

Background: Buprenorphine transdermal system (BTDS), a matrix system, delivers buprenorphine continuously for a 7-day period at 3 dose strengths: 5, 10, and 20 mcg/hour. The active ingredient in BTDS is buprenorphine. The excipients include levulinic acid, oleylolate, povidone, and polyacrylate cross-linked with aluminum.

Objective: To characterize the profile of application site AEs for BTDS in chronic pain studies.

Methods: The incidence of application site AEs during treatment with BTDS (across the run-in, double-blind, and open-label extension periods) was examined using pooled data from 16 studies. The incidences of these AEs between BTDS and placebo were also compared during the double-blind period in placebo-controlled studies; all patients in control arms received placebo patches (identical to BTDS except for absence of buprenorphine). The application site AEs for other marketed matrix-type transdermal patches were reviewed. Ex-US postmarketing surveillance database for products similar to BTDS was searched for severe events.

Results: Of the 6566 subjects, 23.4% experienced ≥1 application-site AE. The most common application-site AEs were pruritus (13.6%) and erythema (8.2%). Most application site AEs were mild or moderate in intensity and none was serious. Treatment discontinuation due to application site AEs occurred infrequently, including pruritus (1.8%) and erythema (1.4%). Of the 887 BTDS-treated and 919 placebo-treated patients in placebo-controlled studies, application site AE rates were higher in BTDS-treated subjects than placebo-treated subjects (16.6% vs 12.7%). The incidence of application AEs associated with BTDS was comparable to other patch products marketed in the US (up to 41%). Rare cases of severe application-site skin reactions with signs of marked inflammation have been observed in clinical trials of BTDS and in ex-US PMS data involving similar products.

Conclusions: BTDS presents a well-tolerated application-site AE profile.

Encore Presentation: American Pain Society 30th Annual Scientific Meeting, Austin, Texas.

14. NKTR-181: A Novel Mu-Opioid Agonist That Exhibits Reduced Abuse Potential and Maintains Full Analgesic Activity Following Repeat Dosing in Preclinical Rodent Models

Presenter: Stephen D. Harrison, PhD

Authors: Stephen D. Harrison, PhD; Juergen Pfeiffer, MS; Irene Choi, PhD; Juli Evans; Dan McWeeney, BA; Phi Quach, BS; P. Trincherio; David V. Gauvin, PhD; Timothy A. Riley, PhD; Stephen K. Doberstein, PhD; Jennifer Riggs-Sauthier, PhD; C. Simone Fishburn, PhD

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Background: NKTR-181 is a novel mu-opioid analgesic engineered using Nektar's advanced polymer conjugate technology. NKTR-181 has significantly less abuse potential in animal models of repeated administration. NKTR-181 also has a significantly reduced rate and extent of CNS exposure relative to oxycodone and is active in multiple preclinical pain models. Properties that make NKTR-181 less attractive for abuse may make it less likely to induce tolerance to analgesia upon repeated administration.

Objective: To assess the abuse liability profile for NKTR-181 using rat models of self-administration (SA) and drug discrimination (DD), and to determine the effect of repeated oral dosing of NKTR-181 in the mouse acetic acid writhing model (AAW).

Methods: Self-administration studies were performed on cocaine-trained rats using intravenous NKTR-181, cocaine, or saline. In the substitution test, a lever test protocol was used in 1-hour sessions on 3 consecutive days, with reinforcement defined as <20% variability over the 3 sessions. In the progressive ratio test, the number of lever presses required to deliver a defined dose was increased until animals no longer worked for reward. DD studies were performed in rats trained to discriminate between oxycodone and vehicle. Animals then received oxycodone or NKTR-181 to determine if either produced a response similar to oxycodone or saline. For AAW, male CD-1 mice received oral doses of NKTR-181 or vehicle once daily for up to 10 days. On days 1 or 10, mice received intraperitoneal 0.5% acetic acid 30 min postdose, and writhes were counted over a 20-min period.

Results: In rat SA studies, NKTR-181 showed no reinforcing properties with response rates similar to saline in the 3-day substitution and progressive ratio tests. Minimum Discriminable Doses for NKTR-181 in the rat DD model were ~30 fold greater than for oxycodone following intraperitoneal and oral delivery, respectively.

Oral NKTR-181 demonstrated full analgesic activity in the AAW model. Repeated dosing with NKTR-181 over 10 days diminished neither the magnitude nor the potency of the analgesic response.

Conclusions: NKTR-181 is a novel mu-opioid analgesic that exhibits no loss of efficacy or potency when tested in a 10-day repeated dosing paradigm. The low abuse liability profile in the rat SA and DD studies, coupled with demonstration of efficacy in multiple preclinical models, suggest that the novel molecular structure of NKTR-181 is responsible for separation of abuse liability and efficacy.

15. Phase 1 Study of Oral NKTR-181, a Novel Opioid Analgesic with Reduced Abuse Potential and Favorable Safety Profile

Presenter: Lynn Webster, MD

Authors: Lynn Webster, MD; Matthew Iverson, MPH; Robert Medve, MD; Aleksandrs Odinecs, PhD; Michael A. Eldon, PhD, FCP

Background: NKTR-181 is a novel mu-opioid analgesic molecule engineered using Nektar's small-molecule polymer conjugate technology and in clinical development for treatment of chronic pain. We hypothesize that by reducing the rate of CNS uptake as compared to widely used opioids, analgesia can still be achieved but acute CNS effects such as euphoria, respiratory depression, and

sedation will be reduced. NKTR-181 acts in vitro and in vivo as a mu-opioid agonist and displays antinociceptive activity in preclinical models with maximal activity comparable to that of oxycodone and morphine but has a significantly lower abuse liability in animal models at analgesic doses. In addition, the chemical structure of NKTR-181 prevents its conversion into a free or abusable form of an opioid, independent of formulation.

Objective: To determine the safety, tolerability, pharmacokinetics, and opioid pharmacodynamics of single oral doses of NKTR-181 in healthy subjects.

Methods: Seven groups of 15 subjects received single 10 to 500 mg oral doses of NKTR-181 solution (n=12) or placebo (n=3). Serial clinical observations included cold pressor test (CPT) and pupillometry; blood samples for PK were obtained, permitting characterization of drug effect and exposure over time. Pharmacokinetic and pharmacodynamic analyses were used to characterize the time courses of drug exposure and effect across doses.

Results: NKTR-181 achieved dose-linear pharmacokinetics, substantial bioavailability, and plasma half-life of approximately 12 hours following administration as an oral liquid. Although NKTR-181 was rapidly absorbed and detected in plasma within 15 minutes, the time course of miosis lagged the time course of NKTR-181 in plasma, consistent with the reduced rate of CNS uptake observed preclinically. The extent and duration of opioid effect, based on the time course of miosis, increased with administered dose, with the time of maximum miosis between 4 and 6 hours, and duration up to approximately 16 hours. The extent and duration of analgesic effect based on CPT parameters of Time to Pain Perception and Pain Tolerance also increased with administered dose. NKTR-181 was well tolerated at all doses, with few reports of AEs until the highest dose level tested (500 mg) when mild nondose-limiting AEs characteristic of an active opioid agonist were reported.

Conclusions: Oral NKTR-181 solution demonstrates linear pharmacokinetics with a half-life and duration of opioid action that should allow once or twice daily dosing without use of a sustained release formulation. NKTR-181 has the potential to be a highly effective analgesic with a favorable safety profile and reduced potential for abuse or misuse.

16. Endocrine Abnormalities after 20 Years of Opioid Therapy

Presenter: Forest Tennant MD, DrPH

Authors: Forest Tennant MD, DrPH; Allen Hassen, MD, MHA

Background: Few studies are available on the long-term outcome of pain patients maintained on opioids. Although opioid suppression of hormones in the pituitary-adrenal-gonadal axis, particularly testosterone, is well known, little is known about additional hormone suppression. Available studies have been done only in patients treated with opioids for relatively short time periods.^{1,2}

Objective: To determine hormone abnormalities in pain patients who have been maintained for 20 or more years on high dose opioids.

Methods: Eighteen patients with intractable pain in a rural California county clinic were maintained on opioids under the auspices of the California Intractable Pain Act for 20 or more years. The 10 male and 8 female adults self-administered over 300 mg equivalent of morphine daily. All had detectable opioids in body fluids.

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No hormone replacement was prescribed by the pain treatment clinic. Each patient had an 8:00 AM fasting serum specimen taken and tested for cortisol, pregnenolone, testosterone, estrogen, corticotropin (ACTH), and follicle stimulating hormone (FSH).

Results: Hormone abnormalities were extremely varied. Only one (5.6%) patient was normal on all six assays. The most common abnormality was low FSH in 6 (33.3%) and low testosterone in 8 (44.4%). One (5.6%) patient each had low pregnenolone and estrogen levels, and 2 (11.9%) had low cortisol levels. High serum levels were pregnenolone (1, 5.6%), ACTH (4, 22.2%), estrogen (1, 5.6%), and cortisol (4, 22.2%).

Conclusions: This study provides additional evidence that the major effect of opioids on the endocrine system is suppression of FSH and testosterone. Suppression may also affect other hormones, including cortisol, estrogen, and pregnenolone. The surprising outcome here is that high levels of ACTH, estrogen, pregnenolone, and cortisol were present in some patients, indicating that severe pain and its endocrine response may not sufficiently be controlled by high-dose opioids.³ The clear conclusion here is that patients with intractable pain must be routinely monitored with pituitary-adrenal-gonadal axis screening and clinically treated for deficient or excessive hormone levels.

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Neuropathic Pain

17. Immunomodulatory Effect of Pregabalin on Spleen Cells in Neuropathic Mice

Presenter: Ho Kyung Song, MD

Authors: Ho Kyung Song, MD; You Jin Kang, MD

Background: Dysregulation of sensory, autonomic, endocrine, and immune systems after tissue injury affect the healing process and can lead to the development of neuropathic pain. The pain is a mental stressor that also interrupts the balance of immune responses that are essential to the body's defense mechanisms. Pregabalin, (S)-3-(aminomethyl)-5-methylhexanoic acid, has clinical and laboratory efficacy in a variety of neuronal diseases, including neuropathic pain. However, several immunological abnormalities, such as suppressed reactivity of lymphocytes to mitogen or NK cell activities, which can lead to impeded tissue healing, metastasis, or subsequent infection, have been described in patients undergoing antiepileptic drug therapy.

Objective: To verify immunomodulation in a neuropathic animal model caused by antinociceptive effect of pregabalin, we assessed the tumoricidal activity of the isolated splenic NK cell and the proliferation of the splenic lymphocytes derived from mitogenic stimulation by PHA.

Methods: The neuropathic model was induced by chronic constriction injury (CCI) to the left sciatic nerve in male BALB/c mice. The mice were categorized into four groups. C: control+saline, CP: control+pregabalin, N: CCI+saline, NP: CCI+pregabalin. Pregabalin was administered orally twice a day for a week from day 2 of operation at a dosage of 30 mg/kg and the antinociceptive effect was measured using a dynamic plantar aesthesiometer. On the 7th day of the treatment, splenic NK cell cytotoxicity was determined by LDH (lactate dehydrogenase) assay with YAC-1 target cells at the ratio of 80:1, 40:1, or 20:1. The proliferative response of splenic lymphocytes to PHA was measured by bromodeoxyuridine (BrdU) detection with an ELISA kit and compared to the C group.

Results: In neuropathic mice, significant allodynia was present on day 2 ($P<0.05$). Mechanical threshold was significantly increased by pregabalin treatment ($P<0.05$). NK cell cytotoxicity and proliferation of splenic lymphocytes were increased by CCI ($p<0.001$) on day 7, but pregabalin treatment suppressed the NK cell cytotoxicity and lymphocytes proliferation ($P<0.05$).

Conclusions: Splenic NK cell activity and lymphocyte proliferation to mitogenic stimulation were increased in neuropathic mice, but these reactions were suppressed by pregabalin treatment.

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18. Safety and Efficacy of NGX-4010, a Prescription-strength Capsaicin 8% Patch for the Management of Postherpetic Neuralgia (PHN) in the Older Population

Presenter: Lynn Webster, MD

Authors: Gordon Irving, MD; Miroslav Backonja, MD; Lynn Webster, MD; Jeffrey K. Tobias, MD; Geertrui F. Vanhove, MD, PhD; and Susy Chen, MD

Background: NGX-4010, a capsaicin 8% patch, has been shown to significantly reduce pain in patients with postherpetic neuralgia (PHN).^{1,2}

Objective: Integrated data from four randomized, double-blind, 12-week controlled PHN studies investigated NGX-4010 efficacy and safety in the older population subgroup (median age 80 years).

Methods: Included were 305 patients (≥ 73 years) receiving a single 60-minute treatment with NGX-4010 and 277 patients receiving a low-dose (0.04%) capsaicin control patch. Endpoints included the mean percentage change from baseline in "average pain for the past 24 hours" Numeric Pain Rating Scale (NPRS) score and the proportion of patients with $\geq 30\%$, $\geq 50\%$, or ≥ 2 units decrease in NPRS scores. Adverse events (AEs) were also evaluated. NGX-4010 decreased pain associated with PHN in the older patient subpopulation.

Results: The NGX-4010-treated group experienced a mean percentage NPRS score reduction from baseline of 25.8% compared with 17.1% in control ($P=0.0005$); 35.4% of NGX-4010-treated group achieved $\geq 30\%$ reduction in NPRS scores (26.0% for control,

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$P=0.0164$); 23.6% had a reduction of $\geq 50\%$ in NPRS scores (12.6% for control, $P=0.0009$); and 33.8% had a decrease of ≥ 2 units (28.4% for control, $P=0.0002$) during weeks 2 to 8. Similar results were obtained during weeks 2 to 12. The most common AEs in the older NGX-4010 patients were capsaicin-related application-site erythema, pain, papules, and pruritus ($>5\%$), and their incidence and severity were similar to the younger NGX-4010 patients. Most of these AEs were mild to moderate and self-limited. **Conclusions:** These data demonstrate that a single application of NGX-4010 can produce significant pain reduction for 12 weeks in older patients with PHN. The most common AEs were application-site events, and the incidence and severity were similar between the older patients compared to the younger.

References:

1. Backonja M. NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomized, double-blind study. *Lancet Neurol.* 2008;7:1106-1112.
2. Irving GA. A multicenter, randomized, double-blind, controlled study of NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia. *Pain Med.* 2011 Jan;12(1):99-109.

Encore Presentation: Presented at the American Pain Society 30th Annual Scientific Meeting, May 19-21, 2011, Austin, Texas.

19. Efficacy and safety of NGX-4010, a Prescription-Strength Capsaicin 8% Patch, as Monotherapy for the Treatment of Postherpetic Neuralgia

Presenter: Geertrui F Vanhove, MD

Authors: Gordon A. Irving, MD; Miroslav Backonja, MD; Richard Rauck, MD; Jeffrey K Tobias, MD; Geertrui F. Vanhove, MD

Background: NGX-4010 is a prescription-strength capsaicin 8% patch indicated for the management of neuropathic pain associated with postherpetic neuralgia (PHN).

Objective: To determine the efficacy and safety of NGX-4010 when used as monotherapy for the treatment of neuropathic pain associated with PHN.

Methods: Integrated data from 295 patients treated with a single, 1-hour NGX-4010 application and 280 patients treated with a single, 1-hour application of a low-dose (0.04%) capsaicin control patch were analyzed. Patients were not receiving other topical treatments or treatment with systemic neuropathic pain medications defined as anticonvulsants, non-SSRI antidepressants, or opioids. The mean percentage change from baseline to weeks 2–8 in “average pain for the past 24 hours” Neuropathic Pain Rating Scale (NPRS) score, recorded daily, was the primary endpoint. Response and Patient Global Impression of Change (PGIC) analyses were also performed. Safety assessments included adverse events (AEs).

Results: During weeks 2 to 8, patients who received NGX-4010 reported significantly greater reductions in NPRS scores compared with controls (-36.5% vs -26.2% , $P=0.0002$). In addition, significantly more NGX-4010 patients compared with controls achieved a $\geq 30\%$ pain reduction from baseline (52% vs 39%, $P=0.0037$), a $\geq 50\%$ pain reduction from baseline (34% vs 24%, $P=0.0117$) or a ≥ 2 unit pain reduction from baseline (45% vs 33%, $P=0.0018$). Furthermore, PGIC analyses at week 8 showed that

significantly more NGX-4010 patients felt much or very much improved compared to controls (45% vs 29%, $P=0.0002$). Similar results were seen during weeks 2 to 12 and at week 12 (PGIC). Transient, self-limited, mostly mild to moderate application-site reactions including erythema and pain were the most common AEs. **Conclusions:** These results suggest that, when used as monotherapy, NGX-4010 significantly reduces pain from PHN. NGX-4010 is generally well tolerated with local, transient application-site reactions as the most common AEs.

Encore Presentation: Presented at the 63rd Annual Meeting of the American Academy of Neurology, April 6-9, 2011, Honolulu, Hawaii.

20. Titration with Gabapentin in Postherpetic Neuralgia (PHN)

Presenter: Jennifer Miller, PhD

Authors: Michael Sweeney, MD; Jennifer Miller, PhD; Phaedra Johnson, MS; Rachel Halpern, PhD; Laura Becker, MS; Robert Dworkin, PhD

Background: Gabapentin is recommended as first-line treatment for postherpetic neuralgia (PHN) by the American Academy of Neurology and other national and international organizations. It is usually given 3 to 4 times per day and must be titrated to an effective dosage over several weeks. It is not known how many patients with a confirmed diagnosis of PHN complete gabapentin titration to an effective dosage and continue therapy in clinical practice in the community.

Objective: To examine titration of gabapentin to effective dosage levels among patients with PHN treated in community practice settings.

Methods: Administrative claims data from a large US health plan were used to identify commercial and Medicare Advantage enrollees with PHN who initiated treatment with gabapentin from July 2005 to February 2010. The date of the first gabapentin pharmacy claim was designated as the index date. Patients were required to have at least 6 months of complete data preceding and 12 months following the index date (pretreatment and follow-up, respectively) and to have evidence of PHN (ICD-9-CM code 053.1x) during pretreatment or on the index date. Patients with epilepsy (ICD-9-CM 345.XX) were excluded. Mean daily dosage, duration of therapy, number of prescription fills, and time to reach maximal dose were examined during the 12-month follow-up period.

Results: A total of 939 patients (mean age 63.8 years, males 39%, Medicare Advantage 26%) met all study entry criteria. Patients were generally healthy, with an average Charlson Comorbidity Index score of 1.05. The mean daily dosage (SD) of gabapentin during the follow-up period was 826 (559) mg. Neurologists prescribed higher dosages on average than did general practice physicians, with mean daily dosages (SD) of 883 (668) mg and 755 (529) mg, respectively. The mean maximum dosage (SD) for patients with at least 14 days on one dosage was 970 (738) mg, with an average time to reach maximum observed dosage of 30 days (71). Only 134 (14.3%) patients were titrated to the FDA-approved effective dosage level of $>1,800$ mg during the follow-up period. Patients remained on gabapentin for an average of 73 days prior to any gaps in therapy of >30 days, and had an average of 3.08 prescription fills; however, 494 (52.6%) patients filled only a single prescription during the follow-up period.

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Conclusions: In community practice settings, only 14% of patients with PHN were titrated to an effective dosage of gabapentin.

References: This study was supported by Depomed Inc.

Postoperative Pain

22. Microencapsulated Bupivacaine Relieves Acute Pain for 72 h in Rats

Presenter: Clifford J. Herman, PhD

Authors: Rachit Ohri, PhD; Phillip Blaskovich; Jeffrey Wang, MD; Lan Pham; Gary Nichols, PhD; Bill Hildebrand; Daniel Costa; Nelson Scarborough, PhD; Cliff Herman, PhD; Gary Strichartz, PhD

Background: Postoperative pain is physiologically limiting, psychologically stressful, and a major factor in delaying hospital discharge.

Objective: In order to address acute postoperative pain in the first 48 h to 72 h after surgery, a controlled release, microencapsulation formulation was developed for the local anesthetic bupivacaine. Microencapsulation has been used previously for several hydrophobic molecules.¹

Methods: Microencapsulation of bupivacaine was achieved with a 75:25 ratio poly-lactide-co-glycolide (PLGA) polymer. Microparticles were generated using a proprietary oil-in-water emulsion/solvent evaporation method. These microparticles had a bupivacaine loading of 60% (w:w) and a mean diameter of 65 to 70 microns (\pm SD of 12 to 15 microns), based on Coulter Counter particle sizing. Scanning electron microscopy (SEM) and Raman spectroscopy were employed to determine microparticle morphology and drug-polymer domain-distribution, respectively. Further characterization of these microparticles was pursued using X-ray diffraction (XRD) for characterizing crystalline domains, differential scanning calorimetry (DSC) for characterizing thermal transitions, and gas physisorption for surface porosity quantification. Importantly, release profile kinetics determined using a United States Pharmacopoeia (USP) Type-2 dissolution apparatus showed that these microparticles generated a sustained release in vitro over 48 h to 72 h. Neurobehavioral evaluation of the bupivacaine microparticle formulation was pursued in rats. Hyperalgesia after incision along the lateral edge of the paw² was assessed by mechanosensitivity to a painful stimulus, using a stiff (15g) von Frey filament. Responses were measured preoperatively and at the following postincisional times: 0h, 2h, 6h, 1d, 2d, 3d, 4d. The study included comparison of hyperalgesia when the sciatic nerve innervating the paw was blocked by bupivacaine HCl dissolved in saline, microparticles without drug, and the slow-release bupivacaine microparticle formulation. For each experimental group, eight animals were evaluated at each time point.

Results: While the bupivacaine HCl (0.5% w/v in saline) had antihyperalgesic efficacy through 2h, the bupivacaine microparticles provided postincisional pain relief through 72 h. The pain scores for the bupivacaine microparticles were 50-70% lower at all time points through 72 h when compared to placebo microparticle spheres (no drug) ($P < 0.001$).

Conclusions: These preclinical data provide encouraging in vivo *proof of principle* for 72 h of analgesia with the bupivacaine microparticle formulation.

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23. An Open-label Pilot Study Evaluating a Heated Lidocaine/Tetracaine Patch in the Treatment of Pain Associated with Shoulder Impingement Syndrome

Presenter: Richard Radnovich, DO

Authors: Richard Radnovich, DO; Michael Smith; Thomas Marriott, PhD; James Heusner, MD

Background: Synera® (lidocaine 70 mg and tetracaine 70 mg) heated topical patch is approved for use on intact skin to provide local dermal analgesia for superficial venous access and dermatological procedures. The depth and duration of local anesthesia it provides suggest that it may be useful in the relief of pain associated with musculoskeletal structures lying close to the surface of the skin.

Objective: To evaluate the potential usefulness of Synera for the off-label treatment of pain associated with shoulder impingement syndrome (SIS).

Methods: This was a 2-week, open-label, outpatient study in 20 adult subjects with SIS, diagnosed by detection of tenderness at the attachment site of the rotator cuff tendons and positive Hawkins and Neers signs. Subjects had symptoms for at least 2 weeks and baseline pain intensity of ≥ 4 on an 11-point Numeric Pain Rating Scale (NPRS). Subjects applied 1 patch directly to the affected shoulder for 2 to 4 hours twice daily for 14 days. No other SIS pain medications were allowed. Outcome measures were NPRS of pain intensity (average and worst pain over the last 24 hours) and pain interference with specific activities of daily living, range of motion, and Patient Global Assessment of Treatment Satisfaction (PGAS, 5-point scale).

Results: Baseline mean NPRS for average pain was 5.6 (range 4 to 8). Over the 2-week treatment period, NPRS (mean \pm standard deviation, n=19) for average pain and worst pain decreased by 41% ($\pm 42\%$) and 44% ($\pm 7\%$), respectively. Pain interference with general activity, normal work, and sleep decreased by 38% ($\pm 46\%$), 37% ($\pm 48\%$), and 43% ($\pm 47\%$), respectively. Both measures of range of motion showed improvement; mean internal rotation increased 29° ($\pm 21^\circ$) and mean abduction increased 41° ($\pm 43^\circ$). Sixty-three percent of the subjects had a ≥ 2 -point decrease from baseline in NPRS for average pain and 53% of subjects had a ≥ 3 -point decrease. Most subjects (53%) were satisfied or very satisfied with their treatment. The patch was well tolerated by all subjects; 1 subject was lost to follow-up. The most common AEs were mild or moderate application-site erythema (50%) and mild headache (20%); no subjects discontinued due to AEs.

Conclusion: In this open-label study in patients with pain associated with SIS, Synera effectively reduced pain intensity, decreased pain interference with activities of daily living, and increased range of motion.

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Psychological Aspects

24. Depression, Primary Care, and Pain

Presenter: Meghan Gannon, MSPH

Author: Meghan Gannon, MSPH

Background: Depression is common to the primary care setting, with several quality gaps noted in the literature¹⁻⁵. Pain can be associated with depression and is becoming an ever-increasing reason for primary care visits.

Objective: The objective of this program is to improve the interaction and support of primary care practices to patients with depression.

Methods: This program evaluates practice data before and after the Quality Improvement (QI) intervention to provide “snapshots” of the practice. The data include clinical information related to the patients’ diagnoses and management of their depression, as well as a practice survey assessing the practice’s attitudes, knowledge, and beliefs of screening and managing patients with depression.

The intervention consists of a novel educational program developed by experts in the field of practice improvement related to depression. Monthly QI coaching conference calls complement the educational intervention and are led by QI faculty. These calls are divided between beginner and advanced calls. Beginner calls are didactic in nature and offer lessons on the chronic care model, practice improvement, and the Plan Do Study Act (PDSA) process.

Advanced calls are interactive and offer the practices a chance to receive guidance from experts on their practice redesign as well as provide peer-to-peer coaching for fellow participants in the field.

Results: There are 36 physicians enrolled in the study. Currently we are in the baseline abstraction phase of the program and will have preliminary results to present at the time of the conference. Practices are now beginning their practice redesign work.

Conclusions: This study is ongoing.

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25. Detection of Depression with Comorbid Pain Using Biomarkers

Presenter: Bo Pi, PhD

Authors: Bo Pi, PhD; Linda M Thurmond; PhD, Katie M, Smith PhD; John A Billello, PhD

Background: Epidemiologic studies indicate that depression is a common comorbidity accompanying chronic pain states. Emerging evidence suggests pathophysiologic mechanisms that underlie the coexistence of depression and chronic pain states. A biomarker panel and algorithm for depression diagnosis has been developed consisting of 10 biomarkers associated with the neurotrophic, metabolic, inflammatory, or HPA axis pathways. Clinical validation in general psychiatric practice settings showed discrimination of patients with depression (n=80) from normal controls (n=43) (P=< 0.00001) and a clinical sensitivity of 90% and specificity of 87%.

Objective: To determine whether a blood-based test for depression could identify depression comorbid with chronic pain. Comorbid depression can complicate the presentation, clinical course, and response to treatment of patients with chronic pain.

Methods: Patients from community psychiatric practices were referred for testing based upon the clinician’s discretion. The majority of patients had recurring depressive symptoms and/or were patients who were difficult to manage or were noncompliant. The study enrolled a total of 98 patients, 80 of whom (81% compliance) had a blood sample drawn. The mean age of the study population was 48.5±12.6 with a range of 21 to 80 years. Fifty-six (70%) were female and 24 (30%) were male. Ten biomarkers were quantified by validated immunoassays for each patient serum sample, and a score was calculated from a proprietary algorithm.

Results: While 16 of 80 subjects had no comorbidity listed, the majority of the enrolled subjects had a variety of comorbidities, with some of the most common being arthritis, diabetes, hypertension, obesity, and chronic pain. Eighteen of 80 patients had chronic pain comorbid with depression. Six of 18 had chronic pain as the only comorbidity. The remaining 12 patients had pain and arthritis (8/12); pain and obesity (3/12), or pain and hypothyroidism (1/12). The MDD scores for depressed subjects with pain and at least one other comorbidity were consistent with a high probability of MDD. Interestingly, of the six patients with only chronic pain, four had a likelihood of depression of >90% and two had 10% and 33% likelihoods.

Conclusions: Comorbid depression can complicate the presentation, clinical course, and response to treatment. This preliminary study shows a biomarker test can identify depression in patients with comorbid chronic pain.

Thursday, September 22

Arthritis

26. Topical Diclofenac Sodium Gel in Older and Younger Patients

Presenter: Bobbie-Sue Brown, MS

Authors: Herbert S. B. Baraf, MD, F. Michael Gloth, MD; H. Richard Barthel, MD; Morris S. Gold, ScD; Roy D. Altman, MD

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Background: Nonsteroidal anti-inflammatory drugs have dose-related risks for gastrointestinal, cardiovascular, and renal adverse events (AEs), particularly in elderly patients. Topical NSAIDs reduce systemic NSAID exposure, potentially reducing these risks.

Objective: To evaluate the efficacy and safety of topical diclofenac sodium 1% gel (DSG) versus vehicle in younger (25–64 y) or older (≥ 65 y) patients with knee osteoarthritis (OA).

Methods: Data were pooled from three 12-week, randomized, double-blind trials. After a 1-week analgesic washout, patients with Kellgren-Lawrence grade 1 to 3 knee OA applied 4 g of DSG or vehicle 4 times daily to 1 knee. Efficacy outcomes were Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain (0–20) and physical function (0 to 68) subscales, a global rating of disease (GRD; 100-mm visual analogue scale [VAS]), and pain on movement (POM; 100-mm VAS). ANOVA was used to compare efficacy (DSG vs vehicle) by age (25–64 or ≥ 65 years). A flare design was used that defined a subset of patients who experienced increased pain during the washout period (modified efficacy subpopulation [MES]).

Results: The MES included 602 younger (aged 25–64 y) and 374 older (aged ≥ 65 y) patients. In younger patients, improvement at week 12 (least squares mean [standard error]) was greater with DSG versus vehicle for WOMAC pain (-5.8 [0.3] vs -4.7 [0.3], $P=0.007$), WOMAC physical function (-17.9 [0.9] vs -14.2 [0.9], $P=0.002$), GRD (-29.5 [1.6] vs -23.8 [1.6], $p = 0.01$), and POM (-37.3 [1.8] vs -29.0 [1.8], $P<0.001$). Among older patients, improvement was greater with DSG versus vehicle for WOMAC pain (-5.3 [0.3] vs -4.1 [0.4], $P=0.02$), WOMAC physical function (-15.5 [1.1] vs -11.0 [1.1], $P=0.004$), and POM (-33.7 [2.2] vs -26.4 [2.2], $P=0.02$). Efficacy of DSG did not differ significantly between younger and older patients: WOMAC pain ($P=0.85$) and physical function ($P=0.70$), GRD ($P=0.86$) and POM ($P=0.81$). Application-site dermatitis was the only treatment-related AE significantly more frequent with DSG versus vehicle in younger (4.0% vs 0.7%) and older (5.8% vs 0.4%) patients.

Conclusions: Topical DSG was effective and generally well tolerated regardless of age, supporting its use for relief of knee OA pain in younger and elderly patients.

Disclosure: Supported by Endo Pharmaceuticals Inc.

Encore Presentation: Published manuscript (Baraf et al, *Drugs Aging*. 2011;28:27-40).

27. Integrating Arthritis Self-management and Exercise

Presenter: Anita D. Mendelson MSc, BMR (PT)

Authors: Anita Debbie Mendelson MSc, BMR (PT); Angela Chan MHS, BPT

Background: Individuals with arthritis, compared to people with other chronic conditions, report poorer self-rated health, more depression, more frequent contact with health professionals, and greater need for help with daily activities. Effective management must focus on helping people live successfully with their condition and address both psychosocial and physical needs. The Program for Arthritis Control Through Education and Exercise - PACE-Ex™ is an arthritis self-management program that aims to empower people to take an active role in their health and learn and practice skills to effectively manage their condition. Facilitated by health care

professionals, over an 8-10 week period, meeting twice weekly, participants engage in one hour of interactive group discussion, condition-related information sharing, problem-solving, and goal-setting, followed by one hour of group warm water exercise.

Objective: To examine the impact of PACE-Ex on participants' self-efficacy for condition management, self-management behaviors, goal-achievement levels, walking, and condition impact on their daily lives.

Methods: As part of regular program delivery, a battery of outcome measures (Activities Balance Confidence Scale, Stanford Chronic Disease Questionnaire, Health Education Impact Questionnaire [HeiQ], goal attainment scaling and 2 Minute Walk Test) is administered pre- and post-program. Post-program focus groups are also conducted. A recent retrospective review of pre/post data was conducted on participants who completed PACE-Ex over the 3 last years. Pre/post data was analyzed using Wilcoxin tests.

Results: PACE-Ex participants ($n=83$) had mean age 70.9 (± 11.5) years and living with arthritis mean of 14.1 (± 11.7) years.

Participants showed statistically significant improvements in time spent exercising and communication with physician, and less interference of condition on day-to-day activities and 2 minute walk test ($P<0.05$). HeiQ domains which showed the greatest change from pre- to post-program were healthy lifestyle behaviours, ability to monitor condition, and skills and techniques to effectively self-manage. Over 60% of arthritis participants attained or exceeded their long-term goal. During post-program focus group, participants reported better understanding of their condition, increased knowledge of accessing resources, greater motivation to participate in physical activity, not feeling as alone or fearful about their health, and valuable learning/sharing with others in similar situations.

Conclusions: PACE-Ex supports individuals living with chronic conditions to adopt healthy behaviours and develop skills to manage their condition and its daily challenges.

Chronic Pain Issues

28. Wide Abdominal Rectus Plication for Chronic Low Back Pain

Presenter: Joseph P. Mulka, MD, PhD.

Authors: Robert M. Oneal, MD; Joseph P. Mulka, MD, PhD; Paul Shapiro, MD; David Hing, MD; Christi Cavaliere, MD

Background: A previous report demonstrated that the wide abdominal rectus plication (WARP) abdominoplasty is an effective treatment modality in select patients with low back pain who failed to achieve relief with conservative therapy.^{1,2}

Objective: To investigate the effectiveness of this treatment for patients with chronic, intractable low back pain and marked lower abdominal muscular laxity.

Methods: The authors studied 8 female patients who presented with chronic low back pain and marked lower abdominal wall muscular laxity. All had failed to respond to conservative management for their chronic back pain. They all underwent WARP abdominoplasty.

Results: There were no significant complications in this series, and all the patients had prompt and prolonged alleviation of their back pain based on the Oswestry Disability Index.³ Length of follow-up ranged from 2 to 11 years.

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Conclusions: The WARP abdominoplasty may be an alternative option for patients with chronic intractable low back pain and marked lower abdominal wall muscular laxity who have failed conservative management. The WARP abdominoplasty tightens the lateral abdominal muscular complex which is contiguous with the thoracolumbar fascia.⁴ Since the thoracolumbar fascia originates on the lumbar spine bony prominences, the WARP abdominoplasty changes the biomechanics of the lower trunk by creating increased intraabdominal pressure and increased core muscular control. This likely reduces static and dynamic stresses on the pain generating structures in the lumbar spine and leads to a decrease in pain.⁵⁻⁶

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29. Chronic Pain Management Through Disrupting Tidal Entrainment of Neural Synchrony

Presenter: Lawrence Robbins, MD

Authors: Lawrence Robbins, MD; L. B. Siegel, MD; S. Ouyang, PhD; H. Sun, MD; C. C. Leith, PhD

Background: There is a common feature in many conditions such as temporal lobe epilepsy (TLE), chronic migraine (CM), fibromyalgia (FM), and their frequent psychiatric comorbidities. Most of these patients experience their "bad days" and "good days," apparently in relapsing-remitting-like cycles. This feature was largely ignored by most investigations until the advent of the adapted diffusion tensor imaging approach (aDTI) that detects baseline neural impulses in axonal fiber tracts.

Objective: We developed a tidal entrainment (TE) theory to interpret baseline neural hyperactivity data from two experiments, allowing us to argue TE as a fundamental and common phenomenon in altered neurobiology in many seemingly unrelated conditions.

Methods: Seven patients with CM (19-47 y, 6W, 1M) and 7 matched controls were in the CM experiment. All 7 patients had transformed from migraine to CM. In the FM experiment, there were 8 FM patients (31-51 y, all women) and 8 matched, healthy controls. All subjects were evaluated by aDTI that used the phenomenon of

discharging axonal fibers exhibiting a minute reduction in fractional diffusion anisotropy (FA).

Results: In the brainstems of the CM group, multiple loci of reduced diffusion anisotropy ($P < 0.001$) were localized in the cerebral peduncle bilaterally, in the middle cerebellar peduncle on the right side, in the midline midpons, and in the upper medulla on the left. In the FM group, loci of reduced diffusion anisotropy of statistical significance ($P < 0.001$) were found in the brainstem and white matter components of the central pain matrix including the anterior cingulate cortex, insular cortex, and orbitofrontal cortex. The baseline hyperactivity in each case resembles in many ways the hypersynchrony of neurons in TLE. In CM there are indeed reported "migraine-generator" neurons in the brainstem, as in TLE the epileptogenic cells in the hippocampus. These neurons fire adversely as pathologic pattern generators, entraining and kindling normal and distributed synchronies into a greater and pathological one. As the entrainment tide flows, the patient may experience a premonitory awareness, a bad-day attack, aggravation, or seizure. When the tide reaches the mood or reward circuits, depression or other psychiatric disturbances may occur. Good days may return following a possible postdromal phase as the tide ebbs.

Conclusions: Chronic pain management is a task of tidal entrainment disruption as it best explains once perplexing multi-indications of anticonvulsants, DBS, TMS, and VNS, most of which tend to break the neural hypersynchrony. aDTI has demonstrated its sensitivity in detecting and monitoring the tidal entrainment dynamics.

30. Do Recovering Teen Insights Affect HCPs' Opioid Prescribing?

Presenter: Angela T. Casey, MPhil

Authors: Angela T. Casey, MPhil; James W. Barrett, BS; Patrick Dwyer

Background: Clinicians play a vital role in preventing abuse of prescription drugs, together with government, patients, parents, and manufacturers. Clinicians are often unaware of the fate of medications they prescribe, and may unwittingly fuel abuse/diversion, despite well-intentioned prescribing. Legitimate access to controlled substances is necessary for public health, but clinicians have a responsibility to minimize potential for abuse/diversion. Adolescents/young adults are particularly at risk. **Objective:** To develop an educational initiative for clinicians to reduce risk of adolescent/young adult prescription medication diversion/abuse.

Methods: A CME/CE initiative consisting of a regional symposium (2009), live teleconferences/webinars (2009), and archived webinar (2010-2011) was developed and presented by pain and addiction experts. The educational format uniquely featured recovering high school students recounting experiences with prescription drug abuse/addiction. The activities' impact was assessed by baseline, postassessment (included standard questions and participants' intentions to change their practice), and 2-month outcomes surveys.

Results: Of a total of 629 participants, 487 baseline and 352 postassessment surveys were completed; 107 opted to participate in the 2-month outcomes, of which 40 responded (37.4% response). Two hundred twenty-six (65.1%) postassessment respondents stated an intention to change their practice or seek additional information on this topic. Twenty-seven of 40 outcomes respondents (67.5%) at

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2 months reported practice change, 6 (15.0%) reported practice change and intention to change further, and 4 (10.0%) reported no practice change but still intended to change.

Outcomes data demonstrated sustained practice change regarding patient education procedures:

Percentage of respondents who “always”/“usually” educate patients:	Baseline	Postassessment (intention to change)	2-month outcomes
About their responsibility to safeguard prescriptions	49.2%	87.8%	82.5%
About young family members/visitors seeking prescription drugs to abuse/divert	37.9%	81.8%	71.8%
How to dispose of medications	39.7%	86.9%	66.7%

Outcomes data also demonstrated sustained practice-change around prescribing opioids:

Percentage of respondents who “always”/“usually”:	Baseline	Postassessment (intention to change)	2-month outcomes
Screen for mental health/substance use disorders/addiction when prescribing controlled substances	54.2%	83.7%	72.2%
Routinely ask patients about alcohol use, particularly heavy episodic (binge) drinking	63.1%	80.6%	80.7%
Queried a prescription monitoring program database	37.6%	71.3%	78.6%

Conclusions: This educational initiative was an effective way to change clinicians’ behaviors to curb prescription medication diversion/abuse. The influence of the adolescents’/young adults’ insights is demonstrated by comments such as:

- “First person narrative was most effective (student).”
- “Interaction with the young adult panelists was crucial to demonstrating the real harm that can come from careless prescribing.”
- “We prescribers need (teens’/young adults’) input to reduce diversion of meds.”

31. Incidence and Impact of Pain Conditions and Comorbid Illness

Presenter: Jessica A. Davis, MPH

Authors: Jessica A. Davis, MPH; Rebecca L. Robinson, MS; Trong Kim Le, MPH, MS; Jin Xie, MS

Background: Pain is one of the most disabling, burdensome, and costly conditions in the United States.¹ Individuals with comorbid conditions have been found to have higher health care expenditures.² Little is known about the rate and impact of multiple painful conditions.

Objective: To characterize a broad range of pain condition cohorts by demographic, clinical, treatment, and economic factors reported in Thomson Reuters’ MarketScan United States Commercial and Medicare Supplemental retrospective claims databases.

Methods: Adults (n=1,211,483) with at least 1 pain condition during the study period from 2005 through 2007 were classified using International Classification of Diseases, 9th Edition (ICD-9) codes into 23 pain cohorts based on the first diagnosis present during the study period.

Results: Musculoskeletal pain conditions were among the most prevalent, including lower back pain (35.0%), osteoarthritis (30.1%), and fibromyalgia (6.24%). Across cohorts, the mean number of comorbid pain conditions ranged from 1.39 (cancer pain and migraine) to 2.65 (multiple sclerosis [MS] pain). High rates of mental health conditions were found in cohorts with HIV-associated and phantom limb pain (42.59% and 36.10%) and were lowest among cohorts with rheumatoid arthritis and psoriatic arthropathy (12.73% and 13.31%). Rates of sleep disorders ranged from 5.47% (painful bladder syndrome) to 11.59% (MS pain). Overall, patients averaged 3.53 pain medications yearly. The highest annual total health care costs were for the cancer pain cohort, and the lowest costs were observed in the post-herpetic neuropathy, surgically induced pain, migraine, and irritable bowel syndrome cohorts. Costs attributed to pain were highest among MS, HIV, and cancer pain cohorts. The highest pharmaceutical costs were observed in the HIV pain cohort.

Conclusions: These findings underscore the heterogeneity of patients with pain in terms of burden of illness, costs to the health care system, and complexity of commonly co-occurring disorders.

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32. Chorionic Gonadotropin Initial Doses For Intractable Pain

Presenter: Forest Tennant MD, DrPH

Authors: Forest Tennant MD, DrPH; Allen Hassen, MD, MPA

Background: Human chorionic gonadotropin (HCG) is a pituitary hormone found in both sexes. It has receptors throughout the nervous system including glial cells, thalamus, and hippocampus.¹ It has shown neural healing capability in rats that have had spine transection.² Preliminary clinical trials in a small number of intractable pain patients indicate that it may ameliorate pain, reduce opioid dosages, and produce pain-free hours.

Objective: To determine an initial starting dose for subcutaneous and sublingual HCG in intractable pain patients who have central pain.

Methods: Subjects were 22 adult intractable pain patients maintained on daily opioids who claimed constant pain except when asleep. All had pain for over 5 years and were assumed to have some central pain, as they had all failed interventions and treatments directed at peripheral pain sites. Patients were started on 125 U/ml HCG given 3 times a week by sublingual drops or subcutaneous injections. Over a 3-month period patients were instructed to progressively increase frequency and dosage until they required a smaller opioid dosage, perceived less pain, and experienced increased energy.

Results: Of the 22 subjects, 16 (72.7%) reached the 3 end points and reported a decrease in opioid dosage, reduced pain, and more energy. The effective, minimal sublingual dosage was 250 U/day (1750 U/week) or 500 U subcutaneously 3 times a week, (1500 U/week). The minimal time to achieve the 3 end points was two weeks. Six patients reported no effects of HCG.

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Conclusions: There are now large numbers of patients with intractable pain who are humanely maintained on opioids for symptomatic and palliative care. They apparently have central pain, as they do not respond to standard, peripheral interventions and treatments. What is needed are central pain treatment agents that will permanently reduce pain and lower the requirement for opioids. A major clinical obstacle in the use of HCG is that its effective dosage is unknown, and this investigation provides an initial starting dosage for HCG. Open trails of HCG to date, although not effective in all intractable pain patients, call for further study.

References:

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33. Pain and Sleep Associated with Working Memory in Adults, 50+

Presenter: Brianne Levine, BA and Jordan K. Aquino, BS

Authors: Brianne Levine, BA; Carter C. Rakovski, PhD; Barbara J. Cherry, PhD; Brian Follick, BA; Jordan K. Aquino, BS; Topaz Slater, BA; C. Jessie Jones, PhD

Background: The theory of distraction control suggests that the ability to inhibit distractions plays an important role in higher-order cognition. In the following analysis, working memory is measured by the Brown-Peterson Task (BP), a reading-with-distraction paradigm. Research using the BP has shown significant age differences in recall. Studies have linked depression, pain, and fatigue with impaired working memory in older and clinical populations.

Objective: The purpose of this secondary analysis is to explore the relationships among pain, sleep, and working memory in adults. It is expected that lower scores on the BP will be associated with higher scores in pain and on feeling rested after sleep.

Methods: The purpose of this study, conducted at California State University, Fullerton, in 2010, was to investigate physical and cognitive functioning of adults with and without fibromyalgia. Two self-report questions were included in this analysis: *number that best describes experience with: 1) pain in the last week* (0=no pain to 10=extreme pain) and *2) feeling rested after sleeping in the last week* (0=awoke fully rested to 10=not rested at all).

The Brown-Peterson (BP) is a short-term memory task with distraction. Participants are read aloud a string of three letters and asked to remember them, then asked to count backwards, by threes, from a three digit number, for a time (0, 9, 18, and 36 seconds), then asked to recall the three letters. Memory was measured by number of correct responses (0-15, high scores indicate better recall). Descriptive statistics were calculated. Pearson correlations were used to test the associations among sleep, pain, and memory. A linear regression model was fit, with memory as the dependent variable and age, fibromyalgia, sleep, pain, and depression (Beck Depression Index) as independent variables.

Results: About half of the sample reported having fibromyalgia (55.7%). Respondents (mean age=64.7) averaged 4.0 and 4.5 on the pain and sleep symptoms, respectively. Both pain and sleep were

significantly correlated with working memory ($P<.05$ and $P<.01$). The more pain and sleep problems participants reported, the fewer correct responses they scored on the BP. The model explained 21.4% of the variance in memory ($R\text{-square}=0.214$). Sleep, pain, and fibromyalgia were not significant predictors; age and depression were significant predictors ($P<.01$ and $P<.05$).

Conclusions: Results suggest that more pain and less sleep were associated with poorer recall and depression and age-predicted recall performance. Future research should investigate medications associated with working memory and test pain management as a means to improve cognitive functioning.

34. Long-term Analysis of Pregabalin for pDPN

Presenter: Birol Emir, PhD

Authors: Roy Freeman, MD, PhD; Raymond Cheung, PhD; Birol Emir, PhD

Background: Pregabalin is approved for the management of painful diabetic peripheral neuropathy (pDPN).

Objective: To examine pooled safety and efficacy findings from 7 long-term, open-label (OL) extension studies of pregabalin (75-600 mg/day) in pDPN.

Methods: Patients with pDPN who participated in double-blind, randomized, clinical trials of pregabalin were eligible to enroll in the OL extension studies, which were of up to 2 years' duration. Mean daily dosage was monitored and pain levels evaluated quarterly on a 100-mm visual analogue scale (VAS). Concurrent self-reported analgesic medications were categorized as likely or not likely to affect efficacy. Medications categorized as likely to affect efficacy included tricyclic agents, norepinephrine and serotonin reuptake inhibitors, anticonvulsants, topical analgesics, and opioids. Data are expressed as mean \pm standard deviation unless otherwise indicated.

Results: The pooled population included 1426 patients aged 21-86 years (91.7% white; 59% male). Most common dosage was 300-449 mg/d (40.0% of patients) followed by 600 mg/d (32.4%), <300 mg/d (17.3%), and 450-599 mg/d (10.4%). Marked reductions in VAS pain score from baseline (64.6 ± 20.6) to endpoint were evident in the first quarter of the OL extension (30.3 ± 23.7) and remained stable through to endpoint (35.9 ± 28.2). Change in VAS from baseline to endpoint was significantly different for patients taking concurrent medications likely to affect efficacy vs concurrent medications unlikely to affect efficacy (-25.6 vs -31.5 ; difference 6.4 [95% CI: 0.3-9.5]; $P<0.0001$). A similar difference was found when patients were stratified as naïve (those who received placebo in the double-blind studies; $n=515$; 5.6 [0.6-10.6]; $P=0.0284$) or non-naïve (those who received pregabalin in the double-blind studies; $n=896$; 6.4 [2.5-10.3]; $P=0.0014$). The adverse event (AE) profile was consistent with the known profile of pregabalin, with most AEs being mild to moderate in intensity.

Conclusions: For patients with pDPN, the efficacy of pregabalin for pain relief is durable for at least 2 years. Taking concurrent medications known to affect efficacy influences reported pain reductions. Long-term use of pregabalin was generally well tolerated.

Disclosure: This study was supported by Pfizer Inc.

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35. Preemptive Ketamine in Knee Surgery Performed in Spinal Analgesia.

Presenter: Dorte Due-Rasmussen, MD

Authors: Dorte Due-Rasmussen, MD; Robert Ravnholt Winding, MD; Harold Max Povey, MD

Background: Studies have shown that low-dose ketamine administered before or during surgery in general anesthesia resulted in reduced postoperative morphine consumption. Pain conducting C-fibers activates NMDA (N-methyl-D-aspartate)-receptors in the dorsal root of medulla spinalis thereby causing central sensitization, increased pain perception, and possibly even pain memory. Low-dose ketamine acts as an NMDA-receptor blocker and thereby significantly prevents acute as well as chronic pain. Menigaux¹ found that giving ketamine 0.15 mg/kg intravenously during general anesthesia resulted in reduced postoperative morphine use after knee surgery.

Objective: To assess whether low-dose ketamine can reduce postoperative morphine consumption in patients undergoing knee surgery in spinal analgesia.

Methods: Randomized double blind prospective study. Primary outcome is postoperative morphine intake, secondary outcome is side effects.

Results: 2 x 25 patients anesthetized with intrathecal bupivacaine and then receiving an intravenous infusion of either saline or saline + ketamine, 0.3 mg/kg. Two patients from each group were excluded. We found a significant difference in age between the two groups ($P=0.049$) with a median age in the control group of 73 years and 68 years in the ketamine group (Mann-Whitney U-test).

Postoperative morphine consumption after 24 hours was 29.0 mg in the control group and 38.8 mg in the ketamine group ($P=0.108$) and after 48 hours 51.4 mg and 59.2 mg, respectively ($P=0.258$). VAS pain score as well as side effects (dream intensity and quality, nausea, vomiting, and itching) were not significantly different (Mann-Whitney U-test).

Conclusions: The ketamine group was 5 years younger and had a 7.8 mg higher intake of morphine after 48 hours. A linear regression shows a highly significant inverse correlation between age and morphine consumption: The older the patient, the lower the consumption. Since morphine intake decreases 2 mg per yearly increase in age, it totally eradicates the already insignificant difference in morphine consumption between the groups.

Spinal analgesia locally blocks afferent and efferent nerve input. Administering further analgesic treatment such as intravenous ketamine may not make any difference because the nerve input is already blocked. It also explains our not finding a morphine-reducing effect. Finally, the dose of ketamine (0.3 mg/kg) in the study might have been too low.

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The authors wish to thank The Department of Biostatistics, University of Aarhus, Denmark, for helping with data analysis.

Fibromyalgia

36. Understanding Fibromyalgia: Online Patient Survey of NFA Members

Presenter: Angela T. Casey, BSC, MPhil

Authors: Angela T. Casey, BSC, MPhil, Richard L. Abbot Jr, BA; James W. Barrett, BS; Rae Marie Gleason

Background: A spectrum of symptoms constitutes fibromyalgia (FM), but patients differ in how they manifest these symptoms and in the impact on their quality of life (QOL).

Objective: To gain insights into patients' experiences with FM symptoms, diagnosis, and treatment, in order to develop educational activities to help clinicians provide optimal care.

Methods: An email was sent to 85,000 National Fibromyalgia Association (NFA) members on 8/26/2010, directing patients to complete a voluntary, anonymous online survey.

Results: By 9/9/2010, 10,017 responses were received (95.5% female, 4.3% male). Symptoms experienced by $\geq 30\%$ of patients at a severity of $\geq 8/10$ were chronic, widespread pain (CWP), problem sleeping, fatigue, sensitivity to touch, difficulty concentrating, poor memory, depression, joint pain, stiffness, and sensitivity to noise/light/odor/cold. At least 40% of respondents rated the following symptoms as "very" or "extremely" disruptive to their QOL: CWP, problem sleeping, fatigue, problem with physical function, difficulty concentrating, poor memory, joint pain, and stiffness. Asked how many work days respondents missed over the past year because of FM, 51.4% were not employed, 11.1% missed >20 days, 9.1% missed 10 to 20 days, 17.7% missed 1 to 9 days, and 10.7% did not miss any days. Activities that $\geq 50\%$ of respondents reported had been limited "a lot" by FM were vigorous activities (eg, sports, lift heavy object), housework, lift/carry groceries, bend/kneel/stoop, and walk continuously for 20 minutes. Respondents were diagnosed by a rheumatologist (44.6%), general/family practitioner (28.3%), internist (9.0%), neurologist (4.2%), and pain specialist (3.6%). Overall, 32.1% reported a "very difficult" experience in receiving a FM diagnosis (24.4% described it as "somewhat difficult").

Only 2.6% of patients were "extremely" satisfied with their current treatment, and 9.5% were "very" satisfied (38.6% were "not at all" or "not very" satisfied). At least 50% of FM patients "strongly agreed" that:

- Patients need physicians to help them explain their condition to family, friends, coworkers, and employers
- Physicians should help patients to communicate the symptoms they are experiencing
- Patients have encountered ≥ 1 physician who questioned the legitimacy of the FM diagnosis
- Patients had ≥ 1 experience where a physician did not take them seriously

But <10% "strongly agreed" that physicians are:

- Well trained to diagnose and treat FM
- Compassionate with their FM patients

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Conclusions: FM patients experienced a spectrum of symptoms that affect their QOL. Many reported difficulty with diagnosis, and few were very satisfied with their treatment. Clinicians can use these insights to improve patient care.

Encore Presentation: A small amount of data will be presented during a CME teleconference/webinar activity in June 2011. The majority of data in this (AAPM) poster presentation will be new data.

37. Hospitalization Charges for Fibromyalgia in the United States, 1999 to 2007

Presenter: Mark G. Haviland, PhD

Authors: Mark G. Haviland, PhD; Jim E. Banta, PhD, MPH; Peter Przekop, DO, PhD

Background: The economic burden of fibromyalgia is substantial, yet little is known about costs when patients are admitted to the hospital with fibromyalgia as the primary diagnosis. Moreover, in few fibromyalgia studies are there sufficient numbers of men and nonwhite participants to study potential gender and racial/ethnic factors.

Objective: To evaluate hospital discharge data for patients admitted for fibromyalgia: (a) estimate total hospitalization costs and (b) determine factors associated with variation in these costs.

Methods: Data were from the Nationwide Inpatient Sample (NIS), which is the largest all-payer inpatient-care database in the United States (covering about 90% of all hospital discharges). Selected for study were patients with the International Classification of Diseases, 9th revision, Clinical Modification FM diagnosis code (729.1, Myositis and Myalgia, unspecified) from the years 1999 to 2007. Total Consumer Price Index (CPI) adjusted (to 2007 dollars) charges were estimated, and a multivariable linear regression model was run with SAS 9.2.

Results: Over the 9-year span, an estimated 63,772 patients – 20,004 (31.4%) men and 43,768 (68.6%) women – were admitted with fibromyalgia as the primary diagnosis. Survey-adjusted total Consumer Price Index (CPI)-adjusted charges were estimated to be \$836,484,216 (\$271,564,313 for men and \$564,919,903 for women). Just over a half of the total charges were billed to Medicare or Medicaid. Mean charges per hospitalization were slightly higher for men (\$14,405) than for women (\$13,328). Mean charges were lowest for whites (\$13,268) and higher for blacks (\$16,529) and Hispanics (\$16,078). Race/ethnicity is masked for approximately 25% of these hospitalizations, so the race/ethnicity multivariable analyses include only an estimated 9,580 white, 2,700 black, and 1,965 Hispanic men; and 21,845 white, 5,820 black, and 3,309 Hispanic women. Survey-adjusted multivariable linear regression models were run after excluding those with masked race data. Gender and race were not significant in this model. Hospital-level measures (Census region, bed size, rural/urban, teaching status, ownership type, and year) explained 8.49% of variations in charges and patient-level measures (age, gender, race/ethnicity, number of procedures, primary payer, and Charlson Comorbidity Index) explained 3.47% (combined hospital + patient total = 11.96%). The strongest predictors of charges were region of the country (charges lowest in the West), number of procedures (positive increase), and hospital ownership type (charges highest at for-profit hospitals).

Conclusions: Average hospitalization costs for fibromyalgia from 1999 to 2007 were just under \$100 million a year. More effective outpatient treatment for fibromyalgia may decrease the need for hospitalization and thus lower the overall cost of treatment.

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38. Fibromyalgia Symptom/Function Correlations With Response

Presenter: Birol Emir, PhD

Authors: Lesley M. Arnold, MD; Gergana Zlateva, PhD; Alesia Sadosky, PhD; Birol Emir, PhD; Ed Whalen, PhD

Background: The Outcome Measures for Rheumatoid Arthritis Clinical Trials (OMERACT) Fibromyalgia Working Group recently proposed that fatigue, multidimensional function, and sleep disturbance, in addition to pain and tenderness should be included as key symptom and function domains in the assessment of patient response to fibromyalgia treatment with a goal of improving assessment of treatment response. An important step in this process is to understand which of the proposed clinical variables identified by the OMERACT fibromyalgia initiative drive patient perception of improvement.

Objective: The objective of the study was to conduct an analysis of pooled data from clinical trials of pregabalin in patients with fibromyalgia to determine which fibromyalgia symptom and function domains drive patient perception of improvement.

Methods: Data from three double-blind, placebo controlled trials (NCT00230776, NCT00645398, and NCT00333866) of pregabalin in fibromyalgia patients were pooled for this analysis. Changes in independent variables, including the Medical Outcomes Study 36-item Short-Form Health Survey, Medical Outcomes Study–Sleep Scale, sleep quality, and pain scores from the daily pain diary, Fibromyalgia Impact Questionnaire, and Multidimensional Assessment of Fatigue were analyzed as predictors of outcome on the dependent variable, Patient Global Impression of Change (PGIC). Correlation analysis assessed relationships between the independent variables and PGIC. Cluster analysis identified dependencies among variables, and a least absolute shrinkage and selection operator technique and stepwise logistic regression determined rank order of variables.

Results: Improvement in PGIC at endpoint showed highest correlation with pain improvement, fatigue, sleep, and work and physical function ($0.4 < r < 0.6$). Cluster analysis identified three main clusters of symptoms at endpoint: mood (anxiety and depression), pain and sleep, and function and fatigue. Pain was ranked as the most important outcome explaining variability in PGIC, followed by fatigue and sleep.

Conclusions: In support of the OMERACT group's push to expand the domains considered when assessing treatment response, pain, fatigue, and sleep associate most strongly with improvement in PGIC. Physical- and work-related function also correlated with patients' overall assessment of improvement. These domains and their respective outcome measures can be used to improve assessment of patients' response to treatment.

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Arnold, LM, et al. Correlations between fibromyalgia symptom and function domains and patient global impression of change: a pooled analysis of three randomized, placebo-controlled trials of pregabalin. *Pain Med.* 2011;12(2):260-7.

39. Pregabalin for Fibromyalgia with Comorbid Osteoarthritis

Presenter: Birol Emir, PhD

Authors: Lesley Arnold, MD; Birol Emir, PhD; Lynne Pauer, MS; Fangzi Huang, BS

Background: The central nervous system has been linked to the generation and maintenance of chronic pain in disease states such as fibromyalgia and osteoarthritis (OA).¹ Patients with fibromyalgia may also have OA as a comorbid condition. Pregabalin, an $\alpha 2\delta$ ligand, is approved in the US to treat fibromyalgia and peripheral neuropathic pain. It is not indicated for OA.

Objective: To assess whether pregabalin treatment outcomes differ between fibromyalgia patients with or without comorbid OA from four phase 3 pregabalin clinical trials (total of 2748 patients, 687 of them on placebo) in fibromyalgia.

Methods: All four studies had the same primary endpoint; the endpoint mean pain score derived from the subjects' daily pain diaries. We restricted the subgroup analysis to this common primary endpoint. Patients with comorbid OA (18.9% overall) were allowed in the studies if pain symptoms from OA did not confound the assessment of pain due to fibromyalgia. Endpoint mean pain was analyzed using an analysis of covariance with terms for treatment, study (or center if applicable), OA status, baseline mean pain score value as a covariate, and treatment by OA status as an interaction term. The percentage of patients with comorbid OA was summarized by study and treatment. Least squares (LS) mean treatment differences were calculated for OA vs non-OA patients in each of the 4 trials and then on the pooled trials using last observation carried forward (LOCF) and baseline observation carried forward (BOCF). The relationships between treatment and OA status and pain relief estimations for approved doses of pregabalin 300 mg/day and 450 mg/day versus placebo using LOCF and BOCF data were assessed.

Results: LS mean difference and 95% confidence intervals in pain scores did not statistically differ between OA and non-OA subgroups in any of the four trials. There were no significant interactions between treatment and OA status (pooled LOCF $P=0.135$; pooled BOCF, $P=0.224$).

Conclusions: This post hoc subgroup analysis suggests that the pregabalin efficacy over placebo is similar whether the patients had comorbid OA or not. However, one must be cautious interpreting these results as the power to uncover the true effect is likely very low and no multiple tests adjustments were done.

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Disclosure: This study was supported by Pfizer Inc.

40. Variations in Managing Fibromyalgia by Physician Specialty

Presenter: Stephen Able, PhD

Authors: Stephen Able, PhD; Yi Chen, MS; JiayingGuo, MS; Kurt Kroenke, MD; Madelaine Wohlreich, MD; David Williams, PhD; Bill McCarberg, MD; Rebecca Robinson, MS

Background: Fibromyalgia (FM) is characterized by chronic, widespread pain and associated symptoms and is often comorbid with other conditions. It is treated by physicians from multiple specialties who employ a variety of treatment strategies.¹

Objective: To evaluate the role of physician specialty on patient and physician characteristics among patients initiating new treatments for FM.

Methods: Baseline data (collected from 7/2008 to 5/2010) were analyzed from REFLECTIONS, a prospective, observational study.² Broad categories of providers known to treat FM enrolled patients from 58 outpatient sites in the United States and Puerto Rico. Data were collected via physician surveys, office visit forms, and telephone interviews with patients (n=1700). Pair-wise comparisons of rheumatologists (n=54), primary care physicians (PCPs; n=25), and pain or physical medicine physicians (PPM; n=3) were made using chi-square and Fisher's exact tests for categorical variables and t-tests for continuous variables.

Results: Physicians were mostly male (72.9%), 49.5 [9.8] (mean [standard deviation, SD]) years of age and 15.6 [9.2] years in practice, with no significant differences among specialties. Widespread pain (85.8%), fatigue (83.7%), and sleep disorders (73.8%) were frequent among treated patients, with only modest differences reported by specialty. Symptoms associated with mood were commonly noted by PCPs (69.9%), but not PPMs (33.3%; $P<.05$). Physicians expressed a high level of confidence diagnosing FM (overall mean [SD]=4.4 [0.7] on a 5-point rating scale), with greater confidence among rheumatologists (4.5) than PCPs (4.1; $P<.05$). Physicians were more confident in treating FM with medications (4.3 [SD=0.8]) than with alternative therapies (3.4 [SD=1.1]), although confidence with alternative therapies was numerically much higher (4.7 [SD=0.6]) among PPMs. Patient satisfaction, reported as excellent to good for 61.8% of all physicians, was higher for rheumatologists (63.5%) and PPMs (68.0%) than for PCPs (56.5%; P for both $<.05$).

Conclusions: This analysis compares physician practice characteristics, physician attitudes, and patient profiles of three categories of physicians: rheumatologists, pain and physical medicine specialists, and primary care physicians. While broadly similar, there are notable differences among these factors across these specialties, which may impact treatment patterns and patient outcomes.

References:

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2. Robinson RL, Kroenke K, Mease P, et al. Burden of Illness and Treatment Patterns for Patients with Fibromyalgia: Baseline Findings from the REFLECTIONS Study. Submitted for publication, *J Pain.*

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41. Milnacipran Improves FM Symptoms, Regardless of Severity

Presenter: Julie Frisolone, PharmD

Authors: Robert H. Palmer, MD; Yong Wang, PhD; Julie Frisolone, PharmD

Background: In several clinical trials, milnacipran was effective for treating the multiple symptoms of fibromyalgia (FM). It is not known whether the severity of pain or overall FM symptoms at the time of treatment initiation may influence the efficacy of milnacipran.

Objective: To evaluate the impact of baseline pain and overall FM symptom severity on the efficacy of milnacipran in patients with FM.

Methods: Data were pooled from 3 similarly designed trials in which patients were randomized to placebo (n=1133), milnacipran 100 mg/day (n=1139), or milnacipran 200 mg/day (n=837). Efficacy assessments were a pain responder analysis ($\geq 30\%$ improvement from baseline in 24-hour recall VAS pain scores), Patient Global Impression of Change (PGIC) responder analysis (rating of “very much improved” or “much improved”), and a 2-measure composite responder analysis (individual patients were required to meet both pain and PGIC responder criteria). Data were stratified by baseline pain severity (VAS score < 60 [moderate]; ≥ 60 to 70 [severe]; > 70 [very severe]) or overall FM severity (Fibromyalgia Impact Questionnaire [FIQ] total score < 39 [mild]; 39 to < 59 [moderate]; ≥ 59 [severe]). Results are reported for observed cases (OC) at the 3-month endpoint.

Results: Milnacipran treatment, compared with placebo, resulted in significantly greater pain, PGIC, and 2-measure responder rates, regardless of baseline pain severity group ($P < .05$, both doses) with odds ratios (OR) ranging from 1.7 to 2.5 for pain responders, 1.7 to 2.8 for PGIC responders, and 1.5 to 3.0 for 2-measure responders. Similarly, in all baseline FIQ severity subgroups, pain, PGIC, and 2-measure responder rates were significantly greater with milnacipran treatment than with placebo ($P < .05$, both doses; ORs, 1.6 to 4.0), except in the small group of patients with an FIQ total score < 39 for 100 mg/day 2-measure composite responders (n=42; OR, 2.2) and 200 mg/day pain responders (n=26; OR, 1.7).

Conclusions: In conclusion, milnacipran treatment resulted in significant multidimensional improvements in pain and global status, regardless of baseline pain severity or FM severity.

Encore Presentation: Presented previously at the 30th Annual Scientific Meeting of the American Pain Society, May 19-21 in Austin, Texas.

42. Pain/Fatigue Relationship in Milnacipran-Treated Patients

Presenter: Julie Frisolone, PharmD

Authors: Robert H. Palmer, MD; Yong Wang, PhD; R. Michael Gendreau, MD, PhD; Julie Frisolone, PharmD

Background: In addition to chronic widespread musculoskeletal pain, patients with fibromyalgia (FM) commonly report fatigue as a major symptom. Results from several clinical trials have shown that milnacipran significantly improves both pain and fatigue in patients with FM. However, the relationship between these 2 symptom domains in milnacipran-treated patients has not been well characterized.

Objective: To examine the relationship between fatigue and pain improvements in patients who are treated with milnacipran for the management of FM.

Methods: Data were pooled from 3 phase III studies in patients with FM randomized to placebo (n=1133), milnacipran 100 mg/d (n=1139), or milnacipran 200 mg/d (n=837). After a dose-escalation phase, patients underwent 12 weeks of stable-dose treatment. Fatigue was measured by using the Multidimensional Fatigue Inventory (MFI), and pain was measured by using a VAS pain scale (0-100). In order to evaluate the impact of baseline fatigue severity on pain improvement with treatment, changes in pain were assessed in patients stratified into tertiles based on their baseline MFI total scores (ie, MFI ≤ 63 ; MFI > 63 and ≤ 74 ; MFI > 74). Pearson correlation coefficients were determined for the relationship between improvements in MFI total score and improvements in pain VAS.

Results: At the 3-month endpoint, significant improvements over placebo with both doses of milnacipran were observed in MFI total score ($P < .01$). Milnacipran 200 mg/day treatment resulted in significant improvements in all MFI subscale scores vs placebo ($P < .05$); milnacipran 100 mg/day significantly improved general fatigue, physical fatigue, and reduced motivation subscale scores vs placebo ($P < .05$). Milnacipran-treated patients stratified to all baseline fatigue intensity tertiles had significantly reduced pain VAS scores ($P < .05$, vs placebo). Improvements in MFI total score correlated only moderately well with improvements in pain VAS (milnacipran, $r = 0.4729$; placebo, $r = 0.3898$).

Conclusions: These results suggest that milnacipran treatment improves fatigue in patients with FM and improves pain, regardless of baseline levels of fatigue. Furthermore, improvements in fatigue and improvements in pain did not appear to be strongly correlated, suggesting that both domains should be assessed independently.

Encore Presentation: Presented previously at the 30th Annual Scientific Meeting of the American Pain Society, May 19-21 in Austin, Texas.

43. A 3-Year, Open-Label Study of Milnacipran for Fibromyalgia

Presenter: Jolan Turner-Rosenthal, PhD

Authors: Lesley Arnold, MD; Allan Spera, BA; Arlene Baldecchi, MT (ASCP), CCRA; Yong Wang, PhD; Jolan Turner-Rosenthal, PhD

Background: Milnacipran is approved for the management of fibromyalgia (FM), a chronic disorder characterized by widespread pain and other symptoms that adversely affect function and health-related quality of life. Because FM is a chronic disorder, long-term efficacy is an important treatment goal.

Objective: To evaluate the long-term safety and efficacy of milnacipran for the management of FM, an open-label, flexible-dose study was conducted in patients with FM over a period that could exceed 3 years.

Methods: Patients in this study (n=1227) were required to have successfully completed previous milnacipran studies. This study consisted of a 2-week washout period, a 2-week dose-escalation period (to milnacipran 100 mg/day), an 8-week stable-dose period (at milnacipran 100 mg/day), and a flexible-dose period (milnacipran 50-200 mg/day) for the remainder of the 3 year study. Key efficacy outcomes included 24-h and weekly recall VAS pain (0-100 mm scale), Patient Global Impression of Change (PGIC), Patient Global Disease Status (PGDS), SF-36 Physical Component Summary (PCS), and the Brief Pain Inventory (BPI) (0-10 scale). Efficacy results are reported as mean changes from study baseline following the 2-week washout period.

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Results: Of the 1227 patients, 47.7% were considered completers, with 206 patients reaching the final visit and 379 being currently enrolled when the study terminated. At the final visit, patients treated with milnacipran demonstrated improvements in pain, with a mean reduction from baseline in 24-h recall VAS pain scores of 23.1 mm (observed cases). Improvements in VAS weekly recall pain, BPI scores, global status (PGIC, PGDS), and physical function (SF-36 PCS) were also observed with milnacipran treatment. The most common treatment-emergent adverse events (TEAEs) over the 3-year period were nausea, headache, hypertension, and sinusitis. TEAEs led to study discontinuation in 20.9% of patients, most commonly because of nausea.

Conclusions: The findings provide support for sustained long-term efficacy (in some cases exceeding 3 years of continuous usage) and tolerability of milnacipran in the treatment of FM.

Encore Presentation: Presented previously at the 30th Annual Scientific Meeting of the American Pain Society, May 19-21 in Austin, Texas.

44. Milnacipran Associated with More Good Days for FM Patients

Presenter: Steven I. Blum

Authors: Steven I. Blum, MBA; Joel M. Trugman, MD; Stavros Tourkodimitris, PhD

Background: Fibromyalgia (FM) can have a significant impact on patient's quality of life. The Good Days Questionnaire for FM (GDQFM) contains several items from the Centers for Disease Control and Prevention Health Related Quality-of-Life (CDC-HRQOL) measure (also known as the Healthy Days Measures), a patient-reported outcomes instrument used to measure health-related quality of life.

Objective: To compare treatment outcomes measured by Good Days among patients who discontinue or continue long-term treatment with milnacipran (MLN).

Methods: This randomized, double-blind, placebo-controlled, parallel-group discontinuation study investigated patients who had been treated with MLN for a duration of up to 4.5 years (range: 18 to 54 months) in previous MLN clinical trials. Following a 4-week open-label treatment period, patients who experienced $\geq 50\%$ reduction in their visual analog scale (VAS) pain score [from pre-MLN exposure to current status] and were being treated with MLN 100-200 mg/d (ie, primary analysis population) were randomized 2:1 to MLN (n=100) or placebo (PBO; n=51). The GDQFM and SF-36 were administered during the 12-week double-blind treatment period. Change from baseline (randomization) was analyzed using ANCOVA and LOCF imputation. The relationship between the Bad Physical and Mental Days was explored by cross-tabulation across both treatment arms (n=150). Pearson correlations evaluated the correlation between Bad Physical and Mental Days with the SF-36 Physical (PCS) and Mental Component Summaries (MCS), respectively.

Results: MLN-treated patients had a significantly greater number of Good Days/wk than PBO-treated patients at all study visits and at the end of the 12-week double-blind treatment period. Patients randomized to continue MLN had 3.0 (2.41) mean (SD) Good Days/wk compared to 2.5 (2.23) Good Days/week for PBO (LSMD = 0.8 Days/wk; 95% CI = [0.0-1.6]; $P < 0.05$). Distribution of Bad Physical Days differed significantly from the distribution of Bad

Mental Days in the same subjects ($P < 0.001$). Cross-tabulation showed that 65.3% of patients had more Bad Physical Days, 15.3% had more Bad Mental Days, and 19.3% had the same number of Bad Physical and Mental Days. The number of Bad Days due to Physical Health and Mental Health was moderately highly correlated with the SF-36 PCS ($r = -0.5161$) and MCS ($r = -0.6398$), respectively.

Conclusions: Among patients who received long-term treatment with milnacipran, those who continued on treatment with milnacipran had significantly more Good Days compared to patients who discontinued treatment. Patients who continued milnacipran treatment had 0.8 more Good Days/week, which extrapolates to an additional 42 Good Days/year. Patients with fibromyalgia were more likely to experience Bad Days because of physical health than mental health.

Encore Presentation: European League Against Rheumatism (EULAR) 2011 Annual European Congress of Rheumatology, May 25-28, 2011, London, UK (abstract accepted for online publication only in abstract form).

45. Pain and Aerobic Endurance Among Adults 50+ With and Without FM

Presenter: Jordan K. Aquino, BS

Authors: Jordan K. Aquino, BS; Dana N. Rutledge, PhD, RN; Brianne Levine, BA; C. Jessie Jones, PhD

Background: Losing functional independence is a universal concern. Aerobic endurance is associated with functional independence. Research has indicated that individuals need to walk approximately 440 yards to be functionally independent.¹ Decreases in aerobic endurance (AE) have been documented among persons with fibromyalgia (FM).²

Objective: The purpose of this study was to determine the association between perceived pain and number of yards walked among older adults with and without fibromyalgia.

Methods: The sample of 115 ambulatory community-dwelling persons (mean age 65 years; 81% female; 60% sedentary/underactive) included 64 persons with FM. All participants completed a 6-minute walk test to assess the number of yards walked. Perceived pain scores were recorded on a self-reported scale of 0 to 10, with higher scores indicative of worsening pain. Bivariate correlations were used to evaluate potential covariates. Linear regressions determined associations between pain and AE, taking age and depression into account.

Results: Persons with FM reported more pain than their healthy counterparts (5.6 vs 2.0, $P < .0001$) and walked less than those without pain (515 vs 616 yards, $P < .0001$). In persons with FM, pain shows a likely association with AE ($P = .056$), taking into account age and depression; a model with all three variables accounts for 28% of the variance in endurance. In persons without FM, pain is not associated with AE when age and depression are accounted for; age and depression account for 10% of variance in endurance. Both samples were small, so these analyses should be considered exploratory.

Conclusions: Our findings support past studies showing age and depression as affecting AE in persons over 50 years. They point to the potential association of pain on endurance in persons over 50 with FM. Clinicians should evaluate AE in persons with FM. Patients who have deficits should be encouraged to take part in acceptable aerobic activities (walking, cycling, pool exercise), as aerobic exercise

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may have a positive effect on physical performance, including AE.³ This discussion should include the feasibility of how to manage pain and exercise together.

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2. Jones CJ, Rutledge DN, Aquino J. Predictors of physical performance and functional ability in people 50+ with and without fibromyalgia. *J Aging Phys Activ*. 2010;18:353-358.
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46. Loss of Response Following Milnacipran Discontinuation

Presenter: Jolan Turner-Rosenthal, PhD

Authors: Philip Mease, MD; Yimin Ma, PhD; Arlene Baldecchi, MT (ASCP), CCRA; Joel Trugman, MD; Jolan Turner-Rosenthal, PhD

Background: Milnacipran has demonstrated efficacy in managing pain, fatigue, and other fibromyalgia (FM) symptoms in several 3- to 6-month double-blind, placebo-controlled trials and in 6- to 9-month open-label extension studies. Patients who completed these studies and who were enrolled in a long-term, open-label study of milnacipran (up to 3.25 years) were eligible for this 17-week randomized, double-blind, placebo-controlled, discontinuation trial.

Objective: This study was designed to evaluate the effect of discontinuation of long-term milnacipran treatment on the symptoms of FM.

Methods: Patients were enrolled and treated with open-label milnacipran 50 to 200 mg/day for 4 weeks (at same dosage as in previous study, Poster No. 53). At the end of the 4-week period, patients taking milnacipran ≥ 100 mg/day and achieving a $\geq 50\%$ reduction in visual analog scale (VAS) pain score from premilnacipran exposure to current status were randomized 2:1 to double-blind treatment with milnacipran (ie, milnacipran continued) or placebo (ie, milnacipran withdrawn) for 12 weeks. The primary efficacy parameter was the time to loss of therapeutic response (LTR), with LTR defined as an increase in VAS pain score to $< 30\%$ reduction from premilnacipran exposure or a worsening of fibromyalgia requiring an alternative treatment. Time to LTR was analyzed by using Kaplan-Meier estimates by treatment group and the log-rank test.

Results: Time to LTR was significantly shorter for patients withdrawn from milnacipran (n=50) than those continuing milnacipran (n=100, $P=.0004$). The median time to LTR was 56 days (95% CI, 28-85) for patients withdrawn from milnacipran and not calculable for patients continuing milnacipran because half of those patients had not lost therapeutic response by study end. At the end of double-blind treatment, 64% of patients withdrawn from milnacipran experienced LTR vs 35% of patients continuing milnacipran. Discontinuation due to treatment-emergent adverse events occurred in 2 milnacipran-treated patients (2.0%) and no placebo-treated patients.

Conclusions: In patients who have been treated with milnacipran for up to 3.25 years, the loss of therapeutic response upon discontinuation of treatment provides further evidence of the efficacy of milnacipran as a treatment for FM.

Encore Presentation: Presented previously at the 30th Annual Scientific Meeting of the American Pain Society, May 19-21 in Austin, Texas.

47. Nociceptive Pain Sources in Fibromyalgia

Presenter: Jeff Sarkozi, MD, FRCPC

Author: Jeff Sarkozi, MD, FRCPC

Background: Fibromyalgia (FM) is a condition characterized by widespread pain and painful tenderness to exogenous stimulation. Central sensitization to externally induced nociceptive stimulation has been well documented. However, no intrinsic source for the pain modified by central sensitization has been identified.

Objective: To identify intrinsic nociceptive pain drivers in FM.

Methods: A retrospective study was undertaken of the presenting clinical features of 100 adult fibromyalgia patients (89 females, 11 males) assessed in a rheumatology practice with a specialty interest in FM. Patients fulfilled the 1990 American College of Rheumatology criteria for the classification of FM. Patients with known secondary FM were excluded from this study. All patients participated in an extended assessment of all musculoskeletal complaints, sleep disturbances, fatigue, and psychological issues and underwent a comprehensive general and musculoskeletal examination.

Results: Patient history identified symptoms of osteoarthritis (OA) and degenerative disc disease (DDD) involving the cervical spine (CS) in 97%, lumbosacral spine in 96%, and thoracic spine in 41%. Symptoms of OA were reported in the knee joints (KJ) in 62%, metatarsophalangeal joints (MTPJ) in 37%, ankles in 35%, first carpometacarpal joints (FCMCJ) in 27%, temporomandibular joints (TMJ) in 27%, wrist joints in 25%, metacarpophalangeal joints (MCPJ) in 21%, finger proximal interphalangeal joints (FPIPJ) in 34%, and finger distal interphalangeal joints (FDIPJ) in 12%. Generalized widespread aching was reported by 41%. Examination revealed osteophytes at the FCMCJ in 90%, FDIPJ in 76%, FPIPJ in 31%, and first MTPJ in 60%. FCMCJ subluxation was noted in 90%. Distinct joint line painful tenderness or pain with motion was identified in the CS in 100%, knee patellofemoral joint in 73%, FCMCJ in 61%, MTPJ in 48%, FPIPJ in 24%, first MCPJ in 21%, FDIPJ in 20%, TMJ in 14%, hip joint in 12%, and medial or lateral KJ in 12%. Periarticular findings included trochanteric bursitis in 40%, plantar fasciitis in 26%, subacromial bursitis/supraspinatus tendinitis in 21%, medial or lateral epicondylitis in 8%, and painfully tender flexor tendon nodules in 16%. Examination for painful soft tissue tenderness revealed an average of 16 FM tender points. Diffuse, nondistinct, widespread tenderness throughout all 4 extremities was noted in 52%.

Conclusions: These results identify the presence of widespread polyregional musculoskeletal nociceptive pain drivers in nonsecondary FM patients. The data suggest that adults with nonsecondary FM have: 1) primary generalized OA predominantly involving the neck and back with associated DDD and a variable combination of tendinitis, bursitis, and fasciitis and 2) increased nociception to these and induced painful stimuli.

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Migraine

48. Molecular Probe of Chronic Migraine Pain

Presenter: Lawrence Robbins, MD

Authors: Lawrence Robbins, MD; C. C. Leith, PhD

Background: Both water and ions pass through ion channel proteins in the membrane of conducting axons. The ion flux determines the membrane potentials, while the water flux indicates the propagation of neural impulses in axons. Less explored is the fact that the water flux is always many times greater than the ion flux. We have developed a new imaging approach — the adapted diffusion tensor imaging (aDTI) — to detect this water flux, and thus, the abnormal baseline neural activity in chronic migraine.^{1,2} We focus on the brainstem, where the nociceptive pathways and antinociceptive circuits are localized. Imaging of brainstem function may help in understanding chronic migraine (CM).

Objective: To test the hypothesis that there is abnormal baseline neural activity in the brainstem in CM headache and to prove that this abnormality can be captured by magnetic resonance imaging of the water flux through protein channel pores.

Methods: Seven CM patients (ages 19 to 47 yr) and 7 matched controls were evaluated using aDTI. All 7 patients had transformed from migraine without aura to CM. All images were acquired using a 1.5T MRI system. A time series of raw aDTI images was acquired from every subject in analogy to fMRI data acquisition, from which the fractional diffusion anisotropy (FA) time series was derived. FA was a convenient mathematical representation of water flux through protein channels such that increased neural impulses elevate this water flux and reduce FA. The statistical parametric mapping method was employed to perform a group analysis on FA time series at every voxel, allowing the capture of minute FA changes in 3D in patients compared to controls.

Results: In the brainstem of the patient group, multiple loci of reduced FA or elevated neural activity ($P < 0.001$) were localized in the cerebral peduncle bilaterally, in the middle cerebellar peduncle on the right side, in the midline midpons, and in the upper medulla on the left. No abnormalities were found in the controls.

Conclusions: aDTI demonstrates its sensitivity in detecting abnormal baseline neural activity. It reveals loci of elevated neural impulses in the resting state of these CM patients. It is superior to fMRI as it does not depend on neurovascular coupling that is still poorly understood. There is no need for uncomfortable or painful stimuli to patients in aDTI scans. aDTI may help shed new light on functional and, perhaps, reversible changes in patients with chronic migraine, creating new opportunities in evaluating drug targeting and efficacy.

References:

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49. Prevalence of Chronic Migraine (CM), Headache-related Disability and Sociodemographic Factors in the US Population: Results from the American Migraine Prevalence and Prevention (AMPP) Study

Presenter: Catherine C. Turkel, PhD

Authors: Dawn C. Buse, PhD; Michael L. Reed, PhD; Kristina Fanning, PhD; Aubrey Manack, PhD; Daniel Serrano, PhD; Catherine C. Turkel, PhD, PharmD; Richard B. Lipton, MD

Background: CM is broadly defined by the presence of migraine with headaches ≥ 15 days/month. A recent review of 16 international population-based studies using various criteria reported CM prevalence ranging from 0.9% to 5.1%, with most estimates in the range of 1.4% to 2.2%.

Objective: To estimate prevalence of CM in the US population and characterize persons with CM by sociodemographic subgroups and headache-related disability.

Methods: In 2004, we mailed surveys to sample of 120,000 US households stratified to represent US Census data. Headache frequency, symptoms, sociodemographics, and headache-related disability (MIDAS) data were obtained. Surveys were returned by 162,756 individuals aged ≥ 12 , and 28,621 reported severe headache. CM was defined as ICHD-2 migraine with headache frequency ≥ 15 headache days/month; EM > 15 headache days/month. Crude and sociodemographically adjusted prevalence ratios (PRs) were generated and EM and CM groups were contrasted by MIDAS grades.

Results: 19,189 individuals (11.79%) met ICHD-2 criteria for migraine (17.27% of females, 5.72% of males) and 0.91% met criteria for CM (1.29% of females, 0.48% of males). Prevalence of CM varied by age, and rates were highest for both females (1.9%) and males (0.8%) in the age range 40 to 49. Prevalence was also 1.9% among females aged 19 to 29, followed by 1.8% among females age 30 to 39. When compared with persons aged 12 to 17, adjusted prevalence ratios in 40 to 49 age group were: females 4.71 (95% CI 3.24-6.83), males 3.31 (95% CI 1.99-5.49.) Rates of CM were higher in African-Americans (females: 1.7%, males: 0.7%) than in Caucasians (females: 1.2%, males: 0.5%), although race was not an independent predictor after adjusting for sociodemographics. Rates of CM were inversely correlated with annual household income and ranged from 2.6% in females and 1.3% in males in households with annual household incomes $< \$22,500$ to 0.5% of females and 0.2% of males among households with average annual incomes $\geq \$90,000$ (adjusted PR females: 0.16 (95% CI 0.12-0.20), males: 0.19 (95% CI 0.15-0.24). Severe-headache-related disability (MIDAS Grade IV) reported by 37.97% of CM vs 9.51% of EM respondents.

Conclusions: In this US population sample, prevalence of CM was nearly 1% (0.91%) and varied by sociodemographics. CM prevalence was highest among females, African-Americans, persons in mid-life, and households with the lowest income. In adjusted models, gender, age, and household income persisted as significant independent predictors; race did not. Higher rates of CM in African-Americans may be due to the influence of socioeconomic (SES) status. Low SES may operate through stress, poor access to medical care, or other factors. The highest grade of headache-related disability was significantly greater among persons with CM.

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References:

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Encore Presentation: 15th Congress of the International Headache Society, June 23–26, 2011, Berlin, Germany.

50. Costs Associated with Lost Productive Time Among Working Adults with Chronic and Episodic Migraine in the United States (US) and Canada

Presenter: Lisa M. Bloudek, PharmD, MS

Authors: Gregory A. Maglinte, PhD; Lisa M. Bloudek, PharmD, MS; Michael E. Stokes, MPH; Leandra Wells, PhD, MBA; Andrew M. Blumenfeld, MD; Richard B. Lipton, MD; Dawn C. Buse, PhD; Werner J. Becker, MD; Teresa K. Wilcox, PhD

Background: Migraine is a complex, debilitating neurological condition that significantly affects mental and physical functioning and produces substantial occupational disability.

Objective: To evaluate the impact of chronic migraine (CM) and episodic migraine (EM) on lost work time and productivity costs in the US and Canada.

Methods: Cross-sectional data were collected via a web-based survey from January to February 2010. Respondents were classified as CM (≥ 15 headache days/month) or EM (< 15 headache days/month). Number of days missed from work or school and number of days where productivity at work or school was reduced by $\geq 50\%$ over the last 3 months was assessed using the Migraine Disability Assessment Questionnaire. Country- and gender-specific wage rates were collected separately and applied to lost work time and productivity data to estimate lost labor costs (2010 US and Canadian dollars). Analyses of lost productive time and costs were conducted among those reporting full-time or part-time employment.

Results: Among US participants employed either full- or part-time ($n=203$), those with CM missed an average (\pm SD) of 2.5 ± 4.9 days from work in the last 3 months versus 1.9 ± 2.8 days for EM ($P=0.66$). In Canada ($n=52$), CM participants missed 3.6 ± 5.6 days from work compared to only 0.8 ± 1.6 days for EM ($P=0.09$). Days where productivity was reduced by $\geq 50\%$ was also higher among CM compared to EM for US (14.6 ± 14.2 vs 4.1 ± 4.4 ; $P<0.0001$) and Canada (20.2 ± 18.2 vs 3.0 ± 3.7 ; $P<0.001$). Total lost time and productivity costs were \$816 higher in the last 3 months for CM compared to EM in the US ($\$1,324\pm 1,286$ vs $\$508\pm 527$; $P<0.0001$), and \$1,735 higher in Canada ($\$2,096\pm 1,744$ vs $\$361\pm 498$; $P<0.0001$).

Conclusions: CM was associated with significantly greater lost productivity and higher lost labor costs compared to EM in the US and Canada.

Encore Presentation: 62nd Annual Meeting of the American Academy of Neurology; April 9-16, 2011; Honolulu, Hawaii, USA.

51. Health Care Resource Use and Costs Among Patients with Chronic and Episodic Migraine in the United States

Presenter: Sepideh F. Varon, PhD

Authors: Michael E. Stokes, MPH; Sepideh F. Varon, PhD; Sean D. Sullivan, PhD; Andrew M. Blumenfeld, MD; Richard B. Lipton, MD; Peter J. Goadsby, MD, PhD; Teresa K. Wilcox, PhD

Background: Migraine is a common, disabling neurological disorder that imposes a significant burden on patients and health care systems.

Objective: The purpose of this study was to evaluate resource use (RU) and associated costs in chronic migraine (CM) and episodic migraine (EM) patients in the United States (US).

Methods: Cross-sectional data were collected via a web-based survey from February to April 2009. Respondents were classified as CM (≥ 15 headache days/months) or EM (< 15 headache days/month). Data collection included baseline demographic and clinical characteristics and medical RU for headache treatment (clinician and emergency department [ED] visits and hospitalizations over the last 3 months and medications over the last 4 weeks). Unit cost data were collected separately from the web-based survey using publicly available sources and applied to RU profiles. Cost estimates were annualized and presented in 2010 \$US. Cost calculations included imputation of missing RU data using mean values of the non-missing participants. Group comparisons of medical RU were made using Fisher's exact test. The RU profile of patients with costs above the 99th percentile was examined; one patient was excluded from this analysis because of *potentially* unreliable data (45 ED visits within a 3-month period).

Results: The study evaluated total of 1,204 participants with migraine. Participants with CM were more likely to have had a primary care provider or neurologist/headache specialist visit compared to EM ($P<0.001$). 4.9% of CM and 3.2% of EM patients were treated either in an ED or hospital for headache ($P=0.35$). Similar proportions of CM and EM patients (83%) also reported having used headache-related medication over the last 4 weeks ($P=1.00$). Mean total annual per-patient costs (\pm SD) were \$2,608 higher for CM than for EM ($\$4,140\pm \$5,332$ vs $\$1,532\pm \$3,224$, respectively, $P<0.001$).

Conclusions: CM was associated with higher medical RU and total costs compared to EM.

Encore Presentation: 62nd Annual Meeting of the American Academy of Neurology; April 9-16, 2011; Honolulu, Hawaii, USA.

52. OnabotulinumtoxinA for Treatment of Chronic Migraine: Pooled Results From the Double-Blind, Randomized, Placebo-controlled Phase of the PREEMPT Clinical Program

Presenter: Catherine C. Turkel, PharmD

Authors: David W. Dodick, MD; Sheena K. Aurora, MD; Catherine C. Turkel, PharmD, PhD; Ronald E. DeGryse, MS; Stephen D. Silberstein, MD; Richard B. Lipton, MD; Hans-Christoph Diener, MD; and Mitchell F. Brin, MD

Background: Chronic migraine (CM) is a prevalent, disabling, and undertreated neurologic disorder. Few preventive treatments have been investigated; onabotulinumtoxinA is the only approved therapy for CM.

Objective: To assess the efficacy and safety of onabotulinumtoxinA (BOTOX®) for the prophylaxis of headaches in adults with CM.

Methods: Two phase 3, 24-week, double-blind, parallel-group, placebo-controlled studies (PREEMPT 1 and 2) followed by a 32-week, open-label phase, evaluated the efficacy and safety of onabotulinumtoxinA in CM (ICHD II migraine and ≥ 15 headache days/month). Qualified subjects were randomized (1:1) to injections

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of onabotulinumtoxinA (155 U-195 U) or placebo every 12 weeks for 5 (double-blind 2, open-label 3) cycles. Key endpoints were mean change from baseline in frequency of headache days (primary PREEMPT 2) and headache episodes (primary PREEMPT 1) at week 24.

Results: Pooled analyses of 1384 randomized adults (onabotulinumtoxinA n=688, placebo n=696) demonstrated a large mean decrease from baseline for key endpoints (headache days and headache episodes), and for almost all secondary variables favoring onabotulinumtoxinA at week 24 (headache days: -8.4 onabotulinumtoxinA, -6.6 placebo; $P<0.001$; headache episodes -5.2 onabotulinumtoxinA, -4.9 placebo; $P=0.009$) and all other time points. The percentage of patients who had $\geq 50\%$ reduction from baseline in headache days at week 24 was significantly greater for onabotulinumtoxinA (47.1% onabotulinumtoxinA, 35.1% placebo; $P<0.001$). The only efficacy variable that did not show a significant difference at week 24 was overall acute HA medication use (all categories; $P=0.247$). However, a significant between-group difference in triptan use reduction was observed ($P<0.001$). Most AEs (62.4% onabotulinumtoxinA, 51.7% placebo) were mild to moderate in severity, with few discontinuations (2.8% onabotulinumtoxinA, 0.7% placebo) due to AEs.

Conclusions: This pooled analysis of the PREEMPT trials supports the efficacy, safety, and tolerability of onabotulinumtoxinA for the prophylaxis of headache in adults with CM.

Encore Presentation: EHMTIC 2010: European Headache and Migraine Trust International Congress, October 28-31, 2010, Nice, France.

53. OnabotulinumtoxinA for Chronic Migraine: PREEMPT Trials Establish a Safe and Effective Dose and Injection Paradigm

Presenter: Catherine C. Turkel, PharmD

Authors: Andrew M. Blumenfeld, MD; Stephen D. Silberstein, MD; David W. Dodick, MD; Sheena K. Aurora, MD; Catherine C. Turkel, PharmD, PhD; William J. Binder, MD

Background: Chronic migraine (CM) is a prevalent, disabling, undertreated neurologic disorder. OnabotulinumtoxinA is the only approved therapy for CM. Various onabotulinumtoxinA dosages and injection paradigms have been evaluated in studies for prevention of headache including migraine, but until recently, none is uniformly safe and effective for the treatment of CM.

Objective: To establish a safe and effective onabotulinumtoxinA dose and injection paradigm for patients with CM.

Methods: The PREEMPT clinical program (2 phase 3, 24-week, double-blind, parallel-group, placebo-controlled studies, followed by a 32-week, open-label phase) evaluated the efficacy and safety of onabotulinumtoxinA in CM (ICHD II migraine and ≥ 15 headache days/month). Randomized patients received a minimum dose of 155 U onabotulinumtoxinA or placebo administered as 31 fixed-site, fixed-dose injections across 7 specific head/neck muscle areas (corrugator, procerus, frontalis, temporalis, occipitalis, cervical paraspinal, and trapezius). Patients with predominant pain location(s) could receive up to 40 U additional onabotulinumtoxinA (maximum dose 195 U) or placebo injections to one or both sides in up to 3 muscle groups (occipitalis, temporalis, and trapezius). Using

a sterile 30-gauge, 0.5 inch needle (with a Luer Lock) intramuscular injections of 0.1 mL/site (5 U) of onabotulinumtoxinA or placebo were administered every 12 weeks (double-blind: 2 cycles), followed by onabotulinumtoxinA (open-label: 3 cycles).

Results: The PREEMPT dose (onabotulinumtoxinA 155 U to 195 U) and injection paradigm demonstrated that onabotulinumtoxinA yielded significant improvements over placebo across multiple headache symptom measures including reduction in headache days: -8.4 onabotulinumtoxinA/-6.6 placebo; $P<0.001$ (pooled data). OnabotulinumtoxinA using this injection paradigm was safe and well tolerated. No new safety findings emerged throughout the 56-week studies.

Conclusions: OnabotulinumtoxinA injections using the “modified” follow-the-pain model was safe and effective in the PREEMPT clinical program and provides an evidence-based injection strategy to optimize clinical outcomes for patients with CM.

Encore Presentation: EHMTIC 2010: European Headache and Migraine Trust International Congress, October 28-31, 2010, Nice, France.

54. Refractory Chronic Migraine: Long-Term Follow-up Using a Refractory Rating Scale

Presenter: Lawrence Robbins, MD

Authors: Lawrence Robbins, MD; Brooke Bassett, NP-C

Background: Refractory chronic migraine (RCM) is often associated with disability and a low quality of life (QOL). Long-term outcomes for patients with RCM have not been well studied. There is a need to categorize these patients according to severity. We used a unique RCM severity rating scale, tracking the clinical course over ten years.

Objective: To evaluate long-term outcomes in patients with refractory chronic migraine (RCM) using a unique refractory rating scale.

Methods: Retrospective chart review. Inclusion: patients with RCM >18 years who had been patients at the headache center for at least 10 years, 2000-2010. The study comprised 129 patients (108 female, ages 19 to 72 and 21 male, ages 31 to 69). RCM diagnosis was made using criteria suggested by the Refractory H/A Special Interest Section of AHS (*Headache*. 2009;49:509-518). Using a refractory scale (RS), the patients were given an initial severity core, 2 to 10 (10=worst). The scale = a) Refractory to preventives, 2 points. b) Refractory to abortives, 2 points. One point added for each: c) >10 years of H/A. d) 25+ days/month of H/A. e) Two of the following associated medical conditions: IBS/fibro/painful bladder syndrome/chronic pelvic pain/TMD/fatigue. f) Significant psychiatric issues (severe Axis I, any Axis II (personality disorder). g) Disability (work or home). h) Severe medication overuse. The patients were grouped according to the RS: 2-4 = mild, 5-7 = moderate, 8-10 = severe. QOL: determined by adding pain, functioning, and mood scores (3-30, 30 = worst). Pain Level: VAS, 1-10 (10 = worst).

Results: As of 2000, 129 RCM patients had been given a severity score (2 to 10). 24 pts. = mild, 67 = moderate, 38 = severe. QOL: for mild patients, average QOL improved 35% from 2000 to 2008-2010 ($P<0.001$, Effect Size (ES) = 2.07). 66% improved 30% or more. For moderate patients, average QOL improved 32% ($P<0.001$, ES = 1.3), while 57% improved 30% or more. Severe group: average QOL improved 33% ($P<0.001$, ES = 1.5), and 61% improved 30% or

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more. QOL was the same or worse in 4% of mild, 16% moderate, and 18% severe patients. At the end of the study, QOL levels were still significantly lower in the severe group than in the mild or moderate groups. Pain Level (1 to 10): For the mild group, pain scores declined over 10 years by an average of 45% ($P < .001$, $ES = 2.55$); 80% of the mild group had pain levels decline 30% or more. In the moderate group pain declined an average of 42% ($P < .001$, $ES = 1.3$); 72% had pain levels decline 30% or more. In the severe group, pain declined an average of 36% ($P < .001$, $ES = 2.16$) 71% had a decrease of 30% or more. Pain was the same or worse in 4% of mild, 15% of moderate, and 18% of severe groups. Pain levels remained higher in the severe group, over the others. ANOVA for pain-change scores yielded no difference among groups. Medications: Overall, the meds that helped significantly over the 10 years included opioids (63%) frequent triptans (31%), butalbital (17%), botulinum toxin type A (16%), stimulants (12%), and other "various" preventives (9%).

Conclusions: Patients with RCM were rated using a refractory scale and their courses followed over 10 years. Sixty percent of RCM patients had at least a 30% improvement in QOL, while only 15% remained the same (or declined); 73% had a 30% or more decline in pain level over 10 years. In the severe group, QOL and pain improved, but after 10 years still lagged behind the mild and moderate patients. Opioids and (frequent) triptans were the most commonly used medications.

55. Rates and Predictors of Remission from Chronic Migraine (CM) to Episodic Migraine (EM): Results from the American Migraine Prevalence and Prevention (AMPP) Study

Presenter: Aubrey Manack, PhD

Authors: Aubrey Manack, PhD; Dawn C. Buse, PhD; Daniel Serrano, MA; Catherine Turkel, PharmD, PhD1; Richard B. Lipton, MD2

Background: Each year, approximately 2.5% of episodic migraineurs develop chronic migraine (CM). Though predictors of progression have been studied, data are limited on CM remission and persistence.

Objective: To estimate remission rates for CM and assess potential predictors of remission from CM to EM.

Methods: In 2005, questionnaires were sent to 24,000 sufferers of severe headache identified in a previous US population survey and followed annually in 2006-2007. CM subjects (ICHD-2 migraine; ≥ 15 headache days/month) were identified in 2005 and had 3 consecutive years of follow-up. To assess predictors of remission, two migraine groups were compared: *persistent* CM (ie, met criteria for CM in 2005 and CM or high-frequency EM [HFEM: 10-14 headache days/month] in 2006-2007) and *remitted* CM (ie, met criteria for CM in 2005 but had low-frequency EM [LFEM: 0-9 headache days/month], probable migraine, tension-type headache, other episodic headache, or no headache in 2006-2007). Demographic variables, body mass index (BMI), depression (PHQ-9), age of onset, allodynia (ASC), medication use, and headache-related-disability (MIDAS) were examined as predictors by assessing among and within group effects.

Results: Subjects included 383 individuals with CM in 2005 who contributed 3 years of data; 64% ($n=292$) were classified as *persistent* CM while 26% ($n=100$) were classified as *remitted* CM. With regard

to predictors of remission, all models adjusted for age, sex, race, population density, geographic region, and income. Exploratory analyses suggested that depression, MIDAS, BMI, age of onset, allodynia, medication use by class, and overuse did not significantly predict remission. Current use of preventive therapy predicted remission; however, those CM sufferers using preventives were half as likely to remit [OR(95%CI)=0.48(0.28,0.84)].

Conclusions: Over 2 years, the majority of CM sufferers were persistent. Preventive treatment was associated with a lower rate of remission, perhaps because CM sufferers on prevention are a more severe subgroup with a worse prognosis.

Encore Presentation: 2nd European Headache and Migraine Trust International Congress (EHMTIC), Nice, France. October 2010.

Multidisciplinary Care

56. Perceived Physical and Mental Health and Comorbid Diseases among Women with Irritable Bowel Syndrome, Fibromyalgia, Neither, or Both Disorders

Presenter: Peter Przekop, DO, PhD

Authors: Peter Przekop, DO, PhD; Mark G. Haviland, PhD; Yan Zhao, MD, PhD; Keiji Oda, MPH; Kelly R. Morton, PhD; Gary E. Fraser, MD, PhD

Background: Functional pain disorders are commonly encountered by physicians, and they remain very difficult to treat. Little is known about patients' perceptions of these diseases. Such knowledge could help advance insights into a possible common underlying pathological basis for these diseases and could help improve our understanding of these patient groups while ultimately improving treatment strategies. Two of the most common disorders encountered and which frequently co-occur are irritable bowel syndrome (IBS) and fibromyalgia (FMS).¹

Objective: To assess common and distinguishing factors among people with a physician-given diagnosis, we compared groups with IBS, FMS, IBS+FMS to each other and to a group with neither disease. Comparisons were made on respondents' perceptions of a number of indices, including stressors, physical and mental health, and comorbidities.

Methods: This is a secondary data analysis. Participants in the present study were 3811 Caucasian women responding to the Biopsychosocial Religion and Health Study survey (control $n=3213$, IBS $n=366$, FMS $n=161$, IBS+FMS $n=71$; average age for all groups was early to mid 60s). To compare stressor and physical/mental health profiles across the four groups, we used one-way analyses of variance and chi-squared tests (with Tukey-Kramer and Tukey post hoc tests, respectively); $\alpha=.05$.

Results: Women with IBS reported more stressful events, worse physical and mental health, and more general medical, pain, and psychiatric comorbidities than women in the control group but fewer stressors and better health than women with FMS and those with both diseases. Overall, women with both diseases had the worst life experiences (stressors)/physical and mental health profiles and more comorbidities.

Conclusions: Perceived disease burden increased from IBS through FMS to IBS+FMS. These results identify subgroups of patients with

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progressively worse perceived pain profiles and may suggest a common underlying pathological process of chronic pain.

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57. Topical Hormone Administration by Radiofrequency Energy

Presenter: Forest Tennant MD, DrPH

Authors: Forest Tennant MD, DrPH; Allen Hassen, MD, MHA

Background: The use of intralesional hormones, particularly the glucocorticoids, is a standard practice in pain treatment. Delivery of the hormone into the painful lesion has traditionally been done by injection or iontophoresis, which delivers the hormone through the skin by electric current differentials. Injections are not only invasive but may miss the target area and be ineffective. Iontophoresis of hormones has not been widely adopted since it is relatively ineffective, probably because of shallow penetration below the skin.

Objective: To determine whether pulsed radiofrequency energy can drive intralesional hormones into a peripheral pain site.

Methods: The patients had common, acute ambulatory pain problems: lumbar back sprain (8), cervical-shoulder sprains (8), facial trauma (2), plantar fasciitis (3), knee sprain (2), and amputation stump inflammation (2). One of the following hormone preparations was applied to the painful area: prednisone 15 mg or medroxyprogesterone 30 mg in 1 ounce of a soluble base cream. A pulsed radiofrequency energy device (Provan[®]) was applied over the painful area. Its electromagnetic energy is delivered through an 8-inch square pad that is pressed against the painful area, which is covered with the hormone cream. The energy wave is preprogrammed to be pulsed at a frequency of 27.12 MHz over 30 minutes. During the 30 minutes, a hormone inspection was done every 10 minutes to determine whether the cream had disappeared by absorption through the skin.

Results: The topical hormone was absorbed and required replacement 1 or 2 times during every treatment. All patients reported pain reduction and more flexibility immediately following the treatment. These benefits remained for variable time frames until a second treatment was necessary or the acute painful injury resolved.

Conclusions: Radiofrequency energy is an electromagnetic energy wave that is known to reduce pain and edema and promote regeneration of injured, painful tissue. It appeared to be very effective in driving therapeutic hormones through the skin and into the injury site. The authors conclude that this technique offers a simple, practical way to drive hormones into a painful lesion, and further studies should be done to determine whether radiofrequency and other energy waves are the preferred methods to deliver hormones to peripheral pain sites.

58. An Algorithm to Improve Communication Between Pain Medicine Physicians and Primary Care Providers

Presenter: Harris Shaikh, MD

Authors: Harris Shaikh, MD; William Grubb, MD; Shihlong Yeh, MD; Sana Shaikh, MD; Genevieve Rojo, RN; Ahdev Kuppasamy, MD; Richard Baloti, MD; Christine Hunter, MD

Background: Pain management specialists use interventions and medications to manage acute and unstable pain. Stable chronic pain can then be managed by primary care physicians (after pain specialist consultation) to provide an efficient and holistic approach to patient care.

Objective: A model to improve communication between the pain management specialist and primary care providers to produce efficient and optimal care for patients with chronic stable pain.

Methods: A consultation request form supported an algorithm to foster better communication between pain medicine and primary care physicians. Patients with unstable pain are defined as having acute pain or chronic pain requiring an intervention after the failure of an upward titration of medication. Patients with stable, chronic pain are defined as those not requiring interventions other than downward titration of pain medications. The algorithm delegates acute pain management to the pain specialist and chronic pain management to the primary care provider, with guidance from the pain specialist.

Results: The structured evaluation form created to facilitate communication has allowed for greater efficiency in the pain management practice. It also allows primary care providers to manage patients with chronic pain who have multiple comorbidities.

Conclusions: The referral algorithm allowed for greater efficiency and optimal care as fewer resources were used for patients that were best managed by their primary care provider. Optimal patient care was possible because of the implementation of structured communication with primary care providers using forms with a systematic algorithm for the appropriate triage and referral of patients to and from the pain specialist.

The algorithm is useful to both the pain specialist and the primary care provider because it offers guidelines by which patients are appropriately managed in either setting. It also allows for better communication with primary care providers who are adjusting pain medications with guidance from a pain specialist. Patients with multiple comorbidities can be better managed by a primary care provider without the fear of ambiguous guidelines for pain management. In this way a pain specialist can avoid managing medical problems that are beyond the scope of the pain practice.

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