

### Evaluating patient education material of medications commonly used in palliative care

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#### Purpose

Palliative care is a specialized medical care for patients with serious illnesses; it focuses on providing patients with relief from symptoms such as pain, dyspnea, agitation, secretions, anxiety, and nausea. A number of medications are commonly used to treat the above listed symptoms. Often times, these medications are prescribed based on a non-Food and Drug Administration (FDA) approved indication. Patient information material is a major source of knowledge for patients and their families. The aim of this study is to evaluate patient information material of medications used in palliative care and its availability in different languages; specifically focusing on drugs prescribed under off-label indication.

#### Method

A list of medications was compiled from the International Association of Hospice and Palliative Care (IAHPC) as well as drugs commonly used in palliative care clinical practice. The medications' patient information material was then evaluated for inclusion of palliative indications and its availability in multiple languages. Four drug information databases and resources were consulted for that purpose: Lexi-Comp, Micromedex, Drug Facts and Comparison, and Medline Plus. In addition, a total of 10 palliative care specific websites were also checked for availability of patient drug information material.

#### Results

A total of 40 medications were identified as commonly used in palliative care, 17 were prescribed based on their FDA approved indication, 16 were prescribed based on non-FDA approved indications, and 7 were being used for both approved and nonapproved indications in palliative care. Upon consulting the different resources, comprehensive patient education material was available only for medications used based on their FDA approved indication. Micromedex had the highest percentage (28.6%) of off-label uses in palliative care for healthcare providers. Compared to other databases, Lexicomp provided the most (26.8%) patient education material about medications use in palliative care under non-FDA indication. Facts and Comparisons had the least amount of information regarding palliative non-FDA indications for both providers and patients (17.9% and 1.8% respectively). Although, MedlinePlus is a commonly utilized database for patient information, it was not found to be the best source for non-FDA indications in palliative care. Patient education materials were available in multiple languages for all drugs commonly used in palliative care. For non-FDA approved indications, the patient education material did not clearly address palliative indications. These indications were, at best, extrapolated from the FDA approved indication as in the case with gabapentin (used for neuropathy) or mentioned under the side effects profile, as it is the case with scopolamine for dry mouth. Palliative care organizations provided a wealth of information about the definition and goal of PC, however when the drugs used were mentioned it was only in the context of symptom management; patient education material was not available.

#### Conclusions

There is definitely a need for the development of patient education material in regard to medication used in palliative care. This will provide both patients and their families with integrated, coherent information about their prescription drugs, in addition to increasing medication adherence. All of these will greatly improve overall quality of patient care.

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### Effect of alkaline diet and PH on chronic pain

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#### Purpose

Chronic pain afflicts 100 million Americans and costs the economy billions of dollars in lost productivity and expenses.

Though reasons for chronic pain are multi factorial, chronic latent metabolic acidosis is hypothesized to make the pain symptoms worse by lowering the intracellular levels of magnesium. Intracellular magnesium is crucial for proper metabolism of vitamin D. Vitamin D when deficient worsens chronic pain. By reducing the metabolic acid load, by supplementing alkaline food in the diet, we may be able to reduce the pain symptoms in these patients.

With advent of industrial revolution, the human diet has changed dramatically. There is net deficiency of potassium and bicarbonate intake (such as potassium available from fruits and vegetables) while there is excessive sodium and chloride intake. Increased load of metabolic acids with high protein, low carbohydrate and fiber leads to unusual strain on the renal system to excrete the metabolic acids in urine.

Foods can be categorized by the potential renal acid loads. Fruits, vegetables, fruit juices, potatoes, are alkali and phosphorus rich. They have a negative renal acid load. Whereas, grain products, meats, dairy products, fish, are low in alkali and phosphorous content. They have a positive renal acid load. In a prospective study 20 patients suffering from chronic pain was enrolled in the study and effect of supplementation of alkaline food on chronic pain was studied.

#### Method

The patients who were suffering from chronic pain for more than 6 months, and who were using daily narcotic medications to control their pain, with average pain scale of 5/10 on the VAS score were enrolled in this study. This study will try to answer the question if chronic pain and narcotic intake is reduced by incorporating alkaline food in the diet. Total of 20 patients were enrolled but only 11 patients followed through up to 8 weeks of the study. Patients with metabolic diseases such as diabetes, hepatic or renal diseases were excluded from the study.

The patients were given a list of alkaline foods and were instructed to include at least 5 servings of the alkaline food every day. The patients kept a detailed log of their alkaline food intake, pain score, and the number of pain pills used every day.

At each visit for the study, the patient's urine pH and salivary pH were measured using pH strips. Their blood pH was extrapolated by measuring end tidal CO<sub>2</sub> measured by Capnometry. Pain score on VAS scale and narcotic pill intake were documented. Measurements were made at the beginning of the study, and subsequently after 4 week and 8 week intervals.

Any change in the intensity of pain, change in intake of pain pills will attempt to be correlated with the changes in urinary, blood and salivary pH as a result of alkaline diet intake.

## Results

The mean VAS pain score at baseline was 7/10. This reduced to 6.1/10 at the 4 week measurement point. This further reduced to 6/10 at the 8 week measurement time. There was a 10% reduction in the intensity of pain documented by the subjects.

The mean intake of short acting narcotics at baseline was at 2.1 pills/day. At 4 week measurement it reduced to 1.8 pills/day and further reduced to 1.2 pills/day at the 8 week measurement time. There was a 10% reduction in the intake of pain pills during the study period.

There was also an of 5% improvement in the mean duration of sleep, as measured at 8 week interval of the study.

The mean urinary pH at baseline was 6.9. This changed to 6.8 at 4 week measurement. At the 8 week measurement point urinary pH remained at 6.8. There was not a statistically significant change in urinary pH as a result of alkaline diet.

The mean salivary pH at baseline was 6.0. This was reduced to 5.9 at the 4 week measurement. Furthermore at 8 week measurement time, the salivary pH reduced to 5.8. Again, there was not a statistically significant change in salivary pH as a result of alkaline diet.

The study attempted to correlate the measurement of end tidal CO<sub>2</sub> using capnography as an indicator of blood pH. The mean end tidal CO<sub>2</sub> at baseline was 32.9. At 4 week measurement time it changed to 34.0 and at 8 week measurement time it was at 32.4. There was no statistically significant change in the end tidal CO<sub>2</sub>.

## Conclusions

The study indicates that there is a 10% reduction in the subjective VAS pain score and pain pill intake by incorporating an alkaline diet. The study failed to establish any statistically significant change in urinary pH, end tidal CO<sub>2</sub> or salivary pH. ( $P > .05$ )

Alkaline diet optimizes the function of enzyme systems and vitamin D function by increasing the intracellular magnesium levels.

This study showed improvement in pain and narcotic intake, but no significant change in pH. More studies are needed in this regard to demonstrate any benefit of alkaline diet on chronic pain, muscle mass and vitamin D metabolism.

## Evaluation of the *in vitro* human trunk skin percutaneous absorption of ketamine HCl, gabapentin, clonidine HCl and baclofen using the Franz Skin Finite Dose Model

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### Purpose

The *in vitro* human trunk skin percutaneous absorption of transdermal compounded formulations containing 4 active substances—ketamine HCl, gabapentin, clonidine HCl, and baclofen— incorporated simultaneously in Lipoderm and also in Lipoderm ActiveMax, was evaluated using the Franz Skin Finite Dose Model. Currently, it is common practice to combine multiple active substances in pain management therapy and the 4 active substances were selected due to their frequent use in topical pain compounded formulations. The Franz Skin Finite Dose Model has proven to be a valuable tool for the study of percutaneous absorption and to accurately predict *in vivo* percutaneous absorption kinetics. Therefore, the Franz Skin Finite Dose Model was selected to evaluate the total absorption, rate of absorption and the skin content of the 4 active substances simultaneously applied to the outer surface of the skin.

### Method

The percutaneous absorption of the 4 active substances was measured using *ex vivo* human trunk skin, without obvious signs of skin disease, from the posterior torso of 3 male donors (Black and Caucasian races). The skin samples were dermatomed, cryopreserved, sealed in a water-impermeable bag and stored at approximately -70°C, prior to skin preparation. Topical pain compounded formulations containing ketamine HCl 5% (w/w), gabapentin 10% (w/w), clonidine HCl 0.2% (w/w), and baclofen 2% (w/w), incorporated simultaneously in Lipoderm and also in Lipoderm ActiveMax, were applied to the skin sections (5  $\mu\text{L}$  formulation/ $\text{cm}^2$ ) and their percutaneous absorption was evaluated over a period of 48 hours. The skin sections were mounted in Franz diffusion cells allowing the skin to be maintained at a temperature and humidity that match normal *in vivo* conditions. One nondosed diffusion cell was included per donor as a blank control. A receptor solution was placed bathing the inner surface of the skin sections in order to measure the rate of appearance of the 4 active substances. During the exposure period, samples of the receptor solutions were removed at pre-selected times (2, 4, 8, 12, 24, 32 and 48 hours) and were analyzed for ketamine HCl, gabapentin, clonidine HCl, and baclofen content using the HPLC/MS analytical method. After the last sample of the receptor solutions (collected at 48 hours), the skin sections were cleansed, tape stripped (to remove the stratum corneum) and separated into the epidermis and dermis to evaluate the skin content of the 4 active substances.

### Results

The total absorption, rate of absorption and the skin content (distribution) of the 4 active substances were determined for a total of 7 Lipoderm and Lipoderm ActiveMax test formulations containing ketamine HCl 5% (w/w), gabapentin 10% (w/w), clonidine HCl 0.2% (w/w), baclofen 2% (w/w), and propylene glycol 10% (w/w). The absorption results indicate the percutaneous absorption of the active substances through the skin whereas the distribution results indicate the percutaneous absorption into the skin. The total absorption and the skin content were determined after 48 hours from a single application of the transdermal compounded formulations in the skin sections. The total absorption corresponded to the total recovered in the receptor solutions and the skin content corresponded to the mass recovered in the stratum corneum, dermis and epidermis ( $\mu\text{g}/\text{cm}^2$ ), of the 4 active substances. The rate of percutaneous absorption, on the other hand, is a time-averaged value and it was determined as the mean flux of the active substances, collected at the receptor solutions ( $\mu\text{g}/\text{cm}^2/\text{h}$ ), over the 48-hour period. The absorption and distribution profiles of each active substance were similar for all 7 Lipoderm and Lipoderm ActiveMax test formulations. The rate of percutaneous absorption showed a rapid penetration to a peak flux for gabapentin and

baclofen occurring approximately 1 hour after dose application, and approximately 4 hours for ketamine HCl. Clonidine HCl exhibited a rapid penetration to an initial peak flux occurring 1 hour after dose application, but also a secondary peak at approximately 40 hours, possibly due to a depot of some of the applied dose in the epidermis, followed by a slow decline in flux thereafter. Mass accountabilities ranged from 85% to 115% of the applied doses across all test formulations.

## **Conclusions**

The 4 active substances—ketamine HCl, gabapentin, clonidine HCl, and baclofen—incorporated simultaneously in Lipoderm and also in Lipoderm ActiveMax, penetrate through and into *ex vivo* human trunk skin, following topical application of the transdermal compounded formulations. It is concluded that the transdermal bases Lipoderm and Lipoderm ActiveMax are indicated in pain management therapy for the preparation of multidrug topical compounded formulations.

## Descriptive analysis of claims-based recurrent low back pain in the medical adult population of a Canadian province

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### Purpose

Low back pain (LBP) is a frequent and costly health condition. Lifetime prevalence reaches an average of 39%, with a large variability depending on the surveyed population and/or the LBP definition. In a lifetime, recurrent episodes will be the reality of a large subset of the LBP population. Likely, 1 out of 4 patients presenting with an acute LBP episode might experience a LBP recurrence within one year. The body of knowledge on the prevalence of recurrent LBP is still limited. This study sought to present a descriptive analysis on the epidemiology of recurrent LBP in a medical population. A new methodology is also proposed to identify true cases of incident recurrent LBP.

### Method

Using the Canadian province of Quebec medical administrative physicians' claims database, prevalent claims-based recurrent LBP cohorts were built for the years 2000 to 2007 from the medical records of 401,264 patients. The annual prevalence was categorized by sex and 5-year age categories. The medical history of the 81,329 patients from the 2007 prevalent cohort was then screened for a retrospective period of 11 years. Patients with a previous episode of LBP were excluded. Positive predictive values (PPV) and Kappa statistics were calculated to determine the optimal clearance period for capturing true incidence cases.

### Results

We observed a decrease from 1.64% to 1.33% in the LBP annual prevalence between 2000 and 2007 for men. This decrease was mostly observed between 35 and 59 years of age. Older women ( $\geq 65$  years) were 1.35 times more at risk to consult a physician for LBP in a recurrent manner than older men. The 5-year incidence rate of adult claims-based recurrent LBP was 325 per 100,000 person-years. Males of 18 to 34 years of age were found 1.18 times more at risk than their counterparts. Altogether, elderlies over 80 years had 52% more new cases than the 18-34 group. The annual incidence decreased by 12% between 2003 and 2007. More than 65% of the diagnoses were tagged as nonspecific. Half of incident patients had between 3 to 6 recurrences in their first year, while 24% had 7 to 10 visits following their first episode.

### Conclusions

The prevalence and incidence rate of claims-based recurrent low back pain was found to decrease between 2000 and 2007 in the adult population of the province of Quebec. This could be the result of accessibility issues or general practitioners' shortage and a greater rate of consultation in complementary and alternative medicine. The elders were however shown at greater risk to consult more for LBP in the medical system. With our aging population, this will need to be closely watched as it might impact the healthcare system in the short term.

## Consequences of OxyContin patient access restrictions on healthcare utilization and costs

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### Purpose

Long-acting opioid analgesics (LAOs) are used for treating moderate-to-severe chronic pain in a variety of conditions. OxyContin<sup>®</sup> (oxycodone hydrochloride controlled-release) is an opioid agonist with abuse-deterrent characteristics and is a Schedule II controlled substance. OxyContin is indicated for the management of moderate to severe pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time. Health plan benefit designs vary in terms of patient access to OxyContin, ranging from relatively open access with moderate out-of-pocket (copay) patient expense, to access restrictions that may include a higher copay expense, as well as requirement for prior authorization (PA) before coverage. This study evaluated the impact of health plans' increasing such access restrictions for OxyContin on the health plans' overall healthcare utilization and cost of managing patients utilizing LAOs.

### Method

A retrospective-cohort analysis using claims data from the IMS Integrated Data Warehouse (pharmacy claims, medical claims) and the IMS Formulary Focus database was conducted. Adult patients with at least one prescription claims (first claim = index date) for a LAO and at least 6 months of plan enrollment postindex were identified from plans that increased OxyContin access restrictions during the period from 7/1/2009 to 12/31/2011, while the complete study period was from 1/1/2009 to 12/31/2012 allowing for pre and post access restriction measurements. Access restrictions included plans imposing PA on OxyContin (the PA group) and plans moving OxyContin to a higher tier copay (the tier change [TC] group). Patients were assigned to either the pre-restriction group or the postrestriction group according to whether their index prescription fell into the pre or postrestriction period specific to each health plan. Patients were segmented into Medicare Part D or commercial insurance for prescription coverage, forming 4 study groups: commercial PA, commercial TC, Medicare PA, and Medicare TC, and were assigned in a hierarchical manner first to the PA groups. Pharmacy (LAOs, short-acting opioids and nonopioids) utilization, medical resource unit utilization (office visits) and billed charges were measured for 6 months following each patient's index date and were compared between the pre- and postrestriction cohorts within each study group. Bootstrapping t-test and generalized linear models with gamma distribution and a log-link were utilized to test the differences in resource utilization and costs, respectively.

### Results

More than 20 health plans imposed PA or TC restrictions during the 2009-2011 period, the number varying over time. The prerestriction sample consisted of 2199, 1980, 2417, and 9818 patients in the commercial PA, commercial TC, Medicare PA and Medicare TC groups, respectively. The postrestriction sample consisted of 709, 1068, 3010, and 8798 patients in the commercial PA, commercial TC, Medicare PA, and Medicare TC groups, respectively. The commercial population was 55% female, with a mean age of 55 years; the Medicare population being older (59 years) and more female (62%) than the commercial population. The Charlson comorbidity index and other patient characteristics were comparable between the prerestriction and postrestriction cohorts. The most common pain-related diagnoses were back, joint and soft-tissue disorders; approximately 10% of patients had a cancer diagnosis, suggesting the population was composed primarily of chronic nonmalignant pain patients, potentially an overweighted disability population. There was a significantly larger mean number of office visits 6 months postindex per patient comparing the pre-restriction to the postrestriction study groups ( $\Delta = 2.49$  [ $P < .001$ ]) for Commercial PA,



$\Delta = 1.41$  [ $P = .008$ ] for Commercial TC,  $\Delta = .90$  [ $P = .010$ ] for Medicare PA,  $\Delta = 1.03$  [ $P < .001$ ] for Medicare TC). Comparing mean 6-month costs between the pre- vs postrestriction cohorts, there were significantly higher medical and total (pharmacy + medical) costs and nonsignificant decreases in pharmacy costs in all study groups in the postrestriction cohorts. Mean 6-month costs were \$1,131 ( $P < .001$ ) higher in the commercial PA group, \$660 ( $P = .0094$ ) higher in the commercial TC group, \$699 ( $P < .0001$ ) higher in the Medicare PA group, and \$564 ( $P < .0001$ ) higher in the Medicare TC group. Analysis of the subset of patients appearing in both pre- and postrestriction study groups found a similar trend in increased office visits and total costs in the postrestriction study groups, but was insufficiently powered to provide statistical significance.

## Conclusions

This retrospective study suggests that implementing access restrictions on OxyContin may increase the number of office visits, office visit related costs and total healthcare costs for patients receiving LAOs, without an offsetting decrease in pharmacy costs, and implementing such strategies may impose a net cost increase to payers. Health plans should consider such unintended consequences of such access restrictions.

## Evaluation of the abuse potential of an extended-release hydrocodone bitartrate tablet formulated with OraGuard™ technology in nondependent, recreational opioid users

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### Purpose

Extended-release (ER) formulations of opioid analgesics may reduce dosing frequency; however, required increases in drug load may lead to abuse associated with drug tampering. This randomized, double-blind, triple-dummy, placebo-controlled, crossover study examined the relative abuse potential of crushed and intact ER hydrocodone bitartrate tablets compared with immediate-release (IR) hydrocodone. ER hydrocodone employs OraGuard™ technology, a novel platform that is intended to protect against rapid release of hydrocodone when tablets are comminuted (ie, broken into small pieces by crushing, milling, grating, or grinding) and provide resistance against dose dumping when tablets are taken with alcohol.

### Method

Healthy adult subjects with a history of recreational opioid use who were not dependent on opioids were enrolled. Eligible subjects who were able to tolerate a 45 mg dose of IR hydrocodone and differentiate the effects of hydrocodone and placebo were randomized to the double-blind crossover portion of the study. Subjects received single doses of each of the following (with a 14-day washout between doses): intact 45 mg ER hydrocodone tablet, crushed 45 mg ER hydrocodone tablet, 45 mg IR hydrocodone powder in a noncarbonated beverage, and placebo. Relative abuse potential was assessed by a series of tests over 72 hours after each treatment. The primary pharmacodynamic measure was maximum effect ( $E_{max}$ ) of drug liking ("at the moment" liking assessed using question 1 of the Drug Liking and Effects Questionnaire [DLEQ1]) based on a 100-point Bipolar Visual Analog Scale (VAS; 0 = strong disliking, 50 = neutral, 100 = strong liking). Subjective secondary pharmacodynamic evaluations included analysis of the overall scores on the Drug Liking VAS and assessment of the balance of drug effects, positive drug effects, negative drug effects, sedative drug effects, and other drug effects of each treatment based on answers to questions on the DLEQ, scores on the Take Drug Again Assessment and Price Value Assessment Questionnaire, and responses on subscales of the Addiction Research Center Inventory. Pupillometry was assessed as an objective secondary measure of other drug effects. Safety and tolerability was also assessed throughout the study.

### Results

Forty-nine subjects were enrolled in the relative abuse potential assessment. Intact ER hydrocodone demonstrated significantly lower drug liking compared with IR hydrocodone based on DLEQ1  $E_{max}$  (53.9 vs 85.2 [ $P \leq .0022$ ]) and Overall Drug Liking VAS (49.2 vs 75.0 [ $P \leq .0022$ ]) measures. Crushed ER hydrocodone also demonstrated significantly lower drug liking compared with IR hydrocodone when assessed by both measures (DLEQ1  $E_{max}$  66.9 vs 85.2 [ $P \leq .0022$ ] and Overall Drug Liking VAS 59.0 vs 75.0 [ $P \leq .0022$ ]). Outcomes for other secondary measures were consistent with these results. No serious adverse events were reported during the study. The incidence of adverse events was lower with intact ER hydrocodone (53%) than with IR hydrocodone (79%) and crushed ER hydrocodone (73%). No new safety signals were observed with ER hydrocodone.

### Conclusions

The abuse potential for intact and crushed ER hydrocodone developed with OraGuard™ technology, as assessed by peak and overall drug liking, is significantly lower than for IR hydrocodone in healthy, nondependent, recreational

opioid users. Balance of drug effects, positive and negative drug effects, and sedative drug effects were also diminished with intact and crushed ER hydrocodone tablet compared with IR hydrocodone. Single 45-mg doses of ER hydrocodone (crushed and intact) were generally well tolerated, with a comparable incidence of adverse events with IR hydrocodone and crushed ER hydrocodone and a lower incidence with intact ER hydrocodone.

## Effects of renal impairment and hepatic impairment on the pharmacokinetics of hydrocodone after administration of a novel extended-release hydrocodone tablet formulated with OraGuard™ technology

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### Purpose

In the United States, hydrocodone is available for the treatment of pain only in immediate-release formulations in combination with other analgesics such as acetaminophen or ibuprofen. A new, extended-release (ER) hydrocodone-only tablet was developed that employs OraGuard™ technology. OraGuard™ is a novel platform intended to protect against rapid release of hydrocodone when tablets are comminuted (ie, broken into small pieces by crushing, milling, grating, or grinding) and provide resistance against dose dumping when tablets are taken with alcohol. Because impairment of renal or hepatic function has the potential to alter the metabolism and elimination of medications, 2 open-label, single-dose, parallel-group studies were conducted to assess the effects of renal impairment (study 1) and effects of hepatic impairment (study 2) on the pharmacokinetics of hydrocodone after administration of the ER hydrocodone tablet. In study 1, the pharmacokinetics of hydrocodone were assessed after administration of a single 45-mg dose of ER hydrocodone to naltrexone-blocked subjects with normal renal function or varying degrees of renal impairment (mild, moderate, or severe impairment or end-stage renal disease [ESRD]). In study 2, the pharmacokinetics of hydrocodone were assessed after administration of a single 15-mg dose of ER hydrocodone to subjects with normal hepatic function or moderate hepatic impairment who were not concurrently receiving naltrexone.

### Method

Subjects participating in study 1 had normal renal function or mild (creatinine clearance >50-80 mL/min), moderate (30-50 mL/min), or severe renal impairment (<30 mL/min), or ESRD (hemodialysis for ≥6 months prior to study enrollment). In this study, eligible subjects received a single 45-mg dose of ER hydrocodone on the morning of day 1 after an overnight fast. Subjects in study 1 also received 50-mg doses of naltrexone at 15 and 3 hours before administration of ER hydrocodone and 9 and 21 hours after administration of ER hydrocodone. Subjects participating in study 2 had normal hepatic function or moderate hepatic impairment (Child-Pugh Classification score 7-9 points). In this study, eligible subjects received a single 15-mg dose of ER hydrocodone on the morning of day 1 after an overnight fast. Subjects in study 2 did not concurrently receive naltrexone because the prescribing information for naltrexone urges careful consideration be given to the use of this medication in individuals with active liver disease. Therefore, the lowest dose of ER hydrocodone was administered in study 2. In both studies, blood samples for pharmacokinetic measurements were obtained pre-dose and through 144 hours postdose; pharmacokinetic parameters included maximum observed plasma hydrocodone concentration ( $C_{max}$ ) and area under the plasma hydrocodone concentration vs time curve from time 0 to infinity ( $AUC_{0-\infty}$ ). Safety was also assessed throughout both studies.

### Results

Evaluable pharmacokinetic data were available for 48 subjects in study 1. Mean  $C_{max}$  in subjects with normal renal function or mild, moderate, or severe renal impairment or ESRD was 28.6, 33.4, 42.4, 36.5, and 31.6 ng/mL, respectively; mean  $AUC_{0-\infty}$  was 565, 660, 973, 983, and 638 ng•hr/mL, respectively. Systemic exposure to hydrocodone was up to 70% higher in subjects with moderate or severe renal impairment vs other renal function categories, likely owing to uremia, which can reduce drug metabolism in patients with advanced chronic kidney disease who are not receiving dialysis. No serious AEs were reported in study 1. One subject with normal renal

function was withdrawn from the study because of an AE of vomiting approximately 90 minutes after administration of ER hydrocodone (considered not treatment-related). The incidence of AEs was similar between subjects with normal renal function (57%) and those with mild (38%), moderate (44%), or severe renal impairment (33%) and ESRD (56%). Evaluable pharmacokinetic data were available for 16 subjects in study 2. Mean  $C_{max}$  in subjects with normal hepatic function or subjects with moderate hepatic impairment was 10.1 and 13.0 ng/mL, respectively; mean  $AUC_{0-\infty}$  was 155 and 269 ng•hr/mL, respectively. Systemic exposure to hydrocodone was ~70% higher in subjects with moderate hepatic impairment vs normal hepatic function, likely the result of a change in bioavailability due to intrahepatic shunting and the reduced ability of the liver to clear the drug. No serious AEs were reported in study 2, and no subjects were withdrawn because of AEs. The incidence of AEs was the same among subjects with normal hepatic function (38%) and those with hepatic impairment (38%).

## Conclusions

Total systemic exposure to hydrocodone was up to 70% higher in subjects with moderate to severe renal impairment or moderate hepatic impairment than in subjects with normal organ function. Although  $C_{max}$  was typically higher in the impaired populations, the effect was less pronounced. ER hydrocodone was generally well tolerated after single 45-mg doses administered with naltrexone blockade in study 1 and single 15-mg doses administered without naltrexone blockade in study 2. However, physicians should be aware of the potential for higher systemic exposure in renally or hepatically impaired populations when titrating to an effective dose of ER hydrocodone.

## Assessment of residents with pain in a long-term care facility

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### Purpose

Pain management of elderly residents in long-term care (LTC) facilities presents clinical challenges and has been transformed by the requirements of the F-Tag 309 component of the Centers for Medicare & Medicaid Services (CMS) Quality Indicators Survey (QIS). F-Tag 309 is concerned with the identification of LTC residents who are in pain and with their assessment and management. The Minimum Data Set (MDS) includes Section J which details the pain management and assessment interview process. The purpose of this research was to evaluate pain management and assessment in the LTC setting utilizing the MDS.

### Method

This was a retrospective, cross-sectional cohort project. The study population included residents from a single LTC facility assessed for pain using the MDS 3.0 Section J. The consultant pharmacist collected the data using the facility's computer system (MEDITECH, Westward, MA). Information was gathered using paper data collection forms and these were entered into Microsoft Access for analysis. Descriptive statistics were used when reporting the results. To detect a difference in mean numeric rating scale (NRS) scores for residents on a scheduled pain medication regimen vs those not on such a regimen, a 2-sample t-test using Minitab was employed. Residents under the age of 18 or those without MDS 3.0 Section J records were excluded. Residents aged 90 or older had their age set at 90 to protect patient privacy and for HIPAA compliance.

### Results

The sample consisted of 265 residents. The mean age was 82 years and most (76%) were female. Section J0100 was completed for all residents. Within the last 5 days, nearly half (46%) had been on a scheduled pain medication regimen with 27% receiving PRN pain medicines, and 17% meeting both criteria. Approximately 11% received a nonmedication intervention for pain and 10% were on PRN pain medication without a scheduled pain medication. Based on MDS data, pain assessment interviews and caregiver assessments were to be conducted in 70% (185/265) and 30% (80/265) of residents respectively. Interviews conducted by facility staff identified 36 of the 185 residents (20%) with pain or hurting within the last 5 days. Of these, 44% said they experienced pain "occasionally" but 33% experienced pain "almost constantly" and 19% "frequently." The impact of pain on function was also assessed (Section J0500). Thirty-six percent said pain made it hard for them to sleep at night and 25% said they had limited their day-to-day activities because of pain. Pain intensity was assessed using the numeric rating scale (NRS) and/or the verbal descriptor scale (VDS). The mean NRS score was  $7.5 \pm 2.4$  (2-10). Of those who had their pain intensity assessed using the VDS, most (53%) described their pain as "moderate" but 21% said it was "severe" or "very severe." Assessment of pain intensity using the NRS revealed those not on scheduled pain medication had scores similar to those receiving pain medication (7.6 and 7.4, respectively;  $P = .841$ ). Caregiver assessment of pain occurred in only 12% of the eligible residents. For those residents who, according to caregivers, are rarely/never understood ( $n = 80$ ) only 12% had a staff assessment for pain.

### Conclusions

Section J in the MDS contains information about the management and assessment of pain that can be used to evaluate its treatment and identify gaps in care. In our analysis, resident interviews were conducted more

frequently than staff assessments to detect and evaluate pain. Interviews conducted by facility staff identified 20% of residents with pain or hurting within the last 5 days. Most residents said they experienced pain "almost constantly" or "frequently," which impacted their ability to function. In this sample, residents not on a scheduled pain medication regimen experience pain similar to those on a scheduled pain medication regimen.

## The impact of pharmacist driven E-FORCSE education on physician controlled substance prescribing practices

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### Purpose

Prescription drug abuse continues to be a problem in the United States. Controlled substances have become increasingly popular and the epidemic of nonmedical use of these medications is on the rise. In order to combat this epidemic, statewide Prescription Drug Monitoring Programs (PDMP) have been developed and are fully operational in 42 states. These programs allow prescribers, pharmacists, and select law enforcement personnel to track prescriptions dispensed for controlled substances. The PDMP in Florida, Electronic-Florida Online Reporting of Controlled Substances Evaluation Program (E-FORCSE) allows the tracking of Schedule II, III, and IV medications. Although all controlled substances dispensed in the state of Florida are required to be reported to E-FORCSE, it is not mandatory for this information to be viewed prior to prescribing controlled substances. Since it is not mandatory to review E-FORCSE reports, the benefits of this program have yet to be fully determined. It is hypothesized that increased awareness and education about the benefits of E-FORCSE will decrease unnecessary controlled substance prescribing.

### Method

Shands Jacksonville internal medicine residents' controlled substance prescribing rates will be evaluated before and after clinical pharmacist intervention. The intervention provided will entail generation and analysis of E-FORCSE reports for patients seen by the internal medicine residents. Change in controlled substance prescribing rates will be evaluated for 26 medical residents by looking at 3 month time periods exactly one year apart. Additionally, confidence in controlled substance prescribing will be evaluated with the use of a survey administered at the conclusion of the study.

### Results

In the historical time period between December 1, 2011 to February 28, 2012, 11.1% of prescriptions were written for controlled substances. In the intervention period, between December 1, 2012 to February 28, 2013, 10.7% of prescriptions were written for controlled substances. This computes to a total controlled substance prescribing rate reduction of 0.4%. When stratified into the 2 separate medical resident classes, the second year medical residents actually increased controlled substance prescribing from the historical to intervention period by 0.5% (9.9% to 10.4%). On the other hand, the third year medical residents had a reduction in controlled substance prescribing by 1.0% (11.9% to 10.9%). When the survey was administered at the conclusion of the study, all 26 medical residents (100%) indicated that their confidence in appropriate controlled substance prescribing was increased. Additionally, the survey revealed that the information on the E-FORCSE reports did affect the prescribing practice of the internal medical residents. When asked if the reports confirmed, altered, or had no effect on prescribing decisions, 100% of the medical residents indicated that the reports affected prescribing practice. Of this 100%, 42% indicated the reports confirmed their prescribing decision, 27% indicated it altered their prescribing decision, and 31% indicated it both confirmed and altered their prescribing decision depending on the patient.

### Conclusions

The controlled substance prescribing rate may not be indicative of the impact of this study. Ideally, the controlled substance prescribing rate was reduced for inappropriate indications but may have been increased for appropriate indications based on the increase in prescriber confidence. Therefore, the greatest impact of this study is believed to



be the increase in prescriber confidence and effect on prescribing practice. Additionally, this study heightened awareness and education on E-FORCSE which in turn should increase utilization by the internal medicine residents in the future.

## **Retrospective Analysis of the Clinical and Economic Results (R.A.C.E.R.) of genotyping chronic pain patients to guide medical detoxification of prescription opioid analgesic abuse (RxO): 2-year study**

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### **Purpose**

Genetic factors contribute to 60% of prescription opioid (RxO) pain medication misuse; however, genetic testing of a patient's predisposition is not widely utilized yet. Many patients fail medical detoxification and experience high relapse rates. The annual direct healthcare costs of an opioid abuser are eight times that of a nonopioid abuser, and overall, the cost burden of prescription opioid abuse is larger than heart disease. Genetic testing may help identify patients at risk for tolerance, dependence and abuse of prescription drugs. It may be a cost-effective means to improve therapeutic decisions in pain management, guide medical detoxification, and constrain spiraling pharmaceutical costs. The objectives of this study are to evaluate the clinical and economic outcomes of a medical detoxification program and develop an algorithm to predict patient treatment outcome based on patient narcotic genetic profile.

### **Method**

The study evaluated 148 patients diagnosed with a workplace injury, most frequently low back pain and lumbar radiculopathy, comorbid chronic pain syndrome, and comorbid psychiatric condition along with taking prescription opioid pain medication. Patients who enrolled in an integrated medical detoxification program were genotyped with TaqMan SNP genotyping assays using the proprietary Proove Narcotic Risk Genetic Test, and followed for 2-years to evaluate their clinical and economic outcomes. TreeNet-based class prediction modeling was used to discern patients with successful outcome from those with treatment failure.

### **Results**

122 patients achieved a successful treatment outcome—50% reduction in both pain VAS and ADL measurements and termination of RxO pain medication utilization at 90 days and over a 2-year follow-up period. Over a 2-year period, study subjects who completed successful treatment are estimated to have achieved a 4:1 cost-benefit analysis, saving workers' compensation payers over \$4M. In addition, the narcotic genetic panel is able to distinguish patients with successful outcome from those with treatment failure. It has 85% sensitivity, 88% specificity and a PPV of treatment success (97.2%) and NPV of treatment failure (56.1%), suggesting a role for genotyping pain management patients for RxO to guide medical detoxification.

### **Conclusions**

In this study, a multivariant narcotic risk genetic panel may be predictive of response to medical detoxification, and the study also suggests a potential economic benefit of genotyping chronic pain patients for RxO tolerance, dependence, or misuse.

## Observational study to calculate addictive risk to narcotics due to genetic predisposition in chronic pain patients

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### Purpose

Genetic factors contribute to approximately 50% to 60% of prescription narcotic pain medication abuse or misuse but are generally not evaluated in clinical practice. Pain, especially for a patient genetically predisposed to neurochemical deficiencies in the mesolimbic dopamine system of the brain, often presents an epigenetic dilemma in which the patient shows greater susceptibility to prescription drug dependence (PDD) or other substance use disorders (SUD). The objective of this study is to evaluate a scoring algorithm of single nucleotide polymorphisms affecting neurochemistry of the mesolimbic reward system to determine whether it is predictive of prescription drug dependence and/or chronic pain syndrome.

### Method

Chronic pain patients diagnosed with prescription drug dependence (PDD) (n = 10), diagnosed with chronic pain syndrome (CPS) (n = 3), both prescription drug dependence and chronic pain syndrome (n = 35) and chronic pain patients without either diagnosis (n = 24) for a total of 72 patients. Subjects were genotyped with the Proove Narcotic Risk Genetics Profile using TaqMan SNP genotyping assays (Life Technologies, Carlsbad, CA). A scoring algorithm, the Dependence Risk Index (DRI) score was calculated to determine elevated risk based on genetic predisposition.

### Results

Subjects with a DRI of greater than or equal to 20 had a positive predictive value (PPV) 80% of having either PDD or CPS vs those subjects without either diagnosis ( $P < .028$ ,  $\chi^2$  of 10.87, sensitivity of 77%, specificity of 63%).

### Conclusions

By considering a Dependence Risk Index (DRI) score, clinicians may be able to identify patients at greater risk for prescription pain narcotic medication abuse or misuse due to genetic predisposition. Further research with larger patient population is required to stratify low, moderate and high risk, as well as variations between ethnicities and gender.

## Swimming suppresses interleukin-6 overloading and inflammation in neuropathic rats

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### Purpose

Neuronal inflammation plays an important role in peripheral neuropathy after chronic constrictive injury (CCI). The purpose of this study was to evaluate the effect of exercise on neuropathic pain, interleukin-6 (IL-6), and inflammation in a rat model of CCI.

### Method

This experimental protocol was approved by the Institutional Animal Care and Use Committee of China Medical University, Taichung, Taiwan, and conformed to the recommendations and policies of the International Association for the Study of Pain (IASP). A peripheral nerve injury was performed in male *Sprague-Dawley* rats via placing 4 loosely constrictive ligatures around the sciatic nerve. Animals were randomly divided into 4 groups: sham operated (SO), SO with swimming exercise (SOSE), CCI, and CCI with swimming exercise (CCISE). We observed temporal course of thermal hyperalgesia and mechanical allodynia as well as the expression of IL-6 and histopathological analyses of the sciatic nerve.

### Results

We showed that CCI rats after swimming exercise prevented this decrease in thermal withdrawal latency and mechanical withdrawal threshold significantly compared with CCI rats without exercise ( $P < .05$ ) on day 22 after CCI. There are no significant differences between SO and SOSE for thermal withdrawal latency and mechanical withdrawal threshold. CCISE rats exhibited lower IL-6 expression than the CCI rats ( $P < .05$ ) on day 22 after CCI. Immune cell infiltration significantly decreased, which demonstrated less inflammation in the injured-treated (exercise) animals compared with the injured-nontreated animals.

### Conclusions

Swimming exercise improves neuropathic pain behavior, inflammation, and IL-6 overexpression of the sciatic nerve in a rat model of CCI. Our data support the usage of physical exercise as a nonpharmacological method for the therapy of neuropathic pain.

## Changes in rates of doctor-shopping following the introduction of a reformulated ER oxycodone product

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### Purpose

In August 2010, Purdue Pharma introduced reformulated OxyContin (ORF) that is intended to deter crushing and that forms a gel when dissolved. The new formulation is intended to deter abuse through routes that require tampering. This study examines whether there was a decline in rates of "doctor-shopping" of ER oxycodone manufactured by Purdue following the introduction of ORF. It was hypothesized that there would be a reduction in doctor-shopping due to reduced demand for ORF for abuse or diversion and that the decline in doctor-shopping rates would be greater for characteristics associated with abuse such as younger age, male gender, higher dosage strength, and cash payments.

### Method

Two data sources were used to estimate changes in rates of doctor-shopping. National trends were assessed using IMS LRx longitudinal patient data for over 150 million patients covering approximately 65% of retail prescriptions filled in the US. Data from the Ohio prescription monitoring program covers all prescriptions for scheduled medications dispensed to outpatients from retail pharmacies in the State of Ohio. Doctor-shopping was defined as obtaining prescriptions from at least 3 pharmacies and 2 prescribers during a period of overlapping prescriptions in a 6 month period based on a published approach (Cepeda, et al, 2012). Rates were calculated by dividing the number of individuals who met this definition by the number who received a prescription in a 6-month period. Doctor-shopping rates were also estimated for comparator opioids: immediate-release (IR) single entity (SE) oxycodone (IMS, Ohio PMP), and hydrocodone (Ohio PMP) to determine whether changes in doctor-shopping rates were specific to OxyContin. Rates were compared in the 1-year pre-ORF period (July 2009-June 2010) to the post-ORF periods of 1 year for IMS (Jan-Dec 2011) and 6-months (Jan-July 2011) for Ohio PMP. The period from Jul-Dec 2010 was a transition period in which both original and reformulated OxyContin were widely available in pharmacies. Given the lack of a gold-standard definition of doctor-shopping, rates were stratified by 1) prescriptions for high-dosage strengths, 2) cash payments, 3) patient age and 4) sex. In addition, rates were estimated using different thresholds of number of prescribers/pharmacies used to obtain opioids during periods of overlapping prescriptions.

### Results

In the IMS dataset, rates of doctor-shopping for OxyContin during the year prior to introduction of ORF were higher for men (0.26%) vs women (0.16%) and for younger ages (eg, 0.47% for age 18-29 years old vs 0.12% for 55-64 years old). Nearly two-thirds (62%) of doctor-shopping events for OxyContin involved cash payment and nearly half (47%) included 80 mg tablets. Overall, rates of doctor-shopping for OxyContin decreased 40% from the year before (Jul 2009 to Jun 2010) to after ORF introduction (Jan to Dec 2011), from 0.22% to 0.13%. The magnitude of decline was larger for doctor-shopping events involving cash payment (52%), 80 mg dosage strength (52%), and both (61%). Declines in rates of doctor-shopping were highest for 18-29 year-olds (64%) and for males (46%). There was a systematic increase in the magnitude of decline in rates of doctor-shopping for OxyContin as the threshold for defining doctor-shopping increased. For example, although there was a 40% decline in rates of doctor-shopping based on a threshold of at least 3 unique pharmacies and 2 prescribers during periods of overlap, there was a 62% decline when the threshold defining doctor shopping was increased to 4 pharmacies and 3 prescribers. In contrast to the findings for OxyContin, there was a 9% increase in rate of doctor-shopping for IR SE oxycodone over the same period. Data from the Ohio PMP yielded a similar pattern of findings: there was a 29% decline in doctor-shopping for

OxyContin using a threshold of 3 pharmacies/2 prescribers and 43% decline for a threshold of 4 pharmacies/3 prescribers, with larger changes in doctor-shopping rates for younger individuals and males, and for prescriptions involving cash payments, and high-dosage strengths. The magnitude of decline in doctor-shopping was larger for OxyContin than for IR SE oxycodone and hydrocodone.

## **Conclusions**

These findings indicate that the rate of doctor-shopping for OxyContin declined following introduction of its reformulation with abuse-deterrent properties. During the same time frame no similar decline occurred for comparators of other oxycodone and hydrocodone products. Declines were larger for indicators associated with increased risk for abuse and diversion, including younger age, men, high-dosage strength and cash payment. Declines in rates for OxyContin were greater for definitions with increasing levels of specificity. Findings from this study suggest that the reformulation of OxyContin has resulted in reduced demand for this product for the purpose of abuse and diversion.

## Safety and efficacy of gastroretentive gabapentin in real-world clinical practice for treatment of patients with postherpetic neuralgia (PHN)

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### Purpose

Clinical trials do not always accurately reflect the efficacy and safety of a drug in real-world clinical practice. Therefore, a phase 4 open-label study was conducted to assess the safety and efficacy of once-daily G-GR in a relatively unselected group of patients with PHN in real-world use.

### Method

This was an open-label, multicenter study in patients  $\geq 18$  years who had active PHN. To reflect clinical practice, exclusion criteria were limited to those in the product label. Eligible patients were titrated to a dosage of 1800 mg/day G-GR over 2 weeks, for total treatment of 8 weeks, followed by a 1-week dosage taper for patients who did not wish or could not continue PHN treatment with G-GR. Patients visits occurred at the baseline/dosing, at the end of Week 2 (end of titration), end of Week 8 (end of treatment or early termination), and by phone at the end of the taper week. At each office visit, the pain intensity was assessed using a visual analog scale (VAS), and both the pain intensity and its interference with daily life were assessed using the Brief Pain Inventory (BPI). Patient/Clinician Global Impression of Change (PGIC/CGIC) scales were completed at Week 8. Adverse events (AEs) were assessed at the Week 2, Week 8, and posttapering phone visits. The protocol was IRB approved and all patients provided informed consent.

### Results

The safety population included 197 patients, and the efficacy population included 190 patients. Adherence to the dosage regimen was high: 89.8% of patients did not miss any doses at Week 2 and 68.9% of patients did not miss any dose at Week 8. The mean percent change in VAS scores from Baseline to Week 2 was -26.5%, and -30.6% from Baseline to Week 8. The proportion of patients with  $\geq 30\%$  reduction in VAS scores from Baseline to Week 2 was 45.8%, and 53.2% from Baseline to Week 8. The proportion of patients with  $\geq 50\%$  reduction in VAS scores was 40.5% at Week 2 and 33.2% at Week 8. Pain scores (worst, least, average, and current pain) on the BPI were all significantly reduced by Week 2 and Week 8 (all  $P < .0001$ ). All BPI interference scores (general activity, mood, walking ability, normal work, relationships, sleep, and enjoyment of life interference scores) and the average of the BPI interference scores were also significantly reduced at Week 2, and continued to decrease until Week 8 (all  $P \leq .0001$ ). For the PGIC and CGIC, 51.1% and 53.3% of patients, respectively, were considered "Very much" or "Much" improved at Week 8 compared with symptoms at study entry.

G-GR was generally well tolerated. A total of 100 (50.8%) patients reported at least one AE, and 37 (18.8%) patients discontinued the study due to AEs. No patient died and 5 (2.5%) patients experienced serious AEs (none was deemed by investigators to be related to treatment with G-GR). The most common G-GR-related AEs were dizziness (13.7%) and somnolence (5.6%). The prevalence of all AEs decreased rapidly, and by the end of the titration period had reached sustained low levels of  $\leq 1.5\%$ .

### Conclusions

In real-world clinical practice, G-GR appears to be an effective and well tolerated treatment option for PHN. Once-daily G-GR not only significantly reduced pain intensity but also improved patients' quality of life.



## Abuse potential of oxycodone/naloxone solution administered intravenously in nondependent recreational drug users with moderate opioid experience

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### Purpose

Opioid analgesics are an important component of modern pain management, however their abuse and misuse have created a serious and growing public health problem. To achieve the desired reinforcing effects, abusers often tamper with dosage forms, including by crushing, chewing, and dissolving in solution, so that more drug becomes systemically available more quickly via various routes of administration including intravenous injection (IV), intranasal insufflation, and oral ingestion. Controlled-release opioid products are particularly likely to be abused via tampering because they contain higher amounts of opioid and because tampering may reduce or eliminate the intact dosage form's controlled-release properties.

OXN, a twice-daily oral controlled-release formulation of oxycodone hydrochloride and naloxone hydrochloride (O to N ratio: 2/1 by weight), is under development in the US for management of moderate to severe chronic pain. Due to its low oral bioavailability ( $\leq 2\%$ ), naloxone is unlikely to affect the analgesic properties of oxycodone when OXN is administered orally as intended. If OXN is crushed and dissolved in a small volume of aqueous media for IV abuse, the extracted naloxone component, a potent opioid antagonist, will be 100% systemically available and is expected to greatly reduce the agonist effects of the concomitantly extracted oxycodone. This study was designed to characterize the IV abuse potential of OXN as compared to oxycodone alone and placebo. IV abuse of OXN was simulated by IV administration of a 2:1 ratio oxycodone:naloxone solution, a composition consistent with laboratory simulations of OXN tampering and extraction for IV administration.

### Method

This was a single-center, double-blind, randomized crossover study to evaluate the IV abuse potential, pharmacokinetics (PK) and safety of oxycodone/naloxone IV solution (ratio: 2/1) in male (N = 21) and female (N = 3) healthy nondependent recreational drug users (aged 20 to 54 years) experienced with opioids. The study consisted of 4 phases: screening, qualification, treatment, and follow-up. Treatments, injected IV within 1 min, were oxycodone 0.07 mg/kg + naloxone placebo, oxycodone 0.07 mg/kg + naloxone 0.035 mg/kg, or oxycodone placebo + naloxone placebo. Subject qualification required adequate differentiation between placebo and oxycodone following single-blind IV administrations. Qualified subjects were to receive all 3 treatments in a randomly assigned treatment sequence from two 3x3 Williams squares. Treatments were separated by 5-10 day washouts. Pharmacodynamic (PD) and PK assessments were conducted up to 6-8 h postdose. PD assessments included visual analog scales (VAS) for 'At the Moment Drug Liking', 'Overall Drug Liking', 'Take Drug Again', High, Good Effects, Bad Effects, Feeling Sick Effects, and Alertness/Drowsiness, and the Subjective Drug Value (SDV) procedure. Both Drug Liking scales were bipolar (0 = Strong Disliking, 50 = Neutral, 100 = Strong Liking). Pupillary responses were measured. Safety evaluations included physical examination, 12-lead electrocardiograms, continuous cardiac monitoring, vital signs, clinical laboratory, medication history, and adverse events. Plasma oxycodone and naloxone concentrations were determined and PK parameters were derived using noncompartmental methods. Descriptive statistics, 95% confidence intervals and P values for treatments and treatment differences for appropriate PD values or derived endpoints (minimum effect [E<sub>min</sub>], maximum effect [E<sub>max</sub>], time-averaged effect) were computed.

## Results

Mean 'At the Moment Drug Liking' VAS  $E_{max}$  for oxycodone (96.4) was significantly higher than for oxycodone/naloxone (56.5) or placebo (48.7), with no significant difference between oxycodone/naloxone and placebo. Mean 'Overall Drug Liking' VAS  $E_{max}$  showed similar differences among the treatments with values of 79.5, 49.5, and 46.0 for oxycodone, oxycodone/naloxone, and placebo, respectively. Mean 'Take Drug Again' VAS  $E_{max}$  was 82.0, 37.0, and 34.5 for oxycodone, oxycodone/naloxone, and placebo, respectively. Mean Good Effect VAS  $E_{max}$  was 94.0 for oxycodone as compared to values of 20.0 and 2.7 for oxycodone/naloxone and placebo, respectively. A similar pattern among treatments was observed for High VAS. Bad Effects and Feeling Sick VAS scores were minimal for all treatments. Mean SDV  $E_{max}$  was low for placebo (\$0.86) and oxycodone/naloxone (\$3.38), and much higher for oxycodone (\$25.06). Pupillometry demonstrated characteristic opioid-induced miosis following oxycodone alone, with significantly smaller changes and a delayed time course following oxycodone/naloxone, and no notable changes following placebo.

Following oxycodone/naloxone vs oxycodone administrations, respectively, comparable oxycodone mean  $C_{max}$  (98.6 vs 81.3 ng/mL) and similar mean AUC (116 vs 115 ng\*h/mL),  $T_{max}$  (0.05 vs 0.05 h),  $t_{1/2}$  (3.5 vs 3.4 h) and CL/F (47.0 vs 47.8 L/h) were observed. Following oxycodone/naloxone administration, mean  $C_{max}$ , AUC,  $T_{max}$ ,  $t_{1/2}$  and CL for naloxone were 25.3 ng/mL, 12.7 ng\*h/mL, 0.05 h, 1.2 h, and 217 L/h.

PD responses to oxycodone alone corresponded with oxycodone systemic concentrations over time. Oxycodone/naloxone coadministration resulted in significant attenuation of oxycodone effects.

The most common TEAE was euphoric mood, which was highest for oxycodone (73.9%; 17 subjects), and considerably lower for oxycodone/naloxone (8.3%; 2 subjects). Two subjects experienced SAE's of ventricular tachycardia, 1 following oxycodone/naloxone treatment and 1 placebo (discontinued). Overall, the incidence of typical opioid treatment-emergent AEs was lower for oxycodone/naloxone compared to oxycodone.

## Conclusions

This study characterized the abuse potential of IV injections of oxycodone/naloxone solution (simulating IV abuse of OXN), oxycodone alone, and placebo, in experienced opioid abusers. Significant reductions in the magnitude of drug liking and of other measured PD effects were observed following oxycodone/naloxone, as compared to oxycodone alone. These reductions demonstrate that the systemic naloxone concentrations observed following simulated IV abuse of crushed and extracted OXN tablets were sufficient to substantially reduce abuse potential, compared to IV injection of oxycodone alone. It is anticipated that this abuse potential reduction will contribute to corresponding reductions in abuse liability in real-world settings.

## A mixed-methods approach to patient and provider satisfaction with pain education

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### Purpose

Patient education is a central component in high-quality integrated care of chronic pain patients. The number of pain management programs in the research literature continues to grow. Patient satisfaction has been associated with better health status, improved engagement in personal healthcare, and reductions in primary care use; conversely dissatisfaction is commonly associated with disenrollment in programming. Less often, the satisfaction of the healthcare providers involved in the facilitation of health education programs has been examined. Literature in the area of provider satisfaction tends to examine workload, job satisfaction, and managed care rather than the impact, utilization, and perception of patient levels of satisfaction of programming. Furthermore, few studies have dealt with both patient and provider perceptions simultaneously. The purpose of the current study was to assess patients' and providers' satisfaction with a 12-week "Pain Education School" program within the initial 2-year phase of implementation. The current mixed-method research study was designed using Morgan's Priority-Sequence Model as a guide. Quantitative methodology was utilized to examine the participant and provider reported satisfaction. Qualitative methodology was employed as a complementary follow-up in order to provide interpretations and explore underlying themes or indicators associated with the reported quantitative satisfaction.

### Method

This is a retrospective study of data that were obtained from anonymous postintervention satisfaction surveys of 219 veteran patient participants between 26-84 years old, and 37 provider participants who facilitated the program. The majority of patient participants were enrolled in a health education program at a Midwestern VA medical center between November 6, 2009-January 20, 2012, while some joined from off-site community-based outpatient clinics utilizing picture telephone technology. "Pain Education School" consists of 12-weeks of 1-hour classes with an additional 1-hour introduction class during the first week. Over the course of the program, 22 modules are presented (averaging 30 minutes each). Classes are scheduled on a rotating basis regardless of the patient participant's entry point—the provider participants rotate on a schedule, not the patient participants. The presenter participants are healthcare providers of the VA that have expertise in the specific module presented. Participants completed the "Pain Education – End of School Survey: Opinion/Satisfaction Survey" at postintervention, while program facilitators completed the "Provider Satisfaction and Program Evaluation" after the 2-year phase. Descriptive statistics were used to quantify survey data. Emerging themes were collated to depict a set of finalized thematic maps to visually represent the patterns inherent in the qualitative data.

### Results

Quantitative findings suggest that patient participants reported learning "new and useful" information ( $M = 4.62$ ,  $SD = 0.82$ ); perceived the program as "easy to understand" ( $M = 4.62$ ,  $SD = 0.70$ ); used the learned information ( $M = 4.58$ ,  $SD = 0.77$ ); and recommended the program to others ( $M = 4.71$ ,  $SD = 0.74$ ). Results indicate that provider participants perceived the goals and services of the program to be "clear" ( $M = 4.35$ ,  $SD = 0.79$ ); the strategies utilized to have "influenced" their practice ( $M = 4.06$ ,  $SD = 1.03$ ); the methods of communication with the coordinators as "helpful" ( $M = 4.29$ ,  $SD = 0.85$ ); and the program as having a "positive" impact on their service ( $M = 4.33$ ,  $SD = 0.72$ ). Additionally, providers received fewer complaints regarding pain medications ( $M = 3.59$ ,  $SD = 0.87$ ); had fewer walk-ins for pain management issues ( $M = 3.29$ ,  $SD = 0.92$ ); spent more time with their patients on other medical problems ( $M = 3.94$ ,  $SD = .75$ ); and felt more comfortable in managing chronic pain due to the

program ( $M = 3.76$ ,  $SD = 0.90$ ). Results also enumerated provider participants' level of utilization of the program, including the extent to which providers have "referred patients" for this service ( $M = 2.17$ ,  $SD = 0.71$ ); the extent to which providers have utilized as "a resource for assistance with chronic pain management" ( $M = 1.83$ ,  $SD = 0.72$ ); and the extent to which providers have utilized "the service as a resource for...other nonpain cases" ( $M = 1.89$ ,  $SD = 0.83$ ). Finally, results indicated provider participants' perception of patient levels of satisfaction ( $M = 3.11$ ,  $SD = 0.90$ ). Qualitative findings produced key themes, subthemes, and example quotations from the satisfaction surveys and will be illustrated on the poster presentation.

## **Conclusions**

The current study allowed for the identification of key treatment elements from the patient's perspective, having both practical and theoretical implications in furthering the development and implementation of health education programs for chronic pain. Unlike previous studies, this study allowed for providers who facilitate the program to also have a voice. This comprehensive participant-centered approach is particularly important when determining satisfaction. Our study also provided a fuller investigation of satisfaction often inaccessible through traditional quantitative methods by utilizing a multimethods approach. This information is invaluable to the providers aiding in the facilitation of the program.

## **An examination of change in distress across cognitive behavioral and acceptance and commitment therapy group sessions for chronic pain**

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### **Purpose**

Numerous studies support the efficacy of cognitive behavioral therapy (CBT) and acceptance and commitment therapy (ACT) in treating chronic pain. Yet, when comparing CBT and ACT protocols to manage idiopathic, noncancer pain among veterans (Cosio, 2012), only significant main effects over time were found for psychological distress as measured by the Brief Symptom Inventory-18 (BSI-18; Derogatis, 2000). These findings were congruent with past literature which recognized CBT and ACT as empirically-supported treatments for pain-related anxiety (Bailey, et al, 2010) and other anxiety-related problems (Ruiz, 2012), but this evidence-base largely examines preintervention to postintervention changes. The validity of pre- and postassessments has been called into question (Kazdin, 2003); perhaps utilizing another measure of distress, specifically the Beck Anxiety Inventory (BAI; Beck, et al, 1988), may serve as corroboration when measuring distress in the current veteran sample.

Experiment 1: The purpose of the first study sought to examine the criterion-related validity of the BAI and BSI-18, and whether the BAI was an adequate, unidimensional appraisal of distress among veterans.

Research has proposed that the mechanism of change in CBT and ACT is “fear-avoidance” (Lethem, et al, 1983; Vlaeyen, et al, 1999; 2000). Questions remain largely unanswered as to why and how this paradigm works across the course of treatment for chronic or persistent, noncancer pain.

Experiment 2: The purpose of the second study was to compare the process of change in psychological distress for the CBT and ACT pain groups measured by BAI scores every week over an 8-week period.

### **Method**

Ninety-six adult veterans (86% men; 14% women), 29-81 years old, elected to seek either an ACT (n = 50) or CBT (n = 46) treatment group for chronic or persistent, noncancer pain at a Midwestern VA Medical Center between November 3, 2009 and November 4, 2010. Veterans had mixed idiopathic chronic pain conditions, including back, neck, extremity, head, and fibromyalgia/soft tissue pain. Veterans elected to participate in either treatment group following the completion of a 12-week preliminary pain health education program (Cosio, et al, 2012; Cosio & Lin, in progress). The 12-week CBT treatment group followed an empirically supported, "Treatments that Work" manualized protocol (Otis, 2007). The 9-week ACT treatment group followed an amalgamation of established protocols (Dhal, et al, 2005; Vowles and Sorrell, 2007) and a self-help workbook (Dahl and Lundgren, 2006). Veterans completed preassessments and postassessments utilizing the BSI-18 at the first and last session of each of the pain group interventions (Cosio, 2012), and the BAI during groups Session #2—Session #8 as a process measure.

Experiment 1: In the first study, the relationship between the BAI and the BSI-18 was measured using Spearman's correlation. The 21 items of the BAI were then subjected to principal components analysis (PCA) to cross validate the measure's factor structure.

Experiment 2: The primary outcome analysis for the second study was a 2 x 7 repeated measures (RM) multivariate analyses of variance (MANOVA). A trend analysis was computed to explore whether there was a linear, quadratic, cubic, etc, relationship between intervention condition and time employing polynomial functions.

## Results

Experiment 1: The mean baseline BSI-18 global distress score was 25.63 (SD = 13.06), and the BAI baseline total score was 19.50 (SD = 11.231), which reflect moderate levels of distress. An ANOVA revealed there was no significant difference between the CBT and ACT groups on baseline BSI-18 scores,  $F(1,94) = 3.122, P = 0.080$ , and the baseline BAI total scores,  $F(1,94) = 1.038, P = 0.311$ . The BSI-18 ( $\alpha = .837$ ) and the BAI ( $\alpha = 0.913$ ) were both found to have good internal consistency. The Spearman correlation between the BAI and BSI-18 was  $r_s = .746, P = .000$ . Inspection of the correlation matrix revealed the presence of many coefficients of .3 and above. The Kaiser-Meyer-Olkin value was .851 and the Barlett's Test of Sphericity reached statistical significance  $P = .000$ . PCA revealed the presence of 5 components with eigenvalues exceeding Kaiser's criterion of 1.0, with the first explaining 38.52% of the variance. An inspection of the screeplot revealed a clear break after the first component. When examining the scree test and the results of the parallel analysis, only one component had an eigenvalue exceeding the corresponding criterion value for a randomly generated data matrix of the same size.

Experiment 2: A 2 x 7 RM MANOVA found a significant "Intervention x Time" interaction,  $F(6, 87) = 2.180, P = .052$ , Wilk's Lambda = .869 and a main effect for "Time,"  $F(6, 87) = 2.339, P = .038$ , Wilk's Lambda = .861. The Mauchly's Sphericity Test result was .052 ( $P = .000$ ). Greenhouse-Geisser Epsilon (G-G  $\epsilon, P = .039$ ) and Huyn-Feldt Epsilon (H-F  $\epsilon, p = .037$ ) calculations adjusted for the lack of sphericity. Polynomial functions indicate that the linear ( $P = .104$ ) and the cubic ( $P = .466$ ) components were not significant, but the quadratic ( $P = .052$ ) component was significant for "Intervention x Time." Therefore, the groups show different quadratic trends over time. There was not a significant treatment effect for "Intervention,"  $F(1, 92) = .009, P = .924$ .

## Conclusions

While prevailing literature clearly demonstrates the efficacy of CBT and ACT for the treatment of chronic pain, research has traditionally focused on changes in symptoms from pre- to posttreatment. Following PCA with parallel analysis to confirm the use of the BAI as an adequate measure for distress among veterans with chronic pain, participants completed BAI's weekly throughout group treatment in ACT or CBT group interventions. While MANOVA results indicate significantly lower levels of distress by the end of treatment, trend analysis revealed distinctive processes of change between groups. Implications related to underlying mechanisms, timing, and patterns of change are discussed.

## OnabotulinumtoxinA (Botox®) for the management of chronic postradiation fibrosis pain

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### Purpose

To describe a novel use of onabotulinumtoxinA as a simple, safe and effective management option for pain and tissue tightness seen in postradiation fibrosis syndrome in the neck and upper torso. A case of severe postradiation fibrosis with pain presenting 11 years following composite excision of adenoid cystic carcinoma of the tongue and floor of the mouth and radical neck surgery) will be discussed in detail. Surgery also involved reconstruction with a pectoralis major myocutaneous flap. This was followed by radiation therapy with resultant tissue atrophy and fibrosis. Initial treatment also included the use of hyperbaric oxygen.

### Method

64 y/o male presented with complains of right-sided neck and shoulder pain as well as range of motion restrictions. Pain had evolved over a decade, following surgery to remove an adenoid cystic carcinoma for the tongue and floor of mouth (composite excision and radical neck dissection) 11 years before presentation. He had also received several courses of radiation therapy with resultant osteoradionecrosis and infectious complications. The pain became progressively worse, particularly over the prior 5 years.

The patient's pain was treated with opioids with only suboptimal results. He had a history of substance abuse overused/misused opioids on several occasions, prompting his primary care provider to seek pain management consultation for other treatment alternatives. He had received some trigger point injections with modest, yet short-lived relief.

On exam, there was atrophy of the pectoralis major and trapezius. He had very visibly tight right sternocleidomastoid and platysma muscles; these were very hard and somewhat tender to palpation. He had very limited left head rotation and left lateral bending as well as extension; other movements appeared to be functional. Range of motion of the shoulder was functional with a painful arc past 60° of abduction and positive impingement signs. Spurling's Maneuver was negative and muscle stretch reflexes were symmetric.

### Results

Screening EMG of the neck and shoulder girdle muscles showed no significant increased involuntary motor unit activity. Insertions were compatible with mostly fibrotic tissue over the right forequarter.

About 2 weeks after the initial visit, OnabotulinumtoxinA (Botox®) injection trial was initiated. The toxin was reconstituted using preservative-free, normal saline solution at a concentration of 50 Units/cc (2 cc per 100 unit/vial) and injections were performed using anatomical landmark guidance with 1/2" 30G disposable hypodermic needle. The following muscles were injected:

- Right sternocleidomastoid: 20 units (divided in 2 places)
- Right splenius capitis: 20 units (divided in 2 places)
- The remaining 60 units were injected subcutaneously over the affected area using a grid pattern over 15 points (4 units/point), for a total of 100 units.

Within a week of the initial injections the patient reported remarkable improvement (reported to be nearly pain-free in the neck and affected forequarter). The patient has received 5 series of injections over a period of 2-and-a-half years, averaging 1 set of injections approximately every 5 months. All procedures have been done similarly with no change in target areas or doses.

### **Conclusions**

OnabotulinumtoxinA (Botox®) should be considered as an option in the comprehensive management of postradiation fibrosis in the cervical and upper torso area. Consistent with other applications, onabotulinumtoxinA (Botox®) appears to have analgesic/pain modulating properties independent of their muscle relaxation effects. This therapy can be safe and remarkably effective when properly utilized.



## Single-dose pharmacokinetics of 1 and 2 tablets of MNK-795 controlled-release oxycodone/acetaminophen tablets (CR OC/APAP) compared with immediate-release oxycodone and acetaminophen

Krishna Devarakonda, Terri Morton, Michael Giuliani, Kenneth Kostenbader, Thomas Barrett  
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### Purpose

Formulations that combine opioid and nonopioid analgesics may provide effective pain relief with lower doses of each agent, which may also translate into improved tolerability. In addition, controlled-release (CR) formulations can reduce the pill burden for patients and potentially improve adherence. MNK-795 (CR oxycodone [OC]/acetaminophen [APAP]) is being developed to manage moderate to severe acute pain that warrants treatment with a controlled-release analgesic. It is the first CR combination OC/APAP analgesic, and is designed to provide fast onset of analgesia (within 1 hour) and sustained analgesia over the 12 hour dosing interval. The tablets employ a dual layer biphasic delivery profile, that when delivered as a single dose (ie, 2 tablets), consists of an immediate-release (IR) component containing 3.75 mg OC/325 mg APAP followed by an extended-release component containing 11.25 mg OC/325 mg APAP. The total APAP dose per tablet is in accordance with the latest requirements from the US Food and Drug Administration (FDA) of  $\leq 325$  mg/dosage unit. This tablet strength was selected to provide effective analgesia while also limiting the total daily dose of APAP (1300 mg; 2 tablets CR OC/APAP every 12 hours) to an amount that is below the current recommended total daily dose (4000 mg). The purpose of this study was to compare the pharmacokinetics, bioavailability, dose proportionality, and tolerability of a single dose (1 or 2 tablets) of CR OC/APAP (7.5 mg OC/325 APAP per tablet) vs an IR formulation of OC/APAP (7.5 mg/325 mg) administered every 6 hours for 2 doses in fasted, healthy subjects.

### Method

This was a single-center, open-label, randomized, phase 1, 3-period, crossover study that included a fourth evaluation period. Fasted, healthy subjects (N = 48) 18 to 55 years of age were randomized to receive 1 tablet of CR OC/APAP taken once (treatment A), 2 tablets of CR OC/APAP taken once (treatment B), and 1 tablet of IR OC/APAP taken every 6 hours for 2 doses (treatment C) in a 3-way crossover design. Subjects who completed periods 1, 2, and 3 returned for period 4 and received 2 tablets of IR OC/APAP every 6 hours for 2 doses under fasted conditions (treatment D). The study included a screening visit and 4 confinement periods of approximately 60 hours each with a minimum of 7 days between the start of each period. Blood was collected predose and at different time points from 15 minutes to 48 hours postdose by venipuncture, and plasma was separated. OC and APAP concentrations were determined using liquid chromatography/tandem mass spectrometry. Analysis of variance was performed to compare treatment conditions A, B, and C using the dose-normalized natural log-transformed PK parameters ( $AUC_{0-\infty}$ ,  $AUC_{0-t}$ , and  $C_{max}$ ), and linear mixed model analysis compared the same PK parameters for treatments D and C. Adverse events were monitored throughout the study.

### Results

Forty-eight healthy adults were enrolled in the study; 33 completed 3 treatment periods, and 27 completed all 4 dosing periods. After administration of CR OC/APAP, the plasma concentrations of OC and APAP rose rapidly, similar to those seen with IR OC/APAP. The median OC  $T_{max}$  was observed at 4 hours and 3 hours after the 1-tablet and 2-tablet doses of CR OC/APAP, respectively. After 1 tablet of IR OC/APAP, peak OC concentrations were observed at 7 hours (1 hr after the second dose), and after 2 tablets of IR OC/APAP at 0.75 hour. Dose normalized  $AUC_{0-t}$  and  $AUC_{0-\infty}$  for OC was comparable across all treatments. The dose normalized  $C_{max}$  for OC was equivalent for the 1- and 2-tablet doses of CR OC/APAP, indicating dose proportionality, and  $C_{max}$  was approximately 20% lower for CR

OC/APAP than for IR OC/APAP. APAP  $T_{max}$  occurred 0.75 hours after dosing with CR OC/APAP for 1 and 2 tablets, respectively, and occurred 0.5 hours after dosing with IR OC/APAP for 1 and 2 tablets, respectively. Dose normalized  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  for APAP were comparable across all treatment groups. In addition, APAP concentrations at 7 to 12 hours after 2 tablets of CR OC/APAP were lower than concentrations after the second dose of IR OC/APAP. Overall, 41 subjects (85.4%) experienced  $\geq 1$  treatment emergent adverse event (TEAE), with TEAEs higher after 2 tablets of IR OC/APAP (75.8%) than after 1 tablet of IR OC/APAP (56.4%), 2 tablets of CR OC APAP (51.2%), and 1 tablet of CR OC/APAP (25.6%). The most frequently reported TEAEs were consistent with those expected from an opioid and were nausea (68.8%), vomiting (39.6%), somnolence (35.4%), pruritus (33.3%), and headache (29.2%). Twenty-one subjects withdrew from the study; 19 were withdrawn because of vomiting per the prespecified protocol.

## Conclusions

CR OC/APAP demonstrated a biphasic delivery of OC, with a rapid rise after dosing followed by CR that peaked at 3 to 4 hours postdose, with plasma OC concentrations prolonged over the proposed 12 hour dosing interval. This first CR combination product containing APAP resulted in APAP concentrations that, after an initial rapid rise, tapered off at 7 to 12 hours postdose. The pharmacokinetic and safety findings of this single-dose study support the safe and appropriate administration of CR OC/APAP for the management of moderate to severe acute pain, and illustrate a unique pharmacokinetic profile for CR OC/APAP.

## Single-dose pharmacokinetics, bioavailability, and safety of MNK-795, a controlled-release oxycodone and acetaminophen combination analgesic (CR OC/APAP), under fed and fasted conditions

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### Purpose

MNK-795 is a novel, controlled-release (CR) combination oxycodone (OC)/acetaminophen (APAP) analgesic (CR OC/APAP) being developed to manage moderate to severe acute pain. CR OC/APAP was studied in clinical trials as 2 tablets every 12 hours. The tablets employ a dual layer biphasic delivery profile, that when administered as a single dose (ie, 2 tablets), consists of an IR component containing 3.75 mg OC/325 mg APAP and an extended-release component containing 11.25 mg OC/325 mg APAP. The total APAP dose per tablet is in accordance with the latest dose limitation imposed by the US Food and Drug Administration of 325 mg/dosage unit. The daily dosage of APAP in 2 tablets of CR OC/APAP taken twice daily is 1300 mg, which is below the current maximum total daily dose of 4000 mg. Because food has demonstrated an impact on the pharmacokinetics (PK) of marketed products using CR technology similar to that of CR OC/APAP, an early assessment of food effects on the PK of CR OC/APAP was performed and indicated that a high-fat meal does not affect the PK of OC and APAP from CR OC/APAP. In the current study, a more thorough characterization of the impact of diet upon the PK of CR OC/APAP was performed. The primary objective of this study was to determine the effect of fed (high- and low-fat diets) vs fasted conditions on the PK profile and bioavailability of OC and APAP from 2 tablets of CR OC/APAP. Safety when administered under fed and fasted conditions was also examined.

### Method

This phase 1 study used an open-label, randomized, single-dose, 3-period, 6 sequence crossover, single-center design, and was conducted in healthy adult subjects (N = 48). Subjects were randomized to receive 2 tablets of CR OC/APAP (ie, 15 mg OC/650 mg APAP) under fed conditions after a high-fat meal (treatment A), 2 tablets under fed conditions after a low-fat meal (treatment B), and 2 tablets under fasted conditions (treatment C). The beginning of each crossover period was separated by a minimum 7-day washout. Blood was collected predose, and samples for PK analysis of OC and APAP were collected at 15, 30, and 45 minutes and at several time points from 1 to 48 hours after dosing. Plasma samples were prepared and analyzed using a liquid-liquid extraction procedure followed by chromatographic separation and tandem mass spectrometry detection of the analytes. Plasma concentration vs time data was used to estimate the PK parameters of OC and APAP. Analysis of variance was performed to compare data from the 3 treatment conditions (A, B, and C) using the natural log-transformed PK parameters ( $AUC_{0-inf}$ ,  $AUC_{0-t}$ , and  $C_{max}$ ), and the Wilcoxon signed-rank test was utilized to compare untransformed  $T_{max}$  and  $t_{lag}$ . Adverse events (AEs) were collected and monitored throughout the study.

### Results

Forty-eight subjects enrolled and received study medication. All subjects were included in the safety analysis; subjects who completed all 3 periods (n = 31) were included in the PK analysis. Both OC and APAP were rapidly absorbed under fasted conditions (median  $T_{max}$ , 3 h and 0.53 h, respectively) with no lag in appearance ( $t_{lag}$ , 0.0 h for both). Administration of CR OC/APAP with food resulted in a slight, but statistically significant, lag of 15 minutes (OC, high-fat and low-fat meal; APAP, low-fat meal;  $P < .02$  for both). The median  $T_{max}$  of OC was significantly delayed by 2 hours with a high-fat meal vs fasted conditions ( $P < .02$ ), whereas the median  $T_{max}$  of APAP was significantly delayed by 1.5 hours with high-fat and low-fat meals vs fasted conditions ( $P < .001$  for both). Compared with CR OC/APAP under fasted conditions, mean total exposure ( $AUC_{0-inf}$  and  $AUC_{0-t}$ ) of OC and APAP were bioequivalent under both

high-fat and low-fat states; mean OC  $C_{max}$  was similar under the high-fat state, and it was slightly increased (25%) under the low-fat state (90% confidence interval was partially contained within the no-effect range); and APAP  $C_{max}$  was decreased by 24% and 23% for high-fat and low-fat conditions vs fasted, respectively. Thirty-three subjects (68.8%) reported  $\geq 1$  treatment-emergent AE (TEAE). The most frequently reported TEAEs were nausea, vomiting, and dizziness, and there were no notable differences between treatment groups. Seventeen subjects terminated early; 14 due to vomiting (withdrawn per protocol) and 3 due to other withdrawal criteria.

## Conclusions

Total OC and APAP exposures (AUC) of CR OC/APAP were not significantly affected by food. Food marginally delayed the  $T_{max}$  of OC and APAP. Minimal changes to  $C_{max}$  for OC and APAP were noted in the presence of food, but these changes were comparable to food effects on peak exposure for other OC and APAP products. In addition, there was no indication that safety was affected by food. The comparable PK and safety findings suggest that CR OC/APAP can be administered with or without food.

## Comparison of the pharmacokinetic profile of MNK-795, a new oral, controlled-release formulation of oxycodone/acetaminophen (CR OC/APAP) analgesic at steady state vs marketed immediate-release tablets

Krishna Devarakonda, Terri Morton, Michael Giuliani, Kenneth Kostenbader, Thomas Barrett  
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### Purpose

The first controlled-release (CR) combination oxycodone (OC)/acetaminophen (APAP) analgesic, MNK-795 (CR OC/APAP), is being developed to manage moderate to severe acute pain that warrants treatment with a CR analgesic. CR OC/APAP is designed to provide a fast onset of analgesia (< 1 hour) and sustained analgesia over the 12 hour dosing interval. The formulation targets controlled medication release in the upper gastrointestinal tract for an extended period of time and incorporates technology designed to provide tamper-resistance and abuse-deterrence. CR OC/APAP employs a dual layer biphasic delivery profile, that when administered as a single dose (ie, 2 tablets), consists of an IR component containing 3.75 mg OC/325 mg APAP and an extended-release component containing 11.25 mg OC/325 mg APAP. The APAP strength follows the limit of 325 mg per tablet required by the US Food and Drug Administration in an effort to reduce the likelihood of drug-induced liver injury. The purpose of this study was to evaluate the steady-state pharmacokinetics (PK) and safety after multiple doses of CR OC/APAP (every 12 h) compared with those following administration of multiple doses of an IR form of OC, IR tramadol/APAP, and IR OC/APAP (every 6 h) in healthy subjects.

### Method

This single-center, open-label, randomized, multiple-dose, 4-period crossover, 4-sequence study was conducted in normal, healthy adults (aged 18-55 years). Subjects were randomly assigned to receive each study medication in 1 of 4 treatment sequences (4 periods, ~7 days each) separated by a minimum of 13 days. Study medications included CR OC-APAP (7.5 mg/325 mg; 2 tablets every 12 h for 4.5 days), IR OC (15 mg; 1 tablet every 6 h for 4.5 days), IR tramadol/APAP (37.5 mg/325 mg; 1 tablet every 6 h for 4.5 days), and IR OC/APAP (7.5 mg/325 mg; 1 tablet every 6 h for 4.5 days). All treatments were administered under fasted conditions. Blood samples for PK analysis of OC and APAP were collected at designated times before and up to 132 hours after dosing. OC PK was compared between CR OC/APAP, IR OC, and IR OC/APAP; and APAP PK was compared between CR OC/APAP, IR tramadol/APAP, and IR OC/APAP. Analysis of variance was performed with the natural log-transformed, dose-normalized (amount absorbed corrected by dose administered) PK parameters ( $C_{max}^{ss}$ ,  $C_{min}^{ss}$ ,  $C_{avg}^{ss}$ , and  $AUC_{0-12h}^{ss}$ ) or natural log-transformed PK parameters (degree of fluctuation around the average plasma concentration at steady state, defined as  $[C_{max}^{ss} - C_{min}^{ss}] / C_{avg}^{ss}$ ). Adverse event monitoring and clinical laboratory testing were conducted.

### Results

Forty-eight adults were enrolled, and data from 24 completers were included in PK analyses. Plasma concentrations of OC and APAP increased rapidly after administration (median  $T_{max}^{ss}$ , 3 h OC; 1 h APAP), and steady-state plasma concentrations of both OC and APAP were achieved within 24 hours of CR OC/APAP initiation. At steady state, dose-normalized peak exposure ( $C_{max}^{ss}$ ) of OC from CR OC/APAP was equivalent to IR OC/APAP and IR OC. Dose-normalized  $C_{min}^{ss}$  and total systemic OC exposure ( $AUC_{0-12h}^{ss}$ ) were also equivalent. Fluctuation of OC plasma concentrations during the dosing interval (every 12 h) for CR OC/APAP was comparable to IR OC (every 6 h) and 23% less than IR OC/APAP (every 6 h). For APAP, dose-normalized  $C_{max}^{ss}$  and  $AUC_{0-12h}^{ss}$  from CR OC/APAP were equivalent to IR tramadol/APAP and IR OC/APAP; however,  $C_{min}^{ss}$  was 21% and 22% lower with CR OC/APAP than for IR tramadol/APAP and IR OC/APAP, respectively. APAP plasma levels of CR OC/APAP fell below those of IR tramadol/APAP and IR OC/APAP approximately 7 hours after dosing on day 5, and were 17% of  $C_{max}^{ss}$  12 hours

after dosing. Fluctuation of APAP plasma concentrations, with respect to  $C_{avg}^{ss}$ , during the dosing interval for CR OC/APAP (every 12 h) was comparable to IR tramadol/APAP (every 6 h) and IR OC/APAP (every 6 h). Approximately 92% of enrolled subjects experienced a treatment emergent adverse event (TEAE), 82.4% during IR OC, 64.5% during IR OC/APAP, 45.5% during CR OC/APAP, and 42.9% during IR tramadol/APAP. The most frequently reported TEAEs during CR OC/APAP were nausea (24.2%), vomiting (21.2%), pruritus (21.2%), headache (15.2%), and dizziness (12.1%). Twenty-two subjects (45.8%) were withdrawn from the study (per protocol) because of vomiting, of which 7 (21.2%) were during CR OC/APAP treatment. No clinically significant treatment-related trends in clinical laboratory assessments or physical examination findings were observed.

## Conclusions

OC and APAP plasma concentrations rose quickly after administration of CR OC/APAP, with a shorter  $T_{max}$  for APAP than OC, and steady-state was achieved within 24 hours for both. At steady-state, CR OC/APAP administered as 2 tablets every 12 hours produced comparable PK to IR marketed products dosed every 6 hours, however with less fluctuation in OC compared with IR OC/APAP and lower trough plasma concentrations of APAP compared with both IR comparators prior to subsequent dosing. These findings support the safe and appropriate administration of CR OC/APAP during the proposed dosing interval of every 12 hours.

## Comparison of the pharmacokinetic profile of a single dose of MNK-795, a controlled-release oxycodone and acetaminophen combination tablet (CR OC/APAP) and marketed immediate-release opioids and opioid/acetaminophen combination tablets

Krishna Devarakonda, Terri Morton, Michael Giuliani, Kenneth Kostenbader, Thomas Barrett  
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### Purpose

The first controlled-release (CR) combination oxycodone (OC)/acetaminophen (APAP) analgesic, MNK-795 (CR OC/APAP), is being developed to manage moderate to severe acute pain that warrants treatment with a CR analgesic. CR OC/APAP employs a dual layer biphasic delivery profile, that when administered as a single dose (ie, 2 tablets), consists of an IR component containing 3.75 mg OC/325 mg APAP and an extended-release component containing 11.25 mg OC/325 mg APAP. This formulation was designed to provide a fast onset of analgesia (< 1 hour) and sustained analgesia over the 12 hour dosing interval. CR OC/APAP incorporates technology designed to provide tamper-resistance and abuse-deterrence. The strength of APAP follows the required maximum of 325 mg in a single tablet by the US Food and Drug Administration in an effort to reduce the likelihood of drug-induced liver injury. The purpose of this study was to evaluate the single-dose pharmacokinetics (PK) of OC and APAP after CR OC/APAP administration compared with the PK following administration of marketed forms of IR OC, IR tramadol/APAP, and IR OC/APAP every 6 hours for 2 doses in healthy subjects.

### Method

This single-center, open-label, randomized, single-dose, 4-period crossover, 4-sequence study was conducted in normal, healthy adults aged 18 to 55 years. Subjects were randomly assigned to receive each study medication in 1 of 4 treatment sequences (4 periods, ~48 h each) separated by a minimum of 7 days. Study medications included: CR OC/APAP (administered one time as two 7.5 mg/325 mg tablets), IR OC (15 mg; 1 tablet every 6 h for 2 doses), IR tramadol/APAP (37.5 mg/325 mg; 1 tablet every 6 h for 2 doses), and IR OC/APAP (7.5 mg/325 mg; 1 tablet every 6 h for 2 doses). All treatments were administered under fasted conditions. Blood samples for PK analysis of OC and APAP were collected at designated times before and up to 36 hours after dosing. The PK of OC was compared between CR OC/APAP, IR OC, and IR OC/APAP; the PK of APAP was compared between CR OC/APAP, IR tramadol/APAP, and IR OC/APAP. Analysis of variance was performed with the natural log-transformed, dose-normalized (amount absorbed corrected by dose administered) PK parameters ( $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$ ). Safety was assessed using standard measures, including adverse event monitoring and clinical laboratory testing.

### Results

Forty-eight adults were enrolled; data from 29 completers were included in PK analyses. Plasma concentrations of OC increased rapidly after administration of CR OC/APAP (median  $T_{lag}$  0 h; median  $T_{max}$  4 h) and OC was slowly eliminated (OC concentration was ~45% of peak exposure ( $C_{max}$ ) 12 h after dosing). OC  $C_{max}$  (dose normalized) from CR OC/APAP was equivalent to that from IR OC, and ~27% lower than IR OC/APAP. The  $AUC_{0-inf}$  of OC from CR OC/APAP (every 12 h) was equivalent to both comparators (every 6 h). Plasma APAP concentrations also increased rapidly after administration of CR OC/APAP (median  $T_{lag}$  0 h; median  $T_{max}$  0.75 h), and APAP concentration was only 18% of  $C_{max}$  12 hours after dosing. Plasma APAP concentrations for CR OC/APAP fell below the levels for the comparators 8 hours after dosing (2 hours after the second dose of the comparator). Total dose-normalized AUC and  $C_{max}$  of APAP from CR OC/APAP were comparable to the AUC and  $C_{max}$  from IR tramadol/APAP and IR OC/APAP. All 48 enrolled subjects received  $\geq 1$  dose of study medication and were included in the safety population. Approximately 60% of subjects experienced treatment-emergent adverse events (TEAEs), 58.1% after IR OC, 37.5%

after IR OC/APAP, 23.1% after CR OC/APAP, and 22.2% after IR tramadol/APAP, the most common were nausea (43.8%), dizziness (33.3%), vomiting (27.1%), headache (20.8%), somnolence (10.4%), feeling hot (10.4%), and pruritus (10.4%). The most frequent TEAEs after CR OC/APAP exposure were nausea (12.8%), dizziness (7.7%), and somnolence (7.7%). All TEAEs were of mild to moderate severity. There were no SAEs reported. No clinically significant treatment-related trends in clinical laboratory assessments or physical examination findings were observed. A total of 13 subjects had protocol-mandated early termination due to vomiting (10 with IR OC, 1 each after CR OC/APAP, IR OC/APAP, and IR tramadol/APAP).

## **Conclusions**

OC and APAP plasma concentrations of CR OC/APAP rose rapidly and, whereas OC concentration was sustained, APAP concentration slowly declined to 18% of the peak at 12 hours, prior to the subsequent dose. The similarity of the relevant PK parameters to those of the IR marketed compounds supports the proposed dosing interval. The PK and safety findings support the proposed 12 hour dosing interval of CR OC/APAP for patients with moderate to severe acute pain.



## Steady-state pharmacokinetics of 1 and 2 tablets of MNK-795, a controlled-release oxycodone and acetaminophen (CR OC/APAP) combination, compared with immediate-release oxycodone and acetaminophen

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### Purpose

The first controlled-release (CR) combination oxycodone (OC)/acetaminophen (APAP) analgesic, MNK-795 (CR OC/APAP), was designed to treat acute pain with 12 hour dosing. CR OC/APAP employs a dual layer biphasic delivery profile, that when delivered as a single dose (ie, 2 tablets), consists of an IR component containing 3.75 mg OC/325 mg APAP followed by an extended-release component containing 11.25 mg OC/325 mg APAP. The total APAP dose per tablet is in accordance with the latest requirements by the US Food and Drug Administration of 325 mg/dosage unit (to reduce the likelihood of drug-induced liver injury), limiting the total daily dose of APAP (1300 mg; 2 tablets CR OC/APAP every 12 hours) to an amount that is below the current recommended total daily dose. CR OC/APAP was designed to provide fast onset of analgesia (< 1 hour) and sustained analgesia over the 12 hour dosing interval. The formulation also incorporates technology designed to provide tamper-resistance and abuse-deterrence. The primary objective of this study was to compare the steady-state pharmacokinetics (PK) of CR OC/APAP administered every 12 hours with IR OC/APAP (7.5 mg/325 mg) given every 6 hours. Secondary objectives included assessing the dose proportionality and safety of CR OC/APAP.

### Method

This single-center, open-label, randomized, multiple dose, phase 1, 3-period crossover study was conducted in normal, healthy subjects (N = 48) 18 to 55 years of age. Subjects received each of 3 treatments under fasted conditions in a randomized order: 1 tablet of CR OC/APAP (7.5 mg OC/325 mg APAP) administered orally every 12 hours for 4.5 days (treatment A); 2 tablets of CR OC/APAP (15 mg OC/650 mg APAP) administered orally every 12 hours for 4.5 days (treatment B); and 1 tablet of IR OC/APAP (7.5 mg/325 mg) administered orally every 6 hours for 4.5 days (treatment C). The study included a screening visit, and 3 confinement periods of approximately 7 days each with a minimum 14-day interval between the start of each period. Blood samples for PK analysis were collected at designated times  $\leq 144$  hours after dosing. OC and APAP concentrations were determined from plasma using liquid chromatography/tandem mass spectrometry. Analysis of variance was performed with the natural log-transformed, dose-normalized PK parameters ( $C_{max}^{ss}$ ,  $C_{min}^{ss}$ ,  $C_{av}^{ss}$ , and  $AUC_{0-12h}^{ss}$ ) or natural log-transformed PK parameters (degree of fluctuation around the average plasma concentration at steady state [DFL], defined as  $[C_{max}^{ss}-C_{min}^{ss}]/C_{av}^{ss}$ ). Adverse events (AEs) and other safety measures were monitored throughout the study.

### Results

Of the 48 subjects enrolled in the study, 33 completed all 3 treatment periods. Plasma concentrations of OC and APAP increased rapidly after administration of both 1- and 2- tablet dosing of CR OC/APAP (OC, median  $T_{max}^{ss}$  2 hours [both]; APAP, median  $T_{max}^{ss}$  0.5 hours [both]). Steady-state for OC with CR OC/APAP (2 tablets) was reached by day 3, and the OC  $C_{min}$  on days 2 to 4 were above 10 ng/mL. Steady-state PK assessments made on day 5 for OC and APAP (dose normalized) showed no difference between the 1- and 2-tablet dosing of CR OC/APAP for  $AUC_{0-12h}^{ss}$ ,  $C_{max}^{ss}$ ,  $C_{min}^{ss}$ ,  $C_{av}^{ss}$ , and DFL. In comparing the steady-state results for OC on day 5 for the 2-tablet dose of CR OC/APAP with IR OC/APAP,  $AUC_{0-12h}^{ss}$ ,  $C_{av}^{ss}$ , and  $C_{min}^{ss}$  were comparable; however,  $C_{max}^{ss}$  and DFL were 16% and 23% lower, respectively. No significant differences were found between steady-state results for  $AUC_{0-12h}^{ss}$ ,  $C_{max}^{ss}$ ,  $C_{min}^{ss}$ ,  $C_{av}^{ss}$ , and DFL for APAP on day 5 for CR OC/APAP (2 tablets) and IR OC/APAP. On day 5, 7 to 12 hours after the last dose of CR OC/APAP (2 tablets), APAP plasma levels tapered off to levels below those observed after an

equivalent dose of IR OC/APAP administered every 6 hours. Forty-two of the subjects (87.5%) reported at least 1 treatment-emergent AE (TEAE). Fewer subjects receiving 1 tablet of CR OC/APAP (47.5%) experienced TEAEs than subjects receiving 2 tablets of CR OC/APAP (70.7%) and IR OC/APAP (73.2%). The most frequently reported TEAEs were nausea (45.8%), pruritus (37.5%), headache (33.3%), dizziness (31.3%), infrequent bowel movements (20.8%), vomiting (20.8%), and somnolence (16.7%). The 10 subjects who experienced vomiting were discontinued early from the study per protocol requirement.

## **Conclusions**

OC and APAP plasma concentrations rose quickly after administration of CR OC/APAP and, although OC was relatively sustained, APAP tapered off during the 12-hour dosing interval. Steady-state dose proportionality was observed with CR OC/APAP. Overall exposure of OC and APAP was comparable between CR OC/APAP and equivalent doses of IR OC/APAP, but CR OC/APAP had lower maximal concentrations of OC with less fluctuation. Safety findings were typical for low-dose opioids. The consistent PK performance of CR OC/APAP and the safety findings support the proposed dosing interval of every 12 hours for the management of moderate to severe acute pain.

## Dose proportionality and linearity of acetaminophen after single or multiple oral doses of MNK-795 controlled-release oxycodone/acetaminophen (CR OC/APAP) tablets

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### Purpose

The first controlled-release (CR) combination oxycodone (OC)/acetaminophen (APAP) analgesic, MNK-795 (CR OC/APAP), is being developed to manage moderate to severe acute pain that warrants treatment with a CR analgesic. The formulation targets controlled medication release in the upper gastrointestinal tract to maximize the bioavailability of APAP, and incorporates technology designed to provide tamper-resistance and abuse-deterrence. CR OC/APAP employs a dual layer biphasic delivery profile, that when delivered as a single dose (ie, 2 tablets), consists of an IR component containing 3.75 mg OC/325 mg APAP followed by an extended-release component containing 11.25 mg OC/325 mg APAP. The total APAP strength per tablet is in accordance with the latest requirements by the US Food and Drug Administration limiting APAP to 325 mg/dosage unit, in an effort to reduce the likelihood of medication-induced liver injury. The purpose of this analysis was to evaluate the dose proportionality and linearity of the APAP component of CR OC/APAP when administered as 1, 2, or 4 tablets (325 mg, 650 mg, or 1300 mg APAP).

### Method

Data were pooled from randomized, crossover, single- and multiple-dose studies conducted in healthy adults (aged 18-55 years). One study enrolled healthy recreational drug users; all other studies enrolled healthy subjects with specific exclusions for drug use. Single oral doses of CR OC/APAP (7.5 mg OC/325 mg APAP) were administered as 1, 2, or 4 tablets (325 mg, 650 mg, or 1300 mg APAP) in 3 separate studies. Multiple doses of 1 or 2 CR OC/APAP tablets (325 mg or 650 mg APAP) were administered every 12 hours for 4.5 days (9 doses) in 2 separate studies. All treatments were administered under fasted conditions. Blood samples for pharmacokinetic (PK) analysis were collected up to 48 hours after a single dose and up to 144 hours after the hour-0 dose for the multiple-dose studies. Plasma was analyzed for APAP using a validated liquid chromatography/tandem mass spectrometry method. Untransformed and log-transformed data for the maximum plasma concentration ( $C_{max}$ ) and total area under the plasma concentration curve ( $AUC_{0-inf}$ ) were evaluated by analysis of variance using the SAS mixed procedure to verify no effect of study, and data were tested for normality.  $C_{max}$  and  $AUC_{0-inf}$  were divided by dose (dose-normalized) for dose proportionality analyses. Dose linearity and proportionality were determined using linear regression of nontransformed data, including 95% confidence intervals (CIs). Safety and tolerability were monitored throughout each study.

### Results

Data from 119 adults (mean age, 29 years) were included in the single-dose studies and 57 (mean age, 32 years) in the multiple-dose studies. After a single dose of CR OC/APAP, both  $C_{max}$  and  $AUC_{0-inf}$  for APAP were linear with respect to dose. Slopes were 6.336 (95% CI, 5.637-7.035) and 41.021 (95% CI, 36.915-45.126) with y intercepts of 467.0 ng/mL and 4024 ng\*hr/mL for  $C_{max}$  and  $AUC_{0-inf}$ , respectively. In addition, dose-normalized  $C_{max}$  and  $AUC_{0-inf}$  values after a single dose of CR OC/APAP were proportional to dose as indicated by linear regression with slopes approximately equal to zero (-0.001 and -0.007, respectively). Similarly, APAP  $C_{max}$  and  $AUC_{0-inf}$  at steady state in the multiple-dose study were linear with respect to dose and were dose proportional. The slope of  $C_{max}$  vs dose was estimated to be 7.079 (95% CI, 5.125-9.032), and the slope for  $AUC_{0-inf}$  vs dose was 40.177 (95% CI, 32.089-48.265). Tests for dose proportionality showed that the slope of dose-adjusted  $C_{max}$  and  $AUC_{0-inf}$  were not statistically

significantly different from zero at steady state (-0.004 and -0.011, respectively;  $P > .05$ ). The most frequently reported treatment-emergent adverse events (TEAEs) were consistent with those expected from an opioid and included nausea, vomiting, pruritus, dizziness, somnolence, and headache. In the lowest dose group (7.5 mg OC/325 mg APAP), nausea was the most common TEAE in the single-dose studies, and headache was the most common TEAE in the multiple-dose studies. In the group receiving 2 tablets (15 mg OC/650 mg APAP), nausea was the most common TEAE for both single- and multiple-dose studies; however, in the single-dose group receiving 4 tablets (30 mg OC/1300 mg APAP), pruritus was the most frequently occurring TEAE.

## **Conclusions**

This first CR OC/APAP formulation was designed to provide a fast onset of analgesia and sustained analgesia over the 12 hour dosing interval. CR OC/APAP exhibits a unique PK profile, and this pooled PK analysis demonstrates dose proportionality and dose linearity of the APAP component of CR OC/APAP when administered as 1, 2, or 4 tablets (325 mg, 650 mg, or 1300 mg APAP) in single doses and at steady state.

## Dose proportionality and linearity of oxycodone after single or multiple oral doses of MNK-795 controlled-release oxycodone/acetaminophen (CR OC/APAP) tablets

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### Purpose

MNK-795 is the first controlled-release (CR) combination oxycodone (OC)/acetaminophen (APAP) analgesic (CR OC/APAP). It was designed to provide fast onset of analgesia (<1 hour) and sustained analgesia over the 12-hour dosing interval. CR OC/APAP employs a dual layer biphasic delivery profile, that when delivered as a single dose (ie, 2 tablets), consists of an IR component containing 3.75 mg OC/325 mg APAP followed by an extended-release component containing 11.25 mg OC/325 mg APAP. In addition, CR OC/APAP incorporates technology designed to provide tamper-resistance and abuse-deterrence. The purpose of this analysis was to evaluate the dose proportionality and linearity of the OC component of CR OC/APAP when administered as 1, 2, or 4 tablets (7.5 mg, 15 mg, or 30 mg OC).

### Method

Data were pooled from randomized, crossover, single- and multiple-dose studies conducted in healthy adults (aged 18-55 years). One study enrolled healthy recreational drug users; all other studies enrolled healthy subjects with specific exclusions for drug use. Single oral doses of CR OC/APAP (7.5 mg OC/325 mg APAP) were administered as 1, 2, or 4 tablets (7.5 mg, 15 mg, or 30 mg OC) in 3 separate studies. Multiple doses of 1 or 2 CR OC/APAP tablets (7.5 mg or 15 mg OC) were administered every 12 hours for 4.5 days (9 doses) in 2 separate studies. All treatments were administered under fasted conditions. Blood samples for pharmacokinetic (PK) analysis were collected up to 48 hours after a single dose and up to 144 hours after the hour-0 dose for the multiple-dose studies. Plasma was analyzed for OC using a validated liquid chromatography/tandem mass spectrometry method. Untransformed and log-transformed data for the maximum plasma concentration ( $C_{max}$ ) and total area under the plasma concentration curve ( $AUC_{0-inf}$ ) were evaluated by analysis of variance using the SAS mixed procedure to verify no effect of study, and data were tested for normality.  $C_{max}$  and  $AUC_{0-inf}$  were divided by dose (dose-normalized) for dose proportionality analyses. Dose linearity and proportionality were determined using linear regression of untransformed data, including 95% confidence intervals (CIs). Safety and tolerability were monitored throughout each study.

### Results

PK data from 119 adults in the single-dose studies and 57 adults in the multiple-dose studies were utilized for this analysis. After a single dose of CR OC/APAP, both  $C_{max}$  and  $AUC_{0-inf}$  for OC were linear with respect to dose as demonstrated by slope ( $P < .001$ ) and intercept not significantly different from zero ( $P > .05$ ). Slopes were 1.050 (95% CI, 0.964-1.136) and 11.093 (95% CI, 10.022-12.165) with y intercepts of -0.417 ng/mL and 7.202 ng•h/mL for  $C_{max}$  and  $AUC_{0-inf}$ , respectively. Dose-normalized OC  $C_{max}$  and  $AUC_{0-inf}$  values after a single dose of CR OC/APAP were proportional to dose as indicated by linear regression with slopes approximately equal to zero (-0.001 and -0.024, respectively). In the multiple dose study,  $C_{max}$  and  $AUC_{0-inf}$  of OC at steady state were also linear with respect to dose and were dose proportional. The slope of  $C_{max}$  vs dose was estimated to be 1.640 (95% CI, 1.308-1.972), and the slope for  $AUC_{0-inf}$  vs dose was 14.151 (95% CI, 11.477-16.824). Tests for dose proportionality showed that the slopes of the dose-adjusted  $C_{max}$  and  $AUC_{0-inf}$  were not statistically significantly different from zero (-0.003 and 0.033, respectively;  $P > .05$ ). The most frequently reported treatment-emergent adverse events (TEAEs) were consistent with those expected from an opioid and included nausea, vomiting, pruritus, dizziness, somnolence, and headache. In the group that was administered 1 tablet (7.5 mg OC/325 mg APAP), nausea was the most common

TEAE in the single-dose studies, and headache was the most common TEAE in the multiple-dose studies. In the group receiving 2 tablets (15 mg OC/650 mg APAP), nausea was the most common TEAE for both single- and multiple-dose studies; however, in the single-dose group administered 4 tablets (30 mg OC/1300 mg APAP, single doses), pruritus was the most frequently occurring TEAE.

### **Conclusions**

CR OC/APAP was designed to treat acute pain with 12-hour dosing. It is the first CR OC/APAP analgesic, and was studied in clinical trials as 2 tablets every 12 hours, and in PK studies as 1, 2, or 4 tablets one time (single-dose) or every 12 hours (multiple-dose). This pooled PK analysis demonstrates dose proportionality and dose linearity of the OC component of CR OC/APAP when administered as 1, 2, or 4 tablets (7.5 mg, 15 mg, or 30 mg OC).

## Duration of use of hydrocodone/acetaminophen, immediate-release oxycodone, and extended-release morphine in a commercially insured population

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### Purpose

Long-term use of hydrocodone/acetaminophen for the treatment of chronic pain in US clinical practice has not been extensively described in the literature. However, one study suggests that the incidence of chronicity among individuals prescribed nonliquid formulations of combination hydrocodone products (Ingenix Employer Solutions) was 2.0%, with chronicity defined by both duration of treatment and dose (ie, at least 20 mg/day during a 3-month period) (poster presentation, APS 2012). Additionally, a drug utilization review conducted by the Office of Surveillance and Epidemiology found that 10% of patients (Source HealthCare Analytics ProMetis Lx<sup>®</sup>) continued hydrocodone combination products for more than 109 days. Hydrocodone/acetaminophen is an immediate-release opioid indicated for the relief of moderate to moderately severe pain; there is limited data to support long-term use. The objective of the current study was to assess among patients newly starting therapy with hydrocodone/acetaminophen the following: 1) the median daily dose, 2) the proportion continuing use >90 days, 3) the number continuing use >90 days, and 4) the diagnoses associated with initial hydrocodone/acetaminophen dispensing among all patients and among the subset who continued therapy for >90 days. Comparator opioid groups used were an immediate-release (IR) opioid, IR oxycodone consisting of both single-entity and combination IRO products, and an extended-release (ER) opioid, ER morphine.

### Method

Using a national commercial insurance database (MarketScan; January 2008 through September 2012), patients  $\geq 18$  years old with a new hydrocodone/acetaminophen (HYD/APAP), IR oxycodone (IRO), or ER morphine (ERM) prescription and 18 months insurance enrollment (6 months before and 12 months after index prescription) were identified. Existing users were excluded in order to include a baseline period for identification of diagnoses and to standardize the follow-up period after the index prescription for calculation of continuous duration of use. It is important to note that the samples were identified separately, so patients newly prescribed HYD/APAP could have also IRO or ERM prescriptions either before, after, or concurrently with HYD/APAP, and vice versa. The IRO sample included both single-entity as well as combination formulations. The primary outcome measure was the number of new users in each sample who were long-term users, defined as those who received >90 days of continuous therapy. Continuous use was defined as a period of opioid therapy with no gaps in supply  $\geq 15$  days; once the patient exceeded this allowable gap, their period of continuous use ended. Patient demographics and clinical characteristics, including opioid use and diagnoses, were also described. Because the pharmacy claims do not contain information about the condition for which drugs were prescribed, diagnoses were temporally linked to medication claims by identifying diagnoses that occurred in the one month prior to or following the index date.

### Results

In the MarketScan Commercial database covering 100 million insured people, there were 4.7 million new HYD/APAP users; 1.8 million new IRO users; and 50,615 new ERM users who met enrollment criteria. The majority of the 3 samples were females (55.3% of HYD/APAP, 58.7% of IRO, and 54.6% of ERM patients); younger individuals (18-34 years) composed a greater proportion of the 2 IR opioids samples (27.6% of HYD/APAP and 27.3% of IRO patients) than the ERM sample (12.5% of ERM patients). The median daily dose of the index prescriptions were as follows: HYD/APAP, 33.3 mg/3000 mg; IRO single-entity, 50 mg, IRO combination products, 37.5 mg; ERM, 45.0 mg. Almost

one-fifth (19.6%, n = 923,594) of the HYD/APAP patients were prescribed  $\geq 4000$  mg APAP at the index prescription. Most (93.4%) of the IRO sample used combination IRO products and only 6.6% used single-entity IRO. Though only a small percentage of the HYD/APAP and IRO users (0.9% and 1.5%, respectively) continued use for more than 90 days, the number of patients meeting this criterion was large (HYD/APAP: n = 42,386; IRO: n = 26,840). In contrast, more than one-quarter of ERM patients (28.4%, n = 14,367) continued use for more than 90 days. The most common pain conditions diagnosed in the month prior to or following the index prescription were back/neck pain (18.4%, 20.4%, and 59.3%, for HYD/APAP, IRO, and ERM, respectively); fractures (15.2%, 18.2%, and 14.1%, respectively); arthropathies, excluding osteoarthritis and rheumatoid arthritis (14.4%, 19.3%, and 25.3%, respectively); and rheumatism, excluding the back (note: also excludes fibromyalgia and neuralgia) (13.0%, 17.1%, and 22.4%, respectively). Among HYD/APAP and IRO users who continued use for more than 90 days, the most common diagnoses were back/neck pain (46.2% and 61.0%, respectively); arthropathies, excluding osteoarthritis and rheumatoid arthritis (24.0% and 23.2%, respectively); rheumatism, excluding the back (18.4% and 19.6%, respectively); and fractures (15.1% and 14.1%, respectively).

## Conclusions

A small proportion of patients who initiated hydrocodone/acetaminophen therapy in the database continued treatment for longer than 3 months; however, the number of patients who continued hydrocodone/acetaminophen was over 40,000, 3 times more than the number of ER morphine users and 1.6 times more than that of IR oxycodone users who continued for longer than 3 months. The most common pain condition among all 3 samples was back/neck pain. In this population of 100 million commercially insured people in the US, hydrocodone/acetaminophen was extensively used to treat chronic pain, 3 times more frequently than ER morphine.



## Clinical characteristics of opioid overdose cases identified in a large commercially insured population

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### Purpose

There is increasing interest in opioid overdose, with recent studies describing an increased risk of overdose at higher opioid doses. However, there remain a number of unanswered questions related to study design issues, potential confounding (particularly confounding by abuse and by indication), and the relative contribution of other risk factors such as sedative hypnotic use. We have replicated this research in a large administrative claims database (MarketScan), identifying cases of opioid overdose using ICD-9-CM codes 965.00 (poisoning by opium [alkaloids], unspecified), 965.02 (poisoning by methadone), 965.09 (poisoning by other opiates and related narcotics). Based on the review of several hundred medical record charts of those diagnosed with opioid overdose or poisoning, a study conducted at Kaiser Permanente (Northwest and Northern California regions) showed that these particular ICD-9 codes are both sensitive and have a high predictive value (PPLP data on file). While our MarketScan analyses demonstrate several strengths, including a large sample size that comprises a large number of cases ( $n = 3,224$ ), information on the severity of the overdose events is limited. Therefore, we have explored the clinical characteristics of overdose cases, including factors such as concomitant diagnoses and treatment setting, to better understand the case population, including potential severity of the overdose event.

### Method

Adults (18-64 years of age) with a new opioid dispensing were identified in the MarketScan Commercial dataset (01/2008-03/2012). Subject observation time continued until the first of either: overdose (specified by the ICD-9-CM codes 965.00, 965.02, 965.09), discontinuation of insurance enrollment, or end of the study period. Overdose case characteristics were described including the treatment setting where cases were identified, ie, 1) hospitalization, 2) inpatient or outpatient emergency room (hereafter referred to as ER cases), or 3) neither hospitalization nor ER (hereafter referred to as other cases). The principal reason for the medical visit was summarized by the primary diagnosis for hospitalized cases, and the primary or first diagnoses for ER and other cases (note: ER and other cases could have more than one primary/first diagnosis, though few did [ $<7\%$ ]). We also explored the prevalence of concomitant diagnoses for poisoning by sedatives/hypnotics/tranquilizers (SHT) and concomitant psychiatric disorders, and other clinical and demographic characteristics. The prevalence of diagnoses for suicides/self-inflicted poisoning by drugs or other substances, as well as accidental poisonings due to analgesics, antipyretics, and antirheumatics were also described.

### Results

In the 9.6 million individuals dispensed a new opioid in the MarketScan Commercial database during the study period, 3,224 cases of overdose were identified (0.02 cases/100 person-years). Approximately half (49%) of the cases were identified based on a hospitalization ( $n = 1,574$ ), 40% by an ER visit/treatment ( $n = 1,298$ ), and 11% from other settings (neither hospitalization nor ER;  $n = 352$ ). Almost all (93%) of the primary diagnosis codes in the hospitalized cases were related to either opioid poisoning (ICD codes 965.00, 965.02, 965.09) (41.9%), other poisoning (15.9%), or psychiatric disorders (35.3%), primarily mood disorders. Among the hospitalized cases, in addition to the overdose poisoning codes used to identify the cases, 28.5% also had a diagnosis for sedative/hypnotic/tranquilizer (SHT) poisoning, 53.8% for psychotropic/other similar drug poisoning (including SHT), 12.3% for a suicide/self-inflicted poisoning by drugs/other substances, and 3.4% for an accidental poisoning by analgesics/antipyretics/antirheumatics. Among the cases identified from an ER visit, the most common first diagnosis was opioid poisoning

(79.7%). Among the ER cases, in addition to the opioid poisoning codes that initially identified the cases, 10.9% of cases had a code for SHT poisoning, 30.6% for psychotropic/other similar drug poisoning (including SHT), 4.4% for a suicide/self-inflicted poisoning by drugs/other substances, and 7.9% for an accidental poisoning by analgesics/antipyretics/antirheumatics. Among the other cases (n = 352), the most common primary diagnoses were related to opioid poisoning (48.6%). In addition to the opioid poisoning codes, 17.6% of these other cases also had a diagnostic code for SHT poisoning, 31.5% for poisoning by psychotropic/other similar drugs (including SHT), 4.8% for a suicide/self-inflicted poisoning by drugs/other substances, and 4.0% for an accidental poisoning by analgesics/antipyretics/ antirheumatics. Despite the identification of overdose cases based on opioid poisoning diagnostic codes, almost half (44%) of the overdose cases had no opioid prescriptions in the 30 days preceding the event.

## **Conclusions**

In conclusion, administrative claims databases are a rich resource of medical/prescription data, and the clinical characteristics of the cases provide further insight into the case severity. Overall, most cases were identified through a hospitalization claim or treatment in an ER setting (89%) and almost half had no recent prescriptions for opioids. Additionally, overdose cases appeared to be complex—co-occurring sedative/hypnotic/tranquilizer poisoning and poisoning by other similar drugs was common, as were psychiatric disorder comorbidities. Clear risk factors for overdose appear to be identifiable including use of psychiatric drugs, and mood or other psychiatric disorders.

## The association between prescribed opioid dose and risk of overdose events—evaluation of the dose-risk response in relation to potential confounding factors

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### Purpose

Policy-makers are considering restrictions on opioid prescribing at dosage strengths above 100 mg/day morphine equivalent dosage (MED) based on 4 published studies. Though these studies are valuable scientific contributions, they may be biased due to uncontrolled differences between people using high vs low opioid doses, and as a result have limitations as a basis for policy setting. Thus, the purpose of this study was to evaluate the risk of opioid overdose associated with prescriptions above 100 mg/day of opioids in 4 new ways:

1. To assess the trend in the dose-overdose relationship above 100 mg/day using 50 mg increments of dosage strength with >3,200 overdose cases as compared to 46 cases in the first paper on the topic,
2. To adjust for use of immediate-release (IR), extended-release (ER), or both, since stratified analyses indicated much higher overdose risk for IR + ER opioid use vs ER use. In addition, IR and ER opioids have different indications (acute vs chronic pain) and are used in different types of patients (eg, knee surgery vs advanced Parkinson's disease) and could result in confounding by indication or channeling bias. Prior published studies have combined IR and ER opioid use into an unstratified amalgamation,
3. To assess the impact of age on the trend in the dose-overdose relationship, since younger people are more likely to abuse drugs than older people and therefore a 100 mg/day limit may have different implications for younger vs older patients, and
4. To assess the impact of concomitant sedative/hypnotic use on the trend in the dose-overdose relationship.

### Method

Using an insurance claims database, the relationship between opioid dose and overdose risk was assessed by calculating the risk of diagnosed opioid overdose per person-years on opioid analgesics in 50 mg/day increments. Two measures of relationship were used: 1) the trend of the overdose risk across dose categories and 2) the relative risk comparing high vs low dose groups. The effect of 4 potential confounders was assessed: type of opioid (IR only, ER only, or both IR and ER), age, concomitant sedative/hypnotic use, and gender. Adults (18-64 years of age) with a new IR or ER opioid dispensing who had at least 6 months of insurance enrollment preceding the qualifying index prescription were identified in the MarketScan Commercial dataset (01/2008-03/2012). Index prescriptions included all opioids except powder formulations of all opioids as well as opium and antitussive formulations of hydrocodone, dihydrocodeine, and codeine. Daily opioid exposure based on prescribed opioid dose was categorized in 50 mg/day increments from 1-49 mg/day to  $\geq 350$  mg/day. Average dose on days used in the 30 day window preceding overdose was calculated for cases. Poisson regression was used to assess differences in dose-overdose relationship between unadjusted and adjusted models.

### Results

In 9.6 million individuals dispensed new opioids, 3,224 overdose cases were identified (0.02 cases/100 person-years). Almost half (44%) of cases had no prescribed opioids in the 30 days preceding the event, and this proportion declined with age, from 59% of 18-24 years olds to 30% of 55-64 years olds. At lower doses, most cases had prescriptions for IR opioids, while at the higher doses (> 100 mg/day), most had prescriptions for ER opioids (with or

without IR opioids). Stratified analyses also revealed a steeper dose-risk response for patients with concomitant sedative/hypnotic prescriptions.

The trend of the relationship between daily dosage strength and overdose risk changed from a 1.33-fold (95%CI 1.29, 1.36) increase per 50 mg increment to 1.12-fold (95%CI 1.08, 1.16) increase after including IR/ER opioid type in the model. After including opioid type, age, and sedative/hypnotic use in the model, there was a significant interaction between dosage strength and age; the trend (per 50 mg increment) was 1.08 (95%CI 0.99, 1.19) for 18-24 year olds, 1.06 (95%CI 0.97, 1.16) for 24-34 year olds, 0.98 (95%CI 0.89, 1.07) for 35-44 year olds, and 1.08 (95%CI 1.03, 1.14) for 45-64 year olds. The goodness-of-fit of the model improved as these covariates were added. Gender did not change the relationship.

When comparing the 2 dose categories just above 100 mg (ie, 100-<150 mg and 150-<200 mg) to the 50-<100 mg category, the crude unadjusted relative risks were 1.15 (95%CI 0.97, 1.38) and 1.61 (95%CI 1.27, 2.04). After adjusting for the opioid type, age, and sedative/hypnotic use, the relative risks decreased to 0.87 (95%CI 0.72, 1.04) and 0.81 (95%CI 0.63, 1.04).

When comparing the highest dose category (>350 mg) to the lowest dose category (1-<50 mg), the crude relative risk was 5.07 (95%CI 3.88, 6.63) and the adjusted relative risk was 1.17 (95%CI 0.86, 1.59).

## Conclusions

In 9 million opioid users (3,224 overdoses), the relationship between opioid dose and overdose risk was diminished considerably after adjustment for opioid type, sedative/hypnotics, and age, suggesting that comparisons of overdose risk in patients prescribed high vs low opioid doses are confounded by different patient types in the groups. After adjustment, opioid type, age, and sedative/hypnotic use remained significant, strong predictors of overdose risk. The high proportion of overdoses without recent prescriptions suggests that many overdoses are from nonprescribed opioids. These results suggest that attempts to reduce overdose risk by simply limiting prescriptions to <100 mg/day may have limited impact.

## Comparative testing of physicochemical properties of reformulated Opana ER and OxyContin

Frank Diana, Cynthia Ciliberto

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### Purpose

The FDA recently granted OxyContin® (oxycodone HCl controlled-release tablets) abuse-deterrent labeling based on a combination of physicochemical properties, abuse liability potential and epidemiologic data. This set a precedent for abuse-deterrent opioid formulations with crush resistant properties, ie, formulations that present physical or chemical barriers to abuse. Opana ER (oxymorphone HCl ER tablets) is a formulation of oxymorphone which is designed to be crush resistant, and is intended to require a higher amount of effort, time, experience and tools to crush or manipulate, when compared to noncrush resistant formulations. Opana ER and OxyContin both use the excipient polyethylene oxide, which provides the extended-release properties of the product and is intended to impair the ability to draw the drug into a syringe by forming a viscous hydrogel when hydrated with small amounts of water. Opana ER and OxyContin use manufacturing processes that are intended to enhance the crush resistance of the tablets. The purpose of this study was to determine the physicochemical characteristics of Opana ER and OxyContin.

### Method

The physicochemical characteristics of Opana ER and OxyContin were evaluated *in-vitro* by third-party laboratories to determine whether the 2 products behaved comparably based on their similar formulation characteristics. These studies were comprised of physicochemical tests to evaluate the potential for crushing and manipulation. Simple and advanced tools were employed to manipulate the products including spoons, hammers, pill crushers, knives, pliers, graters, and grinders. Analyses included breaking force based on the United States Pharmacopeia standard, indentation and compression using a texture analyzer, particle size analysis, and dissolution. Various sample preparation techniques were employed to evaluate the extraction of the active ingredient in water and other solvents.

### Results

Opana ER and OxyContin performed comparably in tests of resistance to physical manipulation. The breaking force was >1000 Newtons for the OxyContin and Opana ER tablets. This is far higher than the 100 Newtons typically required for conventional pharmaceutical tablets. The results of the extraction studies were similar for the 2 formulations. The results of this study demonstrated that Opana ER and OxyContin had similar physicochemical properties and behaved similarly across a battery of *in-vitro* tests.

### Conclusions

Based on these results, both products provided a similar physical/chemical barrier to crushing and manipulation.

## Determination of physicochemical properties of reformulated Opana ER and a generic oxymorphone HCl ER formulation

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### Purpose

In January 2013, FDA issued a guidance document for industry entitled "Abuse-deterrent Opioids - Evaluation and Labeling". The guidance document details the desired physical and chemical properties of an opioid formulation to deter and impede the abuse potential of these products. In early 2012, Endo Pharmaceuticals introduced to the market a reformulated version of Opana® ER (oxymorphone HCl ER tablets) which is designed to be crush resistant (CR). OPANA ER uses the excipient polyethylene oxide, which provides the extended-release properties of the product and is intended to impair the ability to draw the drug into a syringe by forming a viscous hydrogel when hydrated with small amounts of water. OPANA ER uses a manufacturing process that is intended to enhance the crush resistance of the tablets. Recently, generic oxymorphone HCl ER tablets have been approved and have become available on the market. The purpose of this study was to evaluate the physical and chemical properties of a generic formulation and compare the results to those of similar testing performed previously on OPANA ER.

### Method

*In-vitro* tests designed by Endo were conducted by third party laboratories. These tests were comprised of physicochemical testing to evaluate the potential for crushing and manipulation of the generic formulation and subsequent particle size determination. In addition, various sample preparation techniques were employed to evaluate the extraction of the active ingredient in water.

### Results

The generic oxymorphone HCl ER tablets were easily crushed between 2 spoons. The median particle size of the crushed generic product was 0.25 mm. In contrast, when tested using various tools including spoons, hammers, and pill crushers, OPANA ER could not be crushed. A coffee grinder was able to manipulate OPANA ER tablets; however, after 2 minutes of grinding the median particle size still exceeded 1.4 mm. Additionally, the active ingredient from the crushed generic oxymorphone HCl ER tablets was solubilized and readily extracted from the excipients yielding a high percentage of oxymorphone in water. The polyethylene oxide in OPANA ER formed a viscous hydrogel in small amounts of water thereby limiting the amount of active ingredient which could be extracted.

### Conclusions

Based on multiple *in-vitro* studies it was demonstrated that reformulated OPANA ER possessed physicochemical barriers to crushing and manipulation. In contrast, generic oxymorphone HCl ER tablets, which do not possess these physicochemical barriers, were shown to be noncrush resistant and easily manipulated to a smaller particle size. In addition, the active ingredient was more readily extracted from the generic formulation yielding a higher percentage of oxymorphone in water.

## Evaluation of the tamper-resistant properties of MNK-795 controlled-release oxycodone/acetaminophen (CR OC/APAP) tablets

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### Purpose

MNK-795 (CR OC/APAP) is being developed to manage moderate to severe acute pain that warrants treatment with a controlled-release (CR) analgesic. It is the first CR combination oxycodone (OC)/acetaminophen (APAP) analgesic, and was studied in clinical trials as 2 tablets (ie, 15 mg OC/650 mg APAP) administered every 12 hours. The tablets contain polyethylene oxide (Polyox<sup>®</sup>), a release-controlling polymer that targets medication release to the upper gastrointestinal tract for an extended period of time, and incorporates technology with characteristics that could impact the abuse liability of the tablets. A series of *in vitro* studies assessed the ability of CR OC/APAP to withstand physical manipulation and resist attempts to extract a bolus dose by evaluating tablet hardness, particle size and OC yield after milling, OC yield after dissolution in various solvents, as well as syringeability and suitability for intranasal administration.

### Method

The tamper-resistant properties of CR OC/APAP tablets were assessed and compared with those of an existing IR combination of OC/APAP approved by the US Food and Drug Administration at the same dosage strength for each active ingredient. Resistance to tampering using typical means and commonly available tools and solvents was examined with and without preconditioning the tablets by heating/"crisping," freezing, or microwaving. Tablets were then subjected to a variety of particle size reduction methods, such as grinding and crushing, to establish the most appropriate method for subsequent extraction of OC. Six mechanical methods (hammer, pill crusher, mortar and pestle, knife, 2 spoons, and utility knife) and 3 electrical methods (blender, coffee mill, and coffee grinder) for tampering were evaluated. Each method was tested until there was a successful reduction in product particle size, until the tool broke or was rendered unsafe, or until after approximately 10 minutes of attempting to physically break a tablet. The success or failure of these challenges to reduce particle size was assessed visually, and sieving was used to measure particle size reduction quantitatively. Dissolution studies using various household solvents were conducted on intact and mechanically disrupted (after mortar and pestle) dosage forms. Typical approaches to preparing OC for injection were attempted for each product. Experiments mimicking exposure to the mucus lining of the nasal cavity assessed ability to insufflate the powder, and "dose dumping" in alcohol was tested through dissolution in 75 mL of simulated gastric fluid with and without the presence of vodka.

### Results

Compared with IR OC/APAP, CR OC/APAP tablets were more resistant to mechanical and electrical methods of tampering. None of the preconditioning steps demonstrated a clear advantage over manipulations at room temperature. Heating or crisping intact CR OC/APAP tablets resulted in a sticky, gum-like consistency that prevented grinding into a powder. Few methods yielded particle sizes from CR OC/APAP that were conducive to a sieve analysis, and the resultant powder would be expected to contain crushed Polyox<sup>®</sup> in addition to active drug. Dissolution rates for intact CR OC/APAP tablets were generally slower than rates for IR OC/APAP across solvents. Ground CR OC/APAP was more resistant to dissolution in several solvents than the comparator. Syringeability studies demonstrated that when water was added to the crushed tablets, only a small portion of the liquid and active drug could be recovered for both products; however, unlike the comparator, CR OC/APAP produced a semi-solid paste

that was difficult to recover in a syringe. Insufflation experiments found that CR OC/APAP formed a clumpy, solid mass that would likely impede absorption through the nasal mucosa, whereas IR OC/APAP formed a thin, fluid film that could promote absorption through the nasal tissue. IR OC/APAP dissolved rapidly and completely in the presence of simulated gastric fluid with and without alcohol; however, CR OC/APAP demonstrated clear resistance to dissolution under both conditions, with greater resistance in the presence of alcohol.

## Conclusions

CR OC/APAP tablets were more resistant to tampering than IR OC/APAP. Crushing CR OC/APAP was more difficult, and CR OC/APAP had reduced syringeability compared with IR OC/APAP, suggesting that the Polyox<sup>®</sup> in crushed CR OC/APAP will impede snorting and injecting. The results of these *in vitro* tests indicate that CR OC/APAP has physicochemical properties that could deter extraction of a sufficient bolus dose, injection or snorting of the manipulated drug product, and resist dose dumping in the presence of alcohol.



***In Vitro* and human abuse liability assessment: methods and challenges**

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**Purpose**

FDA requires abuse potential assessment of all new CNS drugs, and has issued draft guidance on the assessment of abuse potential, as well as assessment of abuse-deterrent formulations. We will present the basic procedures for *in vitro* and *in vivo* (HAL) assessment, as well as challenges and opportunities posed to researchers in assessing the abuse potential of new drugs and formulations in terms of abuse liability testing.

**Method**

This poster will discuss methods for assessing abuse liability and the implications for labeling, as well as the impact on public health and patient care. These methods are based on guidance documents by FDA as well as our experience using these methods.

**Results**

Methods for abuse liability (AL) testing (including *in vitro* and *in vivo* methods) have been evolving for decades and have demonstrated high validity in the assessment of the relative abuse potential of opioids, stimulants, sedatives, and other drug classes with drugs with known abuse potential and well-studied mechanisms of action. However, the testing of new CNS drugs with less studied mechanisms of action present new challenges because of uncertainties about suitable comparators, making the scheduling and labeling of these drugs more complex. Further, new formulations of existing drugs, particularly drugs designed to be "tamper deterrent" present new challenges for AL testing because of the many ways in which a new formulation might be tampered.

Further, the interpretation of findings for purposes of labeling is challenging because often the main difference between a tampered and untampered drug is the speed of drug delivery, and the "value" of faster drug delivery to drug abusers has not been well studied in opioids. Similarly, new chemical entities (NCEs) that may be prodrugs of already controlled substances or which may theoretically be chemically modified need to be studied for the susceptibility to manipulation. NCEs that bind to known receptors involved in abuse (eg, mu opioid receptor), but have different pharmacokinetic characteristics may also present unique challenges regarding scheduling and labeling.

**Conclusions**

The implications for drug development and regulation are profound and include drug scheduling determinations, the potential for differential scheduling of the same drug with differing formulations, labeling and the nature of the risk mitigation strategies required for drug approval. In addition, more drugs than in the past are likely to require human abuse liability (HAL) assessment to provide FDA with sufficient information upon which to make drug scheduling recommendations as required by the Controlled Substances Act.

## Constipation prevention: a Joint Commission Advanced Practice Certification in Palliative Care Quality Improvement Project

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### Purpose

In September 2011, The Joint Commission (TJC) offered a new certification in Palliative Care to recognize institutions dedicated to improving quality of life in patients with severe life threatening illnesses through physical, spiritual, and emotional support. Abington Memorial Hospital (AMH), a community teaching hospital in the Philadelphia suburbs, was the first hospital in Pennsylvania to receive Advanced Certification in Palliative Care. In order to obtain joint commission certification, 4 performance measures are required, with at least 2 of the 4 measures being of a clinical focus. One performance measure chosen by AMH was the evaluation of an appropriate bowel regimen in patients consulted to the Palliative Care service on active opioid therapy. Constipation is common in patients receiving opioid therapy and can affect quality of life from both physical and psychological distress. Tolerance to the constipation effects of opioid analgesics does not develop. Initiation of a prophylactic bowel regimen is recommended on all patients on opioids without contraindications. This initiative will evaluate the identification and efficacy of bowel regimen recommendations on patients receiving opioids consulted to the Palliative Care service.

### Method

Patients admitted to the Palliative Care (PC) service during the months of November 2011 through February 2012 on ordered opioids were evaluated for effective prophylactic bowel regimens as part of the preliminary joint commission data collection. Exclusion criteria included actively dying patients (within 7 days of admission to the PC service), bowel obstruction, and patients having adequate bowel movements despite lack of a prophylactic constipation regimen. The palliative care service was evaluated on the remaining patients for appropriate bowel regimen recommendations within 24 hours of consult, and whether or not the recommended regimen was effective as defined by having a bowel movement within 72 hours of initial consult. Once the preliminary data was presented to TJC, continued monitoring of 30 patients a quarter with improvement over baseline was the goal for maintaining certification.

### Results

A total of 164 patients out of 411 total consults (39.9%) were receiving opioids at the time of the palliative care consult during November 2011 through February 2012. Sixty-eight (41.5%) met inclusion criteria. Ninety-six patients (58.5%) were excluded due to presence of a bowel obstruction, adequate laxation despite no prophylactic regimen order, or actively dying (as defined for this initiative as within 7 days of death). Recommendations were needed on 44 of the 68 eligible patients meeting inclusion criteria and were made on 37 of these 44 patients (84.1%). Of the 37 patients, 8 patients were unable to be evaluated due to discharge prior to the defined 72 hour time frame. Of the remaining 29 patients, 25 had effective regimens (86%) as defined by a bowel movement within 72 hours after recommendation. Four of 25 patients (16%) did not have a BM within 72 hours after recommendation.

The data was accepted during the certification process with recommendations to continue the initiative by following 30 patients a quarter. During April 2012 through March 2013, follow up data was presented to TJC. One hundred twenty patients were evaluated during this time frame. Of the 120 patients, 63 (52.5%) were not eligible, with reasons similar to the patients meeting exclusion criteria listed above. Of the 57 patients meeting inclusion criteria, recommendations were needed on 43 patients and were made on 37 of the 43 (86%). Of the 37 patients with recommendations needed, 6 were unable to be assessed due to discharge within 72 hours of consult. Effective

recommendations were made in 24/31 patients (79%). Eight of the 31 patients (22%) did not have laxation within the 72 hour time frame identified in the initiative.

### **Conclusions**

The need for a prophylactic bowel regimen in patients on opioids must be individualized. In a palliative care patient, a bowel regimen may be inappropriate due to presence of bowel obstruction, chemotherapy treatments producing diarrhea, adequate bowel movements despite no regimen and actively dying patients. The lack of a prophylactic regimen in a large number of patients at time of consult highlights the need for education on constipation prevention. The palliative care team identified the majority of patients needing a prophylactic bowel regimen at the time of consult but continued improvement is necessary on the appropriate identification and treatment of constipation due to opioids.

## Effect of paroxetine, a CYP2D6 inhibitor, on the pharmacokinetics of hydrocodone and its metabolites following coadministration with a novel hydrocodone single-entity, once-daily, extended-release tablet [HYD]

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### Purpose

HYD is a single-entity, once-daily, extended-release tablet formulation of hydrocodone bitartrate. It is being developed for the management of moderate to severe pain in patients who require a continuous, around-the-clock opioid pain medication for an extended period of time. HYD was formulated with inactive ingredients intended to make the tablet more difficult to manipulate for misuse and abuse.

Hydrocodone undergoes cytochrome P450 (CYP) 2D6 mediated O-demethylation yielding hydromorphone (minor active metabolite) and CYP3A4 mediated N-demethylation yielding norhydrocodone (major inactive metabolite). The concomitant administration of CYP2D6 inhibitors may lead to increases in systemic exposure and may affect safety and tolerability of hydrocodone. The purpose of this randomized, double-blind, 2-period, 2-treatment, crossover, drug-drug interaction study was to investigate the influence of CYP2D6 inhibition by paroxetine (a strong CYP2D6 inhibitor) on the pharmacokinetics (PK) of hydrocodone and its metabolites following oral administration of HYD in healthy subjects.

### Method

Healthy subjects (12 male and 12 female), aged 18 to 50 years received HYD-20 mg with paroxetine in one study period and placebo in the other period. Paroxetine (20 mg tablet) or placebo was administered once daily on days 1-12 (period 1) and days 12-25 (period 2). A single HYD-20 mg tablet was administered once in each study period (on days 10 and 23) in the fasted state. Blood samples for quantitation of hydrocodone and its metabolites in plasma were collected through 80 hours post dose. PK parameters were calculated for hydrocodone and its metabolites, norhydrocodone and hydromorphone. Safety was assessed using adverse events (AE), clinical laboratory tests (biochemistry, hematology, and urinalysis), vital signs and pulse oximetry (SpO<sub>2</sub>) measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings.

Twenty-three subjects completed the study. Twenty-four subjects were included in the safety and PK analyses. One male subject discontinued due to subject's choice. The mean age of the entire study population was 36.0 years.

### Results

The mean systemic exposure (AUC and C<sub>max</sub>) of hydrocodone were similar in the presence and absence of paroxetine. The geometric least square mean (GLSM) ratios (paroxetine/paroxetine placebo) of hydrocodone AUC<sub>t</sub>, AUC<sub>inf</sub>, and C<sub>max</sub> (90% CI) were 105.8 (97.7, 114.6), 105.9 (97.8, 114.6), and 106.0 (92.7, 121.2), respectively, indicating that paroxetine had no meaningful effect on hydrocodone exposure.

The GLSM ratios (paroxetine/paroxetine placebo) of norhydrocodone (major and inactive metabolite) AUC<sub>t</sub>, AUC<sub>inf</sub>, and C<sub>max</sub> (90% CI) were 150.1 (137.4, 163.9), 143.7 (132.6, 155.7), and 148.7 (132.0, 167.4), respectively. These results indicate that norhydrocodone AUC<sub>t</sub> and AUC<sub>inf</sub> in the presence of paroxetine were 50% and 44% higher, respectively, than in the absence of paroxetine. Norhydrocodone C<sub>max</sub> in the presence of paroxetine was 49% higher than in the absence of paroxetine.

For most of the subjects, individual  $t_{1/2}$  and AUC<sub>inf</sub> of hydromorphone, a minor (less than 3% of the parent compound exposure) and active metabolite, were not estimable for the HYD with paroxetine treatment due to the variability of hydromorphone concentrations observed; the majority of subjects had lower limit of quantitation (LLOQ) (0.05 ng/mL) or close to LLOQ levels across the concentration vs time profile. Hence, no statistical analysis was performed for hydromorphone.

There were no deaths, SAEs, or early discontinuations due to treatment emergent adverse events (TEAE). All TEAEs were of mild severity. There were no moderate or severe TEAEs.

### **Conclusions**

Hydrocodone systemic exposure was unchanged when a single dose of HYD-20 mg extended-release tablet was coadministered with the CYP2D6 inhibitor paroxetine at steady state (20 mg once daily for 12 days).

Coadministration of a single oral dose of HYD-20 mg under fasted conditions with paroxetine-20 mg or placebo once daily for 12 days was safe and well tolerated.

## Functional improvement associated with musculoskeletal pain relief following treatment with a heated lidocaine/tetracaine patch: pooled analysis of 4 studies

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### Purpose

The heated lidocaine/tetracaine patch (HLT patch; ZARS Pharma, Salt Lake City, UT) contains a eutectic mixture of lidocaine (70 mg) and tetracaine (70 mg) with an integrated oxygen-activated heating component. The HLT patch is approved for providing local dermal analgesia for superficial venous access and superficial dermatologic procedures. Previous studies of the depth and duration of anesthesia produced by the HLT patch suggest that it may be effective in controlling pain in superficial musculoskeletal structures. In 4 pilot, open-label, phase IIa studies, patients with acute musculoskeletal pain associated with shoulder impingement syndrome (SIS), patellar tendinopathy (PT), carpal tunnel syndrome (CTS), or myofascial trigger points (MTP) demonstrated clinically meaningful improvements in pain, pain interference scores, and physical function following 14 days of twice daily treatment with the HLT patch. The present pooled analysis was conducted to determine correlations between reduction in pain, improvement in pain interference scores, and improvement in function.

### Method

Percent change from baseline to final pain score (patient-reported "average pain," 0-10 scale) was calculated for the patients who completed each of the 4 studies (N = 73). These pain responses were categorized as Worse (<0% improvement), Marginal (0%-<15%), Minimal (15%-<30%), Moderate (30%-<50%), and Substantial ( $\geq$ 50%). Percent functional improvement was estimated as the mean of percent change of pain interference scores for general activity, sleep, and work (0-10 scales) in the SIS, CTS, and MTP studies or as the percent change in Victorian Institute of Sport Assessment (VISA) scores for patients in the PT study. Pearson correlation coefficients (*r*) were calculated for pain and pain interference scores at baseline, percent changes in pain score and pain interference scores, and percent changes in pain score and percent functional improvement.

### Results

Pain scores at baseline were highly correlated with interference scores for general activity ( $r = 0.55$ ,  $P < .001$ ), sleep ( $r = 0.48$ ,  $P < .001$ ), and work ( $r = 0.50$ ,  $P < .001$ ) for the patients in the SIS, CTS, and MTP studies (interference scores were not assessed in the PT study). A similar relationship was seen for baseline pain and VISA scores in patients in the PT study, but the correlation was not significant ( $r = -0.54$ ,  $P = .06$ ). Following 2 weeks of treatment with the HLT patch, percent decrease in pain score was highly correlated with percent decrease in interference for general activity ( $r = 0.63$ ,  $P < .001$ ), sleep ( $r = 0.70$ ,  $P < .001$ ), and work ( $r = 0.66$ ,  $P < .001$ ). Percent increase (improvement) in VISA score in the PT study was not significantly correlated with percent decrease in pain score ( $r = 0.15$ ,  $P = .63$ ). Overall, percent functional improvement was significantly correlated with percent decrease in pain score ( $r = 0.57$ ,  $P < .001$ ). Significant functional improvements from baseline were seen in patients demonstrating Minimal, Moderate, or Substantial improvement in pain score. The 26 patients who had Substantial improvement in pain score demonstrated a functional improvement (mean  $\pm$  SD) of  $60.2\% \pm 44.8\%$  ( $P < .001$ ).

### Conclusions

This analysis shows that there is a significant correlation between improvement in pain and improvement in function after treatment with the HLT patch. Furthermore, patients who experience a  $\geq$ 50% reduction in pain with the HLT

patch have substantial improvements in function, thereby underscoring the importance of this level of pain improvement as a yardstick by which to measure treatment effectiveness. These findings are similar to those reported in other pain conditions.

## Case study describing an innovative biopsychosocial approach in VA primary care for management of persons with persistent pain (PRIME<sub>x</sub>) based upon a systematic review.

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### Purpose

The Institute of Medicine (IOM) report on *Relieving Pain in America* (2011) presents expert findings and recommendations that call for a transformation in the treatment of persons with persistent pain. Treatment strategies must recognize: 1) the biopsychosocial nature of pain; 2) changes in the peripheral and central nervous systems as a result of pain; and 3) the need for individualized treatment emphasizing self-management, especially in primary care.

The IOM report does not provide specific guidelines or parameters for interventions such as type and dosage, partly due to a lack of evidence regarding clinical effectiveness. The IOM report also notes that most biopsychosocial interventions are psychologist-driven and little is known about interventions guided by physical therapists (PTs). The author performed a systematic review to identify existing evidence and developed a pilot program in the VA to implement the IOM recommendations using this evidence. The purpose of this poster is to summarize the findings of the systematic review and to present a case study describing this biopsychosocial approach PRIME<sub>x</sub> (*Pain Rehab Integrating Management and Exercise*).

### Method

Primary research articles were selected for review if they compared usual care (including exercise prescribed by a PT) with a multimodal intervention that included exercise for individuals with persistent pain. Eight clinical trials met the inclusion criteria. While conclusions generally supported multimodal interventions for improving pain and disability, significant variability in type and dosage of intervention was noted. No evidence for a specific intervention or combination of interventions was noted. Dosage was identified as an important factor.

A pilot program was initiated in July 2011 at a VA primary care clinic in Wisconsin. A PT /PT assistant team provided an aggregate of interventions based upon the systematic review. PRIME<sub>x</sub> was offered by PT as an activity-based program to complement the VA's multidisciplinary, education-based pain school.

The individualized interventions included graded exercise, graded exposure, and neuroscience education. Goals reflected IOM recommendations of activity promotion, self-management, and self-efficacy. Treatment model promoted self-efficacy and motivation by emphasizing the 3 fundamental psychological needs of autonomy, competence, and purpose. Frequency was 1-4 visits per month and duration was not specified to reflect the importance of dosage.

When a 22-year-old combat veteran with chronic back and knee pain and mild TBI attributed to multiple IED exposures was not responding to conventional PT, the plan of care was modified to a PRIME<sub>x</sub> approach. Treatment focused on veteran's goal of completing a firefighter training program.

### Results

From January 2012 to May 2013, the veteran participated in 31 total PT visits. Numeric pain rating decreased from 6/10 to 0/10. Activity tolerance improved from inability to squat or lift any weight without an increase in pain to



lifting and squatting with up to 95 pounds without an increase in pain. Functional milestones include completing 2 years of firefighter training program and beginning an internship with a local fire station, running 2 miles without increase in pain, participation in monthly drill for Reserves without an increase in pain, and moving out of parents' home and into his own apartment.

### **Conclusions**

A 22-year-old combat veteran reported decreased pain and improved function after participating in 31 visits/ 17 months of PRIMEx. PRIMEx is an innovative, evidence-based treatment approach integrating graded exercise, graded exposure, and neuroscience education and optimizing treatment dosage and self-efficacy. Primary care physical therapists can incorporate this approach into treatment models that promote safe and efficient use of resources.

## Evidence-based virtual reality for chronic pain self-management: preliminary results

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### Purpose

The overarching goal of this research is to determine if immersive virtual reality (VR) can help patients better manage their chronic pain, and thereby potentially reduce their need for opioid analgesics. This research was designed to explore the potential analgesic effects of immersive VR for chronic pain.

Termed a nonpharmacological adjuvant, VR is a technology that has been shown to reduce the need for opioids for acute pain. While many studies of VR and acute pain are based on pain distraction, at least 2 limitations are evident: it demands the diversion of attention from everyday activities, and its effectiveness is limited to a patient's use of the technology. This is particularly problematic when pain is chronic. To address chronic pain, Mindfulness-Based Stress Reduction (MBSR) is the approach that determined the design of the VR system described here. Since MBSR enhances a patient's awareness of and ability to cope with chronic pain, it may confer benefits beyond VR technology.

Few studies have been undertaken to ascertain what roles may be played by the particular visuals and sounds that comprise a virtual environment. However, VR's effectiveness in addressing conditions such as PTSD suggests its importance. In our studies, the majority of patients reported sensitivity to certain sounds, and a strong preference for representations of nature. In addition, their ability to effect physiological changes that typify MBSR were more successful when specific visual cues did not demand focused attention. These findings guided the design of our VR system.

### Method

Two preliminary studies were conducted to discover what types of visuals are most suitable to help chronic pain patients learn mindfulness-based stress reduction (MBSR) and thereby self-manage their chronic pain. In the first study, electroencephalography (EEG) was used to measure baseline states during relaxation. 16 subjects were divided into 4 conditions; each condition displayed visuals of differing levels of abstraction. In the second study, 74 participants filled out a qualitative questionnaire about what kinds of environments they found most pleasant and relaxing. Based on the results of the 2 studies, we designed a VR environment in which chronic pain patients learn MBSR and may observe their progress in real-time.

Utilizing the results of these studies, a subsequent experiment was designed in which subjects are exposed to a path in a virtual, 3-dimensional forest; a well-known MBSR narration instructs them in MBSR practices. During this process, continuous changes in arousal, measured by galvanic skin response (GSR) data, affects elements that comprise the immersive environment in ways that do not demand focused attention. For instance, the virtual forest appears foggy; as the subject becomes progressively less aroused, the fog clears. In other words, visually abstract cues provide feedback about the effects of MBSR, moment by moment. The goal of this experiment is to enable chronic pain patients to develop skills for self-managing their experience of pain by learning how to affect their psychophysiological states. In this way, patients may accrue another method to address their pain, stress, anxiety, and pain tolerance.

## Results

Issues that are common among chronic pain patients were found to be more prevalent and problematic than initially assumed; few of these issues have been addressed in VR and acute pain studies.

In the first visual experiment, 16 participants participated in the EEG-controlled relaxation experiment. The results of one-way ANOVA suggests that there was a significant effect variable feedback on relaxation levels for 4 types of visual feedback  $F(3,12) = 23.74, P < .0001$ . Furthermore, results of pairwise Tukey's HSD between the condition with highest level of abstraction and the other 3 conditions was statistically significant with  $P$  values of  $< .0001, .0013,$  and  $.0139$ . Results of a qualitative questionnaire suggest that the majority of chronic pain patients (29 of 32) find representations of nature more pleasurable and relaxing than other representations.

Two experiments concerning characteristics of sounds and music revealed that all but 4 chronic pain subjects experienced sensitivity to volume levels and high-pitched sounds, such as those made by birds and brass instruments. Patients reported this an important issue: rather than mere discomfort, several expressed a fear that a "pain event" would be triggered.

Methods of displaying the virtual stereoscopic environment were also explored. The head-mounted display (HMD) commonly used in pain distraction studies was not well tolerated by the majority of subjects who found it too heavy and nausea-provoking. Several subjects prematurely removed the HMD; 2 feared a migraine would be triggered. An alternative stereoscopic display, mounted on a flexible and movable arm, proved less troublesome. This display is not worn, but is maneuvered by subjects to a comfortable position in front of their eyes, considerably reducing skin contact. This display restricts head movement, but was the clear preference. Finally, subjects who found the HMD to be too heavy rated higher visual quality and greater sense of immersion for the alternative display.

## Conclusions

While virtual reality is effective for acute pain, chronic pain requires different approaches to the design of VR systems. Limitations of pain distraction led to the design of a VR system that builds on mindfulness-based stress reduction while findings from careful preliminary studies structured the visual and sonic elements that comprise what patients interact with. A longitudinal study scheduled to begin in October will assess whether VR may prove to be an effective method for self-managing chronic pain, and whether such effects persist beyond VR training.

## Survey of patient perspective on the potential impact of abrupt opioid therapy discontinuation for the management of chronic pain

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### Purpose

Recently-developed algorithms aimed to decrease morbidity and mortality related to chronic opioid-prescribing emphasize frequent assessment for appropriateness of continuing long-term opioid therapy, and when indicated, transition from opioid therapy to alternative therapies for the management of chronic pain. However, opioid discontinuation in some cases seems to be driven by fear of scrutiny by state and federal agencies rather than by medical reasons. Additionally, in many cases, alternative treatments have already been considered before initiation of long-term opioid therapy and found to be not effective. Consequently patients are left with very few viable alternatives to alleviate their pain. The purpose of this pilot study is to highlight the perspective of chronic pain patients treated with opioids when confronted with the possibility of abrupt opioid discontinuation, and its potential impact on patient mood, daily functioning, and quality of life.

### Method

This anonymous and self-administered survey was conducted at a pain clinic in an urban academic hospital setting. Eligibility criteria included chronic pain for 6 months or greater, 18 years of age or older, and the ability to complete the survey in English.

### Results

When patients were asked how they would feel if told their opioids would be discontinued, the responses were: neglected (scale mean 7.1), angry (6.3), helpless (6.7), and upset (7.0) on a scale of 0-10. The majority predicted loss of independence in activities of daily living (scale mean 7.5), inability to enjoy their lives (7.4), and inability to work (7.8). Lastly, participants were asked what they would do if told their opioids were stopped: 86.0% (n = 142) said they would ask for other treatments, 27.2% (n = 43) would change physicians, 11.6% (n = 19) would obtain opioids from friends or family, and 4.2% (n = 7) would engage in illegal activities to obtain opioids, such as forging prescriptions. These 7 patients are among the 19 who would obtain opioids from friends or family. This subset of 19 patients reported higher scores of neglect ( $P = .001$ ), anger ( $P = .000$ ), suspicion ( $P = .019$ ), helplessness ( $P = .004$ ), and upset ( $P = .001$ ), and were more likely to have previously obtained opioids from friends or family ( $P = .023$ ), or bought them from the street ( $P = .008$ ).

### Conclusions

Participants expressed strong feelings of neglect and abandonment when they were confronted with the possibility of abrupt discontinuation of opioids for the management of their chronic pain. Nineteen participants (11.6%) reported they would engage in illegal activities to obtain opioids. These data suggest the possibility of increased drug diversion and utilization of illegal opioids following opioid therapy discontinuation, and that strong negative feelings when confronted with the possibility of abrupt opioid discontinuation and past misuse of prescription opioids may be indicators of risk for future aberrant drug-related behavior. Further research is needed to confirm and expand on these observations.

## Patient perception of nonopioid treatment strategies as substitutes for opioids for the management of chronic pain

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### Purpose

Recent reports of a steep increase in morbidity and mortality attributed to opioids have shifted the center of attention in opioid-prescribing for management of chronic pain from accessibility to safety. Algorithms developed to assist clinicians to assess risk encourage transition to nonopioid alternative treatments when long-term opioid therapy is deemed no longer appropriate. However, in many cases, alternative treatments have already been considered before initiation of long-term opioid therapy and found to be not effective. Consequently, patients are left with very few viable alternatives to alleviate their pain. The purpose of this pilot study is to explore the patient's experience with and perception of various interventional strategies, manipulative and body based therapies, natural products, mind body therapies, or other complementary and alternative medicines (CAM) for the management of their pain, in an effort to identify possible alternatives to opioids that could potentially be offered when opioid therapy is discontinued.

### Method

This anonymous and self-administered survey was conducted at a pain clinic in an urban academic hospital setting. Eligibility criteria included chronic pain for 6 months or greater, 18 years of age or older, and the ability to complete the survey in English.

### Results

Most participants reported never using most of the alternatives listed, including: spinal stimulation, intrathecal therapy, occupational therapy, willow bark, ginkgo biloba, marijuana, ginger, ginseng, hypnosis, tai chi, hydrotherapy, aromatherapy, and music therapy. The most commonly used alternative treatments are: exercise (83.5%, n = 111), physical therapy (78.9%, n = 101), lumbar epidural (71.5%, n = 93), massage (68.3%, n = 86), meditation (66.1%, n = 76), and acupuncture (63.3%, n = 81). The treatment modalities identified to be the most helpful by patients that reported trying them include lumbar epidural (54.8%, n = 51), massage (61.6%, n = 53), and hydrotherapy (61.5%, n = 24). Participants were then asked how helpful these strategies would be for treatment of their pain if their opioids were stopped. The most common response was "no opinion" in regards to most of the treatment strategies. The few treatments more commonly thought be effective in relieving pain in the absence of opioids are lumbar epidural (42.3%, n = 47), exercise (43.2%, n = 48), and massage (42%, n = 47).

### Conclusions

The 3 treatment strategies considered by the more participants to be effective as alternatives to replace opioid therapy were lumbar epidural, exercise, and massage, suggesting that these could be offered to patients when opioid discontinuation is considered. The large number of patients that reported no opinion on the efficacy of other alternative treatments suggests that with more education, more patients might be willing to consider these strategies as alternatives. The complexity of opioid discontinuation necessitates early identification of potential alternative strategies with patient participation, taking into account the patient's experience and preference, in order to provide the best care.

## Abuse potential of oxycodone/naloxone (OXN) tablets administered intranasally in nondependent recreational drug users with moderate opioid experience

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### Purpose

Opioid analgesics are an important component of modern pain management, however their abuse and misuse have created a serious and growing public health problem. Opioid analgesics may be used for nonmedical purposes via intranasal insufflation (IN) by recreational drug users and by more experienced abusers, which contributes to the major public health issue of prescription opioid abuse. Among more experienced nonmedical users, IN is an attractive route of administration. Pharmacological approaches to reduce IN abuse potential of opioids include concurrently administering an opioid antagonist, such as naloxone.

OXN is a twice-daily oral controlled-release combination formulation of oxycodone hydrochloride and naloxone hydrochloride (O to N ratio: 2/1 by weight) under development in the US for management of moderate to severe chronic pain. Due to its low oral bioavailability ( $\leq 2\%$ ), naloxone is unlikely to affect the analgesic properties of oxycodone when OXN is administered orally as intended. However, due to naloxone's higher bioavailability following IN administration ( $\sim 29\%$ ), if OXN tablets are crushed and administered IN, the resulting increased systemic naloxone exposure is expected to meaningfully reduce abuse potential.

This study was designed to characterize the abuse potential of OXN relative to oxycodone powder and to placebo following IN administration in subjects with a history of recreational opioid use.

### Method

This was a single-center, double-blind, randomized cross-over study to evaluate the IN abuse potential, pharmacokinetics (PK) and safety of crushed OXN tablets in male (N = 20) and female (N = 7) healthy nondependent recreational drug users (aged 20 to 50 years) experienced with opioids. The study consisted of 4 phases: screening, qualification, treatment, and follow-up. Treatments, each administered IN within 3 min, were OXN 40/20 mg tablets finely crushed, 40 mg oxycodone powder, and placebo powder. Subject qualification required adequate differentiation between placebo and oxycodone following single-blind IN administrations. Qualified subjects were to receive all 3 treatments in a randomly assigned treatment sequence from two 3x3 Williams squares. Treatments were separated by 5-10 day washouts. Pharmacodynamic (PD) and PK assessments were conducted up to 23-24 h postdose. PD assessments included visual analog scales (VAS) for 'At the Moment Drug Liking', 'Overall Drug Liking', 'Take Drug Again', High, Good Effects, Bad Effects, Feeling Sick Effects, and Alertness/Drowsiness, and the Subjective Drug Value (SDV) procedure. Both Drug Liking scales were bipolar (0 = Strong Disliking, 50 = Neutral, 100 = Strong Liking). Pupillary responses were measured. Safety evaluations included physical examination, 12-lead electrocardiograms, continuous cardiac monitoring, vital signs, clinical laboratory, medication history, and adverse events. Intranasal irritation was assessed. Plasma oxycodone and naloxone concentrations were determined and PK parameters were derived using noncompartmental methods. Descriptive statistics, 95% confidence intervals and P values for treatments and treatment differences for appropriate PD values or derived endpoints (minimum effect [ $E_{\min}$ ], maximum effect [ $E_{\max}$ ], time-averaged effect) were computed.

## Results

Mean 'At the Moment Drug Liking' VAS  $E_{max}$  for oxycodone (94.8) was significantly higher than for OXN (59.1) or placebo (53.2), with no significant difference between OXN and placebo. Mean 'Overall Drug Liking' VAS  $E_{max}$  showed similar differences among the treatments with values of 92.9, 53.4, and 50.3 for oxycodone, OXN, and placebo, respectively. Mean 'Take Drug Again' VAS  $E_{max}$  was 93.6, 42.6, and 30.7 for oxycodone, OXN, and placebo, respectively. Mean Good Effect VAS  $E_{max}$  was 96.6 for oxycodone as compared to values of 38.9 and 9.1 for OXN and placebo, respectively. A similar pattern among treatments was observed for High VAS. Bad Effects and Feeling Sick VAS scores were minimal for all treatments. Mean SDV  $E_{max}$  was low for placebo (\$2.33) and OXN (\$4.28), and much higher for oxycodone (\$35.84). Pupillometry demonstrated characteristic oxycodone-induced miosis following oxycodone, with significantly smaller changes and a delayed time course following OXN, and no notable changes following placebo.

Mean oxycodone  $C_{max}$  was 90.1 and 69.8 ng/mL following IN OXN and oxycodone, respectively. Similar mean AUC (588 vs 591 ng\*h/mL),  $T_{max}$  (1.08 vs 1.11 h) and  $t_{1/2}$  (3.79 vs 3.83 h) were observed for OXN vs oxycodone. For naloxone, mean  $C_{max}$ , AUC,  $T_{max}$ , and  $t_{1/2}$  were 20.2 ng/mL, 29.9 ng\*h/mL, 0.3 h, 4.3 h following OXN administration.

The magnitude and time course of typical PD responses to oxycodone corresponded with systemic oxycodone concentrations following IN oxycodone. However following IN OXN, PD responses to oxycodone were reduced in magnitude, despite similar or greater systemic oxycodone exposure. Systemic naloxone exposure following IN OXN resulted in significant attenuation of oxycodone effects.

No treatment produced significant intranasal irritation. One subject discontinued following an AE of withdrawal after IN OXN. Overall, the incidence of treatment-emergent typical opioid AEs was lower for OXN compared to oxycodone.

## Conclusions

This study characterized the abuse potential of crushed OXN tablets, as compared to oxycodone powder and placebo, following IN administration in experienced opioid abusers. Significant reductions in the magnitude of drug liking and of other measured PD effects were observed following OXN, as compared to oxycodone alone. These reductions demonstrate that the systemic naloxone concentrations observed following intranasal insufflation of crushed OXN tablets were sufficient to substantially reduce abuse potential, compared to insufflation of oxycodone alone. It is anticipated that this reduction in abuse potential will contribute to corresponding reductions in abuse liability in real-world settings.

## The Opioid Abuse Risk Screener (OARS): a highly reliable and valid web-based, comprehensive assessment tool

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### Purpose

Prescription opioid drug abuse has received unprecedented clinical, research, and public policy attention in the past decade; the CDC has declared it an epidemic. Agencies including the DEA, CDC, and FDA have made requirements and policy changes aimed to decrease the opioid abuse problem. The American Pain Society and American Academy of Pain Medicine developed evidence-based practice guidelines for opioid therapy. Their first major recommendation was for careful patient selection and risk stratification. Strong evidence connects psychiatric issues, pain, and substance abuse, yet, to date, few assessments have been developed to evaluate these often co-occurring and sometimes mutually exacerbating factors. Despite practice guidelines and staggering prevalence rates of misuse and overdose, many practitioners are not screening for risk. This may be due to a lack of standardized or comprehensive instruments, cumbersome administration, feeling the data gleaned is not useful, or that they can rely on their own skills. Research suggests even the best trained prescribers are not always successful in accurately screening for risk.

The authors developed a brief, but comprehensive, evidence-based assessment that meets and surpasses clinical practice guidelines. The Opioid Abuse Risk Screener (OARS) was developed as a fully HIPPA-compliant, web-based platform that allows for real-time feedback and a summative report of patient risk. The OARS evaluates patient risk based on critical elements to potential abuse including current and past psychiatric concerns, substance use history, aberrant behaviors, and medical noncompliance and details the risk stratification profile in an immediately accessible, chart ready, color-coded, easy-to-read, summative report.

### Method

The items tested in the present study were derived from an initial item pool of 162 items redundantly covering a range of symptoms, behaviors, and personal history shown by the literature to be of concern when participating in opioid pain therapy. These conceptual domains included emotional disturbance, depression, anxiety, suicidal ideation, history of trauma, symptoms of delusion, noncompliant medical behaviors, personal or family history of substance abuse, behaviors related to intentional misuse of a medication, unemployment, and many other such issues. The initial item pool was reduced in a step-wise fashion over the course of several cycles of data collection and analysis based on the results of classical item analysis as well as exploratory and confirmatory factor analysis. These iterations resulted in a pilot version of the questionnaire consisting of 42 items scored on a 4-point Likert-type scale. These items were administered to a sample of 249 adults including 111 males and 138 females recruited to participate during a consultation at one of several pain clinics in Utah, Idaho, and Arizona. Of the 249 patients, 47% were employed, 63% were married or partnered, 85% were Caucasian, 63% have never smoked, 45% reported seeing 2 or more physicians in the past year that provided pain medications, and 50% reported currently taking opioids for pain.

### Results

Responses to 249 completed questionnaires were first analyzed using classical item analysis techniques in SPSS. Items with low item-to-adjusted-total correlations were deleted. Exploratory factor analysis was then conducted using *Mplus* to obtain an estimate of the number of factors and the degree to which they were intercorrelated. A series of first-order and second-order confirmatory factor analyses was then performed using *Mplus*. Items were deleted if (1) they did not load well on any factor, (2) demonstrated nonnegligible crossloadings on more than one factor, or (3) showed



evidence of correlated error terms. A total of 36 items were retained that loaded on 2 main factors: (1) Emotional Lability (EL), and (2) Aberrant Behavior (AB). Each of these 2 scales showed evidence of a second-order factor structure. The 20 items loading on the EL factor included 5 items from each of 4 different first-order factors: Anxiety, Depression, PTSD, and Quality of Life. The 16 items on the AB scale consisted of 3 different first-order factors including Noncompliance, Risky Behaviors, and Substance Abuse History. The Cronbach's alpha reliability was .938 for the EL scale and .904 for the AB scale. Correlations with the SOAPP-r were .631 for the EL scale and .59 for the AB scale.

## **Conclusions**

The OARS demonstrates excellent internal reliability and validity. Initial indications, through comparisons with the SOAPP-r, suggest strong external (criterion) validity. As it is web-based, it is easy to integrate into clinical practice, is not burdensome for clinic staff to administer or manage nor for patients to complete. The OARS provides accurate, evidence-based, risk stratification and helps ensure patients are provided the most appropriate pain management interventions and overall quality of care. Two large-scale studies designed to further evaluate criterion validity are currently underway and include sensitivity and specificity data comparing OARS results to biological factors (eg, urinalysis) and DOPL reports.

## Treadmill exercise combined with ultrasound treatment attenuated chronic constriction pain in rats

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### Purpose

Ultrasound treatment is used to treat neurological disorder, such as carpal tunnel syndrome. However, the effect and underlying mechanism of ultrasound treatment remains unclear. Previous report also demonstrated that treadmill exercise could alleviate neuropathic symptoms via upregulation of cytokines and related proteins. Therefore, the objective of this study was to determine the effect of ultrasound treatment and combination of treadmill exercise and ultrasound treatment in chronic constriction injury (CCI) induced neuropathic pain in rats.

### Method

Rats were randomly assigned to 5 groups: Naïve, sham operation, CCI with ultrasound treatment (CCI + USD), CCI with treadmill exercise treatment (CCI + TME), and CCI with combine treatment (CCI + TME + USD). Chronic constriction injury was performed on rat's sciatic nerve. Ultrasound treatment was performed 5 days a week for 4 weeks, 1 MHz with 1 w/cm<sup>2</sup> intensity for 5 minutes and started immediately after surgery. One week after surgery, exercise treatment was consisted of 14-16 m/min treadmill exercise with 8% incline grade, 5 days a week for 3 weeks. Thermal hyperalgesia and mechanical allodynia were determined by Plantar Test and Von Frey Aesthesiometer. The expression of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6) and interleukin-10 (IL-10), neurotransmitter substance P and receptor of substance P (neurokini-1, NK-1) in sciatic nerve, branch of sciatic nerve, spinal cord and dorsal root ganglion were determined.

### Results

At 1 hour after treatment, the average withdrawal latency and withdrawal threshold of 3 treatments groups all increased significantly than sham group. These data suggested that all treatments could reverse thermal. The withdrawal latency and withdrawal threshold of CCI + TME + USD group was higher than CCI + USD or CCI + TME groups. There were no significant difference between CCI + USD and CCI + TME groups. After treatment for 4 weeks, the withdrawal latency and withdrawal threshold were indistinguishable between sham and CCI + TME + USD group. In sciatic nerve, the TNF- $\alpha$  level in CCI + TME and CCI + TME + USD groups were lower than that in CCI group and the IL-6 level in CCI + TME and CCI + TME + USD groups were lower than Sham group.

### Conclusions

Ultrasound treatment and its combination treatment with treadmill exercise reversed CCI-induced thermal hyperalgesia, mechanical allodynia and TNF- $\alpha$  overexpression in sciatic nerve.

## Long-term safety and efficacy of lubiprostone in opioid-induced constipation in patients with chronic, noncancer pain: results from a phase 3, open-label clinical trial

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### Purpose

Chronic use of opioid medication for the treatment of noncancer pain results in opioid-induced constipation (OIC) in a significant proportion of patients. Lubiprostone, a locally-acting chloride channel (ClC-2) activator, has been shown to counteract the adverse gastrointestinal effects of opioids via this mechanism in nonclinical studies as well as in two 12-week, placebo-controlled clinical trials. The current extension study evaluates the safety and efficacy of lubiprostone over 9 months of open-label treatment in an OIC population.

### Method

439 adult patients (59.9% female) with confirmed OIC were enrolled from two 12-week, placebo-controlled, double-blinded studies and received lubiprostone, 24 mcg twice daily (BID) for up to 9 months. Inclusion criteria required consistent treatment with a full opioid agonist for the duration of the study. OIC was defined as having, on average, less than 3 spontaneous bowel movements (SBMs)/week during the screening period, and > 1 of the following symptoms for > 25% SBMs during the same period: hard to very hard stools, sensation of incomplete evacuation, or moderate to very severe straining. The primary objective of the study was to evaluate the safety of chronic lubiprostone therapy in patients with OIC. Efficacy outcomes were also assessed.

### Results

Statistically significant changes from baseline were reported at each month for SBM frequency, with mean weekly SBM frequencies ranging from 4.9 to 5.3 SBMs per week, compared to a pre-treatment frequency of 1.4 per week ( $P < .001$  vs baseline at all months). Patient ratings of average degree of straining with SBMs, stool consistency, constipation severity, abdominal bloating, abdominal discomfort, and bowel habit irregularity were also statistically significantly improved from baseline during the entire treatment period ( $P < .001$  at all treatment months). Patient reliance on rescue medication was substantially decreased during the course of the study (33.0% of patients reporting use at Month 1 vs 18.6% at Month 9). Overall, 24.6% of patients reported a treatment-related adverse event (AE) during the 9-month study, the most common of which were nausea, diarrhea, and flatulence (5.0%, 4.6%, and 1.6% of patients, respectively). No treatment-related serious AEs were reported. Nausea and diarrhea were cited as reason for withdrawal in 5 (1.1%) and 5 (1.1%) subjects, respectively, and only 2 cases of nausea and 2 cases of diarrhea were rated as severe.

### Conclusions

Lubiprostone treatment was well tolerated and resulted in overall improvement in symptoms and signs of OIC in this 9-month, open-label study.

### A phase 3, randomized, double-blind, placebo-controlled clinical trial of lubiprostone for the treatment of opioid-induced constipation in patients with chronic, noncancer pain

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#### Purpose

Opioid-induced constipation (OIC) comprises a variety of adverse gastrointestinal effects, including infrequent and incomplete bowel movements, hard stool consistency, straining, abdominal discomfort/pain, and bloating. Lubiprostone is an orally administered, locally acting activator of type-2 chloride channels (ClC-2) that promotes secretion of fluid and chloride into the intestinal tract, facilitating motility and bowel movements. Lubiprostone is indicated for the treatment of chronic idiopathic constipation (24 mcg twice daily [BID]) in adults and irritable bowel syndrome with constipation in adult women (8 mcg BID); in addition, lubiprostone was approved for OIC in adults with chronic noncancer pain (24 mcg BID) in April 2013. The current clinical study assessed the safety and efficacy of lubiprostone 24 mcg BID for the treatment of OIC in patients taking opioids for chronic noncancer pain.

#### Method

This was a randomized, double-blind, placebo-controlled, phase III study conducted at 79 sites in the United States and Canada. Adult men and nonpregnant, nonlactating women with OIC were randomized to receive either placebo or lubiprostone 24 mcg BID for 12 weeks. Inclusion criteria required patients to be on an opioid medication for  $\geq 30$  days prior to screening and throughout the study treatment period. Patients were also required to have  $< 3$  spontaneous bowel movements (SBMs)/week during the screening period, and  $\geq 1$  of the following symptoms for  $\geq 25\%$  of SBMs during the same period: hard to very hard stools, sensation of incomplete evacuation, or moderate to very severe straining. The primary efficacy endpoint was the mean change from baseline in SBM frequency at Week 8 in patients without a dose reduction in study medication. Secondary endpoints included changes from baseline in SBM frequency at Week 12 and overall; percentage of patients with a first postdose SBM within 24 and 48 hours; and overall mean change from baseline in constipation-related symptoms.

#### Results

In total, 418 patients were randomized to receive treatment with lubiprostone 24 mcg BID ( $n = 210$ ) or placebo ( $n = 208$ ). Patients receiving lubiprostone who did not have their dose reduced had a significantly greater change from baseline compared with placebo for SBM frequency at Week 8 (lubiprostone,  $n = 151$ ; placebo,  $n = 159$ ; mean change, 3.3 vs 2.4,  $P = .005$ ; median change, 2.9 vs 1.4). Patients in the entire ITT population who received lubiprostone also had a significantly greater change from baseline compared with placebo for SBM frequency during the overall study period (lubiprostone,  $n = 205$ ; placebo,  $n = 204$ ; mean change, 2.7 vs 2.1,  $P = .004$ ; median change, 2.2 vs 1.6); although the same pattern was observed at Week 12, statistical significance was not achieved. Additionally, a significantly greater percentage of patients treated with lubiprostone compared with placebo reported their first SBM within 24 hours (lubiprostone, 38.8%; placebo 27.8%;  $P = .018$ ) and 48 hours (lubiprostone; 61.2%, placebo 51.7%;  $P = .050$ ) of the first dose. Statistically significant improvements overall with lubiprostone were observed for constipation severity ( $P = .007$ ), stool consistency ( $P < .001$ ), abdominal discomfort ( $P = .024$ ), and straining ( $P < .001$ ). Overall, the most commonly reported adverse events (AEs) were nausea, diarrhea, and abdominal distension; rates of these AEs were higher in the lubiprostone group compared with the placebo group.

Overall, 22 patients discontinued the study due to an AE (placebo, 6 [2.9%] vs lubiprostone, 16 [7.6%]), and no patients died during the study.

### **Conclusions**

Lubiprostone relieved many signs and symptoms associated with OIC, such as SBM frequency at Week 8, first SBM within 24 or 48 hours, constipation severity, stool consistency, abdominal discomfort, and straining; and was well tolerated in patients with chronic noncancer pain.

## Safe and effective high-dose opioid reduction guideline

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### Purpose

Over the last 2 decades, the explosion in opioid use for chronic noncancer pain has raised significant concern about appropriate prescribing practices and patient welfare. This continues to affect patients and prescribers, and has led to intervention by regulatory bodies. The upward trend in opioid prescribing may be attributed to the campaign that educated prescribers about the under treatment of pain and consequently the liberalization of laws governing opioid use. Data suggests that hundreds of thousands of patients nationwide are on potentially dangerous high-dose opioid medications. Physicians may continue these medications for several years and commonly consider dose escalations, attributing this practice to opioid tolerance.

There is little evidence in the literature to support the use of high-dose opioids for chronic pain management. Furthermore, there are limited clinical guidelines to assist in the process of opioid dose reduction and it is unknown if these recommendations can safely and effectively be implemented in high-dose opioid patients.

The primary objective of this study was to develop an opioid dose reduction guideline to be used in high-dose opioid patients who are candidates for opioid reduction. A second objective was to assess pain, depression, and quality of life outcomes after opioid dose reduction.

### Method

This study was conducted at the Kaiser Permanente Greater Southern Alameda Area (GSAA) Chronic Pain Program (CPP). Based on previous experience from the GSAA CPP physician chief, an opioid dose reduction guideline was created to be used for chronic pain patients using high-dose opioids (defined as 300 mg daily oral morphine equivalent or greater). Patients initially agreed to opioid dose reduction after a visit with the Chronic Pain Program physician chief. The guideline for dose reduction was followed and patients were managed by telephone or office visits at least once monthly during the medication taper.

A retrospective chart review of opioid reduction patients from December 2009 to May 2011 was performed. Patients aged 18 to 75 with a diagnosis of chronic pain and an average pain score of 6 or above on an 0 to 10 point Likert scale 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. Electronic medical records were reviewed to assess pain, quality of life, and opioid withdrawal symptoms before, during, and after the opioid taper. Patient-reported pain and quality of life data were collected from the Brief Pain Inventory, and depression data was evaluated using the Patient Health Questionnaire. Statistics were calculated for the change in average opioid dose, pain score, depression score, and quality of life scores using the paired student t-test, and significance was set at a *P*-value of <0.05.

### Results

The opioid reduction guideline will be presented, which provides dosing recommendations for high-dose opioid tapering.

Sixteen patients met inclusion criteria for the retrospective chart review, and outcomes were assessed both before and after opioid dose reduction. The majority of patients were female, which is consistent with the demographics of the CPP. Each patient was diagnosed with more than one chronic pain condition; the most prevalent diagnoses were low back, neck, and migraine pain.

The daily morphine equivalent was significantly reduced from an average of 945 mg to 275 mg over about 17 weeks ( $P < .001$ ). The average pain score was decreased from approximately 7.2 to 4.9 ( $P < .001$ ) based on the Brief Pain Inventory. Depression also improved from an average of 13.5 to 9.5 ( $P < .01$ ) based on the Patient Health Questionnaire. Although the pain interference in mood, walking, work, relationships, and enjoyment of life were reduced following the opioid taper, only pain interference in normal daily activity was significantly lowered ( $P < .05$ ).

Three out of 16 patients did not report any opioid withdrawal symptoms during the medication taper. Six patients experienced withdrawal symptoms only once, and 7 patients experienced withdrawal symptoms more than once throughout the opioid tapering process. The most common opioid withdrawal symptoms were anxiety, sweating or chills, and muscle cramps or spasms. All patients who reported opioid withdrawal were prescribed medications to treat the symptoms, and no significant complications were noted.

## **Conclusions**

The surge in opioid prescribing has led to heightened vigilance by prescribers, patients and regulatory bodies. The existing literature lacks validated recommendations for addressing the large number of patients currently using opioids at high doses. This research provides opioid dose reduction guidelines which were shown to be safe and effective for this patient population. An opioid dose reduction of approximately 70% was achieved with corresponding improvements in pain, depression, and quality of life outcomes. Overall, this study illustrates the benefits of opioid reduction for patients with uncontrolled pain and highlights the need for alternative treatment options for chronic pain patients.

## Effect of hepatic impairment on the pharmacokinetics of hydrocodone and its metabolites following administration of a novel hydrocodone single-entity, once-daily, extended-release tablet [HYD]

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### Purpose

HYD is a single-entity, once-daily, extended-release tablet formulation of hydrocodone bitartrate. It is being developed for the management of moderate to severe pain in patients who require a continuous, around-the-clock opioid pain medication for an extended period of time. HYD was formulated with inactive ingredients intended to make the tablet more difficult to manipulate for misuse and abuse.

To provide guidance to healthcare providers on the appropriate use of HYD, the pharmacokinetics (PK) and safety of HYD has been studied in subjects with compromised hepatic function. The purpose of this open-label, parallel group, single-dose study was to assess the pharmacokinetics (PK) and safety of HYD in subjects with mild, moderate, and severe hepatic impairment in comparison to subjects with normal hepatic function.

### Method

Twenty-seven male and 5 female subjects, aged 18 to 80 years, were categorized using the Child-Pugh classification: 8 mild hepatic impairment (Child-Pugh Class A), 8 moderate hepatic impairment (Child-Pugh Class B), 8 severe hepatic impairment (Child-Pugh Class C), and 8 healthy subjects (normal hepatic function). The group of healthy subjects was matched, to the extent possible, to the group of hepatically impaired subjects for gender, mean age ( $\pm 10$  years), mean body mass index ( $\pm 20\%$ ), and smoking status. Following a 10-hour overnight fast, subjects were administered a single HYD 20-mg tablet. Blood samples were collected at predose and through 168 hours post dose for PK analysis. PK parameters were calculated for hydrocodone and its metabolites, norhydrocodone and hydromorphone. Additional blood samples were collected at predose and 14 hours post dose for ex-vivo plasma protein binding of hydrocodone. Safety was assessed by adverse events (AE), clinical laboratory tests (biochemistry, hematology, and urinalysis), vital signs and pulse oximetry (SpO<sub>2</sub>) measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings.

### Results

Mean  $\pm$  SD area under the curve (AUC) of hydrocodone in subjects with mild hepatic impairment ( $310 \pm 124$  ng·h/mL) was comparable to that in subjects with normal hepatic function ( $342 \pm 37$  ng·h/mL). Mean AUC for subjects with moderate and severe hepatic impairment increased by 14% and 21% as compared to healthy subjects. Mean maximum plasma concentration (C<sub>max</sub>) was comparable across all groups; 16.0, 15.3, 17.0, and 18.4 ng·h/mL in subjects with normal hepatic function and mild, moderate, and severe hepatic impairment, respectively.

Mean AUC values of norhydrocodone, a major inactive metabolite, were 123, 101, 67, and 73 ng·h/mL in subjects with normal hepatic function and mild, moderate, and severe hepatic impairment, respectively. The corresponding mean C<sub>max</sub> values were 4.7, 4.0, 2.3, and 2.2 ng/mL, respectively.

AUC and C<sub>max</sub> of hydromorphone, a minor active metabolite (less than 3% of hydrocodone AUC) had considerable variability with wide 90% confidence intervals across groups.



The mean ex-vivo plasma protein binding (% bound) of hydrocodone in subjects with normal hepatic function and mild, moderate, and severe hepatic impairment were low and comparable at 36.4%, 37.4%, 33.1%, and 34.2%, respectively.

There were no deaths or discontinuations due to treatment emergent AEs.

Clinical laboratory values, vital sign and SpO<sub>2</sub> measurements, and ECG results were similar across the groups.

### **Conclusions**

Following a single HYD 20-mg tablet oral dose, systemic hydrocodone exposure was comparable in subjects with mild hepatic impairment and subjects with normal hepatic function. Systemic hydrocodone exposure was marginally increased in subjects with moderate and severe hepatic impairment, as compared to subjects with normal hepatic function. Hydrocodone plasma protein binding of was similar in healthy subjects and subjects with hepatic impairment.

Administration of a HYD 20-mg tablet under fasted conditions was well tolerated in subjects with normal hepatic function and subjects with mild, moderate, and severe hepatic impairment.

## Effect of renal impairment on the pharmacokinetics of hydrocodone and its metabolites following administration of a novel hydrocodone single-entity, once-daily, extended-release tablet [HYD]

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### Purpose

HYD is a single-entity, once-daily, extended-release tablet formulation of hydrocodone bitartrate. It is being developed for the management of moderate to severe pain in patients who require a continuous, around-the-clock opioid pain medication for an extended period of time. HYD was formulated with inactive ingredients intended to make the tablet more difficult to manipulate for misuse and abuse.

To provide guidance to healthcare providers on the appropriate use of HYD, the pharmacokinetics (PK) and safety of HYD has been studied in subjects with compromised renal function. The purpose of this open-label, parallel group, single-dose study was to assess the PK and safety of HYD in subjects with mild, moderate, and severe renal impairment and end-stage renal disease (ESRD) in comparison to subjects with normal renal function.

### Method

Twenty-seven male and 14 female subjects, aged 18 to 80 years, were categorized based on estimated glomerular filtration rate (eGFR): 8 with normal renal function, 8 with mild renal impairment, 9 with moderate renal impairment, 8 with severe renal impairment and 8 with ESRD. The group of healthy subjects was matched, to the extent possible, to the group of subjects with renal impairment on the basis of gender, mean age ( $\pm 10$  years), mean body mass index ( $\pm 20\%$ ), and smoking status. Following a 10-hour overnight fast, subjects were administered a single HYD 60-mg tablet under naltrexone blockade. Subjects with ESRD were administered HYD 60-mg tablet under naltrexone blockade on 2 occasions separated by a 14-day washout period; once 90 minutes before hemodialysis and once 90 minutes after hemodialysis. Blood and urine samples were collected at predose and through 168 hours post dose for PK analysis. PK parameters were calculated for hydrocodone and its metabolites, norhydrocodone and hydromorphone. Dialysate fluid was collected from subjects with ESRD. Safety was assessed using adverse events (AE), clinical laboratory tests (biochemistry, hematology, and urinalysis), vital signs and pulse oximetry (SpO<sub>2</sub>) measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings.

### Results

Subjects with mild renal impairment showed a slight increase in systemic hydrocodone exposure, AUC (14%) and C<sub>max</sub> (14%), relative to subjects with normal renal function. Subjects with moderate and severe renal impairment exhibited increases in hydrocodone AUC (63% and 58%) and C<sub>max</sub> (23% and 11%), respectively, compared to subjects with normal renal function.

Compared to subjects with normal renal function, ESRD subjects exhibited an increase in systemic hydrocodone exposure (AUC) of 46% when HYD was administered 90 minutes after completion of a dialysis session vs an increase of 5% when HYD was administered 90 minutes before the start of a dialysis session. Regardless of the timing of HYD administration relative to dialysis, hydrocodone C<sub>max</sub> in ESRD subjects was similar to that in subjects with normal renal function.

Norhydrocodone, the major inactive metabolite, showed an increase in AUC by 19%, 73%, and 74% in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function. Norhydrocodone  $C_{max}$  was comparable across the 4 groups.

AUC and  $C_{max}$  of hydromorphone, a minor active metabolite (less than 3% of hydrocodone AUC) had considerable variability with wide 90% confidence intervals across groups.

Hydrocodone renal clearance (CL<sub>r</sub>) in subjects with normal renal function, mild, moderate, and severe renal impairment was 5.3, 3.2, 2.5, and 1.2 L/h, respectively; whereas apparent total body clearance was higher, 83, 89, 52, and 55 L/h, respectively. During hemodialysis in subjects with ESRD, hydrocodone dialyzer clearance (CL<sub>d</sub>) was 9.25 L/h.

There were no deaths or discontinuations due to treatment emergent AEs. One subject (severe renal impairment) had a serious AE of sepsis syndrome (unlikely related to study drug) that resulted in inpatient hospitalization and was resolved by end of the study.

Clinical laboratory values, vital sign and SpO<sub>2</sub> measurements, and ECG results were similar across the groups.

## Conclusions

Following a single HYD 60-mg tablet oral dose, systemic hydrocodone exposure was comparable in subjects with mild renal impairment and subjects with normal renal function.

Subjects with moderate renal impairment, severe renal impairment, and ESRD exhibited systemic hydrocodone exposure (AUC) increases of similar magnitude, 63%, 58%, and 46%, respectively, compared to subjects with normal renal function.

Administration of a HYD 60-mg tablet under fasted conditions with naltrexone blockade was well tolerated in subjects with normal renal function and subjects with mild, moderate, and severe renal impairment and ESRD.

## Treatment of episodic tension-type headache with a novel formulation of ibuprofen sodium

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### Purpose

Episodic tension-type headache (ETTH) is the most common type of primary headache and is often treated with over-the-counter (OTC) analgesics. A single 400-mg dose of standard OTC ibuprofen (IBU) is a well-established, safe, and effective treatment for tension-type headache. Given that achieving rapid relief is a desirable attribute of OTC analgesics, considerable effort has been expended to develop products that enable faster absorption and therefore potentially faster onset of analgesia. Examples of products that possess fast absorption profiles include soft gelatin capsules containing solubilized IBU (ie, soft gels, liquid capsules) and salt-conjugated forms of IBU (eg, arginine, lysine). A novel tablet formulation containing 256 mg of IBU sodium (IBU<sub>Na</sub>, equivalent to 200 mg of standard IBU) has recently been developed. This formulation is absorbed faster than standard IBU tablets and as fast as solubilized IBU and IBU lysine; additionally, it has been shown to have a faster onset of action than standard IBU in a third molar extraction model of dental pain. The purpose of this investigation was to evaluate the overall efficacy and onset of analgesia of IBU<sub>Na</sub> compared with standard IBU tablets and placebo in the treatment of episodic tension-type headache (ETTH).

### Method

Randomized, double-blind (third-party blind), single-center, parallel-group study in otherwise healthy subjects 18-65 years old with a history of  $\geq 4$  ETTH attacks per month for the past 6 months of  $\geq$  moderate severity. Subjects reporting with  $\geq$  moderately severe headache pain were randomized 2:2:1 to single-dose IBU<sub>Na</sub> tablets (2 $\times$ 256 mg; equivalent to 400 mg standard IBU), Motrin<sup>®</sup> tablets (IBU<sub>Mot</sub>; 2 $\times$ 200 mg), or placebo. The double stopwatch method was used to evaluate time to first perceptible pain relief (TFPR) and time to meaningful pain relief (TMPR). At 1, 2, and 3 hours postdose, subjects reported pain severity (4-point Categorical Pain Severity Rating Scale: 0 = none to 3 = severe) and pain relief (5-point Categorical Pain Relief Rating Scale: 0 = no relief to 4 = complete relief). Primary endpoints were the time-weighted sum of pain relief rating (PRR) and pain intensity difference (PID) scores over 3 hours after dosing (SPRID 0-3) for IBU<sub>Na</sub> vs placebo, and TMPR for IBU<sub>Na</sub> vs IBU<sub>Mot</sub>. Secondary endpoints included TMPR; TFPR confirmed by TMPR; PRR and PID scores and their sum (PRID) at 1, 2, and 3 hours postdose; time-weighted sum of PRR, PID, and PRID scores (TOTPAR, SPID, and SPRID) over 2 and 3 hours, respectively; duration of relief; cumulative proportion of subjects achieving MR, FPR (confirmed by MR) at 30 minutes and 1, 2, and 3 hours; cumulative proportion of treatment failures; and proportion achieving complete relief by 1, 2, and 3 hours. Statistical methods included analysis of variance, proportional hazards regression, and Cochran-Mantel-Haenszel test as appropriate.

### Results

A total of 226 eligible subjects were randomized to IBU<sub>Na</sub> (n = 91), IBU<sub>Mot</sub> (n = 89), and placebo (n = 46). Demographics and baseline characteristics were comparable between groups. The mean SPRID 0-3 scores were 9.6, 9.7, and 3.5 for IBU<sub>Na</sub>, IBU<sub>Mot</sub>, and placebo, respectively; each active treatment was significantly superior to placebo ( $P < .001$  for each), but were not significantly different from each other. Median TMPR was significantly faster for subjects in both active treatment groups (IBU<sub>Na</sub> = 40.6 min; IBU<sub>Mot</sub> = 48.5 min) vs placebo ( $> 180$  min;  $P < .001$ ). Although TMPR and TFPR were not significantly different between the IBU<sub>Na</sub> and IBU<sub>Mot</sub> groups ( $P = .253$  and  $.247$ , respectively), using the protocol-specified statistical analysis (proportional hazards), a posthoc analysis using the Gehan-Wilcoxon test, which assigns higher weights to earlier time points, indicated that IBU<sub>Na</sub> provided faster TMPR

and TFPR than IBU<sub>Mot</sub> ( $P = .022$  and  $.018$ , respectively). Mean PRR, PID, and PRID scores for both IBU<sub>Na</sub> and IBU<sub>Mot</sub> were significantly better than placebo at 1, 2, and 3 hours, as were 0-2 and 0-3 hour SPID, TOTPAR, and SPRID scores ( $P < .001$  for all comparisons vs placebo); IBU<sub>Na</sub> and IBU<sub>Mot</sub> scores were not significantly different than each other on any of these measures. A higher percentage of subjects reported confirmed FPR beginning at 0.5 hours in the IBU<sub>Na</sub> group compared with IBU<sub>Mot</sub> (18.7% vs 7.9%;  $P = .033$ ); statistically significant separation from placebo for MPR began at 0.5 hours for IBU<sub>Na</sub> compared with 1 hour for IBU<sub>Mot</sub>. No subjects required rescue medication; none discontinued due to lack of efficacy. No adverse events were reported.

## Conclusions

This study demonstrates that a novel formulation of IBU<sub>Na</sub> is effective and safe in the treatment of ETTH and provides overall pain relief similar to standard IBU. Each treatment was well tolerated. While the onset of analgesia was no different between IBU<sub>Na</sub> and IBU<sub>Mot</sub> tablets in the prespecified analysis, an alternative analysis that assigns higher weight to earlier events revealed significantly faster onset of analgesic effect for IBU<sub>Na</sub> vs IBU<sub>Mot</sub> as measured by TFPR and TMPR. These results are similar to those obtained in a study of dental pain, which found that IBU<sub>Na</sub> was significantly faster than standard IBU.

## A novel formulation of ibuprofen sodium is absorbed faster than standard ibuprofen tablets

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### Purpose

Ibuprofen (IBU) is a widely used, safe, effective, over-the-counter (OTC) analgesic. Rapid onset of action is a desirable attribute of OTC analgesics, and onset of pain relief is associated with rate of absorption. As a result, a number of new formulations have emerged from efforts to develop IBU options with rapid absorption, including solubilized IBU and IBU salt conjugates (eg, IBU lysine, IBU arginine). A novel tablet formulation of IBU sodium (IBU<sub>Na</sub>) is a recent option being investigated. The purpose of this investigation was to characterize the rate and extent of IBU absorption from IBU<sub>Na</sub> compared with that of several other marketed IBU products, including standard and fast-acting formulations. Because food may reduce the rate and/or extent of IBU absorption, the effect of a high-fat breakfast on IBU<sub>Na</sub> absorption was also tested.

### Method

Two randomized, single-dose, open-label, 5-way crossover bioequivalence studies were conducted in healthy volunteers 18-45 years of age. Study 1: In 3 fasting study periods, subjects received 400-mg dose equivalents of IBU, given as IBU<sub>Na</sub> tablets 2x256 mg, Advil<sup>®</sup> Liqui-Gels<sup>®</sup> (IBU<sub>LG</sub>) 2x200 mg, and Motrin<sup>®</sup> IB (IBU<sub>Mot</sub>) 2x200 mg tablets; in 2 study periods within 20 minutes of a standardized high-fat breakfast, subjects received 400-mg dose equivalents of IBU, given as IBU<sub>Na</sub> tablets 2x256 mg and IBU<sub>LG</sub> 2x200 mg. Study 2: In 5 fasting study periods, subjects received 400-mg dose equivalents of IBU, given as IBU<sub>Na</sub> tablets 2x256 mg, Advil<sup>®</sup> Fastgel<sup>®</sup> (IBU<sub>FG</sub>) liquid capsules 2x200 mg, Nurofen<sup>®</sup> (IBU<sub>Nur</sub>) tablets 2x200 mg, Advil<sup>®</sup> (IBU<sub>Adv</sub>) tablets 2x200 mg, and Nurofen<sup>®</sup> Express caplets containing IBU lysine (IBU<sub>Lys</sub>) 2x342 mg. Blood samples were obtained prior to dosing and at 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, and 90 minutes and 2, 3, 4, 6, 8, 10, 12, and 16 hours postdose for assessment of pharmacokinetic parameters (WinNonlin<sup>®</sup> v5.1). Racemic IBU was detected using a validated liquid chromatography with tandem mass spectrometry. Log-transformed area under the plasma concentration-vs-time curve to last observable concentration (AUC<sub>L</sub>) and peak plasma concentration (C<sub>max</sub>) were the primary pharmacokinetic parameters. Treatment differences were analyzed via analysis of variance. Formulations were considered bioequivalent if the 2-sided 90% confidence intervals (CIs) for the least squares means (LSM) ratio between test and reference were between 80% and 125%. Posthoc analyses of time to reach C<sub>max</sub> (T<sub>max</sub>) used the Wilcoxon rank-sum test; Hodges-Lehmann estimates were used to evaluate treatment differences.

### Results

71 subjects (Study 1, N = 36; Study 2, N = 35) were randomized to receive treatment; 4 subjects in Study 1 and 3 in Study 2 discontinued prematurely. In Study 1, AUC<sub>L</sub> (µg·h/mL) was 145.7 for IBU<sub>Na</sub>, 143.8 for IBU<sub>LG</sub>, and 143.4 for IBU<sub>Mot</sub> in the fasted state, and 127.2 for IBU<sub>Na</sub> and 125.9 for IBU<sub>LG</sub> in the fed state. C<sub>max</sub> values (µg/mL) in Study 1 were 50.6, 48.6, and 37.4 for IBU<sub>Na</sub>, IBU<sub>LG</sub>, and IBU<sub>Mot</sub>, respectively, in the fasting state, and 31.5 for IBU<sub>Na</sub> and 34.2 for IBU<sub>LG</sub> in the fed state. The rate and extent of absorption were comparable between IBU<sub>Na</sub> and IBU<sub>LG</sub> in both the fasted and fed states; as expected, food reduced the rate and extent of absorption similarly for both. While fasting, the extent of absorption was similar for IBU<sub>Na</sub> and IBU<sub>Mot</sub>, but IBU<sub>Na</sub> was absorbed significantly faster. In Study 2, AUC<sub>L</sub> (µg·h/mL) was 140.8 for IBU<sub>Na</sub>, 133.8 for IBU<sub>FG</sub>, 140.5 for IBU<sub>Nur</sub>, 140.3 for IBU<sub>Adv</sub>, and 136.4 for IBU<sub>Lys</sub>. Corresponding C<sub>max</sub> values (µg/mL) in Study 2 were 47.0, 46.8, 36.1, 37.7, and 49.9. IBU<sub>Na</sub> was absorbed at an equivalent rate and extent compared with IBU<sub>FG</sub> and IBU<sub>Lys</sub>. The extent of absorption was similar between IBU<sub>Na</sub>, IBU<sub>Adv</sub>, and IBU<sub>Nur</sub>, but the rate of absorption of IBU<sub>Na</sub> was significantly faster. In the fasted state, median IBU<sub>Na</sub> T<sub>max</sub>

was 30-35 minutes, comparable to IBU<sub>LG</sub>, IBU<sub>FG</sub>, and IBU<sub>Lys</sub> (40, 40, and 35 minutes, respectively). Median T<sub>max</sub> was achieved by IBU<sub>Nd</sub> in a much shorter time than with IBU<sub>Mot</sub>, IBU<sub>Nur</sub>, and IBU<sub>Adv</sub> (120, 120, and 82 minutes, respectively). In the fed state, IBU<sub>Nd</sub> and IBU<sub>LG</sub> had the same median T<sub>max</sub> (90 minutes). Adverse events (AEs) were balanced across treatments and mostly mild in severity. The most common AEs were headache and dizziness.

## Conclusions

IBU<sub>Nd</sub> is a novel IBU tablet formulation that is absorbed to the same extent but much more rapidly than standard IBU formulations; maximum plasma concentrations were achieved ~45-90 minutes faster than standard formulations and similar to other fast-absorbed IBU formulations. All IBU formulations were well tolerated; no significant safety findings emerged during these trials. The faster absorption found with IBU<sub>Nd</sub> may translate to a more rapid onset of analgesia.

## A novel formulation of ibuprofen sodium has a faster onset of analgesia than standard ibuprofen tablets in the treatment of postoperative dental pain

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### Purpose

Ibuprofen (IBU), a safe and effective nonsteroidal anti-inflammatory drug (NSAID), is one of the most widely used nonprescription analgesics/antipyretics. Serum concentrations of IBU are highly correlated with level of analgesia; furthermore, the more rapidly IBU is absorbed, the faster the onset of analgesia can occur. As a result, considerable effort has been expended on the development of formulations with this characteristic. A novel tablet formulation of ibuprofen sodium (IBU<sub>Na</sub>) in development has demonstrated faster absorption compared with standard IBU tablets, and similar absorption to that found with solubilized IBU. The purpose of this investigation was to compare the overall efficacy and onset of analgesia of IBU<sub>Na</sub> with standard IBU tablets in the third molar extraction model of dental pain.

### Method

Randomized, double-blind, parallel-group, single-center, 8-hour, inpatient study enrolled healthy adults 16-40 years old undergoing extraction of  $\geq 2$  third molars, with  $\geq 1$  impacted in bone. Eligible subjects with  $\geq$  moderate baseline pain after surgery were randomized 2:2:2:1 to single-dose IBU<sub>Na</sub> (2x256 mg; equivalent to 400 mg IBU), Advil<sup>®</sup> (IBU<sub>Adv</sub>; 2x200 mg), Motrin<sup>®</sup> (IBU<sub>Mot</sub>; 2x200 mg), or placebo, stratified by pain severity and gender. Double stopwatch methodology was used to evaluate time to first perceptible pain relief (TFPR) and time to meaningful pain relief (TMPR). At intervals through 8 hours postdose, subjects reported pain severity (4-point Categorical Pain Severity Rating Scale from 0 = none to 3 = severe) and pain relief (5-point Categorical Pain Relief Rating Scale; 0 = no relief to 4 = complete relief). Primary endpoints were the sum of pain relief and pain intensity difference (PID) scores from 0-8 hours (SPRID 0-8) for IBU<sub>Na</sub> vs placebo and TMPR. Secondary endpoints included TFPR; pain relief (PR) rating, PID, sum of PR and PID (PRID), cumulative proportion of subjects achieving MPR, FPR, and complete relief, and duration of relief at multiple time points from 0-8 hours postdose; time-weighted sums of PID, PR (TOTPAR), and PRID scores at 2, 3, 6 and 8 hours postdose; and global evaluation of pain relief (0 = very poor to 5 = excellent) at 8 hours postdose or at rescue. Statistics included proportional hazards regression, analysis of variance, and Cochran-Mantel-Haenszel test as appropriate. To protect against overall type I error due to multiple comparisons and multiple endpoints, 2-sided treatment group comparisons at the .05 significance level were conducted sequentially.

### Results

A total of 316 eligible patients were randomized to IBU<sub>Na</sub> (n = 95), IBU<sub>Adv</sub> (n = 86), IBU<sub>Mot</sub> (n = 87), or placebo (n = 48), and were included in the efficacy and safety analyses; there were no premature discontinuations. Baseline demographics, pain scores, and surgical characteristics were comparable across treatment groups. The mean SPRID 0-8 score was significantly greater for IBU<sub>Na</sub> and the other active treatments vs placebo ( $P < .001$ ) and was similar for IBU<sub>Na</sub> compared with pooled IBU<sub>Adv</sub>/IBU<sub>Mot</sub> and individual standard IBU treatments. The IBU<sub>Na</sub> group reported TMPR significantly earlier (median 42.4 minutes) than placebo ( $> 8$  hours;  $P < .001$ ), pooled IBU<sub>Adv</sub>/IBU<sub>Mot</sub> (median, 55.3 minutes;  $P < .001$ ), and IBU<sub>Mot</sub> (median, 60.7 minutes;  $P < .001$ ), and trended faster than IBU<sub>Adv</sub> (median, 52.0 minutes;  $P = .075$ ). A significantly higher percentage of subjects achieved MPR with IBU<sub>Na</sub> vs pooled IBU<sub>Adv</sub>/IBU<sub>Mot</sub>, beginning at 30 minutes through 3 hours, as well as at 7 and 8 hours after treatment (all  $P < .05$ ). By study end, 22.9%, 95.8%, 88.4%, 94.2%, and 82.8% of subjects in the placebo, IBU<sub>Na</sub>, pooled IBU<sub>Adv</sub>/IBU<sub>Mot</sub>, IBU<sub>Adv</sub>, and IBU<sub>Mot</sub> groups, respectively, achieved MPR. Median TFPR occurred significantly earlier with IBU<sub>Na</sub> (16.4 minutes) vs placebo



(>8 hours) and vs pooled IBU<sub>Adv</sub>/IBU<sub>Mot</sub> (25.7 minutes), IBU<sub>Adv</sub> (25.1 minutes) and IBU<sub>Mot</sub> (25.8 minutes ( $P < .001$  for all)). IBU<sub>Na</sub> was superior to placebo on other secondary endpoints, including SPRID scores over 2, 3, and 6 hours; time to treatment failure; and global evaluation of study treatment. IBU<sub>Na</sub> was superior to pooled IBU<sub>Adv</sub>/IBU<sub>Mot</sub> and IBU<sub>Mot</sub> on SPRID 0-2 and PID at all time points except hour 6. Most adverse events reported were mild or moderate gastrointestinal disorders (eg, nausea and vomiting) and were similar across treatment groups. Additionally, there were no serious adverse events or discontinuation because of adverse events.

## Conclusions

In a third molar extraction model of dental pain, IBU<sub>Na</sub> (2x256 mg; equivalent to 400 mg IBU) led to significantly faster ( $P < .001$ ) onset of analgesia compared with standard IBU (ie, pooled IBU<sub>Adv</sub>/IBU<sub>Mot</sub>). MPR occurred  $\approx 13$  minutes earlier with IBU<sub>Na</sub> than with the pooled standard IBU; a nearly 20-minute advantage was seen for IBU<sub>Na</sub> vs IBU<sub>Mot</sub>. This novel formulation of IBU<sub>Na</sub> represents a new treatment option for rapid relief of acute pain.

## Prescription amphetamine misuse in pain patients

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### Purpose

Misuse of amphetamines is a hidden public health concern, in which the heaviest users experience many of the same problems as other illicit drug users. High doses of amphetamine increase the risk for compulsive drug abuse. Chronic amphetamine abuse has been shown to result in sleep deprivation, poor nutrition, schizophrenia, psychosis, drug dependence, cerebrovascular accidents, and death. The goal of this study is to describe the frequency of amphetamine misuse among pain patients on prescribed opioids, and the extent to which illicit substances or other medications with abuse potential were identified on urine drug testing (UDT) of these individuals.

### Method

The sample group included 1,493,012 urine samples from 666,481 individuals on prescribed opioid therapy who were drug tested at the request of their clinicians. Patients with amphetamine prescriptions were identified from the requisition. Descriptive data were collected including age, gender, medication prescription history and the results of UDT using mass spectrometry. UDT results were categorized as either coming from nonmisusers of amphetamine—individuals with a positive UDT who have an amphetamine prescription or a negative UDT without an amphetamine prescription, or as samples from misusers of amphetamine—individuals who were prescribed amphetamine but had a UDT negative for amphetamine or individuals without a prescription for amphetamine who had a UDT positive for amphetamine. The prevalence of THC, cocaine, nonprescribed opiates and sedative/hypnotics were compared amongst nonmisusers and misusers.

### Results

The mean patient age was  $49.1 \pm 13.6$  years and 45.0% were male. 30,030 (2%) samples were from individuals prescribed amphetamines, of which 64.6% had positive UDT for amphetamine. 29,788 (2%) samples tested positive for amphetamines were from those without a prescription. The total number of samples from subjects who misused amphetamine was 39,884 (2.7%) vs 1,428,921 (97.3%) who were nonmisusers.

The pattern of test results from patients with an amphetamine prescription that were found not to have amphetamine in their urine was similar to the pattern from those without a prescription for amphetamine where amphetamine was found. Likewise, the pattern of test results from individuals with a prescription for amphetamine where amphetamine was found in the UDT was similar to the patterns of test results from those without an amphetamine prescription where no amphetamine was found in the UDT.

Misusers of amphetamines were more likely than nonmisusers to have a positive UDT for cocaine (3.0% vs 2.1%; RR 1.5; 95% CI, 1.4-1.6;  $P < .001$ ) and THC (18.5% vs 10.0%; RR 1.9; 95% CI, 1.8-1.9;  $P \leq .001$ ). In addition, nonprescribed opiates (23.8% vs 14.6%; RR 1.6; 95% CI; 1.6-1.7;  $P < .001$ ) and nonprescribed sedatives/hypnotics (24.6% vs 14.5%; RR 1.7; 95% CI, 1.7-1.7;  $P < .001$ ) were also more likely to be detected among amphetamine misusers.

### Conclusions

Amphetamine misuse was found in pain patients who were tested for prescription opiates. In this population, misusers of amphetamines were more likely than nonmisusers to have UDT results that were positive for cocaine, THC, and nonprescribed medications with abuse potential.

## Assessment of the pharmacokinetics and safety of oxycodone DETERx administered intranasally in recreational opioid users

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### Purpose

Extended-release (ER) opioid formulations contain high doses of active drug in order to maintain analgesia over a prolonged dosing interval. Abusers frequently tamper with these formulations in an attempt to subvert the time-release mechanism and to access the entire drug load at once. Many conventional ER formulations are susceptible to tampering techniques such as breaking, crushing, or chewing. Crushed ER formulations can then be used intranasally (IN) to achieve rapid onset of euphoric effects.

Oxycodone DETERx is a multiparticulate, ER, abuse-deterrent, bead-in-capsule formulation designed to retain ER properties following common methods of tampering such as crushing, chewing, and preparation for intravenous (IV) injection. In previously reported studies,<sup>1,2</sup> it was shown that oxycodone DETERx beads retained their ER mechanism of drug delivery *in vitro* when subjected to crushing and grinding using readily available household utensils; both the crushed and chewed contents of oxycodone DETERx capsules were also shown to be bioequivalent to intact DETERx capsules *in vivo*. The purpose of this study was to assess the safety and the pharmacokinetics of crushed oxycodone DETERx capsule contents administered IN compared with 2 control treatments: immediate-release (IR) oxycodone powder administered IN and intact oxycodone DETERx capsules administered orally (PO).

### Method

In an open-label, randomized, active-controlled, naltrexone-blocked, 3-treatment, 3-period, crossover comparison study, the safety and pharmacokinetics of crushed oxycodone DETERx IN (40 mg), oxycodone powder IN (40 mg), and intact oxycodone DETERx PO (40 mg) were compared in nondependent, recreational opioid users experienced with IN administration of opioids. Intact study drug was administered as a single, oxycodone DETERx capsule. Crushing of oxycodone DETERx capsule contents was done using the most aggressive particle size reduction method identified in previously conducted crushing studies<sup>1</sup>. Crushed oxycodone DETERx or oxycodone powder was administered using a standardized insufflation (snorting) procedure. For Treatment Periods with IN dosing, blood samples were collected pre-dose and at 5.0, 10.0, 20.0, 30.0, 45.0 minutes and at 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 10.0, 12.0, 18.0, 24.0, 30.0, 36.0, and 48.0 hours post dose. For treatment periods with PO dosing, similar blood sampling times followed pre- and postdose except that within the first hour, only the 15- and 30-minute samples were collected. Plasma samples were analyzed using a LC-MS/MS method. Pharmacokinetic parameters  $C_{max}$ ,  $AUC_{INF}$ ,  $T_{max}$  and Abuse Quotient (AQ) were calculated. Safety and tolerability were assessed through treatment-emergent adverse events, vital signs measurements, oxygen saturation, nasal cavity assessments, hematologic, biochemical, and urinalysis laboratory parameters, and physical examinations.

### Results

A total of 13 subjects completed all treatment periods per protocol. When administered IN, mean  $C_{max}$  of the crushed DETERx capsule contents was significantly lower than that of oxycodone powder. LSMean for  $C_{max}$  of crushed oxycodone DETERx administered IN was 59.04% (90% CI: 55.37-62.96) compared with oxycodone powder administered IN. Mean  $C_{max}$  following IN administration of crushed DETERx capsule contents was also lower than that observed for the intact oxycodone DETERx capsule administered PO. LSMean for  $C_{max}$  of crushed oxycodone DETERx administered IN was 79.57% (90% CI: 72.14-87.77) compared with oxycodone DETERx administered PO. The

median  $T_{max}$  was longer for crushed DETERx capsule contents IN than for oxycodone powder IN. Median  $T_{max}$  for crushed DETERx capsule contents IN and oxycodone powder IN were 5.0 hours and 3.0 hours, respectively. Median  $T_{max}$  of oxycodone DETERx administered PO was 5.03 hours. Oxycodone powder IN had the highest AQ value (42.49 ng/ml/hr); AQ values for crushed oxycodone DETERx IN and intact oxycodone DETERx PO were of similar magnitude (8.46 and 8.37 ng/ml/hr, respectively). Although the rate of absorption for oxycodone powder IN was significantly different from the oxycodone DETERx IN and PO treatments (based on  $C_{max}$  and  $T_{max}$ ), the overall extent-of-absorption was similar for all treatments; the ratios of  $AUC_{INF}$  LSMean values for crushed oxycodone DETERx IN and intact oxycodone DETERx PO relative to oxycodone powder IN were 88.59% (90% CI: 82.48-95.15) and 95.99% (90% CI: 89.64-102.79), respectively. Adverse events were mild across the treatment groups. There were no cases of oxygen desaturation of clinical significance; clinical laboratory values, vital signs, and physical exam results were unremarkable. Nasal cavity examinations revealed need to blow nose in both IN treatment groups at early time points postdose; other nasal findings (irritation, burning, nasal discharge, facial pain/pressure, nasal congestion) were mainly mild across the IN treatments.

## Conclusions

Crushing and snorting oxycodone DETERx capsule contents produces relatively lower plasma concentrations of oxycodone compared with the intact oxycodone DETERx formulation, administered PO, and oxycodone powder, administered IN, indicating that a concentration driven euphoric effect sought by drug abusers may not be achieved after nasal administration of intact or manipulated oxycodone DETERx.

## References

1. Kopecky E, et al. Poster presented at 34<sup>th</sup> Annual Scientific Meeting of the American Pain Society, New Orleans, LA. May 2013.
2. Kopecky E, et al. Poster presented at International Conference on opioids, Boston, MA. June 2013.

## Assessment of the use of oral fluid as a matrix for drug monitoring in patients undergoing treatment for opioid addiction

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### Purpose

Drug testing is an important clinical tool available to physicians who are assessing patient compliance and effectiveness of a drug treatment program. While urine has traditionally been the sample of choice for drug monitoring, oral fluid, being a filtrate of the blood, has several advantages and has shown great promise as a sample matrix for such applications. Oral fluid collection can be accomplished without the need for highly trained medical staff and using a simple, noninvasive, oral fluid collection device, an adequate sample can be obtained in only a few minutes. There has been a significant amount of research done on the use of oral fluid for toxicology applications. However, more studies assessing the utilization of oral fluid drug testing are required to validate its use for clinical drug monitoring goals. The objective of this study was to assess the use of oral fluid as a matrix for clinical drug monitoring by comparing urine drug testing (UDT) and oral fluid drug testing (OFDT) in patients undergoing treatment for opioid addiction. This was accomplished by: 1) assessing positivity rates for drugs in simultaneously collected, paired oral fluid and urine samples from donors undergoing suboxone therapy and 2) to compare positivity rates for illicit drugs and prescription medications from 2 patient groups; one undergoing unobserved urine collections and a second that was tested following observed oral fluid collection.

### Method

Target populations of donors necessary for this study include otherwise healthy males and females between the ages of 18 and 72 who are undergoing suboxone treatment for opiate dependence. Donors were excluded from the study based on known health issues, such as impaired liver or renal function.

Quantisal<sup>TM</sup> oral fluid collection devices from Immulysis Corporation were utilized for specimen collections. These devices are designed to collect 1 mL of neat oral fluid ( $\pm 10\%$ ) from the donor as indicated by a blue color change on the collection adequacy indicator. To ensure the validity of the sample, the donor may not eat or drink for 15 minutes prior to the collection time. The swab is then placed in 3 mL of oral fluid extraction buffer (included with collection device) and capped for transport to the laboratory. Urine samples were collected into approved specimen cups according to standard UDT protocols.

Simultaneous paired oral fluid and urine samples ( $n = 120$ ) were collected from donor participants. Paired specimens were collected at 3 time points during the day at 7 AM, 12 PM, and 5 PM for 2 subsequent days.

Additionally, 2 separate groups of patients provided samples for drug monitoring. One group underwent unobserved urine collections ( $n = 4560$ ) and the second group provided observed oral fluid collections ( $n = 2368$ ).

Once received into the laboratory the oral fluid and urine samples were subjected to EMIT immunoassay screening and LC/MS-MS quantitative drug analysis.

## Results

120 paired oral fluid and urine samples were collected from compliant donor patients at a high volume suboxone clinic and levels of buprenorphine, norbuprenorphine, and naloxone were determined. Additionally, a comparison of results from 6928 patients (4560 unobserved urine collection, 2368 observed oral fluid collection) monitored for heroin metabolite, amphetamine, benzodiazepines, buprenorphine, THC, cocaine, codeine, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone was completed. Results of this study indicated that timed, observed collection of simultaneous urine and oral fluid samples from patients undergoing suboxone treatment for opiate dependence exhibited a very high correlation of positivity rates between the matrices when appropriate cutoffs are applied. In contrast, comparison of comprehensive drug testing results for 4560 patients submitting to unobserved urine collection and 2368 patients undergoing observed oral fluid collection yielded significantly different results in positivity rates for several illicit drugs and prescription medications.

## Conclusions

This study was used to determine the effectiveness of OFDT as a viable drug-monitoring tool since UDT has higher potential for adulteration or substitution. An internal, anonymous survey of clinic patients indicated urine tampering during unobserved collection was common practice. Since observed urine collection is not always practical, OFDT was considered an alternative. Comparison of same-donor urine and oral fluid indicated positivity rates were in agreement. Conversely, comparison of unobserved urine vs observed oral fluid collections yielded significant differences in positivity rates for several drugs of abuse. In conclusion, OFDT effectively detected illicit drug use and noncompliance in this population.

## Identifying clinicians' practice patterns when managing opioid induced constipation in patients on long-term opioid therapy: a descriptive study to inform education needs

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### Purpose

There has been a significant increase in chronic use of opioids in the past 15 years with over 200 million prescriptions for opioids in the US annually. With increased use of opioids, more patients are presenting with opioid-induced constipation (OIC), a subset of opioid bowel dysfunction (OBD). It is estimated that 40% to 80% of chronic opioid users report constipation. Despite the high prevalence of OIC among opioid users, no formal guidelines, diagnostic criteria, or ICD-9 code exists for making a diagnosis of OIC. The purpose of this study was to describe practice patterns of US clinicians with regard to the diagnosis and management of opioid induced constipation (OIC) in adults on long-term opioid therapy and to identify relevant gaps in clinical knowledge.

### Method

To aid in survey creation, 2 focus groups were conducted using nominal group technique via a web interface and teleconference to elicit barriers that clinicians face in diagnosing and managing OIC in patients on chronic opioid therapy. These results framed a case-based survey that was administered between November 2012 to February 2013 to 327 US-based healthcare professionals including primary care physicians (n = 101), pain specialists (n = 151) and nurse practitioners (n = 75) to explore and quantitatively assess their knowledge and practice patterns with respect to the diagnosis and management of OIC in patients on long-term opioid therapy. Descriptive and inferential statistics were utilized to summarize survey responses.

### Results

The far majority (80%-96%) of respondents indicated that the most common side effect experienced with the chronic use of opioids is constipation. Clinicians included constipation (84%-92%) in the top 3 side effects that they would discuss with a patient prior to starting him or her on opioids. Forty percent of pain specialists and a third of PCPs recognized that OIC is a subset of OBD.

A prophylaxis regimen for patients starting on opioids is prescribed less than 40% of the time by half of PCPs and pain specialists and by 27% of NPs. When clinicians do prescribe prophylaxis, they are most likely to use a stool softener, an osmotic laxative, or a high fiber diet. As for initial treatment options for a patient diagnosed with OIC, clinicians are most likely to consider a stool softener, osmotic laxative, or a bulk laxative. The main factors that guide clinicians' treatment decisions for a patient with OIC are bowel movement symptoms, patient experience with previous constipation therapies, patient characteristics, patient access to medication, and patient preference.

49%-61% of clinicians feel that constipation and sedation would most likely result in discontinuation and/or poor adherence to long-term opioid therapy. Similarly, over half (51%-77%) of clinicians feel that the fear of addiction, level of pain control for the patient, and cost of medications are factors that are most likely to limit patient adherence to long-term opioid treatment.

All respondents have some degree of confidence in their ability to manage patients with OIC, however only 26%-33% were "very confident."



Clinicians indicate that the most significant barriers to the optimal management of patients with OIC are patient lack of adherence to treatment recommendations, lack of patients reporting of symptoms and the additive impact of comorbidities on constipation.

### **Conclusions**

These data highlight many gaps in the care of patients with chronic pain and OIC that can be addressed by educational, informational, or policy interventions. Clinicians would benefit from further information on the differentiation of OIC from opioid bowel dysfunction, the importance of open discussion of side effects of opioid therapy with patients at each visit, and identification of treatment choices for patients with OIC.

### Accuracy of the bead-based multiplex xTAG<sup>®</sup> CYP2D6 Kit v3

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#### Purpose

Cytochrome P4502D6 (CYP2D6), a member of the cytochrome P450 superfamily, is involved in the metabolism of drugs and other foreign compounds, as well as the catalysis of steroid hormone biosynthesis. CYP2D6 is required in metabolism of up to 25% of all prescribed medicines including  $\beta$ -blockers, antipsychotics, antidepressants, antiarrhythmic and analgesics such as VICODIN<sup>®</sup>, TYLENOL<sup>®</sup>, OxyContin<sup>®</sup>, and Ultram<sup>®</sup> (acetaminophen, hydrocodone, oxycodone and tramadol). Drug-metabolizing phenotypes can be classified into 4 groups, from lowest level of metabolism to highest level of metabolism: poor metabolizers (PMs), intermediate metabolizers (IMs), extensive metabolizers (EMs), and ultra-rapid extensive metabolizers (UMs). Four categories of alleles exist in the CYP2D6 gene: normal function (\*1 and \*2), reduced function (\*9, \*10, \*17, \*29 and \*41), nonfunctional (\*3, \*4, \*5, \*6, \*7, \*8, \*11 and \*15) and increased function (duplicated or multiduplicated alleles). As the CYP2D6 gene is highly polymorphic, detection and determination of the star genotypes for CYP2D6 can be a time consuming process. In this study, the accuracy of the FDA cleared, bead-based multiplex assay (xTAG<sup>®</sup> CYP2D6 Kit v3) developed by Luminex Toronto was evaluated. This multiplex panel is designed to simultaneously detect 17 star genotypes resulting from the combination of 21 mutations and polymorphisms, including gene duplication, within 7 hours in a single reaction. Data generated from xTAG<sup>®</sup> CYP2D6 Kit v3 may provide useful information to aid clinicians in determining strategies for therapeutics that are metabolized by the CYP2D6 gene product.

#### Method

The clinical study of the xTAG<sup>®</sup> CYP2D6 Kit v3 was evaluated using de-identified archived left-over genomic DNA originally extracted from primary clinical specimens (peripheral blood samples) with different ethnicities and the results compared to DNA sequencing. Four hundred and fifty-nine (459) clinical samples were analyzed in the first experiment. Two hundred and seventy-nine (279) clinical samples were analyzed in the second experiment: sixty-three (63) newly recruited clinical samples, and two hundred and sixteen (216) previously analyzed samples. For the rare \*8 genotype, blended \*8 plasmid samples were tested. These blended \*8 plasmid samples were prepared by the addition of plasmid DNA to genomic DNA to mimic a heterozygous sample. Bidirectional sequencing was used as the comparator method for all alleles (mutations and polymorphisms) in the study.

#### Results

Seven hundred and thirty-eight (738) data points were generated in the entire accuracy study. Accuracy of 99.6% for the first experiment and 100.0% for the second experiment were obtained for xTAG<sup>®</sup> CYP2D6 Kit v3 across all mutant and wild type alleles when compared to bidirectional sequencing.

#### Conclusions

This study demonstrated the accuracy of the xTAG<sup>®</sup> CYP2D6 Kit v3 for simultaneous detection of CYP2D6 mutations and polymorphisms. Both star genotypes and the related mutations and polymorphisms from the clinical samples can be determined in a single reaction. Additionally, the study demonstrated that a wide variety of CYP2D6 alleles exists within North American population.

**Efficacy of an outpatient, multidisciplinary VA pain management clinic: findings from a one-year outcome study**

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**Purpose**

Numerous meta-analyses and critical reviews offer clear evidence that integrated, multidisciplinary chronic pain management programs offer patients the greatest opportunity for relief of their suffering and return to functional lifestyles (Flor, Fydrich, & Turk, 1992; Guzman, Esmail, Karjalainen, et al, 2002; Turk, 2002; Turk & Okifuji, 1998). However, according to the Committee for the Accreditation of Rehabilitation Facilities (CARF), the number of accredited interdisciplinary chronic pain management programs in the US has decreased from 210 in 1998 to only 84 in 2005 (Solochek, 2005). Furthermore, multidisciplinary chronic pain management programs are becoming an "endangered species" due to third-party payers refusing reimbursement for treatment (Turk, 2006). More recent studies have confirmed that interdisciplinary programs were therapeutically effective, but "carving out" practices within these programs had a negative impact on both short-term and follow-up outcome measures (Robbins, Gatchel, Noe, et al, 2003).

The outpatient, multidisciplinary pain management clinic at Jesse Brown VA Medical Center (JBVMAC) opened in April 2009 and was originally staffed by a team of anesthesiologists, pain fellows, anesthesia residents, 2 nurses, and a clinical pharmacist. The clinic gradually expanded services in May 2009 with the addition of an osteopath physician, in September 2009 with a psychologist and physician assistant, and in May 2010 with a neurologist. In light of the unique team composition of the JBVMAC Pain Management Clinic, and in concurrence with the VA's mission to engage in evidenced-based practice, the investigators evaluated the efficacy of the outpatient, multidisciplinary pain management clinic.

**Method**

A total of 546 veterans were consulted to the JBVMAC Pain Management Clinic between February 1, 2010 and January 31, 2011. Of the consulted veterans, 359 completed the intake questionnaire only, 83 completed both the intake and discharge questionnaire, 96 completed the discharge questionnaire only, and 8 were reconsulted to the clinic during the specified time frame.

All veterans completed a pre-treatment intake, which included the Screener and Opioid Assessment for Patients with Pain (SOAPP)<sup>®</sup> Version 1.0 and the Pain Outcomes Questionnaire-VA (POQ-VA) Intake Questionnaire at the initial consult. Veterans were asked to complete the POQ-VA Discharge Questionnaire upon completion of treatment and subsequent discharge from the pain clinic. Veterans voluntarily participated in the treatment provided and were free to withdraw at any time. The current study protocol was reviewed and approved by the affiliated university's Institutional Review Board and the VA's Research & Development office. A waiver of informed consent was granted due to the retrospective nature of the study and the minimal risk to subjects who participated.

Primary endpoints included the change from intake to discharge in the subscales of "Pain," "Mobility," "Activities of Daily Living (ADLs)," "Negative Affect (NA)," and "Fear." Secondary endpoints included average patient satisfaction in treatment and change from intake to discharge in self-reported current use, average duration of use, and average degree of pain relief of opioid medications. Descriptive statistics, repeated measures, paired sample t-tests, and chi-squared tests were used to assess if the difference between outcome measures were statistically significant.

## Results

The majority of veterans (64%) reported a "severe" baseline pain severity (corresponding to a pain score of 7-10 at intake). One hundred sixty-three patients (30%) indicated that low back pain was the pain location most interfering with life while 124 patients (23%) reported more than one location.

At baseline, the average SOAPP score was  $10.47 \pm 8.28$ , indicating that the veterans may require a higher level of monitoring (ie, smaller prescriptions, more frequent visits, referral to a specialist, etc) when prescribing opioids. At intake, 341 patients reported taking opioids regularly while 182 reported not taking any opioids. Those taking opioids reported an average duration of therapy of four and a half years ( $54.39 \pm 83.03$  months) and reported an average degree of relief with opioid use of  $2.57 \pm 0.80$ , with "0" (no relief) and "10" (complete relief).

Patients had a statistically significant decrease in average "Pain" severity from 7.36 to 6.99 ( $P = .000$ ). There were also statistically significant improvements in "Mobility" ( $P = .000$ ), "ADLs" ( $P = .001$ ), "Vitality" ( $P = .000$ ), and "NA" ( $P = .000$ ). There was no significant difference in "Fear" ( $P = .132$ ). There was also a significant decrease in total POQ-VA score ( $P = .000$ ). The number of patients on chronic opioids significantly decreased from 341 to 335 at intake to discharge ( $P = .000$ ). The average duration of opioid therapy did not change, but the average degree of relief increased.

One-hundred eighty patients completed the patient satisfaction questions on the discharge questionnaire on a scale from "0" (no/not recommended) to "10" (complete/strongly recommended). The average score for overall treatment received in the pain clinic was  $8.56 \pm 2.20$ . The average score for patients' perception of staff was  $9.32 \pm 1.51$  and staff competence was  $9.33 \pm 1.41$ . The average score for clinic accessibility was  $8.86 \pm 2.02$  and for pain referrals to others was  $9.04 \pm 2.00$ .

## Conclusions

Patients enrolled in the JBVAMC outpatient, multidisciplinary Pain Management Clinic made significant, albeit small improvements in most of the core POQ-VA Questionnaire outcome measures. There were also fewer patients taking opioids by the end of the study, and those who remained on opioids reported higher relief with opioid use, perhaps in combination with the other treatment modalities implemented in the pain clinic.

Patients discharged from the JBVAMC pain clinic also reported high levels of satisfaction with the care they received.

Despite some limitations, this study shows that participation in an outpatient, multidisciplinary VA pain management clinic resulted in overall improvement.

## Provider perspectives of the value of patient education websites

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### Purpose

In the past decade, the use of computers and the internet has skyrocketed—as has their use as a source of health information. In 2011, 75.6% of American households reported having a computer and 71.7% reported having an internet connection (US Census). The increased availability of internet access has also increased the number of people looking for information related to their health care online (Pew, 2009). In 2001, 40% of US adults reported using the internet to find health information and in 2010 over 50% reported using the internet for this purpose (Bessiere, 2010).

Because of the increase in autonomy to find health information, it is imperative that patients are able to access correct health information and find websites that cover self-management. Studies have shown that computer based education for patients can improve patient knowledge, and skill development (Portnoy, 2008). For patients to benefit from online resources, they must access websites that are accurate, informative, and helpful. Healthcare providers, as trusted, knowledgeable resources are in a great position to recommend websites which would be most beneficial to their patients. However, little research has been done on this topic.

While there are many tools for the dissemination of patient education, this study focused on online education; specifically, how providers are finding out about patient education websites, what websites they are recommending to their patients, and what factors might support or inhibit recommendations of patient education websites.

### Method

A literature search was conducted using PubMed and Google Scholar to find articles related to the dissemination of patient education materials from providers to patients. No articles were found specifically addressing this topic, however there were 13 articles found relating to the dissemination of research and clinical findings into medical practice. Six of these articles specifically articulated themes related to barriers physicians may face in translating research findings and recommendations into practice. We compiled a list of 28 possible barriers listed among the 6 articles then discussed how each barrier could be related to provider dissemination of educational materials. We developed 17 items about the reasons providers would or would not provide patient education websites to their patients. Items were answered on 5 point Likert scale from Strongly Disagree (1) to Strongly Agree (5).

### Results

The sample consisted of 11 arthritis pain health experts. We focused our analysis on the 8 respondents who reported that they recommend patient education websites to their patients. All of the providers said they are aware of existing patient education websites, and 75% are familiar with the types of information on those sites. These providers also reported that they believe it is helpful to their patients to recommend these websites (88%), and that patients are interested in receiving these materials (100%). Providers are also confident in the quality of information on the websites and agree that their patients will obtain accurate information (75%). Also, providers believe that patients will still come to them with questions even if the patients are given education websites (75%).

Of the 3 respondents who do not recommend patient education websites, some of their concerns include: that recommending these websites is not helpful to the patients; they are not confident in their ability to recommend good websites; and they do not have time to recommend the websites to their patients.

## Conclusions

This pilot study contributes preliminary data on why providers may or may not recommend patient education websites. This can help to encourage other providers to recommend these materials in the future. The study limitations include that our study population were pain experts who were recruited through an online education tool, and asked to give feedback on an online program. We believe these methods attracted more people who are interested in online patient education. Further research is needed with a more diverse provider population to assess factors that may affect provider's dissemination of patient education websites.

**Sensorium: an immersive virtual environment for relaxation and stress management**

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**Purpose**

Sensorium is an immersive virtual reality (VR) system designed and developed by 3 senior undergraduate student researchers that renders visible inner states by changing visual and aural stimuli in a virtual environment according to bodily responses. Using galvanic skin response (GSR) technology, the system provides users with a way to reduce their stress in a fun and safe environment by understanding and learning how to change their psychophysiological states. The results of our study suggest that immersive VR that integrates biofeedback technology promotes relaxation through associative cause and effect. Astonishingly, 99% of users reported their relaxation improved after their virtual reality session with Sensorium, leading to reduced stress. Literature supporting this finding indicates a reduction in stress facilitates a reduction in symptoms of pain, therefore supporting to the existing paradigm of the pain studies lab at Simon Fraser University that virtual reality and biofeedback can be used to promote meditative practices.

**Method**

For the study, participants rated their levels of relaxation from 1 (very stressed) to 10 (very relaxed) on a Likert scale. They were run through the experiment for 5 minutes with solely the GSR attached in order to gain a baseline reading. Following this, they put on our head-mounted display and engaged in the world for another ten minutes, giving them the opportunity to look around and experiment controlling how relaxed they were. After the experiment, the participant filled out a final survey with questions about their experience and how effective the system was for facilitating their relaxation.

**Results**

The result for the mean value for the pre-session relaxation level was 5.857 (SD = 1.925), and the mean for the postsession relaxation level was 6.900 (SD = 1.364). Postsession data shows that none of the users who reported a pre-session relaxation level of less than 5 left with an equal or increased level of stress. Notably, 64% of participants agreed that spending time in the VE was beneficial for entering a meditative state. After running a t-test, we found a significant effect for the use of VR on relaxation levels:  $t(72) = 4.43$  with  $P < .0001$ . Aspects of the VE that had a strong impact on relaxation according to quantitative and qualitative data include: a synthesized auditory musical element attached to the GSR reading, the swaying of the grass, and the leaves falling from the trees. The next step is to reduce the complexity of the VE in response to user feedback.

**Conclusions**

To advance the evidence of the benefits of Sensorium, we plan to test it with people who are living with chronic pain. We anticipate that by introducing Sensorium to this group, participants will have the opportunity to learn about their psychophysiological states, shape an improved sense of agency they have over their bodily pain, and learn coping strategies to relieve stress with techniques such as mindfulness-based stress reduction (MBSR).

## Effect of topical diclofenac (Pennsaid) on clinical neuropathic pain

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### Purpose

Neuropathic pain is a chronic pain condition that results from injury or disease of the peripheral and/or central nervous system. Despite extensive research over the last several decades, neuropathic pain remains difficult to manage. One of the primary reasons is the lack of effective pharmacotherapy for neuropathic pain conditions. Although several categories of medications such as tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, anticonvulsants and opioids are currently being used, their efficacy remains largely uncertain. Importantly, there is a significant heterogeneity with regard to the clinical presentation and associated comorbidity of patients suffering from neuropathic pain. On the other, the role of NSAIDs in neuropathic pain management has been proposed although its clinical efficacy, particularly its topic effect, remains unknown.

The study objective was to gather preliminary data to determine whether topical diclofenac (Pennsaid) would reduce clinical pain and improve both quantitative sensory testing (QST) and functional status in subjects with peripheral neuropathic pain.

### Method

After IRB approval, we conducted a prospective, randomized, double-blinded placebo-controlled, crossover study to examine whether Pennsaid would improve peripheral neuropathic pain. Subjects who met the inclusion criteria were randomized to receive placebo or Pennsaid during the first phase and then be crossed over into the second phase to receive Pennsaid or placebo. Subjects with neuropathic pain conditions, specifically who have the clinical features of postherpetic neuralgia (PHN) and complex regional pain syndrome (CRPS) were included. The study period was between May of 2012 and March of 2013. We gathered the demographic information, pain history, SF-36, QST data (warm threshold, heat pain threshold, heat pain tolerance, temporal summation to a train of 4 identical thermal stimuli). The entire study took 5 weeks (phase I: 2 weeks; washout: 1 week; phase II: 2 weeks) including 4 office visits and 2 phone interviews. Paired t-test was used to compare outcomes before and after Pennsaid or placebo treatment. A *P*-value of  $< .05$  is considered to be statistically significant (\*).

### Results

Twenty-eight subjects completed the study, including 12 male and 16 female subjects with the mean age of 48.8 (22-68y); 3 had PHN and 25 had CRPS. After 2 weeks of topical application of Pennsaid, subjects with neuropathic pain showed reduced VAS pain score (before:  $5.7 \pm 0.3$ ; after:  $4.8 \pm 0.3$ ;  $P < .05$ ), decreased constant (before:  $5.2 \pm 0.5$ ; after:  $4.0 \pm 0.5$ ;  $P < .05$ ) and burning (before:  $4.3 \pm 0.5$ ; after:  $2.7 \pm 0.5$ ;  $P < .05$ ) types of pain, as well as decreased self-reported hypersensitivity of the painful area (before:  $3.8 \pm 0.6$ ; after:  $2.7 \pm 0.5$ ;  $P < .05$ ). This self-reported improvement was accompanied by a positive change in QST results, reflected by a decrease in pain summation (a correlate of the wind-up phenomenon). In contrast, there were no differences in both clinical and QST outcomes in the same subjects before and after a 2-week application of placebo (DMSO). There were no reported complications in subjects treated with either Pennsaid or placebo.

### Conclusions



The data from this preliminary, prospective, randomized, double-blind, and placebo-controlled cross-over study indicate that application of topical diclofenac lotion (Pennsaid) could reduce clinical pain of neuropathic characteristics. This reduction of clinical pain also corresponds with a decrease in pain summation as measured by QST, a psychophysical measurement of pain sensitivity.

## Lubiprostone for treatment of opioid-induced constipation does not interfere with opioid analgesic effects in patients with noncancer pain

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### Purpose

This posthoc analysis of pooled data from three 12-week, randomized, double-blind, placebo-controlled trials evaluated whether oral lubiprostone, approved in April, 2013 for the treatment of opioid-induced constipation (OIC) in adults with chronic noncancer pain, interferes with opioid analgesia.

### Method

Patients  $\geq 18$  years old on a stable opioid dose and having  $< 3$  spontaneous bowel movements per week were randomized to twice-daily (BID) lubiprostone 24 mcg ( $n = 659$ ) or placebo ( $n = 641$ ). In one trial, patients receiving diphenylheptane opioids (methadone or propoxyphene) were excluded. Analgesic interference was assessed using patient-reported Brief Pain Inventory-Short Form (BPI-SF) scores and by changes in morphine-equivalent daily (ie, opioid) dose (MEDD). Scores for the BPI-SF domains of pain interference and pain severity (including "worst pain") could range from zero (none) to 10 (maximum).

### Results

Mean BPI-SF domain scores were similar between the lubiprostone and placebo groups at baseline; these scores remained generally stable and were similar between the groups at months 1, 2, and 3. The mean changes from baseline in BPI-SF scores were statistically similar between treatment groups at each month. The mean changes from baseline in MEDD were also statistically similar between treatment groups at each month.

### Conclusions

Lubiprostone 24 mcg BID did not interfere with the analgesic effect of opioids in adult patients with chronic noncancer pain and OIC.

## Lubiprostone significantly improves constipation induced by nonmethadone opioids in patients with chronic, noncancer pain: results from a phase 3, randomized, double-blind, placebo-controlled clinical trial

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### Purpose

Opioid-induced constipation (OIC) is a common and debilitating side effect of long-term opioid use. Lubiprostone, a locally acting chloride channel (ClC-2) activator, has been shown previously to counteract the adverse gastrointestinal effects of nonmethadone opioids by promoting secretion of fluid and chloride into the intestinal tract, facilitating motility and bowel movements. Lubiprostone is indicated for the treatment of chronic idiopathic constipation (24 mcg twice daily [BID]) in adults and irritable bowel syndrome with constipation in adult women (8 mcg BID); lubiprostone was approved for the treatment of OIC in adults with chronic noncancer pain (24 mcg BID) in April 2013. The current study presents a placebo-controlled, phase 3 trial of orally administered lubiprostone in patients with OIC taking opioids for chronic noncancer pain.

### Method

This randomized, double-blind, placebo-controlled safety and efficacy study was conducted at 103 sites in the United States and Europe between December 2010 and November 2011. Adult men and nonpregnant, nonlactating women with confirmed OIC were randomized evenly to receive either lubiprostone 24 mcg BID or placebo BID for 12 weeks. Inclusion criteria required consistent treatment with a full-agonist opioid, other than methadone or another diphenylheptane opioid, from at least 30 days prior to screening and throughout the study. Patients must also have reported, on average, less than 3 spontaneous bowel movements (SBMs)/week during the screening period, and  $\geq 1$  of the following symptoms for  $\geq 25\%$  SBMs during the same period: hard to very hard stools, sensation of incomplete evacuation, or moderate to very moderate straining. The primary efficacy endpoint was the overall SBM response rate, defined as having 3 or more SBMs per week for at least 9 weeks, and at least 1 additional SBM over mean baseline SBM frequency during every treatment week with observed data. Those patients with fewer than 9 weeks of observed data were automatically considered nonresponders. Secondary endpoints included changes from baseline in weekly, monthly, and overall SBM frequency; time to first SBM; and overall mean changes from baseline in OIC-related symptoms. For the primary efficacy endpoint, groups were compared using the Cochran-Mantel-Haenszel method, stratified by pooled site. All statistical tests were 2-tailed with a significance level of  $\alpha = 0.05$ .

### Results

In total, 431 patients were randomized to treatment with lubiprostone or placebo. Significantly more patients in the lubiprostone group than in the placebo group were overall SBM responders during the 12-week treatment period (27.1% vs 18.9%;  $P = .030$ ). Overall, weekly mean changes from baseline in SBM frequencies demonstrated the superiority of lubiprostone over placebo overall and at every treatment week, with statistical significance achieved overall ( $P = .001$ ) and at 9 of the 12 treatment weeks ( $P \leq .040$ ). In addition, median time to first SBM was significantly shorter for patients treated with lubiprostone vs placebo (23.5 vs 37.7 hours;  $P = .004$ ), with a significantly higher proportion of patients treated with lubiprostone reporting their first SBM within 24 ( $P = .008$ ) and 48 ( $P = .007$ ) hours after the first dose compared with placebo. Straining, stool consistency, and constipation severity were also statistically significantly improved in patients treated with lubiprostone vs placebo ( $P = .004$ ,  $P < .001$ , and  $P = .010$ , respectively). The most common adverse events (AEs) reported by patients treated with lubiprostone were

diarrhea (11.3%), nausea (9.9%), and abdominal pain (7.1%); among patients who received placebo, the corresponding incidences of these AEs were 3.8%, 4.7%, and 0.0%, respectively. The incidence of serious AEs (SAEs) was similar in the placebo (2.8%) and lubiprostone (3.3%) groups; no SAEs were considered related to treatment with lubiprostone.

### **Conclusions**

Lubiprostone significantly improved SBM response and OIC symptoms in patients with OIC and chronic noncancer pain in this 12-week, placebo-controlled study. Lubiprostone was well tolerated in this patient population.

## Prescribing opioid treatment and abuse-deterrent formulations: a perspective from pain specialists

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### Purpose

Prescription opioids can be subject to misuse, abuse, and diversion for nonmedical use. The scope of problems and consequences, including death and healthcare burden, is substantial. Prescription opioids are involved in an alarming proportion of pharmaceutical-related overdose deaths. Gaining an understanding of the factors that influence how opioids are prescribed and the perceived need for abuse-deterrent formulations is relevant for reaching optimal prescribing practices and treatment outcomes. A survey of healthcare providers was conducted with the aim of describing some attitudes and perceptions related to mitigating the risks associated with prescription opioid treatment and the use of abuse-deterrent formulations.

### Method

Attendees of 2 live symposia were surveyed using a written feedback form at the conclusion of national pain specialist conferences in April and May 2013. The survey questions were presented to a sample of 210 audience members; this group was predominantly composed of practicing pain specialists. The survey and symposia were sponsored by Pfizer.

Attendees were asked to indicate their level of agreement with 5 statements related to mitigating the risks associated with prescription opioid therapy:

- Prescription opioid medications are just one treatment option and should not be used first line for most patients.
- Managing the potential for prescription opioid misuse, abuse, and diversion is a real concern in my practice.
- Risk-mitigation strategies should be applied universally to all candidates for prescription opioid therapy.
- There is a need for practical office-based tools to help me employ opioid risk-mitigation strategies.
- Abuse-deterrent formulations should be considered when prescribing opioid therapy.

Respondents indicated their level of agreement on a 7-point scale, with 1 representing "Strongly Disagree" and 7 representing "Strongly Agree." Written feedback forms were obtained from 40% of symposia attendees (n = 83). The number of respondents varied per question, and all data were summarized using descriptive statistics.

### Results

Seventy percent (52/74) of respondents indicated strong agreement (a rating of 6 or 7 on a 7-point scale) that prescription opioid medications should not be used first line for most patients. Eighty percent (55/69) indicated strong agreement that managing the potential for misuse, abuse, and diversion is a real concern in their practice setting. Seventy-nine percent (58/73) indicated strong agreement that risk-mitigation strategies should be applied universally with all candidates for prescription opioid therapy. Seventy-five percent (55/73) indicated strong agreement that there is a need for practical office-based tools to facilitate implementation of risk-mitigation strategies. Lastly, 81% (60/74) indicated strong agreement that abuse-deterrent formulations should be considered when prescribing opioid therapy. The proportion of respondents indicating disagreement (ratings of 1, 2, or 3 on a 7-point scale) was very low across all 5 statements, ranging from 3% to 8%.

## Conclusions

Prescribing chronic opioid therapy requires understanding of the risk for misuse, abuse, and diversion. The survey results suggest a need for education around placement of opioid therapies among other therapies. The findings reveal significant concern regarding misuse, abuse, and diversion of prescription opioids in the practice setting. Additionally, the survey highlights the need for office-based tools to facilitate risk-mitigation strategies. Respondents also showed a high level of willingness to universally apply risk-mitigation strategies and incorporate abuse-deterrent formulations as a component of risk mitigation. Further research is needed with larger sample sizes and across additional physician groups who prescribe opioid therapy.

## Successfully improving the practice of chronic pain management: an innovative personalized education approach

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### Purpose

Continuing medical education (CME) can help physicians sharpen their skills at assessing and treating patients with chronic pain and improve patient outcomes. Traditionally, this has been done through self-assessment and self-directed learning models. However, recent research has shown that physicians have limited ability to accurately assess their own needs. Physicians often participate in education that reinforces what they already know and are less likely to identify programs that target unmet needs. Recent research has also demonstrated that tailored content that matches the needs of learners is often more effective than more generic information. To provide tailored content specific to the needs of primary care physicians (PCPs) involved in the management of chronic pain, Medscape, LLC and CE Outcomes, LLC, developed an innovative online learning model called the Personalized Learning Program. This program intended to address the following identified education gaps: limited ability to use validated instruments for pain assessment and appropriate patient conversations to identify the type, severity, intensity, duration and underlying pathophysiology of the chronic pain; lack of patient communication on functional goal setting related to chronic pain as a part of the treatment regimen and to provide access to multidisciplinary resources; and limited competency in prescribing appropriate pain therapies based on an understanding of the underlying pathophysiology of different pain conditions and the mechanisms of action of treatments, as well as the ability to navigate multiple and sometimes conflicting guidelines on the treatment of chronic pain.

### Method

PCPs completed an online, baseline clinical self-assessment intended to identify their practice gaps from current evidence-based guidelines and recommendations in the management of chronic pain. On the basis of the results of the self-assessment, PCPs were provided an individualized learning plan. Each plan included links up to 6 CME activities that were developed by Medscape, LLC to specifically address the educational gaps, skills or performance needs of PCPs involved with chronic pain management. At the conclusion of each activity, learners were presented with postassessment questions which were replicated from the baseline self-assessment and aligned to that activity. Responses to the baseline self-assessment and postassessment questions were then analyzed. Comparisons were made between the responses of each physician to the baseline self-assessment with the responses of the same physician following participation in the education, in order to demonstrate improvement in knowledge and performance decisions associated with the education. The differences between baseline self-assessment and postassessment responses for each matched PCP set were aggregated as a measure of the impact of the education. Additionally, the PCP learner sample was compared to a demographically similar group of PCPs who did not participate in the education, to serve as the control group. Data for the control group were captured through the distribution of the baseline self-assessment survey among a random sample obtained from a proprietary database of PCPs.

### Results

Participants of this educational curriculum (N = 277) were 36% more likely to make evidence-based decisions in chronic pain management (actual effect size of 0.55). Participants postactivity compared to participants at baseline were more likely to select the Brief Pain Inventory questionnaire to characterize how a patient's pain impacts daily function (46% vs 15%,  $P < .001$ ), and to conduct a thorough physical examination for patients with chronic pain prior to developing a treatment plan (76% vs 64%,  $P = .02$ ). Participants postactivity were more likely to utilize a form to identify achievable goals prior to determining the treatment regimen (72% vs 47% baseline,  $P = .001$ ; vs 35%

controls,  $P < .001$ ), and to accurately recognize physiologic chronic pain (21% vs 6%,  $P = .05$ ). More participants postactivity compared to baseline participants indicated that a preferred strategy for a patient presenting with chronic pain and inadequate relief on current opioid therapy would be to establish realistic goals (74% vs 32%,  $P = .002$ ). Participants postactivity were more likely to recognize that NSAIDs are not recommended for neuropathic pain (84% vs 30% baseline,  $P < .001$ ; vs 38% controls,  $P < .001$ ), to categorize non-CNS tissue damage as nociceptive pain (postactivity 59% vs 80%,  $P = .002$ ; vs controls 58%,  $P = .01$ ), to select the Neuropathic Pain Questionnaire as the most appropriate assessment tool for a patient with neuropathic pain (82% vs 61% baseline,  $P < .001$ ; vs 50% controls,  $P < .001$ ), to recognize that treatment plans should include discussion of functional goals and treatment expectations (95% vs 85% baseline,  $P < .001$ ; vs 87% controls,  $P = .02$ ), and to select serotonin-norepinephrine reuptake inhibitors as an appropriate class of antidepressants for treating low back pain (69% vs 28% baseline,  $P < .001$ ; vs 47% controls,  $P < .001$ ).

## Conclusions

Tailored education that identifies specific educational needs of physician learners and then guides them to activities and resources that address those needs, rather than reinforcing information they have already mastered, is a unique and innovative approach to online instructional design. Such an individualized approach to online CME education can result in significant increases in evidence-based practices among PCPs related to the assessment, diagnosis and treatment of patients with chronic pain.



**KP201. A novel opioid pain therapy with reduced abuse potential and improved safety**

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**Purpose**

The misuse, abuse and diversion of opioid pain medications have continuously increased for over a decade. In 2008, for the first time, more deaths were caused by drug overdoses in the US than by motor vehicle accidents. The majority of these drugs were prescription pain killers. As a result, physicians, the FDA, lawmakers and advocacy groups have expressed an urgent need for abuse-deterrent pain treatments.

**Method**

Typical approaches to reduce abuse have been through formulations, which have demonstrated some success but still represent only a marginal improvement over nonabuse-deterrent products. KP201 is a novel prodrug of hydrocodone, which, when taken orally as indicated, is hydrolyzed during first-pass metabolism to release the active opioid. The enzymatic hydrolysis, however, is significantly less efficient after intranasal administration compared to the oral route. KP201's inherent molecular properties provide a differential and preferred way to address narcotic abuse.

**Results**

Preclinical studies suggest that KP201 has unique abuse-deterrent properties that significantly limit the exposure to hydrocodone upon intranasal administration. Despite having the same oral bioavailability as currently marketed, immediate release hydrocodone products, KP201 is poorly water soluble and thus cannot be efficiently formulated for intravenous injection, another route of opioid abuse. In addition, KP201 is resistant to chemical and physical extraction methods.

Besides its abuse-deterrent features, KP201 also has the potential to prevent or reduce opioid-induced constipation (OIC) which afflicts a large number of patients receiving opioid therapy. Unlike peripheral  $\mu$ -opioid receptor antagonists intended to compensate for the constipatory effects of concomitantly administered opioid pain treatments, data from a validated motility study in rats suggest that KP201 may not cause OIC in the first place, because it is pharmacologically inactive and thus does not interact with the enteric  $\mu$ -opioid receptors.

**Conclusions**

KP201 is a novel hydrocodone prodrug with abuse-deterrent properties that is also tamper resistant and has the potential to reduce or prevent opioid-induced constipation.

## Effect of banning office dispensing of controlled Substances II-III in Florida

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### Purpose

In 2010, Florida was the overwhelming leader nationwide in controlled substance dispensing. This resulted in an annual increase in statewide prescription drug related deaths from 2007-2011. Most significant, due to its popularity on the "street", was oxycodone. Partially in response to this, the state of Florida legislature adopted House Bill 7095 which took effect July 1, 2011. This bill, among other regulatory aspects over pain clinics, banned dispensing of Schedule II and III substances from offices. This abstract will outline the effect that banning office dispensing of CS II-III had on overall dispensing of oxycodone, as well as prescribing of CS II-III to workers compensation (WC) patients.

### Method

Automation of Reports and Consolidated Orders System (ARCOS) monitors DEA controlled substances from their point of manufacture until reaching the retail dispensing site. ARCOS data was used to analyze the annual amounts of oxycodone dispensed in the state from 2009-2012. WC information was extracted from the Medi-Span<sup>®</sup> database.

### Results

In 2010, ARCOS data showed that 90 of the top 100 (and 49 of the top 50) oxycodone purchasing physicians in the nation were located in Florida. In 2011 only 13 dispensers on that list were located in Florida. No Florida doctors are on that list in 2013. Oxycodone purchases by physicians decreased 98% when comparing January-September 2010 and the same period in 2011. Pharmacy purchases during that same period decreased by 9%. For WC patients seen 3-6 months after operation or injury, 26.7% were dispensed CSII-III medication in the 6 month period before the ban. After the onset of the ban 22.6% of WC patients were prescribed CSII-III medications.

### Conclusions

Many aspects of pain clinic practice were affected by state of Florida legislative reform, such as implementation of an electronic prescription drug monitoring system, professional and educational physician requirements, implementation of medical care guidelines and establishing criminal penalties for violations. While these contributed to the decrease, banning CS II-III dispensing from offices directly resulted in a decrease in oxycodone dispensing in Florida. The ban on dispensing resulted in a decrease in prescribing CS II-III to workers compensation patients.

## Characteristics of patients treated with extended-release tapentadol since market launch: a retrospective analysis of administrative claims from a large, national health plan

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### Purpose

Approximately 100 million Americans experience chronic pain at an annual costs estimated at \$560-\$635 billion in 2010 dollars ( \$261-\$300 billion in healthcare costs and \$297-\$336 billion in lost productivity; Institute of Medicine, 2011). Opioids are the mainstay treatment for moderate to severe pain (Chou, et al, 2009), with long-acting formulations commonly used to treat chronic pain, defined as pain that lasts for at least 3 to 6 months. Extended-release tapentadol (TAP ER), available since September 2011, is a mu-opioid agonist and norepinephrine reuptake inhibitor indicated for the management of moderate to severe chronic pain and neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults. Given that TAP ER is the first new molecular entity in the long-acting opioid (LAO) market in many years, there is a paucity of information on its real-world use, specifically data on the characteristics of patients receiving TAP ER. The purpose of this analysis was to characterize patients treated with TAP ER and to compare their demographic and health status characteristics with those prescribed 2 of the most commonly prescribed branded long-acting opioids, oxycodone CR (OXY CR) or oxymorphone ER (OPN ER), using data elements available from administrative claims.

### Method

This retrospective analysis used administrative claims data from a large national health plan. The study population comprised adult commercial and Medicare Advantage members with  $\geq 3$  pharmacy claims for either TAP ER, OXY CR, or OPN ER from September 2011 through November 2012. The first observed claim for one of the LAOs of interest served as the "index LAO" and the fill date served as the "index date." All patients were required to: (1) have continuous enrollment in the health plan for 180 days before and 120 days after the index date (baseline and follow-up periods, respectively); and (2) have no claims for the index LAO during baseline. Demographic characteristics of interest included age, sex, and insurance type. Health status variables (measured during baseline) included general comorbidities, Charlson comorbidity index (CCI) score (Quan, et al, 2011) and individual chronic pain conditions: arthritis/arthropathies, back pain, cancer, migraine, musculoskeletal pain (other than back pain), and neuropathic pain. Chronic pain conditions were identified by the presence of at least 2 medical claims with relevant International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes that were at least 30 days apart. Demographic characteristics were compared descriptively between the TAP ER cohort and each of the OXY CR and OPN ER cohorts using t-tests for continuous variables and chi-square statistics for categorical variables. A Bonferroni approximation adjusted for multiple paired comparisons (Abdi 2007); the adjusted *P*-value was equal to  $\alpha/\text{number of comparisons}$ , or 0.025 (0.05/2). No additional analytic adjustments were performed.

### Results

A total of 666 TAP ER, 6,627 OXY CR, and 1,229 OPN ER patients met all aforementioned inclusion criteria and were assigned to the cohorts of interest. The mean (standard deviation) ages (years) were 51.2 (12.8), 55.8 (14.2), and 50.9 (12.4), in the TAP ER, OXY CR, and OPN ER cohorts, respectively ( $P < .001$  TAP ER vs OXY CR). The TAP ER cohort had a higher percentage of females (62.3%) than either the OXY CR (50.9%) and OPN ER (52.5%) cohorts (both at  $P < .001$ ). The most prevalent chronic pain conditions observed for the TAP ER cohort were back pain (70%), neuropathic pain (41%), arthritis/arthropathies (33%), and musculoskeletal pain (30%). TAP ER patients had

significantly higher rates of back pain than OXY CR patients (70% vs 50%,  $P < .001$ ) and higher rates of neuropathic pain than either OXY CR or OPN ER (41% vs 23% or 32%, respectively, both  $P < .001$ ).

### **Conclusions**

In this analysis of the first months of real world utilization of TAP ER, back pain and neuropathic pain were the most commonly occurring pain conditions, each present at higher rates compared with the rates in the other index LAO cohorts. TAP ER patients were also significantly more likely to be female than patients receiving OXY CR or OPN ER. These findings, representing early use of a new product, may change over time as prescribers gain additional experience with this therapy.

## A comparison of the daily average consumption (DACON) and pharmacy costs of 3 commonly prescribed oral long-acting opioids: tapentadol ER, oxycodone CR, and oxymorphone ER

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### Purpose

Chronic pain has been estimated to impact up to 40% of Americans and can result in substantial healthcare utilization and absenteeism. Long-acting opioids (LAOs) are a mainstay of treatment for patients with chronic pain. Compared to short-acting opioids, the sustained release twice daily dosing of LAOs may provide improved pain control. Two commonly used LAOs for patients with chronic pain are oxycodone controlled release (CR) and oxymorphone extended release (ER). Studies of these LAOs suggest that patients may increase their initially prescribed dosage over time (ie, dosage creep), and their daily average consumption (DACON) may exceed the expected 2 tablets per day. Additionally, increased medication use has cost implications. Payers have implemented a variety of programs to ensure appropriate use of LAOs, including prior authorizations and quantity limits. Currently, it is unclear whether the same degree of dosage creep or DACON above 2 tablets daily applies to tapentadol ER, an oral LAO approved for the management of moderate to severe chronic pain in adults. This study evaluates medication utilization patterns and pharmacy costs for tapentadol ER compared to oxycodone CR and oxymorphone ER users.

### Method

Pharmacy claims from the Source Healthcare Analytics database from 03/2011-08/2012 were analyzed. The first dispensing of an oral LAO (index medication: tapentadol ER, oxycodone CR, or oxymorphone ER) was defined as the index date. LAO users  $\geq 18$  years old, with  $\geq 180$  days of clinical activity prior to the index date,  $\geq 120$  days of clinical activity following treatment initiation, and receiving at least 90 days therapy of the index medication were included. The initial 30 days postindex date was used as a titration period and the subsequent 90 days were used for the DACON measurement. LAO users were required to have at least 90 days of the index medication during the DACON measurement period and were excluded if other LAOs were used. All comparisons contrasted the tapentadol ER group to the oxycodone CR and oxymorphone ER groups separately. The primary objective was to compare the DACON, a measure of the average number of tablets dispensed per patient per day, between the comparison groups during the 90-day measurement period. The results were also generated among the subset of users using the highest tablet dosage strength (tapentadol ER 250 mg; oxycodone CR 80 mg; oxymorphone ER 40 mg). In addition, the mean dose increase from first to last dispensing and the mean drug costs (based on wholesale acquisition costs) were compared during the 90-day measurement period. Statistical inference was assessed using chi-square tests for categorical variables and Student's t-tests for continuous variables. No adjustment was made for multiplicity.

### Results

A total of 12,175 LAO users (tapentadol ER:  $n = 1,046$ ; oxycodone CR:  $n = 9,152$ ; oxymorphone ER:  $n = 1,977$ ) were identified and formed the study population. The mean age was 51.1, 54.5, and 49.2 years for the tapentadol ER, oxycodone CR, and oxymorphone ER groups, respectively; 62.0%, 55.2%, and 56.4% were female. The mean DACON was significantly lower in the tapentadol ER group at 1.96 tablets compared to the oxycodone CR group at 2.37 tablets ( $P < .001$ ) and compared to the oxymorphone ER group at 2.19 tablets ( $P < .001$ ). Tapentadol ER was also associated with a more stable and predictable medication utilization than oxycodone CR and oxymorphone ER, as evidenced by a lower standard deviation for DACON (0.45, 0.90, and 0.75 for the tapentadol ER, oxycodone CR,

and oxymorphone ER groups, respectively). Among the subset of LAO users who received the highest dosage strength, those receiving tapentadol ER were dispensed significantly fewer tablets per day compared to the other 2 groups (tapentadol ER: 1.93 vs oxycodone CR: 3.12 [ $P < .001$ ]; vs oxymorphone ER: 2.51 [ $P < .001$ ]). When comparing the daily dose increase from the first to the last dispensing during the 90-day measurement period, the mean percentage increase was lower in the tapentadol ER group (12.1%) compared to oxycodone CR (15.3%,  $P = .047$ ) and oxymorphone ER (15.1%,  $P = .109$ ) groups. Among the subgroups with musculoskeletal pain, a similar pattern of dose escalation was observed (tapentadol ER = 11.5% vs oxycodone CR = 15.2%,  $P = .088$ ; vs oxymorphone ER = 19.1%,  $P = .016$ ). The mean total drug cost for the LAOs during the 90-day measurement period was significantly lower in the tapentadol ER group (mean = \$1,047; 95% CI: \$1,023-\$1,070) compared to the oxycodone CR (mean = \$1,210; 95% CI: \$1,188-\$1,232,  $P < .001$ ) and oxymorphone ER (mean = \$1,384; 95% CI: \$1,342-\$1,426,  $P < .001$ ) groups.

## Conclusions

On average, patients treated with oxycodone CR and oxymorphone ER received a significantly higher number of tablets per day compared to tapentadol ER users. The DACON was also more stable and predictable for tapentadol ER users than for patients receiving the other 2 LAOs, with differences more pronounced at the highest tablet dosage strength. These factors contributed to significantly lower pharmacy costs for use of tapentadol ER compared to oxycodone CR and oxymorphone ER.

## Relationship between oxycodone pharmacokinetics and subjective drug effects following oral administration of an immediate-release combination of oxycodone and acetaminophen and MNK-795 controlled-release oxycodone/acetaminophen (CR OC/APAP) tablets

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### Purpose

Prescription opioids are most commonly abused through the oral route of administration. Certain pharmacokinetic (PK) properties of these medications, including a rapid time to maximum plasma concentration ( $T_{max}$ ) and greater maximum plasma concentration ( $C_{max}$ ), have been associated with greater subjective drug liking and reinforcing effects, and tend to be preferred by drug abusers. Conversely a medication with a longer  $T_{max}$  would be expected to have delayed reinforcing effects, be less preferred, and have reduced human abuse liability. The purpose of this analysis was to compare the PK and pharmacodynamic (PD) properties of the first controlled-release (CR) combination oxycodone (OC)/acetaminophen (APAP) analgesic, MNK-795 (CR OC/APAP), with those of immediate-release (IR) OC/APAP, and to examine the correlation between PK parameters (eg,  $C_{max}$  and area under the plasma concentration–time curve [AUC]) and PD parameters for the primary measures of drug liking, drug high, and good drug effects in recreational opioid users. Reduced drug liking, drug high, and good drug effects have been specified as reflecting reduced human abuse liability. CR OC/APAP was developed to manage moderate to severe acute pain that warrants treatment with a CR analgesic, and was designed to provide tamper-resistance and abuse-deterrence.

### Method

This single-center, randomized, double-blind, double-dummy, active- and placebo-controlled, crossover study was conducted with non-opioid-dependent male and female subjects who reported  $\geq 5$  occasions of recreational prescription opioid use over the past 12 months, including  $\geq 1$  occasion during the past 12 weeks. To enter the treatment phase, subjects had to prove nondependence via a naloxone challenge test, then tolerate and accurately discriminate IR OC (15 mg)/APAP (650 mg) from placebo. Subjects received one treatment of the following in each of 7 periods: placebo, intact 15 mg/650 mg CR OC/APAP, intact 15 mg/650 mg IR OC/APAP (low-dose, intact); intact 30 mg/1300 mg CR OC/APAP, intact 30 mg/1300 mg IR OC/APAP (high-dose, intact); crushed, encapsulated 30 mg/1300 mg CR OC/APAP, and crushed, encapsulated 30 mg/1300 mg IR OC/APAP (high-dose, crushed). Oxycodone and acetaminophen PK parameters, including  $C_{max}$ ,  $T_{max}$ , and AUC at 0-1 h, 0-2 h, 0-4 h, 0-8 h, 0-12 h, and 0-infinity were determined. Abuse potential was assessed with 100-point visual analog scales of subject-reported drug liking, drug high, and good drug effects. PD measures included peak drug effects ( $E_{max}$ ), time to  $E_{max}$  ( $TE_{max}$ ), and area under the effect curve (AUE) assessed at multiple time points from 0 to 12 hours. The PK/PD relationship was evaluated by calculating correlation coefficients between these parameters (eg,  $C_{max}$  vs  $E_{max}$  and  $AUC_{0-x}$  vs  $AUE_{0-x}$ ).

### Results

A total of 61 subjects met criteria and entered the treatment phase; 55 completed all 7 treatment periods. Oxycodone  $C_{max}$  values after administration of intact doses of CR OC/APAP were half (30.5 ng/mL [high-dose, intact], 14.0 ng/mL [low-dose, intact]) of the values observed with the corresponding intact doses of IR OC/APAP (61.9 ng/mL [high-dose, intact], 32.8 ng/mL [low-dose, intact]). In addition, median  $T_{max}$  was significantly longer for CR OC/APAP (2.1 h [high-dose, intact], 3.1 h [low-dose, intact]) compared with the same dose of IR OC/APAP (1.1 h for both high- and low-dose intact conditions;  $P < .001$ ), representing relative increases in median  $T_{max}$  of 91% and 181%, respectively. Oxycodone AUC values up to the first 4 hours after administration were also lower for intact doses of

CR OC/APAP compared with intact doses of IR OC/APAP; however, overall exposure, as evidenced by  $AUC_{0-\infty}$ , was equivalent between formulations. High-dose CR OC/APAP  $C_{max}$  was similar for the intact and crushed formulations (30.50 ng/mL vs 31.10 ng/mL, respectively); however, median  $T_{max}$  for the crushed CR OC/APAP was delayed by 1.5 hours (3.6 h vs 2.1 h [high-dose, intact]), representing a 71% relative increase in  $T_{max}$  after crushing. Furthermore, CR OC/APAP (high-dose)  $AUC_{0-1h}$  was greater for the intact formulation (13.0 ng·h/mL vs 1.9 ng·h/mL) and  $AUC_{0-2h}$  was twice as high (36.7 ng·h/mL vs 17.3 ng·h/mL) vs crushed conditions. In general, drug liking, drug high, and good drug effects were greater for IR OC/APAP compared with CR OC/APAP (crushed and intact), and were numerically or statistically lower for crushed CR OC/APAP compared with intact CR OC/APAP. Moreover, a strong correlation was demonstrated between the PK parameters of  $C_{max}$  and  $AUC_{0-x}$  and PD parameters of  $E_{max}$  and  $AUE_{0-x}$ , respectively, for all drug liking, drug high, and good drug effects in this trial ( $R^2 = 0.711-0.997$ ).

## Conclusions

CR OC/APAP has a controlled-release profile with lower  $C_{max}$  and longer  $T_{max}$  for OC than IR OC/APAP while maintaining the same extent of exposure. The PK profile of oral CR OC/APAP was strongly correlated to perceived drug effects. Crushing CR OC/APAP slowed the rate of release of OC and had similar or less drug liking, drug high, and good drug effects than the comparable dose of intact CR OC/APAP. Importantly, CR OC/APAP may be the first opioid formulation with a demonstrated reduction in abuse-related subjective effects relative to the IR formulation following intact or crushed oral administration.



## Comparison of subjective drug effects of orally administered MNK-795 controlled-release oxycodone/acetaminophen tablets (CR OC/APAP) vs immediate-release oxycodone/acetaminophen tablets in recreational users of prescription opioids

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### Purpose

Immediate- and extended-release (ER) formulations containing oxycodone (OC) are among the prescription opioids that have the highest risk of abuse, and ER OC is primarily abused orally. Drug abusers may seek to defeat the extended-release characteristics of OC formulations by crushing or chewing the tablets to extract an oral bolus dose with rapid onset of subjective effects that have been associated with drug abuse. MNK-795 (CR OC/APAP) is the first controlled-release (CR) combination OC/acetaminophen (APAP) analgesic. It is being developed to manage moderate to severe acute pain that warrants treatment with a CR analgesic. CR OC/APAP incorporates technology designed to provide tamper-resistance and abuse-deterrence. This study evaluates some subjective effects that have been associated with drug abuse, comparing those of intact and crushed CR OC/APAP with intact and crushed immediate-release (IR) OC/APAP.

### Method

This study utilized a single-center, randomized, double-blind, double-dummy, active- and placebo-controlled, crossover design. Healthy male and female nondependent, recreational opioid users who reported  $\geq 5$  occasions of use over the past year, including  $\geq 1$  occasion within the past 12 weeks, were studied. Absence of physical dependence was confirmed by naloxone challenge test, and subjects had to tolerate IR OC 15 mg/APAP 650 mg and accurately discriminate it from placebo to enter. The treatment phase consisted of 7 periods, with a 72-hour washout between treatment administrations. Subjects received one treatment of the following in each of 7 periods: placebo, intact 15 mg/650 mg CR OC/APAP, intact 15 mg/650 mg IR OC/APAP (low-dose, intact); intact 30 mg/1300 mg CR OC/APAP, intact 30 mg/1300 mg IR OC/APAP (high-dose, intact); and crushed, encapsulated 30 mg/1300 mg CR OC/APAP, crushed, encapsulated 30 mg/1300 mg IR OC/APAP (high-dose, crushed). The primary outcome measures were 100-point visual analog scales (VAS) of subject-reported drug liking, drug high, and good effects. Pharmacodynamic measures included peak drug effects ( $E_{max}$ ; primary), time to  $E_{max}$  ( $TE_{max}$ ), and area under the effect curve (AUE) assessed at multiple time points from 0 to 12 hours. Pharmacodynamic statistical analyses were performed on least-squares mean differences using a linear, mixed-model analysis of variance with fixed effects for sequence, period, and treatment, and a random effect for subjects nested in sequence. Least-squares mean differences along with 95% CIs were constructed for all pair-wise comparisons between treatments. Data were adjusted for multiple comparisons. Safety assessments were also conducted.

### Results

Analyses were performed on 55 subjects that completed the treatment phase. The  $E_{max}$  of the subject reports of drug liking, drug high, and good drug effects for high-dose, intact CR OC/APAP were significantly lower ( $P < .001$ ) than for high-dose, intact IR OC/APAP (liking, 26.4 vs 35.6; high, 47.9 vs 76.0; good effects, 55.4 vs 75.3). The  $E_{max}$  for drug liking, high, and good effects for high-dose, intact CR OC/APAP was also significantly lower ( $P < .02$ ) than for low-dose, intact IR OC/APAP.  $TE_{max}$  was longer for high-dose, intact CR OC/APAP compared with high-dose, intact IR OC/APAP, but only the difference for drug liking (1.7 vs 1.2;  $P < .05$ ) reached statistical significance. AUE at early time points (ie, 0-1 h and 0-2 h) for these ratings were also significantly lower for high-dose, intact CR OC/APAP compared with high-dose, intact IR OC/APAP ( $P < .01$  for each comparison). AUE for drug high remained significantly

lower at later time points (0-4 h, 0-8 h, and 0-12 h;  $P < 0.01$  for each comparison). AUE for good effects was lower during the 0-4 h, 0-8 h, and 0-12 h time intervals, but only the difference for AUE<sub>0-4 h</sub> was statistically significant ( $P < .001$ ). AUE for drug liking was more comparable at these time points. Comparisons of the lower doses and crushed formulations also demonstrated significantly lower  $E_{max}$  for drug liking, high, and good effects ( $P < .001$ ) for CR OC/APAP vs IR OC/APAP. Importantly, crushing CR OC/APAP did not increase its subject-reported effects, producing similar or significantly less drug liking, high, and good effects than the same dose of intact CR OC/APAP or IR OC/APAP. Moreover, crushed CR OC/APAP had a significantly longer  $TE_{max}$  ( $P < .02$ ) and significantly lower AUE<sub>0-1h</sub>, AUE<sub>0-2h</sub>, and AUE<sub>0-4h</sub> ( $P < .02$ ) for drug liking, high and good effects than the same dose of intact CR OC/APAP.

## Conclusions

Oral administration of CR OC/APAP resulted in less drug liking, drug high, and good drug effects compared with IR OC/APAP, suggesting potentially lower abuse liability. Crushed CR OC/APAP produced fewer and delayed reports of drug liking, drug high, and good drug effects compared with intact CR OC/APAP and IR OC/APAP, which is unique and in opposition to the effect of crushing other currently available oxycodone formulations. Importantly, CR OC/APAP may be the first opioid formulation with demonstrated reduction in subjective effects that have been associated with drug abuse relative to the IR formulation following intact or crushed oral administration.

## Open-label safety of MNK-795, controlled-release oxycodone/acetaminophen tablets (CR OC/APAP), in patients with osteoarthritis or chronic low back pain

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### Purpose

Combining opioids with acetaminophen (APAP) is safe, effective, and an established approach to the treatment of a variety of pain states. A multimodal approach to therapy combining analgesic agents with different mechanisms of action, such as combining opioid and nonopioid analgesics can reduce the overall dose of each active pharmaceutical ingredient, potentially minimizing side effects. In addition, compared with immediate-release preparations, controlled-release (CR) analgesics generally provide more consistent plasma concentrations throughout the dosing period, minimizing peak-to-trough fluctuations with the convenience of less frequent dosing. MNK-795 (CR oxycodone[OC]/APAP), the first CR combination OC/APAP analgesic product, is designed to treat acute pain with 12 hour dosing. Specifically, it is being developed to manage moderate to severe acute pain that warrants treatment with a CR analgesic. In addition, CR OC/APAP incorporates technology designed to provide tamper-resistance and abuse-deterrence. The primary objective of this study was to evaluate the safety and tolerability of CR OC/APAP with up to 35 days of use in patients who were transitioning from Step 1 to Step 2 of the World Health Organization pain scale. The secondary objective was to evaluate the efficacy of CR OC/APAP using changes from baseline in pain intensity, pain-related quality of life, and disease-specific quality of life.

### Method

This multicenter, phase 3, open-label study included adult ( $\geq 18$  years) patients with a clinical diagnosis of (1) osteoarthritis (OA) of the knee or hip, with moderate to severe pain intensity despite chronic use of stable doses of nonopioid or opioid medications, or (2) chronic low back pain (CLBP) that was moderate to severe in intensity and present for at least several hours a day for  $\geq 3$  months. A 3-day washout period was required. Study medication consisted of 2 tablets of CR OC/APAP (ie, 15 mg OC/650 mg APAP) administered every 12 hours. The first dose of study medication was given under medical supervision, and patients were monitored for 4 hours after the initial dose. Patients who tolerated the first dose (ie, no emesis and no moderate or severe nausea) continued to take 2 tablets of CR OC/APAP every 12 hours for the duration of the study (up to 35 days). Safety and efficacy (modified Brief Pain Inventory-short form, Western Ontario and McMaster Universities Arthritis Index, Roland-Morris Disability Questionnaire) assessments were conducted at baseline and weekly thereafter. Safety and tolerability were evaluated based on time to discontinuation; the occurrence of treatment-emergent adverse events (TEAEs); and changes from baseline in vital signs, pulse oximetry, clinical laboratory test results (chemistry, hematology, and urinalysis), and liver function test (LFT) results (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], lactate dehydrogenase [LDH], gamma-glutamyl transpeptidase [GGT], and total and direct bilirubin).

### Results

Of the 376 patients enrolled ( $n = 141$  OA,  $n = 235$  CLBP), 75.8% completed the study (69.5% OA, 79.6% CLBP). Mean duration of CR OC/APAP exposure was 29.2 days, with duration of exposure  $\geq 10$  days for 82.4% of patients. Mean time to discontinuation was 7.7 days, and the most common reason for study discontinuation was a TEAE (22.7% OA patients, 16.6% CLBP patients). TEAEs that occurred in  $>5\%$  of patients were nausea (23.1%), vomiting (15.2%), dizziness (14.9%), somnolence (11.4%), constipation (11.2%), pruritus (7.2%), and headache (5.1%). Most TEAEs were mild or moderate in intensity;

17 patients (4.5%) reported a total of 22 severe AEs, of whom 10 patients (2.7%) experienced  $\geq 1$  severe gastrointestinal event ( $n = 6$  nausea,  $n = 5$  vomiting, and  $n = 1$  constipation). No AEs of dizziness or somnolence were considered severe. Shifts in LFT results from normal at baseline to elevated at the end of treatment were observed in the following proportions of patients: 6.9% ALT, 5.0% AST, 0.3% ALP, 1.5% LDH, 4.6% GGT, and 0.6% total bilirubin. Ten patients had LFT results during the study that the investigator deemed clinically significant; 5 patients discontinued due to these AEs, and all resolved or were resolving after discontinuation. With the exception of the changes in LFT results, there were no changes in hematology or clinical chemistry that were considered related to CR OC/APAP by the investigator. Changes in physical examination findings, vital signs, and oxygen saturation not clinically significant, with one exception. One patient was found to have hypopnea that was considered related to study medication and resulted in discontinuation. No other patients experienced respiratory depression or orthostatic hypotension. Substantial decreases in pain intensity (worst pain, average pain, and current pain) were observed early in treatment and continued throughout the study for both patient groups (OA and CLBP), with corresponding improvements in quality of life.

### **Conclusions**

Overall, no apparent clinically significant treatment-related trends were observed in clinical laboratory test results, vital signs, pulse oximetry measurements, or physical examination findings. The safety/tolerability profile of CR OC/APAP was consistent with expectations for a low-dose opioid/APAP combination product. This study supports the safety/tolerability of CR OC/APAP (administered as 2 tablets every 12 hours) for up to 35 days, and supports its use for the management of moderate to severe acute pain that warrants treatment with a CR analgesic.

## Efficacy and tolerability of methylnaltrexone in advanced illness patients with opioid-induced constipation: a responder analysis

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### Purpose

Opioid-induced constipation (OIC) is a distressing side effect of chronic opioid therapy, evidenced in up to 90% of advanced illness patients taking long-term opioids. Subcutaneous methylnaltrexone (MNTX) has been shown to be efficacious and safe in this patient population, although factors that determine optimal responsiveness have not been elucidated. The objective of this posthoc analysis was to examine the influence of demographic and baseline characteristics on efficacy and tolerability of MNTX in advanced illness patients with OIC.

### Method

Data were pooled from 2 randomized, double-blind, placebo (PBO)-controlled, phase 3 studies (n = 287) of MNTX (0.15 and 0.3 mg/kg). Subgroup analyses of the primary outcome measure, proportion of patients with a rescue-free bowel movement (RFBM) within 4 hours of first dose, were conducted for gender (female/male), age (<65/≥65 years), primary diagnosis (cancer/noncancer), and baseline morphine equivalent dose (<150/≥150 mg/d).

### Results

Overall, 54.1% and 58.2% of patients treated with MNTX 0.15 and 0.3 mg/kg experienced a RFBM within 4 hours, vs 14.6% for PBO-treated patients ( $P < .0001$  for both doses vs PBO). Responsiveness to MNTX was significantly greater than PBO in all subgroups (range of MNTX responses: 48.1%-73.3%, range of PBO responses: 10.2%-18.8%,  $P < .0001$  for nearly all comparisons). The largest differences from PBO were observed for noncancer patients taking MNTX 0.3 mg/kg (70.0% vs 12.8%,  $P = .0002$ ) and for patients maintained on ≥150 mg/d oral morphine taking MNTX 0.3 mg/kg (73.3% vs 16.7%,  $P < .0001$ ). Common adverse events were abdominal pain (pooled MNTX: 27.9%, PBO: 9.8%), flatulence (13.3%, 5.7%) and nausea (10.9%, 4.9%). Tolerability was generally comparable across subgroups.

### Conclusions

These findings demonstrate that in advanced illness patients with OIC, MNTX produces a rapid and robust laxation response that is consistent across gender, age, primary diagnosis, and baseline opioid use. MNTX 0.3 mg/kg may elicit particularly favorable responses in select subgroups.

## Comparison of the heated lidocaine/tetracaine patch and oral naproxen for treatment of lateral epicondylitis

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### Purpose

Lateral epicondylitis, or tennis elbow, is an overuse injury resulting in pain in the elbow and forearm. Although commonly associated with racquet sports, it occurs more frequently in nonathletes. Initial treatment of lateral epicondylitis is conservative and includes oral and topical nonsteroidal anti-inflammatory drugs, corticosteroid injections, and physical therapy. The results of recent pilot studies showing improvements in musculoskeletal pain suggest that the heated lidocaine/tetracaine patch (HLT patch) may represent an initial conservative treatment for pain associated with lateral epicondylitis. The HLT patch (ZARS Pharma, Salt Lake City, UT) contains a eutectic mixture of lidocaine (70 mg) and tetracaine (70 mg) with an integrated oxygen-activated heating component. The present pilot study was conducted to compare 2 application regimens of the HLT patch and oral naproxen for the treatment of pain associated with lateral epicondylitis.

### Method

Adults ( $\geq 18$  years old) with clinical evidence of lateral epicondylitis and an average pain score for the previous 24 hours of  $\geq 4$  (0-10 scale) were enrolled in the study and randomly assigned to 1 of 3 treatment groups. In Group 1, patients applied a single HLT patch over the affected site twice daily for periods of 4 hours with about 12 hours between applications. In Group 2, patients applied a single HLT patch to the affected site once daily for a period of 12 hours. In Group 3, patients were treated with oral naproxen sodium 500 mg twice daily. All patients were treated for 14 days and were followed for an additional 14 days after cessation of treatment to examine the durability of response. Elbow pain was assessed at baseline, Day 14, and Day 28 using a 0-10 point scale. Patients who left the study for any reason or who were lost to follow-up had all postbaseline pain scores imputed as baseline observation carried forward. In each group, change from baseline was analyzed with a *t*-test.

### Results

Fifty-two patients enrolled in the study and 44 patients completed the study. 3 patients were lost to follow-up and 5 patients withdrew early. At baseline, the mean average pain scores were (mean  $\pm$  SD)  $5.9 \pm 1.7$  ( $n = 18$ ),  $5.8 \pm 1.5$  ( $n = 17$ ), and  $5.2 \pm 2.5$  ( $n = 17$ ) in Groups 1, 2, and 3, respectively. After 14 days of treatment, the mean change from baseline was  $-2.3 \pm 1.6$  ( $P < .001$ ),  $-1.9 \pm 1.7$  ( $P < .001$ ), and  $-1.5 \pm 1.9$  ( $P = .004$ ) in Groups 1, 2, and 3, respectively. In Group 1, 56% of patients experienced a clinically meaningful reduction in pain ( $\geq 30\%$  reduction from baseline). In Groups 2 and 3, a clinically meaningful reduction in pain was reported by 53% and 41% of patients, respectively. In Group 1, 6 of 10 patients (60%) who had experienced a  $\geq 30\%$  reduction in pain maintained their response or continued to improve 14 days after stopping therapy. The durability of the response was similar in Groups 2 and 3, where 50% of the patients in each group with a clinically meaningful reduction in pain maintained their response or improved after 14 days off therapy. Application site rash or erythema was reported by 50% of patients in Group 1 and 18% of patients in Group 2. Two patients in Group 1 withdrew from the study due to application site adverse events. Two patients in Group 3 experienced nausea as an adverse event.

### Conclusions

The HLT patch administered either twice daily or once daily for pain of lateral epicondylitis resulted in a clinically meaningful reduction in pain that was comparable to oral naproxen. The majority of patients maintained their response or continued to improve following 2 weeks of treatment, suggesting a durability of response when used for acute, short-term relief. Based on these results, the HLT patch may represent an alternative initial conservative treatment for lateral epicondylitis pain, and further study is warranted.

## Breakthrough pain and its association with functional status, pain interference, and disability in cancer patients: findings from the National Breakthrough Pain Study

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### Purpose

Few studies have evaluated breakthrough pain (BTP) in community-dwelling populations with cancer and chronic pain. The National Breakthrough Pain Study assessed the prevalence, characteristics, and impact of BTP in a sample of patients from a large commercially-insured population identified from a US administrative claims database. The aim of this subanalysis was to evaluate functional status, pain interference, and disability associated with BTP in cancer patients who reside in the community.

### Method

Administrative claims from the HealthCore Integrated Research Database were used to identify commercially-insured adult patients who had  $\geq 2$  medical claims at an interval  $\geq 3$  months with an ICD-9-CM code indicating a chronic pain condition (cancer or noncancer) and who had  $\geq 3$  opioid prescription claims. Patients were contacted by phone and, after providing verbal consent, responded to a screening questionnaire that identified patients with controlled, persistent pain and queried these patients about the presence or absence of BTP. The Brief Pain Inventory (BPI), Sheehan Disability Scale (SDS), and 12-Item Short-Form Health Survey (SF-12) also were administered by interview. The SF-12 measures physical and mental health based on 12 questions pertaining to the patient's ability to perform activities and emotional problems. Comparisons between cancer patients with BTP and cancer patients without BTP were made using bivariate/unadjusted comparisons. All statistical analyses were performed at 95% significance using 2-sided tests or 2-sided confidence intervals without adjustment for multiplicity.

### Results

Of 2198 patients surveyed, 1279 had controlled, persistent pain. Of these, 145 had cancer pain, 77.2% of whom reported BTP (BTP, 112; no BTP, 33). Cancer patients with BTP had significantly higher total pain interference scores on the BPI than those without BTP (mean  $\pm$  SD:  $34.7 \pm 14.5$  vs  $23.4 \pm 16.7$  [ $P = .003$ ]) and significantly greater global functional impairment on the SDS (mean  $\pm$  SD:  $16.8 \pm 8.3$  vs  $12.4 \pm 8.3$  [ $P = .03$ ]). Cancer patients with BTP also had a significantly lower quality of life compared with those without BTP, as assessed by SF-12 physical component summary score (mean  $\pm$  SD:  $27.8 \pm 9.1$  vs  $32.2 \pm 10.1$  [ $P = .02$ ]); there was no significant difference in the mental component summary score of the SF-12 (mean  $\pm$  SD:  $47.0 \pm 11.9$  vs  $49.4 \pm 11.6$  [ $P = .3$ ]).

### Conclusions

In a sample of commercially-insured, community-dwelling cancer patients, those with controlled, persistent pain and BTP had greater pain-related functional impairments and disability than those with controlled, persistent pain and no BTP. These data suggest that BTP is clinically important among populations receiving cancer care in the community.



## Common-sense opioid prescribing—opioid safety initiative measure at the US Department of Veterans Affairs

Marylee O'Connor, Wafa Samara  
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### Purpose

Opioid Safety Initiative is a pilot program within the Department of Veterans Affairs in select VISN's. The specific aim of this pilot program is to promote the use of the Business Intelligence (BI) tool to:

- Identify veterans who are at immediate, short-term and long -risk of harm associated with high-dose opioid therapy and to develop an individualized clinical action plan to mitigate risks.
- Offer providers education and training to enhance competencies and promote clinical practice guidelines for safe and effective opioid therapy for the management of noncancer related chronic pain.
- Encourage utilization of existing tools and resources to promote organizational/system improvements to support providers in the delivery of safe and effective opioid therapy in the context of an integrated, team based pain management.

### Method

BI tool is used to select patients for a protected peer review process. BI tool looks at several risk factors in order to identify patients for review such as:

- Opioid risk factors such as substance abuse history and concomitant use of CNS depressants
- Opioid and benzodiazepine use
- Chronic opioid patients without a urine drug screen in the last 12 months
- Chronic opioid patients without a visit to their primary care provider in last 6 months
- Chronic high-dose APAP patients
- High-dose opioid patients on >120 mg morphine equivalents a day

Protected peer review will examine the last 24 months of available medical records and will examine things like is there a clear pain diagnosis documented in the chart, is level of analgesia documented at each visit and are aberrant behaviors addressed. Once reviews are completed the goal is to identify areas for improvement consistent with aims of the safety initiative. Up to 5 records for any one provider will be reviewed by an interdisciplinary team using a standard review form that has been developed by the team. Patients being treated through oncology or palliative care services will be excluded. Review instruments will remain at a facility level; however results will be summarized for the VISN.

### Results

Data is now being compiled and is not available for results at this time.

### Conclusions

The goal if this process is to provide information and suggestions to the providers about opioid use and monitoring for patients who are receiving long-term therapy with high-dose opioids that put them at risk of poor outcomes. The VA wants to provide the best pain care possible using the VA/DoD Clinical Practice Guidelines covering the Management

of Opioid Therapy for Chronic Pain along with a stepped-care approach to influence treatment practices that safeguard against harm and misuse

## Relative bioavailability of oral oxycodone/naloxone (OXN) tablets as compared to sublingual naloxone, IV naloxone and oral reformulated OxyContin®

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### Purpose

Oxycodone hydrochloride/naloxone hydrochloride controlled-release tablets (OXN) are being developed by Purdue Pharma L.P. as an oral formulation of oxycodone and naloxone in a fixed 2:1 ratio by API anhydrous weight (w/w) for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. In the United States, OXN is being developed in 3 strengths: 10/5 mg, 20/10 mg, and 40/20 mg intended for BID dosing (approximately every 12 hours).

Oxycodone is a potent opioid agonist with high affinity at mu receptors in the brain, spinal cord and peripheral organs. Oxycodone is orally bioavailable, but naloxone has very low oral bioavailability ( $\leq 2\%$ ), due to extensive first-pass metabolism. Naloxone is a potent mu receptor antagonist and is included for its abuse-deterrent properties and its potential to decrease opioid gastrointestinal side effects. Oxycodone and naloxone are each approved drugs and have been marketed separately in the United States.

This study was performed to compare oral OXN (20/10 mg oxycodone/naloxone tablets) to oral reformulated OxyContin® (20 mg), with respect to oxycodone bioavailability, and to sublingual (SL) Suboxone® (0.5 mg) and intravenous (IV) naloxone (0.4 mg), with respect to naloxone bioavailability.

### Method

Healthy subjects aged 18-55 years were randomly assigned to a treatment sequence in this 4-treatment, 4-period crossover study. The 4 treatments administered were: OXN 20/10 mg as a single oral tablet; Suboxone (buprenorphine 2 mg/ naloxone 0.5 mg) as a single SL film; IV naloxone (0.4 mg/ 1 mL) as a single IV injection and OxyContin® as a single oral 20 mg tablet. Treatments were administered in the fasted state and were separated by 7-day washout periods. Blood samples for determination of oxycodone, naloxone, naloxone-3 $\beta$ -glucuronide, 6 $\beta$ -naloxol and buprenorphine were collected through 72 hours post dose. Systemic exposures to oxycodone and naloxone were characterized. PK parameters were calculated for parent and metabolites measured. Safety was assessed using adverse events (AEs), clinical laboratory tests (biochemistry, hematology and urinalysis), vital signs and pulse oximetry (SpO<sub>2</sub>) measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings.

### Results

Thirty subjects (18 males and 12 females; mean age: 34 years) were included in the safety and PK analyses. Twenty-seven subjects completed the study. Two subjects were discontinued due to TEAEs and 1 subject was discontinued due to administrative reasons.

Peak ( $C_{max}$ ) and total exposure (AUC) following a single dose of oxycodone administered as oral OXN 20/10 mg were bioequivalent to the peak and total exposure of a single dose of oxycodone administered as oral reformulated OxyContin 20 mg.

The absolute bioavailability of naloxone from OXN compared with IV naloxone was less than 1%, as evaluated by dose-normalized AUCt. The bioavailability of oral naloxone from OXN was lower than that of SL naloxone from Suboxone, with a mean dose-normalized AUCt ratio of 12.9%.

For OXN (20/10 mg), SL Suboxone (2/0.5 mg) and IV naloxone (0.4 mg), respectively, the mean (%CV) naloxone AUCt was 0.66 (89.0), 0.22 (46.4) and 2.7(25.1) ng\*h/mL; mean (%CV) C<sub>max</sub> was 0.08 (96.9), 0.10 (46.0), 1.3(29.6) ng/mL.

Treatment-emergent AEs were reported by 5 subjects (19%) after receiving oral OXN, 5 subjects (18%) after receiving SL Suboxone, 4 subjects (14%) after receiving IV naloxone, and 8 subjects (29%) after receiving oral reformulated OxyContin. There were 3 TEAEs reported in at least 2 subjects in any treatment: nausea, dizziness, and headache. Nausea was the most frequently reported TEAE across treatments and occurred most with SL Suboxone and oral OxyContin, less with oral OXN, and the least with IV naloxone. All TEAEs resolved by the end of the study. There were no deaths.

## Conclusions

The absolute bioavailability of oral naloxone from OXN was low (< 1%) and was lower than that of naloxone from SL Suboxone.

Peak (C<sub>max</sub>) and total exposures (AUC) following a single dose of oxycodone administered as oral OXN 20/10 mg were bioequivalent to the peak and total exposures of a single dose of oxycodone administered as oral reformulated OxyContin 20 mg.

The administration of oral OXN (20/10 mg oxycodone/naloxone), SL Suboxone (2/05 mg buprenorphine/naloxone), IV naloxone (0.4 mg), and oral OxyContin (20 mg) as single doses under fasted conditions was safe and well tolerated.

**Effect of ketoconazole, a CYP3A4 inhibitor, on the pharmacokinetics of hydrocodone and its metabolites following coadministration with a novel hydrocodone, single-entity, once-daily, extended-release tablet [HYD]**

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**Purpose**

HYD is a single-entity, once-daily, extended-release tablet formulation of hydrocodone bitartrate. It is being developed for the management of moderate to severe pain in patients who require a continuous, around-the-clock opioid pain medication for an extended period of time. HYD was formulated with inactive ingredients intended to make the tablet more difficult to manipulate for misuse and abuse.

Hydrocodone undergoes cytochrome P450 (CYP) 2D6-mediated O-demethylation yielding hydromorphone (minor active metabolite) and CYP3A4 mediated N-demethylation yielding norhydrocodone (major inactive metabolite). The concomitant administration of CYP3A4 inhibitors may lead to increases in systemic exposure of hydrocodone and may affect safety and tolerability of hydrocodone. The purpose of this randomized, double-blind, 2-period, 2-treatment, crossover drug-drug interaction study was to investigate the influence of CYP3A4 inhibition by ketoconazole (a strong CYP3A4 inhibitor) on the pharmacokinetics (PK) of hydrocodone and its metabolites following oral administration of HYD in healthy subjects.

**Method**

Healthy subjects (13 males and 17 females), aged 18 to 50 years, received HYD-20 mg with ketoconazole in one study period and placebo in the other period. Ketoconazole (200 mg tablet) or placebo was administered every 12 hours for 6 days in each period. A single HYD-20 mg tablet was administered once in each study period (on days 5 and 24) in the fasted state. Blood samples for quantitation of hydrocodone and its metabolites in plasma were collected through 80 hours post dose. PK parameters were calculated for hydrocodone and its metabolites, norhydrocodone and hydromorphone. Safety was assessed using adverse events (AEs), clinical laboratory tests (biochemistry, hematology, and urinalysis), vital signs and pulse oximetry (SpO<sub>2</sub>) measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings.

Twenty-eight subjects completed the study. Twenty-seven subjects were included in the PK analyses. Two subjects discontinued due to subject's choice. The mean age of the entire study population was 29.8 years.

**Results**

The mean AUC<sub>t</sub> and AUC<sub>inf</sub> of hydrocodone were increased by 135% and 133%, respectively, after administration of ketoconazole 200 mg q12h for 6 days. C<sub>max</sub> of hydrocodone increased by 78% in the presence of ketoconazole.

The mean AUC<sub>t</sub>, AUC<sub>inf</sub>, and C<sub>max</sub> of norhydrocodone were decreased by 36%, 34%, and 52%, respectively, in the presence of ketoconazole. Hydromorphone is a minor active metabolite (<3% of systemic hydrocodone exposure). The mean AUC<sub>t</sub>, AUC<sub>inf</sub>, and C<sub>max</sub> of hydromorphone were increased by 195%, 178%, and 95%, respectively, in the presence of ketoconazole.

There were no deaths, serious AEs (SAEs), or discontinuations due to treatment emergent AEs (TEAEs). For the HYD with ketoconazole treatment, a total of 26 TEAEs were reported and 11 of 30 subjects (37%) experienced at least 1 TEAE. For the HYD with placebo treatment, a total of 14 TEAEs were reported and 9 of 28 subjects (32%) experienced at least 1 TEAE. All TEAEs were mild or moderate and resolved by the end of the study. Clinical laboratory values, vital sign and SpO<sub>2</sub> measurements, and ECG results and changes from baseline were similar across the 2 treatments, and no apparent treatment-related trends were observed.

## **Conclusions**

Coadministration of a single dose of HYD-20 mg extended-release tablet with the CYP3A4 inhibitor ketoconazole at steady state (200 mg, q12h for 6 days) increased the systemic exposure of hydrocodone by 135% and decreased norhydrocodone by 34%. However, no appreciable differences were observed on hydromorphone systemic exposure.

Coadministration of a single oral dose of HYD extended-release 20-mg tablet oral dose under fasted conditions with ketoconazole 200 mg q12h for 6 days was safe and well tolerated.

## Intramuscular administration of nucleotides (CMP/UTP) and vitamin B<sub>12</sub> in the treatment of alcoholic polyneuropathy

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### Purpose

The primary study objective was to evaluate the clinical action of the combination of pyrimidine nucleotides cytidine monophosphate (CMP) and uridine triphosphate (UTP) plus hydroxocobalamin in the treatment of patients presenting alcoholic polyneuropathy. Secondary study objectives included assessment of the combination of CMP, UTP, and hydroxocobalamin in the treatment of patients presenting alcoholic polyneuropathy, using clinical, physical, and laboratory endpoints, as well as adverse events assessment.

### Method

The study was performed at UNIFESO university hospital in Rio de Janeiro, Brazil. Eligible subjects included patients of both genders, ages of 18-65, with a clinical presentation of alcoholic polyneuropathy. Patients received a 6-day intramuscular treatment consisting of: CMP 5.0 mg; uridine triphosphate UTP 3.0 mg; hydroxocobalamin 2.0 mg; and lidocaine 20 mg. At each assessment, a medical history was taken, along with physical and laboratory exams (including serum vitamin B<sub>12</sub> levels). Use of concomitant medications and occurrence of adverse events were continuously monitored. Efficacy assessments included a 100mm pain VAS (visual analog pain scale), paresthesia assessment (using the 2-point test), the finger-to-nose test to evaluate motor coordination, and the lower limb vibration perception test. At Assessments 1 and 3, the patient and the investigating physician evaluated the patient's overall condition on a scale of 1-10 points. Results were statistically analyzed using the software GraphPad Prism 5.0. Overall clinical efficacy and tolerability were analyzed via comparison of the results of each assessment in relation to pretreatment values.

### Results

A total of 120 patients were included in the study. 3 study visits were performed: Assessment 1 (pretreatment), Assessment 2 (treatment day 3), and Assessment 3 (treatment day 6). All patients reported consumption of at least 2 alcoholic drinks per day. Pretreatment symptoms included pain (n = 120), paresthesia (n = 47), altered vibration perception (n = 34), and altered motor coordination (n = 18). Mean pretreatment VAS value was 46.78mm. At Assessment 3, mean VAS value decreased to 40.12 mm ( $P < .0001$ ). The increase in serum vitamin B<sub>12</sub> level from Pretreatment to Assessment 3 was statistically significant ( $P < .0001$ ). The number of patients presenting paresthesia decreased significantly ( $P = .0005$ ). While the number of patients presenting pain, altered vibration perception, and altered motor coordination decreased at Assessment 3, these values did not reach statistical significance. There was a statistically significant improvement in the scores of the overall condition assessments performed by the patients and the investigating physician ( $P < .0001$  for both). Twenty-seven patients presented with adverse effects, which were mild or moderate in severity, short-lasting, and none caused withdrawal from the study. The safety assessments performed throughout the study remained did not vary significantly from pretreatment values and remained within normal limits.

## Conclusions

We conclude that the intramuscular administration of uridine, cytidine, and vitamin B<sub>12</sub> was safe and effective in the treatment of patients presenting alcoholic polyneuropathy. The combination reduced pain and paresthesia in relation to pretreatment values, and increased vitamin B<sub>12</sub> levels among affected patients. Our findings are in concordance with data from previously published literature reporting that combination of uridine, cytidine, and vitamin B<sub>12</sub> has had favorable results in variety of peripheral neuropathic pain syndromes, including chronic neuropathic lumbar pain, pain following neurological surgical procedures, neural compression-induced neuralgias, peripheral neuropathies, and pain and paresthesia in patients with vitamin B<sub>12</sub> deficiency anemia.



## Trends in drug and illicit use from urine drug testing from addiction treatment clients

Steven Passik<sup>1</sup>, Howard Heit<sup>2</sup>, Adam Rzetelny<sup>1</sup>, Amadeo Pesce<sup>1</sup>, Charles Mikel<sup>1</sup>, Kenneth Kirsh<sup>1</sup>

<sup>1</sup>Millennium Research Institute, San Diego, CA, USA, <sup>2</sup>Georgetown University School of Medicine, Washington, DC, USA

### Purpose

To present trends in drug use and misuse among people with addiction so that practitioners can remain current in their knowledge to guide their assessment and management of these issues

### Method

De-identified data from Millennium Laboratories (ML) (Q1 2013 for addiction and Q3 2012 for ML Average derived from 80,000 + specimens from all practice types with similar sampling procedures) was used for this project to describe current patterns of drug use among addiction treatment clients.

Selection of practices for inclusion:

Step 1: Identify initial subset of addiction practices that have provided at least one specimen to ML during Q1 2013.

Step 2: Select from subset only practices that exclusively use 11/12-panel cups as their submission protocol.

Step 3: Select only practices that reliably provide medication lists with their submissions.

Step 4: Rank the subset created in step 3 by # of samples submitted during the assessment period (highest to lowest).

Step 5: Create final subset of practices by selecting the #1 ranked practice plus additional practices such that the following rules are obeyed;

- No more than 2 practices from any given state
- At least one of the following conditions are satisfied:
  - Final subset of practices is equal to the entire subset created in step 4
  - Number of specimens submitted by the final subset is greater than 10% of the initial subset identified in step 1
  - And the number of practices in the final subset is equal to, or greater than, 10
- Number of specimens submitted by the final subset of practices approaches but does not exceed 5000 specimens
- And the number of practices in the final subset is equal to, or greater than, 10

### Results

Out of 4299 specimens, 48.5% of specimens were in full agreement with their reported medications. 25.6% of specimens had unreported prescription medications detected and 6.8% had prescription medications not detected. 5.6% of these specimens had illicit substances detected and 9.3% had illicit substances and unreported medications detected. 3493 specimens were tested for opiates with 639 testing positive. 123 of those positive results were false positives. 182 of the specimens were found to be false negatives. 3376 specimens were tested for cocaine with 101 of those results testing positive. 8 of those results were false positives while 38 of those were false negatives.

## Conclusions

Prescription drugs, and the opioid class in particular, have wide ranging impact on society. While pain practitioners are becoming increasingly aware of the need to test patients for medication adherence and are gaining better understanding about abuse and addiction, it is helpful to understand ongoing challenges seen when treating patients for addiction. Likewise, the addiction field needs to be similarly cognizant of UDT and the implications that test results may have on treating patients with addiction and potentially helping to identify early signs of relapse. UDT can be an important tool in pain and addiction treatment.

## Trends in drug and illicit use from urine drug testing from addiction treatment clients

Steven Passik<sup>1</sup>, Howard Heit<sup>2</sup>, Adam Rzetelny<sup>1</sup>, Amadeo Pesce<sup>1</sup>, Charles Mikel<sup>1</sup>, Kenneth Kirsh<sup>1</sup>

<sup>1</sup>Millennium Research Institute, San Diego, CA, USA, <sup>2</sup>Georgetown University School of Medicine, Washington, DC, USA

### Purpose

To present trends in drug use and misuse among people with addiction so that practitioners can remain current in their knowledge to guide their assessment and management of these issues.

### Method

De-identified data from Millennium Laboratories (ML) (Q1 2013 for addiction and Q3 2012 for ML Average derived from 80,000 + specimens from all practice types with similar sampling procedures) was used for this project to describe current patterns of drug use among addiction treatment clients. Steps of practices for inclusion included: Step 1: Identify initial subset of addiction practices that have provided at least one specimen to ML during Q1 2013. Step 2: Select from subset only practices that exclusively use 11/12-panel cups as their submission protocol. (Though office based tests were not necessarily recorded in every case). Step 3: Select only practices that reliably provide medication lists with their submissions. Step 4: Rank the subset created in step 3 by # of samples submitted during the assessment period (highest to lowest). Step 5: Create final subset of practices by selecting the #1 ranked practice plus additional practices such that the following rules are obeyed.

### Results

A total of 48.5% of specimens came back in full agreement with reported medications, while the remainder showed some level of inconsistency, including 9.3% showing positive results for both illicit substances and unreported medications (compared to a prevalence rate of 3.8% from the historical laboratory average from pain and other disciplines). The most often seen illicit and alcohol markers detected were cannabinoids (20.2%) ethyl glucuronide/sulfate (11.7%) and cocaine (3%). Comparing POCT results to LC-MS/MS confirmation for opiates for the addiction specimens, 29.9% of true positives and 22.4% of true negatives were missed by POCT.

### Conclusions

While pain practitioners are becoming increasingly aware of the need to test patients for medication adherence and are gaining better understanding about abuse and addiction, it is helpful to understand the ongoing challenges seen when treating patients for addiction. Likewise, the addiction field needs to be similarly cognizant of UDT and the implications that test results may have on treating patients with addiction and potentially helping to identify early signs of relapse.

### Exploring high rates of abnormal pharmacogenetic findings in a pain practice

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#### Purpose

Pharmacogenetic testing (PGT) holds promise for impacting patient healthcare through increasing efforts towards personalized medicine and hopefully leading to more effective and less toxic medication choices. This technology has specific relevance for chronic pain populations, given that they often have complicated health issues and polypharmacy is common. This retrospective study explores the prevalence of genetic polymorphisms in a specialty pain practice in Louisiana.

#### Method

A retrospective analysis was completed for all patients entering the pain practice between the last week of November, 2012 and the first week of February 2013. PGT was specifically conducted for CYP2B6, CYP2C19, CYP2D6, or UGT2B15 utilizing a noninvasive, saliva-based test.

#### Results

The sample consisted of 61 men (58.7%) as well as 41 women (39.4%) with an average age of 46.7 years (range = 23-83, SD = 11.5 years). Across the CYP2B6, CYP2C19, CYP2D6, and UGT2B15 tests, 164 (42.3%) were Extensive, 99 (25.5%) were Intermediate, 28 (7.2%) were Ultra-rapid and 27 (7.0%) were Poor Metabolizers.

#### Conclusions

While preliminary, the data shows that specialty care clinics may encounter more frequent occurrences of genetic polymorphisms. Caution is needed as this brief report encompasses one pain practice located in a southern state with potentially distinct genetic markers. Further exploration and prospective study is needed.

## Assessing the burden of pain and unmet medical need

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### Purpose

To provide a methodological framework for the assessment of the burden of pain and unmet medical need, at low cost, in both developed and developing countries.

### Method

An assessment was carried out of the potential role of national health surveys and panel data to assess the burden of pain as it relates to (1) pain experience by prevalence, type and chronicity and (2) the impact of pain on quality of life, health status, employment experience and healthcare resource utilization. The literature review pointed to the potential role of pain panels as the most flexible approach. Rather than attempt to piggy-back of large scale national population surveys, whether in the public or private sector, the assessment pointed to the role pain specific panels provide a viable and flexible option. This is seen in the ability to apply validated assessments of screening tools to capture pain type probabilities, the likelihood of chronic pain through prognostic risk scores and the overall experience of pain and associated comorbidities.

At the same time, the assessment pointed to the fact that small, low cost pain experience samples were as robust as large scale surveys and avoided their inherent redundancy.

A key feature of successful and robust burden of pain assessments is the utilization of microdata to estimate multivariate models to assess the independent contribution of pain to the burden of disease. A major rate limiting step is the cost of data acquisition and the constraints imposed by reliance on a fixed panel. Unless costly supplementary analyses are undertaken, key attributes of pain experience and the application of validated instruments to establish clinically meaningful categories are absent.

### Results

Existing panel data assessments point to: (1) the high prevalence of chronic pain (as high as 28% of persons 18 years and over); (2) the significant contribution of daily severe pain (prevalence as high as 10% of population 18 years and over); (3) the role of key comorbidities such as depression and insomnia to the burden of pain, and (4) in multivariate analyses, the dominant and independent contribution of chronic pain to quality of life scores, overall health status, labor force participation, absenteeism and presenteeism, and emergency room visits.

Given the global prevalence of chronic and frequent pain, panel data tailored to pain populations overcome most of the limitations imposed by national population surveys and national panel data, as well as offering a viable low cost option that allows studies to be undertaken within 1 or 2 months. Unlike studies that derive from larger surveys, pain panels (together with nonpain control groups) allow the differentiation of pain types (neuropathic, nociceptive, mixed), prognostic assessments of pain chronicity, the application of validated instruments to capture subject characteristics and the presence of comorbidities. Pain panels to identify these data, to establish control groups and support comprehensive descriptive and multivariate analyses can be generated for the majority of developed and developing countries to give a global perspective on the burden of pain.

## **Conclusions**

Low cost pain panels with their control groups offer a viable option in the assessment of chronic pain. The degree of customization that small sample pain panels allow a comprehensive a flexible vehicle for pain prevalence and burden of pain estimates.

## A multimodal approach to postoperative pain: a new look at an old approach

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### Purpose

Over 90 million US surgical procedures are conducted annually and over 80% of patients report experiencing moderate-to-severe pain after surgery. Inadequately managed postsurgical pain has both clinical and economic consequences such as longer recovery times, delayed ambulation, higher incidence of complications, increased length of hospital stay and potential to develop chronic pain. Generally, opioids are the mainstay option for pain management in patients with moderate-to-severe postsurgical pain and standard treatment paradigms consist of prescribing increased amounts of opioids alongside increased pain severity. However, opioids have been reported to potentially cause significant side effects and increase overall healthcare costs. To improve patient and economic outcomes after surgery, postoperative pain guidelines have suggested incorporating a multimodal/multimechanistic approach to pain treatment. A multimodal approach is the simultaneous use of a combination of 2 or more opioid and nonopioid analgesics that provide 2 different mechanisms of actions. Utilizing a multimodal approach may result in a greater reduction in pain vs single therapies in addition to minimizing opioid use, thus reducing opioid related side effects. However, not all approaches may be effective for all types of surgeries. In addition, not all analgesics may be a viable option for outpatient settings, ambulatory surgery, or the fast-track surgical procedures. Thus, it is important for physicians and patients to have multiple options. Here we present an overview of currently available treatments and provide insight into the recently approved, novel intranasal ketorolac application which can be considered part of a multimodal analgesic regimen when managing moderate-to-severe acute pain.

### Method

A review of the literature was performed in order to provide a timely update regarding past, present, and future multimodal treatment options for postoperative pain. Initially, keywords were generated to search the available literature databases. Keywords were used alone or in combination and consisted of "multimodal analgesia," "multimechanistic analgesia," "postsurgical pain," "postoperative pain," "opioids," "nonsteroidal anti-inflammatories," "acetaminophen," "local anesthetics," "outpatient," "ambulatory," and "fast-track." The keywords listed were placed into the following databases' respective search algorithm: PubMed, EMBASE, Ingentaconnect, BIOSIS Previews, Cochrane Library, and Google Scholar. Articles were reviewed for relevancy by 2 independent authors. Only randomized controlled trials, systematic reviews, and meta-analyses were included.

### Results

The American Society of Anesthesiologists recently published guidelines on acute pain management in the perioperative setting. These guidelines recommend employing a multimodal pain therapy approach to optimize treatment and minimize adverse effects. Guidelines state that unless contraindicated, patients should receive an around-the-clock regimen of NSAIDs, COX-2 inhibitors, or acetaminophen. Nonopioid treatment options used in multimodal treatment paradigms include acetaminophen, NSAIDs, COX-2 inhibitors, ketamine, pregabalin, and gabapentin. A review of randomized controlled trials consisting of acetaminophen, NSAIDs or COX-2 inhibitors reported reductions in opioid consumption, decrease in pain scores and reduction in common opioid side effects such as nausea and sedation. Currently, ketorolac injection is commonly used to manage moderate to severe postoperative pain because it has similar potency to morphine. Ketorolac injection has been shown to have a good safety and

efficacy profile as well as demonstrate opioid sparing effects. However, ketorolac injection may not be suitable for the day surgical outpatient, ambulatory setting, or fast-tracked surgical procedure. Recently, a novel ketorolac intranasal spray (SPRIX<sup>®</sup>, Regency Therapeutics, Shirley, NY) has come to market and has shown efficacy and safety for postoperative pain. Intranasal ketorolac reaches peak plasma concentration in less than 30 minutes, with a median  $T_{max}$  of 45 minutes. Over a 48-hour period, the use of morphine was reduced by 26%-34% overall in the ketorolac group when compared with the placebo group in 2 separate clinical efficacy studies. In addition, at every time point up to 48 hours, pain intensity difference scores were higher for the ketorolac group compared with the placebo group. Intranasal ketorolac was well tolerated in clinical studies; most common side effects included nasal discomfort and irritation. Advantages for this product include: ease of use, patient controlled analgesia (PCA), and fast onset of relief compared to standard oral treatments.

## Conclusions

Postsurgical pain remains poorly managed and improvements in treatment regimens are warranted. Multiple signaling and modulatory pathways may be involved during postoperative pain sensation. Published work utilizing multiple pharmacologic interventions with different mechanisms of action has shown similar or superior efficacy vs individual agents as well as improved safety and tolerability. Nonopioid analgesics such as NSAIDs and COX-2 inhibitors are effective adjuncts to opioid therapy. Newer treatment options, such as intranasal ketorolac, may provide physicians with an additional option for patients who are not receptive to other nonopioid analgesics in addition to providing patients with an at home PCA.



## Preemptive anticipation of diverted opioid abuse: the case for an abuse-deterrent formulation (ADF) of extended-release morphine

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### Purpose

Thomas Aquinas stated: "Nothing is intrinsically good or evil but its manner of usage may make it so." This applies to medication for pain, the single most common reason that people seek medical care. Seventy percent of Americans believe that research into better pain management should be a top priority for medical science. The World Health Organization has advocated that pain relief be considered a fundamental human right. The greater availability of prescription opioids has been associated with their diversion and misuse. Drug abuse deaths have tripled since the 1990s, and 100 Americans die every day from a drug overdose. The abuse of prescription opioid analgesics has been termed a national epidemic and has vast ramifications for patients, the healthcare system, and society at large. The total financial costs associated with prescription opioid abuse (healthcare costs plus lost productivity) have been estimated at \$10 billion annually.

Opioid risk management refers to organized efforts to minimize the harms associated with opioid therapy without limiting access to appropriate opioid therapy. Managing these interlocking public health concerns requires a coordinated effort among many stakeholders, including government and law enforcement entities, prescribers, the healthcare system, patients and their families, and society at large.

The proposed Stop Tampering of Prescription Pill (STOPP) Act of 2012 was intended to allow the FDA to reject a New Drug Application for a non-ADF product of a controlled substance. However, many opioid analgesic products are still available without abuse-deterrence, including the "gold standard" narcotic pain reliever, morphine.

### Method

The authors examined the literature using the PubMed database for reviews and clinical studies from the past 5 years by searching the terms "opioid misuse," "opioid abuse," "abuse-deterrent opioids," and "morphine abuse." The authors also reviewed published reports from several websites: RADARS, the Centers for Disease Control and Prevention, the FDA Law Blog, and National Vital Statistics. These search results were then supplemented with older materials as needed to fill gaps and evaluated in light of the clinical experiences of the authors.

### Results

Opioid abusers exhibit specific drug preferences, based on drug availability, price, peer preferences, withdrawal characteristics, and media attention to a specific drug. Widely available drugs tend to be more misused than harder-to-obtain drugs, where availability is defined by numbers of pills dispensed, prescriptions filled, and individuals who fill at least one prescription per quarter. RADARS System Poison Center data report that hydrocodone is the most-abused drug, but hydrocodone is rarely described by drug abusers as a drug of choice. Many abusers are opportunistic and take multiple drugs, as availability allows; a study of oxycodone-related deaths from 1999 to 2002 found most involved polydrug use patterns.

The choice of OxyContin as the primary drug of abuse dropped from 35.6% of respondents to 12.8% in 21 months when the new ADF (OxyContin OP) came on the market ( $P < .001$ ); in that same time, the selection of other non-ADF opioids as primary drug of abuse increased from 20.1% to 32.3% ( $P = .005$ ). The release of OxyContin OP coincided with an increase in abuse of extended-release oxymorphone. The arrival of ADFs also has coincided with an upsurge in the use of heroin; in Maryland, heroin-related deaths increased 41% from 2011 to 2012 while, at the same time, deaths related to prescription opioids decreased by 15%.

Among opioid abusers, morphine is a well "liked" drug; drug abusers rated it about 70% (100% was most desirable) compared to 80% for oxycodone (a "drug of choice" on the street). Morphine is a widely available, frequently prescribed, and inexpensive. An ADF of extended-release morphine (Embeda, Pfizer) has been withdrawn from the market. The current lack of an abuse-deterrent formulation for extended-release morphine suggests that morphine will be particularly vulnerable to abuse.

### **Conclusions**

It seems likely that the release of abuse-deterrent opioids will result in a redirected increase in the abuse of non-abuse-deterrent long-acting opioids. The specific lack of an abuse-deterrent formulation for extended-release morphine is a gap. The development and approval of an abuse-deterrent formulation extended-release morphine should be a high priority for the healthcare system.

## Evaluating the need for an abuse-deterrent immediate-release formulation of oxycodone

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### Purpose

The increased use of opioid analgesics to treat moderate to severe acute and chronic pain syndromes has benefited many patients, but at a price to public health and welfare. With greater availability of prescription opioids a concomitant increase in the diversion, misuse, and abuse of prescription pain killers has occurred, which has been estimated to cost the US about \$10 billion annually in healthcare-associated costs and lost productivity. In order to allow access to opioid analgesics for the pain patients who need them, comprehensive opioid risk management strategies are necessary, including patient and clinician education, prescription monitoring programs, and abuse-deterrent formulations. Abuse-deterrent formulations exist for some but not all prescription opioids. Our objective was to evaluate the need for an abuse-deterrent formulation of immediate-release (IR) oxycodone.

### Method

The authors searched the PubMed database to using key search terms "abuse-deterrent oxycodone immediate release" and "immediate-release oxycodone" for articles (clinical studies, reviews, editorials) published in the past 3 years. A similar Google search was performed for related news articles. The authors reviewed these materials for relevance to their question about the need for ADF oxycodone IR.

### Results

The US consumed 82% of the world's oxycodone in 2007. Extended-release (ER) oxycodone is currently available in an abuse-deterrent formulation. An abuse-deterrent formulation of IR oxycodone exists but is available only in 5.0 mg and 7.5 mg tablets and is not widely used (Oxecta<sup>®</sup>, Pfizer); no abuse-deterrent formulation exists for IR oxycodone for 15 and 30 mg.

With a higher and less variable bioavailability than morphine, oxycodone scores high in terms of "likability" among abusers with few negative subjective responses. Oral IR oxycodone is better "liked" by abusers than ER oxycodone. A survey of high school students indicated that ER and IR oxycodone were their preferred prescription opioids for abuse.

Oxycodone abuse was rampant in Florida, which once bought 89% of the nation's oxycodone supply; recent legislation has shut down these "pill mills."

In 2010, the market release of an abuse-deterrent formulation for oxycodone ER resulted in a 53% decrease in reports of drug diversion per population and a 50% decrease per unique recipient. The current availability of an abuse-deterrent formulation of ER oxycodone and non-abuse-deterrent formulations of IR oxycodone products makes it likely that oxycodone abuse will simply shift to one of the widely available non-abuse-deterrent immediate release formulations.

A less-discussed role of abuse-deterrent IR oxycodone involves pain patients who are known to be at elevated risk for opioid misuse. Abuse-deterrent products make it possible for prescribers to mitigate the risks of opioid analgesia prescribed for high-risk patients. Fixed-dose combination products including oxycodone are available, but may be contraindicated in patients who must avoid or limit their use of acetaminophen. The availability of an abuse-deterrent IR oxycodone product would permit oxycodone monotherapy for a broad range of patients and be an important addition to the armamentarium for treating pain patients while reducing societal risks of opioid diversion.

## **Conclusions**

As the US migrates to a comprehensive offering of abuse-deterrent prescription opioids, it seems urgent that an abuse-deterrent oxycodone immediate-release formulation 15 and 30 mg be developed. Oxycodone is a frequently abused agent that nevertheless plays an important role in pain management, and immediate-release opioids are important agents for treating postoperative pain and a variety of acute and chronic pain syndromes. Abuse-deterrent immediate release oxycodone would facilitate pain management in high-risk and other patients without compromising pain management.

## Insights into abuse-deterrence: can we avoid both diversion and discrimination?

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### Purpose

The number of drug overdose deaths in the US have more than tripled since 1990 with about 100 Americans dying from a drug overdose every day. About 55% of those who abuse prescription pain relievers say they got the pills from a friend or relative. About 75% of those who misuse prescription opioids take drugs that were originally prescribed for another person. The nonmedical use of prescription pain killers accounted for 43% and 47% of emergency department visits related to drug misuse for boys and girls, respectively, aged 12 to 14 in 2010 and 31% and 45% of boys and girls, respectively, aged 15 to 17. In 2011, about 8 million Americans age 12 and older currently abuse drugs other than marijuana, of which 4.5 million misused pain relievers. In a survey of prescription drug abusers that was conducted from 2010 to 2011, about half said they got the drugs they abused free from a friend or relative, with 80% of these respondents saying the friend or relative had a prescription from just one physician. About 50% of teens opportunistically seek out prescription drugs for recreational use with the notion that prescribed agents are safer than street drugs. To reduce abuse, prescribers may attempt to discriminate between high-risk and low-risk patients. Our objective was to explore the most important ways in which opioids might be diverted for misuse and abuse.

### Method

The authors used the PubMed database and keywords "opioid diversion" and "opioid abuse" to search for recent (<3 years) articles, editorials, clinical studies, and reviews. The authors then examined the literature to determine specific types of diversion.

### Results

Prescription opioid abusers get their drugs through 3 main mechanisms.

#### *Friends and Relatives*

Three out of 4 people who misuse pain medication report that they take drugs prescribed to another, described as a friend or a relative. Prescribers may at times discriminate among patients believed to be at high risk for potential opioid abuse; however, such prescribed drugs may be taken from a legitimate patient's possession by an abuser. For that reason, the use of abuse-deterrent opioid formulations may be an important component in opioid risk management. Such abuse-deterrent products should be prescribed without regard to the individual patient's abuse risk, since the prescriber cannot know who might gain access to the patient's medicine cabinet. Abuse-deterrent formulations are appropriate for all patients, not just those at high risk.

#### *Leftover Pills*

Opportunistic users may take leftover opioids from their own, family, or friends' prescriptions: 37% of students misusing opioids reported using leftover drugs. A study of surgical patients found that, on average, they consumed

only 58% of the prescription pain relievers prescribed and 67% reported having medication left over from the initial prescription. In a study of 250 elective surgery outpatients, most received a 30-pill prescription of an opioid pain reliever but consumed a mean of 10 pills. Most patients are not well informed about how to dispose of prescription narcotics, and may simply keep them without appreciating the risk they present.

### *Doctor Shopping*

Doctor shopping involves posing as a pain patient to obtain multiple prescriptions; a retrospective study of over 146 million opioid prescriptions found less than 1% of those purchasing a prescription could be presumed to be doctor shoppers (consistent with another study of 25 million subjects) although this group bought 1.9% of all opioid prescriptions, composing 4% of the weighted amount dispensed.

### **Conclusions**

Abuse of opioids has led to increased scrutiny and regulations, which may result in undertreatment of pain. The advent of abuse-deterrent opioid formulations is one important solution and an important treatment option in the prescriber's armamentarium. When deciding what to prescribe for a patient, prescribers have the option of using abuse-deterrent formulations exclusively to avoid the appearance of "profiling" or discriminating against particular patients. Further study and analysis are needed as well as public health education about the diversion of prescription pain killers, which play an important role in clinical practice.

## Relative attractiveness of oxycodone/naloxone (OXN): comparative assessment of tampering potential and recreational drug user preferences for different opioid formulations

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### Purpose

The nonmedical use of prescription drugs by recreational drug users and abusers presents a major public health issue. Tampering, eg, crushing, grinding, chewing, or dissolving, is conducted so that a significant amount, or even the entire amount, of the drug becomes available for immediate absorption by parenteral administration, mucosal application, or intentional swallowing of the manipulated dosage form, in order to achieve rapid euphoric effects. Several approaches have been taken to reduce opioid abuse potential via reformulation of existing products with physicochemical resistance properties and addition of antagonist components to produce pharmacological deterrence. OXN is a twice-daily oral controlled-release combination formulation of oxycodone hydrochloride and naloxone hydrochloride in a 2/1 ratio by weight, under development in the US for management of moderate to severe chronic pain. Naloxone is a potent antagonist at mu receptors and is included for its abuse-deterrent properties and to potential to decrease opioid gastrointestinal side effects without affecting the analgesic effect of oxycodone. The attractiveness of OXN relative to other oxycodone formulations was assessed by soliciting the opinion of experienced opioid drug abusers, who have knowledge and experience in misusing and tampering with pharmaceutical opioid products. The current study was designed to investigate how the expected pharmacologic deterrent properties of OXN translated into a decrease in attractiveness to drug abusers in a 'real-world' situation.

### Method

This was a noninterventional, single-session research study conducted in current recreational opioid users who had experience in tampering with and administering prescription formulations by alternative routes of administrations. The study assessed the attractiveness for abuse and tampering with OXN tablets compared to other oxycodone formulations, including original formulation OxyContin tablets, oxycodone immediate-release tablets, Percocet tablets (oxycodone and acetaminophen), Percodan tablets (oxycodone and aspirin), and hypothetical oxycodone transdermal patches. Subjects who reported having tampering experience for the purpose of: (1) oral administration, (2) intravenous (IV) administration, and (3) snorting via physically manipulating drug products (eg, crushing, dissolving, chewing and others) were included and completed the study. Each subject attended one study session lasting approximately 2-3 hours. The assessed endpoints included opioid abuse/tampering history and preferences, Opioid Attractiveness Scale, Value of Product Scale, Likelihood to Tamper Scale, Value of Product-Likelihood to Tamper Index, Overall Desirability Ranking, and Estimated Street value. Responses to open-ended questions were recorded. Descriptive statistics were tabulated and the differences between the formulations were evaluated nonparametrically based on the distribution of data.

### Results

Thirty subjects completed the study (76.7% male, 86.7% white, mean age 39.0 years). Preferred route of administration was reported as oral for 13 (43.3%) subjects, intravenous for 8 (26.7%) subjects, and intranasal for 9 (30.0%) subjects. The majority of subjects ( $\geq 50.0\%$ ) reported prior tampering and abuse experience with OxyContin<sup>®</sup> (original formulation), Percocet<sup>®</sup>, codeine products, Dilaudid<sup>®</sup>, "other" morphine products and Percodan<sup>®</sup>. OxyContin<sup>®</sup> (original formulation) was reported as the most attractive opioid for abuse, and Dilaudid<sup>®</sup> was reported as the second most attractive opioid. All subjects had snorted opioids. Insufflation and chewing were reported as the most common routes of nonmedical administration (both 30%). Most subjects had used intact products by oral ingestion (90.0%) and

reported having chewed opioids (83.3%). All subjects reported crushing for oral or intranasal administration, and had previously chewed products (90.0%) or removed coatings or layers prior to oral intake (73.3%). The majority of subjects reported dissolving products in water, alcohol, or other solvents for oral or intravenous administration. Other tampering methods, such as heating/boiling/melting or chemical extractions were less common ( $\leq 26.7\%$ ). Subjects reported being willing to spend up to 30 minutes tampering with the highest dose of oxycodone (80 mg) compared to the lower doses (10 or 40 mg). From responses to open-ended questions, the presence of naloxone was the main factor deterring OXN abuse, independent of route of administration. Oral and intravenous abusers indicated they would not abuse OXN and that they would inform others of the presence of naloxone and absence of "high". Subjects rated OXN as least attractive and OxyContin® (original formulation) as most attractive. When ranked, OXN had the lowest Overall Desirability and Estimated Street Value, and OxyContin® (original formulation) had the highest; the differences in desirability and street value between OXN and the other oxycodone products evaluated were statistically significant.

### **Conclusions**

OXN was found to be the least attractive of the oxycodone products by recreational opioid users with experience with tampering and various routes of administration, while OxyContin® (original formulation) was the most or amongst the most attractive of the products. Although potential OXN tampering methods were suggested by the intranasal abusers, the overall conclusion of this study is that the presence of naloxone constitutes a significant deterrent against abuse and tampering of OXN.



## Half-value duration analysis for acetaminophen after single and multiple doses of oral MNK-795 controlled-release oxycodone/acetaminophen (CR OC/APAP) tablets

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### Purpose

The first controlled-release (CR) combination oxycodone (OC)/acetaminophen (APAP) analgesic, MNK-795 (CR OC/APAP), was designed to treat acute pain with 12 hour dosing. CR OC/APAP employs a dual layer biphasic delivery profile, that when administered as a single dose (ie, 2 tablets), consists of an immediate-release (IR) component containing 3.75 mg OC/325 mg APAP and an extended-release component containing 11.25 mg OC/325 mg APAP. The total APAP strength/tablet follows the latest US Food and Drug Administration limit of 325 mg/dosage unit. The technology targets its CR properties in the upper gastrointestinal tract to maximize the bioavailability of APAP and produce an extended duration of action. The formulation also incorporates technology designed to provide tamper-resistance and abuse-deterrence. This delivery of APAP results in a rapid rise in plasma concentration (45 min-1 h) with subsequent tapering to approximately 17% to 18% of the peak plasma concentration by 12 hours after dosing. Conventional pharmacokinetic (PK) measures, such as maximum plasma concentration ( $C_{max}$ ) and time to  $C_{max}$  ( $T_{max}$ ), alone may be insufficient to fully describe the performance of CR formulations. Half-value duration (HVD) is a complementary PK measure of the period of time during a dosing cycle that plasma concentrations are equal to or above half of the maximum concentration (50%  $C_{max}$  value); HVD can be used to better describe PK behavior of a modified release product. This analysis evaluated the HVD for APAP after single and multiple doses of CR OC/APAP (2 tablets) compared with IR OC/APAP (1 tablet; 7.5 mg/325 mg) administered every 6 hours.

### Method

Data were obtained from 2 randomized, open-label, crossover studies (1 single dose and 1 multiple dose) conducted in healthy adults (age 18-55 years). Oral doses of CR OC/APAP were administered 2 tablets (15 mg OC/650 mg APAP) administered once in the single-dose study, and 2 tablets administered every 12 hours for 4.5 days (9 doses) in the multiple-dose study. Oral doses of IR OC/APAP were administered as 1 tablet every 6 hours for 2 doses (for a total of 15 mg OC/650 mg APAP over 12 hours) in the single-dose study, and every 6 hours for 4.5 days (18 doses) in the multiple-dose study. All treatments were administered under fasted conditions. Blood samples for PK analysis were collected up to 36 hours in the single-dose study and up to 132 hours after the hour-0 dose in the multiple-dose study. Plasma was analyzed for APAP using a validated liquid chromatography/tandem mass spectrometry (LC/MS) method. HVD (and conventional measures of  $C_{max}$ ,  $T_{max}$ , and area under the concentration time curve [AUC]) for APAP after single and multiple doses of CR OC/APAP were compared with values from IR OC/APAP. For the multiple-dose study, the analysis was performed for both the initial dose period (day 1, 0-12 h) and at steady state (day 5, 0-12-h dosing interval; ie, 96-108 h). Paired 2-tailed *t*-tests were used in statistical analysis. Safety and tolerability were monitored throughout each study.

### Results

PK data from 29 and 24 adults were included in the single- and multiple-dose studies, respectively. Conventional PK measures for APAP were similar for CR OC/APAP and IR OC/APAP in both the single-dose and multiple-dose studies. In the single-dose study, the mean (SD)  $C_{max}$  of APAP was 4654 ng/mL (1360 ng/mL) for CR OC/APAP and 4387 ng/mL (1326 ng/mL) for IR OC/APAP, the median  $T_{max}$  was 0.75 hours for both, and  $AUC_{0-inf}$  was 30759 ng•h/mL and 30368 ng•h/mL for CR OC/APAP and IR OC/APAP, respectively. Values were similar at day 1 and at steady

state in the multiple-dose study, with no accumulation. Peak mean (SD) plasma APAP concentrations at steady state were 4793 ng/mL (1132 ng/mL) for MNK-795 and 4877 ng/mL (1383 ng/mL) for IR OC/APAP. The HVD of APAP was slightly (but not statistically significantly) shorter for CR OC/APAP vs IR OC/APAP after the first administration (mean [SD], 3.68 h [1.80 h] vs 4.41 h [2.34 h], respectively; difference of -0.73 h,  $P = .133$  in the single-dose study; mean [SD] 3.33 h [1.46 h] vs 3.60 h [2.03 h], respectively; difference of -0.27 h,  $P = .520$  on day 1 in the multiple-dose study). During steady state, however, the HVD of APAP with CR OC/APAP was significantly longer than for IR OC/APAP (mean [SD], 4.24 h [1.35 h] vs 3.11 h [1.83 h], respectively, difference of 1.13 h,  $P = .024$ ). Treatment emergent adverse events (TEAEs) occurred in 37.5% and 64.5% of participants while taking IR OC/APAP, and in 23.1% and 45.5% while taking CR OC/APAP, in the single- and multiple-dose studies, respectively. The most frequently reported TEAEs after CR OC/APAP administration were nausea (12.8%), dizziness (7.7%), and somnolence (7.7%) in the single-dose study, and nausea (24.2%), vomiting (21.2%), headache (15.2%), and dizziness (12.1%) in the multiple-dose study.

## Conclusions

This first CR combination OC/APAP analgesic was studied in clinical trials as 2 tablets administered every 12 hours. The current PK analysis showed that the  $C_{max}$ ,  $T_{max}$ , and AUC of APAP with 12-hour dosing of CR OC/APAP (15 mg OC/650 mg APAP) were consistent with IR OC/APAP (7.5 mg OC/325 mg APAP) taken every 6 hours; however, the HVD for APAP of CR OC/APAP was significantly longer with steady-state dosing. These PK findings support the administration of CR OC/APAP every 12 hours for the management of moderate to severe acute pain, and illustrates that CR OC/APAP has a unique PK profile.

## Half-value duration analysis for oxycodone after single and multiple doses of oral MNK-795 controlled-release oxycodone/acetaminophen (CR OC/APAP) tablets

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### Purpose

The first controlled-release (CR) combination oxycodone (OC)/acetaminophen (APAP) analgesic, MNK-795 (CR OC/APAP), was designed to provide fast onset of analgesia (< 1 hour) and sustained analgesia over the 12 hour dosing interval. It is being developed to manage moderate to severe acute pain that warrants treatment with a CR analgesic. CR OC/APAP employs a dual layer biphasic delivery profile, that when administered as a single dose (ie, 2 tablets), consists of an immediate-release (IR) component containing 3.75 mg OC/325 mg APAP and an extended-release component containing 11.25 mg OC/325 mg APAP. The formulation incorporates technology designed to provide tamper-resistance and abuse-deterrence. Conventional pharmacokinetic (PK) measures, such as maximum plasma concentration ( $C_{max}$ ) and time to  $C_{max}$  ( $T_{max}$ ), may be insufficient to fully describe CR formulations. Half-value duration (HVD) is a measure of the period of time during a dosing cycle that plasma concentrations are equal to or above half of the maximum concentration (50%  $C_{max}$  value); HVD can be used as a complementary measure of a PK profile to describe modified release characteristics. This analysis evaluated the HVD for OC after single and multiple doses of CR OC/APAP (2 tablets) compared with IR OC/APAP (1 tablet; 7.5 mg/325 mg) administered every 6 hours.

### Method

PK data from 2 randomized, open-label, crossover studies (1 single dose and 1 multiple dose) conducted in healthy adults (age 18-55 years) were analyzed. Oral doses of CR OC/APAP were administered as 2 tablets (15 mg OC/650 mg APAP) taken once (single-dose study) and 2 tablets administered every 12 hours for 4.5 days (9 doses; multiple-dose study). The same participants also received oral doses of IR OC/APAP during a separate trial period, administered as 1 tablet every 6 hours for 2 doses (for a total of 15 mg OC/650 mg APAP over 12 hours) in the single-dose study and 1 tablet every 6 hours for 4.5 days (18 doses) in the multiple-dose study. All treatments were administered under fasted conditions. Blood samples for PK analysis were collected up to 36 hours in the single-dose study and up to 132 hours after the hour-0 dose in the multiple-dose study. Plasma was analyzed for OC using a validated liquid chromatography/tandem mass spectrometry (LC/MS) method. HVD (and conventional measures of  $C_{max}$ ,  $T_{max}$ , and area under the concentration time curve [AUC]) for OC after single and multiple doses of CR OC/APAP were compared with PK values from IR OC/APAP. For the multiple-dose study, the analysis was performed for both the initial dose period (day 1, 0-12 h) and at steady state (day 5, 0-12-h dosing interval; ie, 96-108 h). Paired 2-tailed *t*-tests were used in statistical analysis. Safety and tolerability were monitored throughout each study.

### Results

PK data from 29 adults in the single-dose study and 24 adults in the multiple-dose study were included. In the single-dose study, the mean (SD)  $C_{max}$  of OC was lower for CR OC/APAP compared with IR OC/APAP (14.28 ng/mL [2.94 ng/mL] vs 19.42 ng/mL [4.62 ng/mL], respectively). The median  $T_{max}$  was observed at 4 h for CR OC/APAP and 8 h (2 hours after the second dose) for IR OC/APAP, and the mean  $AUC_{0-inf}$  for CR OC/APAP and IR OC/APAP (at the same total dose) were comparable (169.34 ng•h/mL vs 171.53 ng•h/mL, respectively) over the dosing period. Consistent with a controlled-release product, the HVD of OC after single doses was significantly longer for CR OC/APAP compared with IR OC/APAP (mean [SD], 9.65 h [2.81 h] vs 5.94 h [2.23 h], respectively, difference of 3.71 h,  $P < .0001$ ). Similar results were seen in the multiple-dose study. On day 1 after initial dosing and during steady state, the  $C_{max}$  was lower for CR OC/APAP vs IR OC/APAP, with similar AUC. The mean (SD) HVD over the dosing interval on

day 1 in the multiple-dose study was significantly longer for CR OC/APAP compared with IR OC/APAP (7.90 h [1.70 h] vs 5.54 h [2.53 h], respectively, difference of 2.35 h,  $P < .0001$ ), as was the HVD at steady state (7.85 h [1.39 h] vs 5.79 h [2.80 h], respectively, difference of 2.06 h,  $P < .001$ ). In the single- and multiple-dose studies, respectively, 37.5% and 64.5% of participants experienced a treatment emergent adverse event (TEAE) after IR OC/APAP, and 23.1% and 45.5% experienced a TEAE after CR OC/APAP. The most frequently reported TEAEs following administration of CR OC/APAP were nausea (12.8%), dizziness (7.7%), and somnolence (7.7%) in the single-dose study and nausea (24.2%), vomiting (21.2%), headache (15.2%), and dizziness (12.1%) in the multiple-dose study.

## Conclusions

Traditional PK measures indicate a lower  $C_{max}$  and equivalent AUC of OC with CR OC/APAP administered as 2 tablets every 12 hours (15 mg OC/650 mg APAP) compared with IR OC/APAP (7.5 mg OC/325 mg APAP) administered as 1 tablet every 6 hours. The HVD measure indicates a longer time above 50% of the  $C_{max}$  for OC plasma concentrations with CR OC/APAP compared with IR OC/APAP. These PK findings support the administration of CR OC/APAP every 12 hours for the management of moderate to severe acute pain, and illustrate a unique PK profile for CR OC/APAP.

## **Intrathecal inhibition of activator protein 1 (AP-1) attenuates spared nerve injury-induced hypernociception and regulates expression of proinflammatory cytokines in mice.**

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### **Purpose**

Neuropathic pain results from nerve damage or dysfunction and induces plastic changes throughout the nociceptive sensory system, which is associated to the painful process' chronification. These changes may be due to the induction and/or repression of genes, which may be modulated by transcription factors. One of the main transcription factor involved in the inflammatory process is the activator protein-1 (AP-1), which is structurally formed by protein families Jun, Fos, ATF (activating transcription factor) or MAF (muscular aponeurotic fibrosarcoma), arranged as homo- or heterodimers connected by a structure called "leucine zipper." The AP-1 appears to be essential for the maintenance of physiological and pathological condition of the immune system, eg, psoriasis, where AP-1 seems to determine which cytokine genes are activated, thus, modulating the progression of the disease. The activation of AP-1 induces the production of proinflammatory cytokines, which can trigger central and peripheral sensitization. Cytokines IL-1 $\beta$  and TNF- $\alpha$ , for example, cause central sensitization via activation of sodium channels resistant to tetrodotoxin 1.8, thus reducing the threshold for activation of these neurons and facilitating the hypernociception. However, the role of AP-1 in the induction and/or maintenance of neuropathic hypernociception is incompletely understood. The present study describes how pharmacological inhibition of AP-1 may be a potential therapeutic strategy for treating neuropathic pain. Our hypothesis is that activation of transcription factor AP-1 would participate in the genesis and/or maintenance of neuropathic pain, by inducing the production/release of proinflammatory cytokines (IL-1 $\beta$  and TNF- $\alpha$ ) in spinal cord of mice.

### **Method**

Female C57BL/6 mice (20-30 g) were housed in temperature-controlled rooms (22-25 °C) with access to water and food ad libitum. All experiments were conducted in accordance with National Institutes of Health Guidelines for the welfare of experimental animals and with the approval of the Ethics Committee of the School of Medicine of Ribeirão Preto (University of São Paulo, Brazil). All behavioral tests were performed between 8 and 17 hours. Each experiment used 5 to 8 animals per experimental group. The animals received inhalation anesthesia (2% isoflurane) and were submitted to an experimental model of neuropathic pain Spared Nerve Injury (SNI). For false operated (sham) mice, the nerve was similarly exposed, but no nerve ligation was carried out. The animals were treated intrathecally (i.t.) with AP-1 inhibitor SR11302 ((E,E,Z,E)-3-Methyl-7-(4-methylphenyl)-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid) in the dose range of 3-100  $\mu$ g/site or vehicle. The mechanical nociceptive evaluation was performed with von Frey filaments. The assessment of the motor activity of the animals was checked by the rota-rod apparatus. After anesthesia (2% isoflurane), the spinal cord of the animals were exposed and the segment L4-L5 of the spinal cord was removed for evaluating the expression of messenger RNA (mRNA) and protein of proinflammatory cytokines were measured by RT-PCR and ELISA, respectively.

### **Results**

Four different protocols were made for intrathecal treatment with an inhibitor of AP-1 (SR11302) to evaluate the mechanical hypernociception by von Frey filaments: 1) Single daily injections immediately prior to the SNI and on days 1, 2, 3 and 4 after SNI triggered hypernociception attenuation only on day 14 after SNI. 2) Single daily injections on days 4, 5, 6 and 7 after SNI triggered hypernociception attenuation in 1-3 hours after the last injection

(day 7). 3) Single daily injections on days 7, 8, 9 and 10 days after SNI triggered hypernociception attenuation in 3-5 hours after each injection, returning to baseline threshold next day. 4) Single injection on day 7 after SNI is enough to attenuated hypernociception in 3-5 hours after injection. None of the aforementioned protocols injections caused motor damage to animals, given by the rota-rod apparatus (data not showed). The behavioral results suggest that AP-1 is involved in the maintenance of neuropathic hypernociception. On the seventh day after SNI, segment L4-L5 of the spinal cords of animals submitted or not to SNI were removed 3 hours after i.t. injection of the inhibitor of AP-1 (SR11302) for RT-PCR and ELISA. The results showed that the SNI surgery causes an increase of approximately 114 and 95 % mRNA expression of IL-1 $\beta$  and TNF- $\alpha$  compared to the sham animals, respectively. This increase was attenuated by approximately 58 and 61% when animals were pretreated (3 hours before) with SR11302. However, these results were not observed in the measure of the expression of these cytokines by ELISA.

## Conclusions

Current treatments for neuropathic pain are only partially effective and additional development is hindered by the incomplete knowledge of how neuropathic pain is induced and maintained. This study shows that the inhibition of transcription factor AP-1 may be a potential analgesic/anti-inflammatory for treating neuropathic pain, since AP-1 inhibitor blocks, for a few hours, the mechanical hypernociception triggered by experimental model of neuropathic pain by reducing the synthesis of pro-inflammatory cytokines IL-1 $\beta$  and TNF- $\alpha$ .

## **Intraplantar pertussis toxin-evoked hypernociception depends on neutrophil migration, proinflammatory cytokines, adaptor molecule MyD88 and toll-like receptor 4**

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### **Purpose**

Pertussis toxin (PTX) is the major virulence factor of *Bordetella pertussis*. This bacterium is characterized as strictly aerobic, nonlactose fermenting gram-negative coccobacillus and causative agent of whooping cough, a highly dangerous and contagious disease which is preventable by vaccination. However, most patients complain of pain at the site of this vaccine. PTX is also frequently used as a pharmacological tool for inhibiting  $G_i$  and  $G_o$  proteins, eg, in studies of the mechanism of action of antinociceptive drugs. Intrathecal PTX induces hypernociceptive signals compared to neuropathic syndromes in rats and mouse. However, the mechanism by which PTX causes hypernociception is poorly elucidated. Therefore, our hypothesis is that the pertussis toxin triggers an inflammatory process, including pain.

### **Method**

Nociceptive evaluation was made through constant and increasing pressure apparatuses on the animal's paw (modified Randall-Selitto and electronic von Frey, respectively). The variation in paw volume was measured by using a hydroplethismometer. The number of neutrophils was indirectly checked by a colorimetric assay which evaluated the myeloperoxidase activity. Cytokine concentration was measured by immunosorbent assay (ELISA).

### **Results**

High doses of PTX ( $0.3 - 1 \mu\text{g.paw}^{-1}$ ) cause mechanical hypernociception in rats, confirmed in mice ( $0,6 - 1 \mu\text{g.paw}^{-1}$ ), and edema, which depends on the neutrophil migration and increased pro-inflammatory cytokine's synthesis/release to the injection's site. Such effects were partially prevented by the pretreatment with intravenous fucoidin or intraplantar indomethacin, atenolol or dexamethasone. Posttreatment with i.pl.morphine inhibited the PTX-evoked mechanical hypernociception. Further, pretreatment with adenylyl cyclase, protein kinase (PK) A or PKC inhibitors also prevented PTX-caused mechanical hypernociception. Mice which are mutant for toll-like 4 receptors (TLR4) and knockout for MyD88 adaptor molecule did not show either i.pl. PTX-evoked mechanical hypernociception or neutrophil migration, when compared to the respective wild type animals.

### **Conclusions**

The present study showed that the pain caused by the vaccine containing PTX may be due to an inflammatory response, with induction of the mechanical hypernociception, edema, neutrophil migration and inflammatory mediators synthesis/release. The mechanical hypernociception seems to depend on the signalization pathway, which involves adenylyl cyclase/protein kinase (PK) A and PKC. The mechanical hypernociception and the neutrophil migration evoked by the i.pl. PTX depend on toll-like 4 receptors, as well as molecule MyD88.

## Comparison of heated lidocaine/tetracaine patch and corticosteroid injection for treatment of shoulder impingement syndrome pain: a 6-week, randomized, open-label study

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### Purpose

Shoulder impingement syndrome (SIS) is a common cause of shoulder pain and limitation of shoulder range of motion (ROM). Treatment of SIS typically begins with conservative therapy that includes oral nonsteroidal anti-inflammatory drugs (NSAIDs) and supervised physical therapy, with the goal of reducing pain and improving strength and function. In patients who fail to respond to this treatment strategy, subacromial injections of a corticosteroid may be of benefit. Recent case reports and a small clinical study suggest that the heated lidocaine/tetracaine patch (HLT patch) may represent an initial conservative treatment for SIS pain. The HLT patch (ZARS Pharma, Salt Lake City, UT) contains a eutectic mixture of lidocaine (70 mg) and tetracaine (70 mg) with an integrated oxygen-activated heating component. Previous studies of the depth and duration of anesthesia produced by the HLT patch suggest that it may be effective in controlling pain in superficial musculoskeletal structures. The present study was conducted to compare the efficacy of the HLT patch vs a single corticosteroid injection in the treatment of SIS pain in a 6-week, randomized, open-label study.

### Method

Patients with unilateral SIS pain of  $\geq 14$  days' duration and an average pain score of  $\geq 4$  (0-10 scale) were enrolled in the study and randomized to treatment with a single HLT patch applied to the affected shoulder twice daily for 14 days or to a single subacromial corticosteroid injection. Patients in the HLT patch group could continue with treatment on an as-needed basis for an additional 2 weeks, with a limit of 2 HLT patches per day. During the final 2 weeks, no additional treatment was allowed. At baseline and at 2, 4, and 6 weeks, patients rated their pain and pain interference with specific activities (0-10 scale). Shoulder ROM (internal rotation and abduction) was measured with a goniometer at baseline and at each study visit. Patients were provided with acetaminophen to use as rescue medication for SIS pain, but patients who used acetaminophen for this purpose on 2 consecutive days were considered treatment failures. These patients, as well as patients with protocol violations or those who had withdrawn from the study, had all postbaseline values imputed as baseline observations carried forward. A *t*-test was used to compare changes from baseline and between-group differences.

### Results

Sixty-five patients were screened; 60 were enrolled in the study (average age = 51, range 18-75 years,  $n = 21$  female) and randomized to either the HLT patch group ( $n = 29$ ) or the injection group ( $n = 31$ ). In the HLT patch group, 2 patients were deemed treatment failures due to acetaminophen use, 3 patients were withdrawn due to protocol violations, and 1 patient withdrew due to an adverse event (increased shoulder pain). In the injection group, 6 patients were deemed treatment failures due to acetaminophen use, and 2 patients were lost to follow-up. Patients in the HLT patch group averaged about 1 patch/day during the 2 weeks of as-needed treatment. Average pain scores at baseline were similar in the HLT patch ( $6.0 \pm 1.6$ , mean  $\pm$  SD) and injection ( $5.6 \pm 1.2$ ) groups. Both groups demonstrated a significant ( $P < .001$ ) reduction in average pain scores at 2 weeks compared with baseline ( $-35\% \pm 29\%$  and  $-42\% \pm 36\%$  in the HLT patch and injection groups, respectively), which were sustained through 6 weeks ( $-43\% \pm 34\%$  and  $-43\% \pm 41\%$ , respectively). No significant differences between the HLT patch and injection groups were seen at any time point. At 6 weeks, 66% of the HLT patch group demonstrated a clinically important ( $\geq 30\%$ )



reduction in average pain score compared with 55% in the injection group. Similar improvements were seen in each group for worst pain and pain interference with general activity, work, or sleep. Significant improvements in ROM were observed for both internal rotation and abduction at 2 weeks in both groups and were sustained through 6 weeks.

## **Conclusions**

The pragmatic dosing of the HLT patch, which was intended to reflect real-world use of analgesics by patients with acute musculoskeletal pain (fixed dosing for 2 weeks followed by as-needed dosing for the subsequent 2 weeks), resulted in a sustained benefit lasting 6 weeks. This benefit was achieved by a noninvasive approach and was similar to that observed in the group of patients who were treated with a single subacromial corticosteroid injection. Based on these results, the HLT patch may represent an alternative initial conservative treatment for SIS, and further study is warranted.

## Should buprenorphine be called a 'partial agonist'?

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### Purpose

It has become somewhat commonplace to read buprenorphine referred to as a 'partial agonist,' but without a reason given. It seems that this characterization is based mainly on *in vitro* laboratory assay results rather than on *in vivo* testing or clinical data. When this is the case, such designation commingles separate pharmacologic principles: intrinsic activity (at the receptor level) and efficacy (applicable only to a specific clinical situation). Because buprenorphine is well suited for transdermal delivery and is being increasingly prescribed in this way for pain relief, an improper characterization based on preclinical assays can result in misperceptions leading to suboptimal use. We review the criteria and evidence to assist in answering the question of whether buprenorphine should be termed a partial agonist.

### Method

The terms 'affinity,' 'intrinsic activity,' 'efficacy,' 'full agonist,' and 'partial agonist' are defined and described, and the distinctions among them are highlighted by illustrative examples. Preclinical *in vitro* assays, *in vivo* animal models, PET scans, and clinical trial results for buprenorphine were obtained from literature sources, reviewed, and are presented. The material is organized in a manner and directed toward addressing the question of whether it is accurate or appropriate to refer to buprenorphine as a partial agonist.

### Results

Buprenorphine has been studied in laboratory assays, animal models, and human clinical trials. These measure 3 related but distinct pharmacologic properties: affinity, intrinsic activity, and efficacy. Affinity represents the chemical interaction between drug and receptor; intrinsic activity represents the biological stimulus imparted by a drug at a receptor; efficacy represents the level of effect. The use of the word efficacy in more than one way has led to confusion, in particular with buprenorphine. Buprenorphine has very high affinity for the m-opioid receptor (MOR). However, it displays low intrinsic activity in *in vitro* assays (<sup>35</sup>S]GTPγS binding). This has led to characterization of buprenorphine as a 'partial agonist' - a compound that produces less than the 100% effect produced by a 'full agonist'. The problem is that 100% depends on the conditions. For example, in the same *in vitro* assays in which buprenorphine is a partial agonist, so is morphine. Efficacy must be measured *in the relevant conditions* and under these conditions, the question is: how much intrinsic activity is needed? The answer will depend on the clinical conditions - that is why designation 'full' or 'partial' agonist is a conditional term, *ie*, situationally-dependent. In the majority of animal models, buprenorphine displays greater than 98% antinociceptive efficacy; it is generally not associated with an analgesic ceiling effect in humans at doses from 0.2 to about 7 mg; and PET scans of human brain have shown that full analgesia is achieved with buprenorphine doses that occupy less than 100% of MOR (the definition of a full agonist). As part of the regulatory approval process, transdermal buprenorphine was tested in clinical trials, which provide an opportunity to assess analgesic efficacy in a variety of specific clinical pain syndromes.

### Conclusions

Terminology used in preclinical studies can lead to erroneous predictions or misperceptions of a compound's clinical efficacy. Thus, it is inappropriate to call a drug 'full' or 'partial' agonist based on these. And a 'ceiling' effect in a preclinical test cannot be assumed to translate to ceiling effect in clinical settings. This principle is particularly relevant to buprenorphine, which can be a full agonist (full analgesic efficacy at less than full receptor occupancy) and a partial agonist (less than full efficacy) at other endpoints, demonstrating the endpoint-dependent nature of these terms.

## Patient satisfaction associated with use of fentanyl sublingual spray for the management of breakthrough pain in patients with cancer of different types and stages

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### Purpose

Breakthrough cancer pain (BTCP) is often inadequately treated with oral short-acting opioids, which negatively impacts quality of life. This analysis examines patient satisfaction in a multicenter, randomized, double-blind, placebo-controlled clinical trial of fentanyl sublingual spray for BTCP in patients with different types and stages of cancer.

### Method

Opioid-tolerant adults (aged 18 years or older) receiving around-the-clock opioids for baseline pain and with 1-4 episodes/day of BTCP were enrolled in a 26-day open-label titration phase (N = 130). Those who successfully titrated to a stable, effective dose (100-1600 mcg) of fentanyl sublingual spray were eligible for enrollment in the 26-day double-blind phase (n = 96), during which patients received 7 active doses of fentanyl sublingual spray and 3 placebo doses in a fully randomized sequence. Patient satisfaction was assessed using the Treatment Satisfaction Questionnaire for Medication (TSQM; 0-100 scale, higher scores indicate greater satisfaction). Patients were instructed to base their responses on results they had historically obtained with their usual breakthrough medication and the study medication posttitration (before randomization). Adverse events (AEs) were recorded.

### Results

The mean (SD) age of patients in the titration phase was 55.6 (12.2) years. The most common cancers were reproductive (30.0%), breast (17.7%), lung (17.7%), skin (12.3%), and head/neck (12.3%). The mean (SD) duration of cancer was 7.5 (9.4) years; 59.2% of cancers were stages 2 (10.8%), 3 (17.7%), and 4 (30.8%). TSQM scores improved after titration; mean (SD) change from baseline to posttitration was 26.1 (20.9) for Effectiveness, 12.5 (30.8) for Side Effects, 8.0 (21.2) for Convenience, and 20.5 (23.1) for Global Satisfaction. Posttitration, 88.5% of patients were satisfied with treatment vs 40.8% at baseline. AEs were reported for 60.0% of patients during titration; nausea (13.1%) was the most common.

### Conclusions

These results suggest that the use of fentanyl sublingual spray for BTCP leads to a high degree of patient satisfaction across a heterogeneous cohort of cancer patients. This is particularly important to healthcare providers who care for patients with cancer and to patients who struggle to achieve BTCP relief.

## The impact of an abuse-deterrent formulation of an extended-release opioid on healthcare utilization and costs

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### Purpose

Pain is an exceedingly common cause of disability in the US Prescription opioids (RxOs) are an important component of modern pain management, but abuse of RxOs has become a serious public health problem in the US In 2011, an estimated 1.8 million Americans aged 12 or older had pain reliever dependence or abuse. Manufacturers of extended-release opioids (EROs) have recently introduced formulations with abuse-deterrent characteristics (hereinafter referred to as "abuse-deterrent formulations" or "ADFs") as one way to hinder manipulation of EROs without negatively impacting appropriate access for pain patients. To date, the impact of ADFs on the healthcare system has not been quantified. This study examined the impact of the introduction of an ADF in August 2010 on healthcare utilization and costs among a commercially-insured population.

### Method

This study used de-identified medical and pharmacy claims data for commercially-insured patients (Truven Health Analytics MarketScan Commercial Claims and Encounters Database). The study period was February 2010 to May 2011, which included a 6-month period before the introduction of the ADF of extended-release oxycodone HCl and a 6-month period after the introduction of the ADF, separated by a 3-month transition period. Patients were included in the study if they were chronic ERO users, defined as patients with at least 120 days' supply of EROs over a 6-month period, had continuous insurance coverage during the entire study period, were aged 18-64 during the entire study period, and had a single "primary" ERO that accounted for at least 70% of their ERO days' supply in the 6-month pre- and post-ADF periods. Patients meeting these inclusion criteria were then divided into 2 mutually exclusive cohorts: (1) patients whose primary ERO in the pre-period was extended-release oxycodone HCl (the non-ADF version) and whose primary ERO in the postperiod was the ADF of extended-release oxycodone HCl, and (2) a reference cohort of patients whose primary ERO was the same in both the pre- and the postperiods (ie, patients who did not switch EROs) and whose primary ERO was not extended-release oxycodone HCl. A difference-in-differences approach was then used to compare healthcare utilization and costs between the 2 cohorts.

### Results

The aforementioned selection criteria resulted in 11,569 patients in the extended-release oxycodone HCl group and 25,124 patients in the reference group. Switching to the ADF of extended-release oxycodone HCl was associated with a 1.4 percentage-point reduction in the likelihood of having an emergency department (ED) visit ( $P = .032$ ) and a 0.8 percentage-point reduction in the share of patients hospitalized ( $P = .131$ ) during the 6-month postperiod, compared to the reference cohort. In addition, switching to the ADF of extended-release oxycodone HCl was associated with a net decrease of 31.3 ED visits per 1000 patients ( $P = .047$ ) and a net decrease of 80.6 days of hospitalization per 1000 patients ( $P = .116$ ) over a 6-month period, compared to the reference cohort. In terms of healthcare costs, patients switching to the ADF of extended-release oxycodone HCl experienced a net reduction in inpatient costs of \$378 ( $P = .0293$ ) and ED costs of \$35 ( $P = .0245$ ) over a 6-month period, compared to the reference cohort.

### Conclusions

This study found that the introduction of the ADF of extended-release oxycodone HCl was associated with reductions in healthcare utilization and costs. Specifically, relative to patients remaining on the same ERO, patients who switched to the ADF of extended-release oxycodone HCl experienced fewer ED visits and hospitalizations, which resulted in a net reduction in associated healthcare costs.

## Hidden costs to employers of opioid abuse—healthcare costs, work-loss costs, and prevalence of opioid abuse among commercially-insured beneficiaries

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### Purpose

Prescription opioid abuse is a significant public health concern in the US. In 2011, an estimated 1.8 million Americans aged 12+ were dependent on or abused prescription pain relievers. In addition to the adverse clinical outcomes associated with opioid abuse, research has identified significant abuse-related economic costs to payers and to society. Much of this research, however, is based on data that pre-date significant private and public efforts to increase awareness of and reduce prescription opioid abuse and may not reflect current abuse prevalence (including diagnosed and undiagnosed abuse), approaches to pain management, and treatment costs. This study's objective was to expand upon previous research to provide updated and comprehensive estimates of the prevalence of diagnosed opioid abuse and the excess healthcare and work-loss costs of abuse among commercially-insured patients from Q1 2006-Q1 2012.

### Method

This study used de-identified administrative claims from a database of beneficiaries covered by large self-insured companies throughout the US (OptumHealth). Patients aged 12-64 with and without diagnoses for opioid abuse/dependence (hereinafter referred to as opioid abuse) were observed over a 12-month observation period centered on an index date. For opioid abusers, the index date was defined as the date of the first opioid abuse diagnosis from Q1 2006-Q1 2012. For controls (ie, nonabusers), the index date was defined as the date of a random medical claim over the same time-period. Finally, all patients were required to have continuous non-HMO coverage in order to ensure that the data captured all relevant drug and medical claims. Opioid abusers were matched 1:1 to controls based on year of index date, availability of work-loss data, baseline healthcare costs, and propensity score to account for baseline differences in demographics, comorbidities, and healthcare resource use. Per-patient total healthcare and work-loss costs in the 12-month observation period were calculated for opioid abusers and compared with that of matched controls to determine the incremental costs of diagnosed abuse. Opioid-abuse-related costs from an employer perspective were calculated by combining the per-patient incremental costs with estimates of prevalence of diagnosed and undiagnosed abuse derived using claims data and secondary sources. Costs were calculated overall and on a per-member-per-month basis from the perspective of a large, self-insured employer and were measured in 2012USD.

### Results

9,291 opioid abusers and 395,901 controls met the inclusion criteria, with abusers having significantly higher rates of baseline comorbidities, including congestive heart failure (1.8% vs 0.6%), renal disease (0.9% vs 0.4%), psychotic disorders (16.2% vs 2.7%), and other mental disorders (27.7% vs 7.2%). After matching, however, baseline patient characteristics and medical resource utilization were well-balanced across cohorts (n = 7,658 opioid abusers, n = 7,658 controls), with baseline healthcare costs of \$3,485 for both abusers and for matched controls.

During the 12-month observation period, matched opioid abusers had significantly more days in the emergency room (2.5 vs 0.8), days in a rehabilitation facility (6.5 vs 0.2), and days hospitalized (4.5 vs 0.9) than did matched controls, which led to per-patient incremental abuse-related healthcare costs of \$10,627 (\$20,343 opioid abusers vs \$9,716

matched controls). In addition, of the 1162 matched pairs with work-loss information available, opioid abusers had \$1,244 in excess work-loss costs compared with matched controls (\$3,773 vs \$2,528), with disability and absenteeism comprising \$505 and \$739 of the overall differential, respectively. In this database, the prevalence of opioid abuse among beneficiaries of large self-insured companies grew nearly 3-fold increase from 2005 to 2011. Using the 2011 prevalence of opioid abuse (18.6 per 10,000) and an implied ratio of diagnosed to undiagnosed abuse of 3.24 derived from claims data and secondary sources, the annual cost of opioid abuse from an employer perspective is estimated at \$5.93 per-member-per-month in healthcare costs and \$6.15 per-member-per-month when including work-loss costs.

Of note, approximately 20% of diagnosed opioid abusers in the sample did not have an insurance claim for a prescription opioid prior to the first abuse diagnosis, suggesting that a substantial share of abusers are obtaining prescription opioids through diversion from family members or from other illicit sources.

(All above comparisons were statistically significant at  $P < .01$ .)

### **Conclusions**

This study examined the economic costs of opioid abuse to employers, as employers pay for a substantial share of healthcare costs through their contributions to employer-sponsored health insurance, and they also bear the burden of lost workplace productivity due to opioid abuse. The results demonstrate that opioid abuse among individuals covered by large self-insured employers imposes substantial costs on employers. Employers may be unaware of the magnitude of this problem, as a large portion of opioid-abuse-related costs are attributable to undiagnosed abuse.



## Prevalence of pain among older adults with COPD and other chronic conditions

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### Purpose

Individuals with COPD may be at increased risk for chronic pain symptoms. The objective of this study is to perform a comprehensive comparison of the annual prevalence of pain (any and chronic) in an older adult population and a subpopulation of individuals with COPD or other chronic conditions.

### Method

Retrospective analysis (1/1/2006 through 12/31/2010) of managed care enrollees (age >40). Besides COPD, chronic conditions included are: Alzheimer's, atrial fibrillation, cancer, chronic kidney disease, acute myocardial infarction, diabetes, heart failure, ischemic heart disease, rheumatoid/osteoarthritis, and stroke/transient ischemic attack. Pain is indicated by ICD-9-CM diagnosis code, nonpharmaceutical pain therapy or prescription claim for pain medication. Extended pain or pain treatment was considered evidence of chronic pain. Adjusted annual prevalence rates (adjusted for age, sex, and Hispanic ethnicity) for individuals with continuous enrollment through each year were estimated using population estimates for the state of New Mexico.

### Results

Adjusted prevalence rates were similar across all years; for brevity, rates for 2010 are stated. *All Enrollees.* More women than men (79.2% vs 66.5%,  $P < .05$ ), and more individuals with chronic disease than those without chronic disease (85.8% vs 62.9%  $P < .05$ ) had evidence of any pain. *Chronic Disease Population, Any Pain.* Evidence of any pain was similar among individuals with COPD and those with non-COPD chronic disease (88.9% vs 85.2%,  $P > .05$ ); however more individuals with COPD had at least 1 pain-related prescription (73.7% vs 63.1%,  $P < .05$ ). *Chronic Disease Population, Chronic Pain.* Percentages with evidence of chronic pain were lower, but still high. A higher percentage of those with COPD compared to those with non-COPD chronic disease (61.8% vs 53.9%,  $P < .05$ ) had some indication of chronic pain, and evidence of chronic pain-related medication use (48.1% vs 35.7%,  $P < .05$ ). Extended use of nonpharmaceutical treatments for pain was less common in this chronic disease population: 10.2% of those with COPD and 11.3% with non-COPD chronic disease ( $P > .05$ ).

### Conclusions

Pain is a very common experience among older adults with chronic disease. Almost 1/2 of those with COPD had evidence of chronic use of pain medication compared to slightly more than 1/3 of those without COPD but with other chronic conditions

## Application of epidural implantable access systems for pain management in incurable patients

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### Purpose

Domiciliary chronic pain syndrome management in incurable patients with disseminated cancer is of paramount importance in improving their quality of life. In Russia, however, this social issue remains unattended and requires novel methods of intractable cancer pain management.

### Method

In the period of 2011-2013, 27 incurable patients with various types of cancer (aged 8 to 15 years; mean age 12.7 years) underwent epidural access system implantation. Epidural space catheterization at the L<sub>3</sub> - L<sub>4</sub> interspace was performed followed by x-ray to ensure the catheter proper placement. A 1 cm skin incision and blunt dissection of the subcutaneous tissue was made at the catheter exit site. A clip for catheter fixation was then inserted into the created subcutaneous space and sewn to the adjacent tissues. The port was implanted into the soft tissues above right ribs 10-12. The catheter was threaded through the subcutaneous tunnel up to the port. The incision above the clip and port was closed in layers. Only Huber needles were used to access the port. The choice of type and dosage of the analgesic was based on the pain syndrome severity, as well as cancer localization and stage.

### Results

The patients noted the improvement in quality of life, improved emotional state, and almost complete pain relief. 1 patient (3.7%) is currently alive, 26 (96.3%) died due to cancer progression. The epidural implantable access system was used for up to 5 months. No infection or occlusion of the system was observed. One patient (3.7%) experienced blood pressure drop due to an opioid analgesic overdose.

### Conclusions

Epidural access systems facilitate pain syndrome management, improve the quality of life, and reduce the opioid dose. If administered otherwise, intravenously or through intramuscular injection, the opioid dose should be gradually increased. Besides, these routes of opioid administration are commonly associated with adverse effects. However the introduction of epidural access systems in the Russian medical setting is stalled due to the absence of qualified medical staff in hospices as well as in outpatient departments which provide in-home care for incurable patients.

## Challenging current pain management: the role of laser medicine for chronic pain conditions

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### Purpose

Laser medicine is a noninvasive, pain-free, light-based therapy that uses red and infrared light to target inflamed, injured and diseased tissues. Photons of light stimulate metabolic energy production, thereby accelerating the healing process. When compared to traditional treatment, patients recover from musculoskeletal and peripheral nerve injuries with less scar tissue, accelerated cell regeneration and improved function. Chronic pain is often caused by the body's inability to progress past the inflammatory phase of injury recovery. Laser medicine targets and resolves inflammation, thereby providing pain relief even for patients suffering from chronic pain conditions.

### Method

Patients suffering from osteoarthritis, fibromyalgia, neuropathic pain, neck conditions, low back conditions, and other joint disorders undergo a laser medicine treatment protocol which includes applications of light-emitting-diode (LED) arrays in the red (660nm, 750 mW) and infrared (840 nm, 1500 mW) range, followed by a laser probe (830 nm, 180 mW) in the infrared light range. Treatments are administered initially 3 times weekly and tapered to weekly or monthly depending on the patient's clinical response.

### Results

Patients normally begin to positively respond to treatment within the first 3 treatments. Patients experience reduced pain levels, increased range of motion and functional capabilities and overall improvement in their quality of life. Several clinical case profiles are presented to highlight the clinical outcomes of laser medicine.

### Conclusions

Unlike traditional modes of pain management, this innovative technologically-based field of laser medicine offers clinicians a solution for pain resolution. By addressing the underlying pathology at the cellular level through increased metabolic energy, enhanced connective tissue repair, nerve function recovery and resolution of the inflammatory process, chronic pain conditions can be resolved without harmful side-effects or interactions with pharmaceuticals.

## Medication use evaluation of high-dose opioids in a Veterans Affairs Medical Center

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### Purpose

Opioid overdose-related deaths have become an increasing concern within the past decade. Among individuals treated with opioids for chronic noncancer pain (CNCP), evidence suggests that high doses of opioids increase risk of fatal overdose. A recent Veterans Affairs study found that patients receiving morphine equivalent dose  $\geq 100$  mg/day had an 8.9-fold increase in overdose risk. Although there is no uniformly accepted definition of 'high dose', the American Pain Society/American Academy of Pain Management (APS/AAPM) and Veterans Affairs/Department of Defense (VA/DoD) guidelines for CNCP management define 'high dose' as morphine equivalent dose  $>200$  mg/day, above which management by a specialist is recommended. These guidelines also recommend a 'universal precautions' approach to opioid prescribing involving careful patient selection and risk management and documentation of patient education and informed consent using a written opioid pain care agreement (OPCA). Routine and random urine drug tests (UDT) are recommended prior to initiating opioids and during treatment with opioids. VA/DoD guidelines also recommend treatment with long acting preparations of opioids for CNCP. There is additional concern with use of concomitant benzodiazepines and opioids as studies have suggested increased risk of central nervous system depression and overdose with this combination. The purpose of this study was to review opioid prescribing practices at doses equal to or greater than 200 mg of morphine equivalents per day.

### Method

The study population for the medication use evaluation (MUE) included patients with CNCP enrolled in primary care at W.G. (Bill) Hefner Veterans Affairs Medical Center. Approval was obtained from Pain Committee at the Medical Center and all reasonable efforts to maintain privacy and welfare of subjects were observed. A retrospective chart review was conducted for patients taking doses  $\geq 200$  mg of morphine equivalent per day. Two hundred and four (204) patients were identified using pharmacy prescription database. Fifty patients were randomly selected for review based on the American Society of Health System (ASHP) criteria for MUE. All patients with CNCP were eligible for inclusion, while the exclusion criteria included patients on opioids for acute pain, cancer pain and long-term care/hospice patients. An in-depth chart review was conducted for each patient and information was recorded regarding the diagnosis of chronic pain, face-to-face appointments with the primary care provider at least every 6 months, signed OPCA, ratio of long acting to short acting opioids, methadone prescribed on an as-needed basis instead of scheduled dosing, presence of at least one UDT in the past year, and presence of a bowel regimen.

### Results

Back pain was the most commonly reported form of chronic pain (92%). The majority of patients reviewed were meeting with their primary care provider face-to-face at least every 6 months (88%). Less than 60% of the patients had an OPCA on file, and approximately half of the patients (52%) were receiving a higher ratio of short acting to long acting opioids, or were only prescribed a short acting opioid. Eighty-five percent (85%) of the patients prescribed an 'as needed' short acting opioid were consistently filling it every month with no time lapse in between fill due dates. Approximately 70% of patients had received a UDT within the past year, while only 38% were on a documented bowel regimen. Of the 7 patients prescribed methadone, 1 patient was issued methadone to be taken as needed. Of all the patients reviewed taking  $\geq 200$  mg of morphine equivalent per day, 44% were also prescribed a concomitant benzodiazepine. Morphine sustained released (50%) and oxycodone (68%) were the most commonly prescribed agents. Based on the MUE results, it is evident that patients are consistently meeting with their primary care providers

every 6 months; however improved utilization of OPCA is needed. The finding of at least one UDT per year for patients on chronic opioid therapy exceeds from other reports in literature, although it still needs improvement. Education regarding the use of long acting opioids is needed to help improve patient compliance and decrease risk of diversion. These results have led to the development of local guidelines requiring OPCA and UDTs for all patients on chronic opioid therapy. There is also addition of clinical pharmacy specialist for pain management to assist primary care providers comanage 'high-risk' patients. Some of our limitations include predominantly male population and lack of access to medications prescribed outside the medical center.

## **Conclusions**

It has been well reported that patients receiving higher doses of prescribed opioids are at an increased risk of overdose. This study elucidates current prescribing patterns for Veterans at our facility receiving high-dose opioids, interventions that can be made to help implement safe prescribing practices, and also further emphasizes the importance of having specific policies and procedures in place for the safe management of opioid therapy in CNCP patients.

## Opioid-sparing effect of alpha-2-delta calcium channel subunit: add-on therapy of gabapentin to sublingual buprenorphine in patients with chronic nonmalignant pain

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### Purpose

Buprenorphine (Bup) is partial  $\mu$ -agonist with limited tolerance and available for the treatment of opioid dependence as well as acute or chronic pain. Gabapentin (GBP) binding to the alpha-2-delta calcium channel subunit, includes the list of first-line medications for the treatment of chronic neuropathic pain. Combination of GBP and morphine achieved better analgesia at lower doses of each drug than either as a single agent<sup>1</sup>). However, there is little data available on concurrent medication of Bup and GBP. In the present study, we investigated the add-on therapy of GBP to sublingual Bup in patients with chronic nonmalignant pain.

### Method

We retrospectively performed a chart review of 15 outpatients (mean age, 62.8 years; range, 26 to 86 years) with chronic nonmalignant pain, who had received the treatment of sublingual Bup under our pain clinic supervision for at least 6 months prior to the add-on GBP therapy during 6 months. They were treated by different 3 physicians, who regulated Bup dosage with an escalating dose of GBP at every visit for better analgesia (less than a visual analog scale 40mm) and relief of adverse effects by Bup and GBP. We recorded the daily dose of sublingual Bup (BD), a visual analog scale (VAS) scores, Bup or GBP-induced side effects, before the add-on GBP therapy (pre) and 6 months after the beginning of the add-on GBP therapy (post). Data were analyzed using paired t-test. P values less than 0.05 were considered significant.

### Results

The mean BD<sub>pre</sub> and BD<sub>post</sub> were  $480.0 \pm 302.8$   $\mu\text{g}$  /day and  $246.6 \pm 176.7$   $\mu\text{g}$  /day, respectively. The mean VAS<sub>pre</sub> and VAS<sub>post</sub> were  $53.3 \pm 16.5$  and  $35.4 \pm 17.7$ , respectively. The mean BD<sub>post</sub> and VAS<sub>post</sub> were significantly lower than the mean BD<sub>pre</sub> and VAS<sub>pre</sub> ( $P = .0038$ ,  $P = .0015$ , respectively). The mean maximal GBP dose was  $940.0 \pm 392.4$  mg (means  $\pm$  SD). No patients experienced a serious adverse event.

### Conclusions

Our results demonstrate that the add-on GBP therapy can provide the buprenorphine-sparing effect and better analgesia in the chronic pain patients with buprenorphine treatment, though this pilot study had the limitation.

**Dose escalation of sublingual buprenorphine in patients with chronic pain: influence of gender or age**

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**Purpose**

Buprenorphine is partial  $\mu$ -agonist with limited tolerance and available for the treatment of opioid dependence as well as acute or chronic pain. However, there is little data available on the rate of dose escalation of sublingual buprenorphine in patients with chronic nonmalignant pain. In the present study, we investigated the rate of dose escalation of sublingual buprenorphine of patients with chronic noncancer pain and the influence of the sex or age on the dose escalation.

**Method**

We retrospectively performed a chart review of 63 patients with noncancer chronic pain, who had the treatment of sublingual buprenorphine under our pain clinic supervision for at least 6 months. They were treated by different 8 physicians and had adjuvant medications (including anti-inflammatory drugs, antidepressants, anticonvulsants, etc) and interventional procedures when indicated. (1) We recorded the daily dose sublingual buprenorphine, VAS scores and opioid-induced side effects at the onset of treatment, 6, 12, 18, and 24 month (mo) after the initiation of sublingual buprenorphine. To assess the dose escalation of sublingual buprenorphine, we evaluated the average monthly rates of dose escalation of sublingual buprenorphine every 6 months. (2) Patients were divided into the following groups according to sex or age: female group (n = 39) and male group (n = 24): younger group (n = 18: 23-59 yo) and older group (n = 35: 62-82 yo). To determine the influence of age, we compared the peak dose of sublingual buprenorphine. Data were analyzed using unpaired t-test and ANOVA and Bonferonni. P values less than 0.05 were considered significant.

**Results**

(1) The average monthly rates of dose escalation for 13-18mo and 19-24mo were significantly lower than the rate for 0-6 mo ( $P < .0001$ ,  $P < .0001$ , respectively). (2) There were no significant differences in the peak dose and the term between female group and male group ( $P = .859$ ,  $p = 0.4404$ , respectively). (3) There were no significant differences in the peak dose and the term between younger group and older group ( $P = .6546$ ,  $P = .5754$ , respectively). We did not find a significant increase in VAS scores and opioid-induced side effects in both groups.

**Conclusions**

The average monthly rates of dose escalation of sublingual buprenorphine significantly diminished from 13 to 24 mo after the initiation. Our results demonstrate that the dose escalation of sublingual buprenorphine may be limited and not influenced by the sex or age.

**Long-term maintenance of improvements in quality-of-life, functionality, and pain interference for moderate-to-severe chronic pain patients receiving continuous treatment of Butrans® (buprenorphine) Transdermal Delivery System (BTDS)**

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**Purpose**

While short-term (1-3 months) efficacy of opioids has been well-established, less evidence exists regarding long-term effectiveness in treating chronic pain. Randomized, placebo-controlled trials of Buprenorphine Transdermal System (BTDS) for chronic low-back pain (CLBP) found treatment effectiveness with regards to pain relief, quality of life, and sleep quality over 12 weeks. Long-term maintenance of these improvements has not been previously examined. This posthoc analysis evaluated long-term outcomes of BTDS treatment among patients with moderate-to-severe CLBP or osteoarthritis (OA).

**Method**

Data were from CLBP or OA patients who opted into an open-label treatment extension phases following several 12-week, double-blind, randomized placebo/active-controlled trials. Following the close of each core trial, patients from all treatment arms received 5, 10, or 20 mcg/hour of BTDS for 6-12 months. Patient-reported outcomes included quality of life (SF-36v2 Health Survey physical and mental summary scores), sleep quality (Sleep Disturbance and Sleep Problems Index from the Medical Outcomes Study Sleep Scale), pain impact (Brief Pain Inventory [BPI] Interference scale), functioning (Oswestry Disability Index total score), and work productivity (overall work impairment scale from the Work Productivity and Activity Impairment questionnaire). Changes over time in each of these outcomes were tested with repeated-measures mixed-effects models that included time (visit month) as a fixed effect and age, gender, core study treatment arm, outcome score at extension baseline, and pain severity at extension baseline as covariates.

**Results**

Time was not significantly related to physical or mental dimensions of quality of life, sleep disturbance, sleep quality, functioning, or work productivity, net of other variables. Time predicted only pain interference, as indicated by a statistically significant increase in the BPI Interference scale—from 2.9 to 3.3, on a 0-10 scale—over 12 months.

**Conclusions**

Significant gains in quality of life, sleep quality, functioning, and work productivity that CLBP and OA patients made during 12-week core trials were maintained over the longer-term, while pain interference increased by a slight degree over 12 months but remained much improved from baseline.



## A retrospective evaluation of painful diabetic neuropathy in a resident internal medicine clinic

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### Purpose

Painful diabetic neuropathy (PDN) is a common complication of diabetes and can significantly impact a patient's life, including mood, sleep, self-worth, independence, ability to work, and overall quality of life. Treatment of PDN is often difficult, and consists of glycemic control in addition to pharmacologic agents for pain such as anticonvulsants, antidepressants, and opioids. This study was completed in the internal medicine clinic (IMC) to 1) identify the prevalence of PDN, 2) evaluate the most common treatment approach to PDN in a clinic with minimal opioid prescribing, 3) compare diabetic treatment intensification goals for hemoglobin A1c (HbA1c), blood pressure (BP), low-density lipoprotein (LDL) cholesterol, and body mass index (BMI) between all diabetic patients within the IMC and diabetic patients with PDN.

### Method

A retrospective chart review of diabetic patients was completed. Active IMC patients, who were defined as any patient with an appointment during the past year, were eligible for inclusion if they had an IMC appointment scheduled between March 2013 and April 2013. Patients were identified based on presence of diabetes and neuropathy/neuropathic pain documented on the problem list or within a patient encounter. Data was collected regarding patient demographics, laboratory parameters, medication regimen, and past medical history.

### Results

A total of 7805 active patients in the IMC were identified, and 1456 (18.7%) had known diabetes. Of the known diabetic patients, 294 had appointments during the one-month study period, and 96 (32.7%) of these patients had PDN. The most common pharmacologic treatment approach was monotherapy with either gabapentin (n = 81, 84.4%) or a tricyclic antidepressant monotherapy (TCA) (n = 4, 4.2%). The most common daily dose of gabapentin was 900 mg, (range 100-3600 mg). The other monotherapy regimens were duloxetine (n = 1), tramadol (n = 1), and pregabalin (n = 1). The remaining patients were receiving combination therapy as follows: gabapentin and TCA (n = 3); gabapentin and duloxetine (n = 1); TCA and tramadol (n = 1); pregabalin, TCA, and tramadol (n = 1). The remaining 2 patients had not yet been started on pharmacologic therapy. For the diabetic outcome of HbA1c <7%, 25% of patients with PDN met this goal as compared to 37% of all diabetic patients in the IMC. For the goal BP <140/80 mmHg, 37% of patients with PDN were at goal as compared to 65% of all diabetic patients. The percentage of patients at goal for LDL <100 mg/dL was 53% for the PDN group as compared to 60% of all diabetic patients, and for BMI <30, the percentage of patients at goal for both patients with PDN and all diabetic patients was 30% and 31%, respectively. Finally, the percentage of patients who met the goal for the HbA1c, LDL, and BP was 7.7% of PDN patients and 9.5% for all diabetic patients.

### Conclusions

This study revealed PDN is prevalent in the diabetic patient population within the IMC. The most common pharmacologic treatment prescribed was gabapentin monotherapy, and combination therapy was rarely used. Additionally, patients with PDN were less likely to achieve the diabetic intensification goals for the specified outcomes as compared to all IMC diabetic patients. Future studies evaluating the efficacy and tolerability of the medication

regimens are recommended, as well as daily patient visit enhancements to improve achievement of diabetic treatment goals within the PDN patient population.

## Open-label extension of a randomized, double-blind, placebo-controlled, phase 3 study of the safety and analgesic efficacy of MNK-795 controlled-release oxycodone/acetaminophen tablets (CR OC/APAP) in an acute pain model

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### Purpose

Multimodal therapy combining oxycodone (OC) and acetaminophen (APAP) is an established approach to the treatment of acute pain. Combining agents with different mechanisms of action can reduce the overall dose required for each component, which may result in an improved side-effect profile.<sup>1</sup> MNK-795 (controlled-release [CR] OC/APAP) is the first CR combination OC/APAP analgesic, and was designed to provide a fast onset of analgesia (< 1 hour) and sustained analgesia over the 12 hour dosing interval. In addition, CR OC/APAP incorporates technology designed to provide tamper-resistance and abuse-deterrence. The current study presents the open-label extension phase of a multicenter, randomized, double-blind, placebo-controlled, parallel group, phase 3 study of CR OC/APAP in patients with moderate to severe acute pain.

### Method

The study consisted of a screening period of between 2 and 30 days before surgery; a randomized, double-blind dosing phase of 2 days (48 hours) postprocedure; and an optional ≤ 14-day open-label extension for qualified patients. Patients undergoing unilateral, first metatarsal bunionectomy who reported at least moderate or severe pain intensity and a numeric rating scale score of ≥ 4 (out of 10) between the hours of 4:00 AM and 12:00 PM on the first postoperative day were eligible to enter the study. During the double-blind phase, patients were randomized to receive 2 tablets of CR OC/APAP (ie, 15 mg OC/650 mg APAP) or placebo administered every 12 hours (0, 12, 24, and 36 hours; 4 total doses). Patients who had a pain intensity score ≥ 3 at completion of the double-blind study could participate in the open-label extension. During the open-label phase, patients were discharged from the surgical clinic and instructed to take 2 tablets of CR OC/APAP every 12 hours until no longer needed. The open-label phase lasted up to 14 days, with clinic visits at days 7 and 14 (± 1 day), followed by a telephone call 7 days (± 2 days) after the last dose. Safety and tolerability were assessed via physical examinations, vital signs, pulse oximetry, and laboratory tests at each visit. In addition, a global assessment of patient satisfaction was obtained at each visit. Adverse events were collected at each visit and the 7-day follow-up.

### Results

A total of 329 patients (CR OC/APAP, n = 166; placebo, n = 163) were enrolled and received ≥ 1 dose of study treatment during the blinded-dosing phase; 293 (89.1%) completed the double-blind phase and, of these patients, 146 (49.8%) entered the open-label extension (77 from prior CR OC/APAP; 69 from prior placebo), with 129 (88.4%) completing the open-label extension. The mean age was 40.6 years, 83.6% were female, and 61.6% were white and 34.2% were black or African American. During the open-label dosing period, 120 patients (82.2%) received ± 20% of the expected doses. At the final visit, 94%, 86%, 83% of patients indicated they were "very satisfied" or "satisfied" with the ease of administration, time for medication to work, and level of pain relief provided by CR OC/APAP, respectively. During the open-label phase, 64 patients (43.8%) experienced a treatment-emergent adverse event (TEAE); the most frequently occurring TEAEs were nausea (17.8%), vomiting (7.5%), and constipation (6.2%). One patient reported 3 severe TEAEs, and 1 reported a serious adverse event (DVT assessed by the investigator as unrelated to study medication). Changes from baseline in laboratory values were generally small and were similar between treatment groups during double-blind periods and similar between the double-blind and open-

label periods. Vital signs during the open-label phase were normal in >90% of patients at any visit. During the open-label phase, ≤1.4% of subjects had shifts from normal to abnormal oxygen saturation at any time point.

### **Conclusions**

CR OC/APAP was well tolerated in this phase 3 open-label extension, and more than 80% of patients were satisfied or very satisfied with treatment. The most frequently occurring adverse events were consistent with those seen with other opioids. Shifts in laboratory test results, vital signs, and oxygen saturation were not clinically significant. CR OC/APAP is an important addition to the armamentarium for patients with moderate to severe acute pain.

### **Reference**

1. Raffa RB. Pharmacology of oral combination analgesics: rational therapy for pain. *J Clin Pharm Ther.* 2001;26(4):257-264.

## A randomized, double-blind, placebo-controlled, phase 3 study of the safety and analgesic efficacy of MNK-795 controlled-release oxycodone/acetaminophen tablets (CR OC/APAP) in an acute pain model

Neil Singla<sup>1</sup>, Thomas Barrett<sup>2</sup>, Lisa Sisk<sup>2</sup>, Kenneth Kostenbader<sup>2</sup>, Jim Young<sup>2</sup>, Michael Giuliani<sup>2</sup>

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### Purpose

The combination of oxycodone (OC) and acetaminophen (APAP) has long demonstrated efficacy in treating acute pain. MNK-795 (controlled-release [CR] OC/APAP) is the first CR combination OC/APAP analgesic, and was designed to treat acute pain with 12 hour dosing. Specifically, CR OC/APAP was designed to provide fast onset of analgesia within 1 hour and sustained analgesia over the 12 hour dosing interval. In addition, CR OC/APAP incorporates technology designed to provide tamper-resistance and abuse-deterrence. The current study is a multicenter, randomized, double-blind, placebo-controlled, parallel group, phase 3 study of CR OC/APAP in patients with moderate to severe acute pain.

### Method

The study consisted of a screening period of between 2 and 30 days before surgery, a randomized double-blind dosing phase of 2 days (48 hours) postprocedure, and an optional  $\leq 14$ -day open-label extension for qualified patients. Patients undergoing unilateral, first metatarsal bunionectomy who reported moderate or severe pain intensity and numeric rating scale score of  $\geq 4$  (out of 10) between the hours of 4:00 AM and 12:00 PM on the first postoperative day were eligible for the study. During the double-blind phase, patients were randomized to receive 2 tablets of CR OC/APAP (ie, 15 mg OC/650 mg APAP) or placebo administered every 12 h (0, 12, 24, and 36 h; 4 total doses). Pain intensity was rated with an 11-point numerical rating scale (0 = no pain; 10 = the worst pain imaginable). The primary efficacy measure was the summed pain intensity difference over the first 48 h (SPID<sub>48</sub>). Other measures included pain intensity difference (PID) and SPID at multiple time points over 48 h, total pain relief over the first 48 h (TOTPAR<sub>48</sub>), and the time to perceptible, meaningful, and confirmed pain relief. Time to relief was measured using a double stop watch method. PID was estimated using multiple imputation techniques and using 6-h censoring for rescue medication (ibuprofen). Safety and tolerability were assessed throughout the double-blind and open-label periods.

### Results

A total of 329 subjects (CR OC/APAP, n = 166; placebo, n = 163) were enrolled and received  $\geq 1$  dose of study treatment during the blinded-dosing phase (blinded safety population); 293 (89.1%) completed the double-blind phase. Efficacy analyses were performed on a modified intent-to-treat population of 303 patients; 150 patients randomized to CR OC/APAP and 153 patients randomized to placebo. The majority of these patients were female (85.1%) and the mean age was 43.0 years. The primary efficacy analysis (SPID<sub>48</sub>) was significantly greater in the CR OC/APAP group compared with placebo, indicating a greater reduction in pain over 48 h for those patients receiving CR OC/APAP (mean [SE], 114.9 [7.64] vs 66.9 [7.60], respectively; treatment difference = 48.0 [10.54];  $P < .001$ ). Mean PID for CR OC/APAP was numerically superior beginning at the earliest time point measured (15 min) and each time point thereafter in the blinded evaluation period; statistical significance was reached 30 min after the first dose. Mean SPID over 0 to 4, 0 to 12, 0 to 24, and 0 to 36 h were all statistically significant vs placebo ( $P < .001$  for all). TOTPAR<sub>48</sub> for CR OC/APAP also indicated significant improvement compared with placebo (mean [SE] = 91.3 [3.47] vs 70.9 [3.39], respectively; treatment difference = 20.5 [4.85];  $P < .001$ ). Median time to confirmed perceptible pain relief was 48 min for CR OC/APAP, and it could not be determined for placebo ( $P < .001$ ). Overall, during the double-blind phase, 37.7% of patients in the safety population (124/329) experienced a treatment-emergent adverse

event (TEAE). TEAEs with CR OC/APAP were consistent with other opioids; nausea (30.7%), dizziness (13.3%), headache (9.6%), vomiting (9.0%), constipation (4.2%), and somnolence (3.6%) occurred with the greatest frequency during the double-blind period. One patient reported a severe TEAE (headache), and none reported a serious adverse event.

### **Conclusions**

CR OC/APAP was efficacious and well tolerated for the treatment of moderate to severe acute pain in an acute postoperative pain model. CR OC/APAP administered twice daily (2 tablets) for 4 doses demonstrated a fast onset of pain relief with sustained analgesia over 48 h following a surgical procedure. These results support that CR OC/APAP may be appropriate for patients with moderate to severe acute pain.

## Biochip based immunoassays for the detection of oxycodone, oxycodone metabolites and hydromorphone from one urine sample

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*Randox Toxicology Limited, Kearneysville, USA*

### Purpose

**Purpose.** The semi-synthetic analgesic drugs of the opioid class: oxycodone (14-hydroxy-7,8-dihydrocodeinone) and hydromorphone (4,5- $\alpha$ -epoxy-3-hydroxy-17-methyl morphinan-6-one) are Schedule II controlled substances (strong potential for abuse or addiction but with legitimate medical use). The analgesic potency and the abuse potential of oxycodone are comparable to morphine. Hydromorphone is more potent than morphine and is also susceptible to abuse. Both drugs can produce adverse side effects, in the case of oxycodone, the adverse side effects limit the maximum tolerated dose. Oxycodone abuse poses a risk of overdose and death. Oxycodone and hydromorphone are metabolised in the liver and excreted primarily via the kidneys. Studies have shown that noroxycodone is the most abundant metabolite of oxycodone in circulation after administration of oxycodone to human subjects. An in vitro study reported that in humans the oxymorphone, formed by O-demethylation of oxycodone by the enzyme CYP2D6, accounts for 13% of oxycodone oxidative metabolism in liver microsomes.

Oxycodone and hydromorphone tests are indicated to monitor their use or misuse. Tests based on immunoassays allow the screening of samples, and only positive test results need confirmation by confirmatory methods such as gas chromatography/mass spectroscopy (GC/MS), high performance liquid chromatography (HPLC). The aim of this study was to develop and evaluate the analytical performance of biochip based immunoassays for the screening of oxycodone, oxycodone metabolites and hydromorphone from a single sample of urine, which will facilitate the testing process by increasing the detection capacity of the screening step.

### Method

**Methods.** Competitive chemiluminescent immunoassays defining discrete test sites on a biochip platform were employed. The biochip (9 mm x 9 mm) is also the vessel where the immunoreactions occur. The light signal generated from each of the test sites on the biochip is simultaneously detected using digital imaging technology. The assays were applied to the Evidence analyser, which incorporates dedicated software to process and archive the multiple data generated. To distinguish positive from negative samples, a normalised value was calculated as percentage of the signal intensity emitted from the cut-off test region relative to the signal intensity emitted from the sample test region. Samples producing a response value > response value of the user-defined cut-off were considered positive (normalised value > 100). Samples producing a response value < response value of the user-defined cut-off were considered negative (normalised result < 100).

### Results

**Results.** The 3 biochip based immunoassays were standardised to oxycodone and presented different cross-reactivity profiles. One of the immunoassays presented the following cross-reactivity profile: 3040.6% (hydrocodone), 1939.4% (ethylmorphine), 497.8% (codeine), 471.1% (dihydrocodeine), 261.3% (hydromorphone), 118.4% (thebaine), 105.5% (heroin), 72.0% (levorphanol), 35.1% (6-monoacetylmorphine), 21.8% (morphine). Another immunoassay detected hydrocodone (%cross-reactivity: 62.2%) and noroxycodone (%cross-reactivity: 27.5%). The third immunoassay detected oxymorphone (%cross-reactivity: 73.8%). For a cut-off concentration of 100 ng/ml, the normalised values of 38, 18, and 24 were obtained for the respective immunoassays and represented the lowest concentrations of oxycodone which could be distinguished from the zero calibrator with a confidence level of 99%. The intra-assay

precision (n = 20) and total precision (n = 80) of the 3 immunoassays for different levels of oxycodone, expressed as %CV, were <8% and <11.5% respectively.

### **Conclusions**

The biochip based immunoassays developed allow the detection of oxycodone, oxycodone metabolites and hydromorphone from a single sample. This increases the detection capacity of the screening step and facilitates the testing process as only positive results require confirmation with other methodologies.



## Simultaneous immunoassays on a biochip platform for the detection of multiple pain relievers from a single urine sample

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### Purpose

Urine drug testing (UDT) is a useful tool in pain management to facilitate the monitoring of the use or misuse of drugs. Acetaminophen (paracetamol) is an analgesic and antipyretic drug with no anti-inflammatory properties, and is one of the most frequently used drugs in intentional overdose, as it is readily available in oral preparations. The widely available nonsteroidal anti-inflammatory drugs ibuprofen and salicylates (derived from salicylic acid) inhibit the synthesis of prostaglandins, which is the cause for their analgesic and anti-inflammatory action. The synthetic analgesic tramadol is classified as a central nervous system drug usually marketed as tramadol hydrochloride; both tramadol and its metabolite (O-desmethyltramadol) are  $\mu$ -opioid receptor agonists. This study reports the analytical evaluation of 4 simultaneous biochip based immunoassays for the detection of acetaminophen and the metabolite NAPQI (N-acetyl-p-benzo-quinone imine), ibuprofen, tramadol and its metabolite O-desmethyltramadol as well as salicylates at therapeutic doses from a single urine sample. This is relevant to facilitate the screening of these compounds to monitor their use or misuse; extended to cases of overdoses.

### Method

Competitive chemiluminescent immunoassays defining discrete test sites on a biochip platform were employed. The biochip is also the vessel where the immunoreactions occur. The light signal generated from each of the test sites on the biochip is simultaneously detected using digital imaging technology. The assays were applied to the evidence analyser, which incorporates dedicated software to process and archive the multiple data generated.

### Results

The acetaminophen assay was standardised to acetaminophen and the %cross-reactivity with the metabolite NAPQI was 37.3%. The ibuprofen assay was standardised to ibuprofen and also detected S-( + )-ibuprofen, iso-propyl phenyl acetic acid, ibufenac and R(-)-ibuprofen (%cross-reactivity: 95.4%, 84.8%, 30.2%, 24.0% respectively). The salicylates assay was standardised to salicylic acid, 4-aminosalicylic acid, 2,3-hydroxy benzoic acid, gentisic acid sodium salt hydrate were also detected (%cross-reactivity: 326.5%, 97.0%, 22.3% respectively). The tramadol assay was standardised to tramadol and the metabolite O-desmethyltramadol was also detected (%cross-reactivity: 26.4%). The limits of detection (LOD) in neat urine sample were 3.66  $\mu\text{g/ml}$  for acetaminophen (assay range: 0-2680  $\mu\text{g/ml}$ ), 17.36  $\mu\text{g/ml}$  for ibuprofen (assay range: 0-2240  $\mu\text{g/ml}$ ), 15.95  $\mu\text{g/ml}$  for salicylic acid (assay range: 0-2640  $\mu\text{g/ml}$ ) and 0.1 ng/ml for tramadol (assay range: 0 -152 ng/ml). The intra-assay precision (n = 20) of the 4 immunoassays for 3 different concentration levels, expressed as %CV, was < 12%.

### Conclusions

The results indicate applicability of the biochip-based immunoassays to the simultaneous sensitive screening of multiple analgesic drugs and metabolites from a single urine sample. This represents a useful analytical tool in UDT to facilitate the screening of samples in order to monitor the use or misuse of these compounds in pain management settings.

**Use of a biomarker panel for the detection of major depressive disorder in centralized intractable pain**

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**Purpose**

To demonstrate that a blood-based profile of biomarkers can identify major depressive disorder (MDD) comorbid with central intractable pain (CIP). Clinically, MDD can complicate the clinical course and response to treatment of patients with chronic pain.

**Method**

The study group consisted of thirty-nine (39) patients with centralized intractable pain (CIP), with a mean age of 45.5 ± 12.3 (range from 24-71 years). Twenty-four (62%) were female and 15 (38%) were male. Each had a blood sample drawn for measurement of serum levels of 9 biomarkers (alpha-1 antitrypsin, Apolipoprotein CIII, Brain Derived Neurotrophic Factor (BDNF), Cortisol, Epidermal Growth Factor, Myeloperoxidase, Prolactin, Resistin, and soluble TNF receptor II) by immunoassay. A proprietary algorithm was used to generate a depression score (range 1-9) using serum biomarker concentration. Biological pathway-specific coefficients (Inflammation, HPA axis, Metabolic and Neurotrophic) were used to create the hyperspace vectors and hypermaps of CIP patients.

**Results**

Twenty-one (54%) of the patients had MDDScores >5 consistent with a diagnosis of MDD and 14 of the 21 patients had an MDDScore of 9. Of the 18 patients with MDDScores of <5, 12/18 had an MDDScore of 1. With the exception of EGF, individual biomarkers showed no correlation to MDDScore. Hypermaps and pathway vector analysis indicated that CIP patients with MDDScores >5 had higher average expression of inflammatory (3.7-fold) and HPA axis biomarkers (11.5-fold).

**Conclusions**

Our results indicate that MDDScore was able to segregate CIP patients into 2 groups based upon the biomarker panel signature. This suggests we may be able to identify CIP patients with a higher probability of comorbid major depression and the suffering that ensues. Additionally, this study supports other evidence that excess inflammation and hyper-arousal of the HPA axis are major clinical problems with centralized, intractable Pain.

**PainWorkbook: an online cognitive-behavioral intervention for chronic pain**

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**Purpose**

Research has shown that cognitive behavioral strategies are useful in the management of chronic pain. Unfortunately, most patients lack access to education on the use of these strategies. We created a 10-chapter, web-based, interactive, cognitive-behavioral pain management workbook and evaluated its benefit in a sample of individuals with chronic low back pain.

**Method**

Study participants were recruited from the internet and screened to ensure that they reported low back pain of at least 6 months duration with an average pain rating of at least 4 on a 0-10 scale. Two hundred forty-seven eligible individuals [73% women, 27% racial/ethnic minority, mean (SD) age = 46.1 (11.7) years, mean (SD) current pain = 6.1 (1.9)] enrolled, completed baseline measures, and were randomly assigned to receive either the online workbook (OWB) or a traditional self-help book (SHB) for low back pain. They were asked to use the OWB or SHB over a 10-week intervention period. Follow-up measures were completed by 232 participants 8 weeks after the intervention period, including the Roland Morris Disability Questionnaire (RMDQ), the interference subscale of the Graded Chronic Pain Scale (GCPS-I), the Chronic Pain Coping Inventory (CPCI), and the Survey of Pain Attitudes (SOPA).

**Results**

Both groups showed significant improvements over time on the RMDQ, GCPS-I, and subscales of the CPCI and SOPA. A series of ANCOVAs was conducted to examine whether, controlling for baseline scores, the OWB group evidenced significantly greater improvement than the SHB group. Results indicated that the OWB group reported marginally more frequent use of exercise as a coping strategy,  $F(1, 229) = 3.88, P = .050$ . With regard to pain attitudes, the OWB group reported a significantly higher sense of control over their pain,  $F(1, 229) = 14.61, P < .001$ , and significantly lower perceived disability,  $F(1, 229) = 4.61, P = .033$ , on the SOPA. SOPA control ( $\beta = -.32, P < .001$ ) and disability ( $\beta = .39, P < .001$ ) subscales were, in turn, significantly related to disability reported on the RMDQ,  $F(2, 228) = 111.72, P < .001$ . The SOPA disability subscale was also significantly related to the GCPS-I ( $\beta = .53, P < .001$ ).

**Conclusions**

Both the SHB and the OWB were associated with significant improvements; however, the OWB appeared to offer greater benefit with regard to pain attitudes and coping. More studies are needed to evaluate the potential effects of the OWB in a clinic setting.

## Culture matters: a web-based training for healthcare providers in cognitive-behavioral pain management

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### Purpose

Cognitive-behavioral pain management (CBPM) techniques such as diaphragmatic breathing, progressive muscle relaxation, and guided imagery have garnered strong empirical support. However, lack of access to provider training is a major barrier to more wide-spread use of CBPM. It is especially difficult for providers to find training in the culturally competent use of CBPM. Cultural competence is particularly important in the use of psychological approaches such as CBPM. Research has shown that cultural groups differ in their acceptance of various kinds of standard cognitive-behavioral approaches. Therefore, this project sought to develop and evaluate a web-based training in culturally competent use of CBPM for healthcare providers, called *Teaching Pain Self-Management: Culture Matters*.

### Method

Primary care providers and oncology specialists were recruited from throughout the United States using an email broadcasting service, weighted so as to oversample from more racially and ethnically diverse states. Providers were screened to ensure that they talk directly with patients about ways to manage their pain. After consenting and completing pretest measures, 180 participants (mean age  $48.1 \pm 10.2$  years, 72% women, 16% non-White, 6% Hispanic; 52% nurse practitioners, 29% physicians, 16% physician assistants) were randomly assigned to receive access to the web-based training (WBT) or to a self-guided learning (SGL) condition in which they were instructed as follows: "Please spend as much time as you feel is adequate to address the study learning objectives...like what you might do if you decided on your own that you wanted to learn more about these topics...When you feel that you have spent an appropriate amount of time researching and learning about the study learning objectives, please complete the postassessment, no later than sometime within the next 14 days." Participants in the WBT condition were given 14 days to review the training and completed the postassessment upon their completion. All who completed the postassessment (N = 136) were compensated with a \$150 Amazon gift card.

### Results

Repeated-measures ANOVA revealed a significant condition by time interaction for ratings of self-perceived competence in using CBPM,  $F(1, 134) = 22.3, P < .001$ ; ratings increased in the WBT condition but not in the SGL condition. Repeated measures MANOVA was used to compare intentions to conduct assessment, use various CBPM techniques, and tailor approaches to the patient's culture in the forthcoming 90 days to self-reported practices over the preceding 90 days, between conditions. Although both conditions reported intentions to use CBPM techniques more frequently in the upcoming 90 days than they had used them in the preceding 90 days, a significant omnibus condition by time interaction,  $F(15, 102) = 3.3, P < .001$ , occurred such that the effect was particularly pronounced in the WBT condition. Furthermore, compared to those in the SGL condition, those in the WBT condition reported spending more time reviewing information and practicing what they learned ( $P < .001$ ). Those in the WBT condition also agreed more strongly that they were likely to use what they had learned in their work ( $P < .001$ ), that the information would help them in their clinical practice ( $P < .001$ ), that the information was complete ( $P < .001$ ), that the information was credible ( $P < .001$ ), and that they would recommend the information to a colleague ( $P < .001$ ). Among those in the SGL condition, only 29% agreed that it was easy to find information on how cultural beliefs

influence the experience and perception of pain and no more than 50% agreed that it was easy to find information on any of the various CBPM techniques they were asked to research.

### **Conclusions**

Results support the utility of the WBT for training healthcare providers to use CBPM strategies in ways that are responsive to patients' cultures. Although large effects were observed for clinical practice intentions, it remains to be seen whether such posttraining intentions will translate into posttraining behaviors. Ninety day follow-up assessments of self-reported posttraining clinical practices are still pending for the majority of the sample. More studies are needed to examine whether cultural tailoring of CBPM techniques improves outcomes among patients from diverse cultural backgrounds.

**Fibromyalgia and bullying: a comprehensive review of the literature**

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**Purpose**

Fibromyalgia is a chronic pain condition in which a person has wide spread bodily pain and tenderness in the joints, muscles, tendons, and other soft tissues. The causes of fibromyalgia are not fully understood, but research has indicated that physical and/or emotional trauma may promote the development of fibromyalgia. Recently, bullying has garnered much attention in the media due to its long lasting effects on a person's psychological and physical well-being. Children and younger adults who experience bullying have both an acute and chronic increased risk to experiencing depression, anxiety, changes in sleep patterns, and poor health. To gain a better understanding of the association between bullying and the development of fibromyalgia, a comprehensive review of the literature was performed.

**Method**

Databases were searched during the time periods of database inception to June 2013 and included MEDLINE, PUBMED, EMBASE, and Google Scholar. The main search terms used included "fibromyalgia," "bullying," "childhood stress," and/ or "chronic pain."

**Results**

Analysis of the literature revealed that fibromyalgia patients were generally associated with more stressful, negative lifetime events as a result of childhood or adult victimization and trauma. In addition, the literature tended to support that female victims were more likely to develop fibromyalgia.

**Conclusions**

Experiencing trauma may reshape the neurotransmitter and endocrine circuits, resulting in the development of increased anxiety, stress, and pain perception. Understanding the consequences of bullying and its association with chronic pain development is important for developing effective therapeutic regimens.

## Challenges of treating patients with chronic pain with dysphagia (CPD): physician and patient perspectives

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### Purpose

Reports indicate that approximately 30% of the American population (~100 million people) suffers from chronic pain. Failure to treat chronic pain effectively can affect many aspects of a patient's life and affect overall quality of life. In addition, undertreated chronic pain is a burden to society, creating a drain on healthcare resources and increasing medical costs. The complexity of patients with chronic pain often creates treatment challenges; many patients are diagnosed with other comorbidities that may contribute to the underlying pain condition or impact treatment regimens and outcomes. One such comorbidity is dysphagia, defined as a difficulty with or inability to swallow. Patients who have dysphagia may be unable to swallow solid, oral analgesics and those with severe dysphagia may require the administration of analgesics through an enteral tube or use an alternative route of administration (eg, transdermal). This condition poses a treatment challenge and may predispose patients with chronic pain with dysphagia (CPD) to medication errors and poorer health outcomes; a result caused by patients' and physicians' attempts to circumvent the swallowing difficulty. To better understand 1) the prevalence of patients with CPD, 2) current treatment practices, and 3) clinical unmet needs in this patient population, 2 informant-specific surveys were administered in order to understand the knowledge, attitudes, and practices of physicians and the beliefs/perceptions of patients regarding the treatment of CPD.

### Method

Using a purposive sampling approach, physicians and patients were recruited for separate surveys regarding CPD. Physician informants in the United States participated in a qualitative phone interview between November and December, 2012. Physicians were identified based on specialty, experience in pain management, prescribing practices, and location. Physicians took part in a semi-structured survey on: prevalence of CPD, patient-physician communication, pain management practices, treatment alternatives, and current unmet needs. Data obtained from physician interviews was combined with results from a comprehensive literature search to calculate the prevalence of CPD.

Patients completed a 30-question, structured, online questionnaire during February 1-15, 2013. An online, convenience sampling approach was used to recruit patients. Participants were recruited through a consumer panel of pre-identified patients with chronic pain. Inclusion criteria included: resident in the United States, ≥18 years, diagnosed with chronic pain, suffering from chronic pain ≥3 months, and using opioid analgesics ≥3 months. The survey consisted of closed- and open-ended questions on: participant demographics, chronic pain diagnosis, type and duration of pain, current treatment(s), medication compliance, opioid analgesic(s) route(s) of administration, presence and prevalence of swallowing difficulty, patient-physician communication, use of nonrecommended methods to assist in swallowing opioids, misuse of opioids, and knowledge and attitudes regarding abuse-deterrent formulations.

Open-ended questions in both surveys were reviewed and coded manually. The frequency of each code was calculated to show the percentage of total respondents who provided each coded response. For all closed-ended

questions, frequency, means, and significance were calculated using SPSS v18.0 (IBM Corporation, Armonk, New York).

## Results

A total of 34 physicians and 1021 patients took part in the surveys. Prevalence of patients with dysphagia was estimated between 10%-15%, which approximates to 37.5 million Americans based on recent US Census Bureau data. Stratification of these patients indicated that 20%-25%, 1%-6%, and 30% of children/adolescents (<19 years old), adults, and the elderly (>65 years old), respectively, experience dysphagia. To determine the overlap of chronic pain and dysphagia, physicians were asked to identify the prevalence of this patient population in their practices. Driven by physician type, primary care physicians reported approximately 5%-10%, oncologists reported 30%-35%, and hospice/palliative care physicians reported 40%-50% prevalence of CPD. Overall, it was estimated that approximately 11% of patients with chronic pain also have dysphagia, which calculates to approximately 11 million Americans with CPD. Physicians indicated that current treatment regimens for patients with CPD consisted of the fentanyl patch, immediate-release opioids, methadone liquid, or extended-release morphine products. Physicians were only moderately satisfied with currently available treatment options. Physicians indicated that they were generally less concerned with opioid abuse and misuse in this patient population; it was indicated that an easy to swallow, extended-release product with abuse-deterrent properties would be welcomed.

Of the 1021 patients surveyed, approximately 30% indicated that they had trouble swallowing or disliked swallowing pills. The majority of patients (80%) indicated that they were not asked about their ability to swallow solid, oral dosage forms by their physician(s). As a workaround for their swallowing difficulties, some patients (16%) indicated that they cut/crush/grind their medication to facilitate swallowing. Most of these patients (65%) did not know that altering tablets could potentially change the drug release (eg, pharmacokinetic) characteristics of the tablet and could lead to serious adverse events, including fatal overdose in the case of opioid analgesics.

## Conclusions

A significant proportion of patients with chronic pain also has dysphagia and cannot swallow solid, oral dosage forms, which poses a treatment challenge for pain specialists and other healthcare providers. Currently available treatment options have limitations; new treatment options would be welcomed by both physicians and patients. Physician and patient education should be enhanced in order to promote awareness of the consequences associated with altering solid, oral analgesic drugs. Facilitating patient-physician communication on this condition may help to improve treatment outcomes.



**Insomnia characteristics and treatment in centralized, intractable pain patients**

Forest Tennant

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**Purpose**

Determine insomnia characteristics and pharmacologic agents that centralized, intractable pain patients find effective. Most centralized, intractable pain patients have constant pain with severe insomnia due to hyper-autonomic arousal and central sensitization. They do not respond well to nonpharmacologic measures. Scant attention has been paid to this clinical problem.

**Method**

Forty (40) patients in treatment for centralized, intractable pain were surveyed with a written questionnaire. They described their pain as constant and associated with severe insomnia. Subjects of inquiry included the specific name of insomnia medication used, the use of opioids at bedtime, length of sleep, and effect of sleep on pain severity.

**Results**

The majority (31; 77.8%) of patients get less than 5 hours sleep at one time. About 70% take a pharmacologic agent to sleep with benzodiazepines the most common class of sleep aids. The remainder take an opioid dose before bedtime. Forty-four per cent (44%) reported they have less pain the day after a good night's sleep.

**Conclusions**

The majority (31; 77.8%) of patients get less than 5 hours sleep at one time. About 70% take a pharmacologic agent to sleep with benzodiazepines the most common class of sleep aids. The remainder take an opioid dose before bedtime. Forty-four per cent (44%) reported they have less pain the day after a good night's sleep.

**Long-term safety and efficacy of human chorionic gonadotropin (HCG) for centralized, intractable pain**

Forest Tennant

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**Purpose**

To determine the safety and efficacy of HCG after one or more years of treatment. Human chorionic gonadotropin (HCG) is comprised of 2 subunits. One contains follicle stimulating hormone (FSH), luteinizing hormone (LH), and thyroid stimulating hormone (TSH). The other unit is anabolic and neurogenic with multiple receptors in the central nervous system. It is now being investigated by the author for centralized, intractable pain since only symptomatic, analgesics are available.

**Method**

Twenty-six (26) centralized intractable pain patients with constant unremitting pain and who have used HCG for periods ranging from 12 to 74 months were evaluated in June 2013. The dosage of HCG used by these patients ranged from 250 to 750 units a day when used sublingually. Those using injections self-administered 1000 units 2 to 3 times a week.

**Results**

All patients reported the attainment of either some pain-free hours, permanent reduction in pain, or less severe flares of pain. All have decreased opioid use ranging from a reduction of 30 to 100%. Two patients no longer use opioids. All report increases in energy and endurance. Subgroups report increases in intellectual functions, sleep, and libido. Side-effects have only been noted in 3 patients and consist of headache (2) and loss of hair (1) which resolved with lowering the HCG dosage.

**Conclusions**

This selected, open-label group of centralized, intractable pain patients appear to have safely and greatly benefited from HCG therapy. Results here cannot be generalized to other pain populations. Considering our lack of therapeutic, curative agents for centralized, intractable pain, HCG should be given clinical trials by other investigators.

**Oxytocin pilot study in centralized, intractable pain patients**

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**Purpose**

To determine if oxytocin shows enough clinical efficacy and safety to warrant clinical investigation in centralized, intractable pain patients. Oxytocin is a hormone naturally produced in the central nervous system of females and males. It has shown multiple neurogenic properties in animal studies.

**Method**

Thirteen intractable pain patients who had centralized their pain were given a starting sublingual oxytocin dosage of 10 units/ml each day. Dosage was titrated upward to as high as 40 units a day over 6 weeks. Patients were evaluated for side-effects, pain relief, and desire to continue therapy. This study began in January 2013 and patient outcomes were determined in June 2013.

**Results**

Nine of the 13 (69.3%) patients reported that oxytocin relieved pain, decreased opioid use, and improved mental abilities. Eight desire to continue therapy. One used oxytocin for approximately months at which time she was able to temporarily cease opioid and oxytocin use. Two patients reported dramatic improvement in pain relief and ability to read, remember, and mentate. The 4 patients who discontinued treatment found oxytocin to either be ineffective or produce the side-effects of headache and dysphoria.

**Conclusions**

Oxytocin should be investigated in centralized, intractable pain patients as there are few treatment alternatives in this population.

**Search for inflammatory markers in centralized, intractable pain patients**

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**Purpose**

To find inflammatory markers other than ESR and CRP. Pain and inflammation are inextricably linked, so biologic markers that indicate the presence of inflammation are critically needed. At this time only the crude erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) assays are generally recognized as clinical inflammatory markers.

**Method**

Thirty-nine (39) centralized, intractable pain patients who were in medical treatment and considered stabilized were simultaneously tested for ESR, CRP, alpha-1 antitrypsin (A1AT), myeloperoxidase (MPO), and soluble tumor necrosis factor alpha receptor type II (TNFR).

**Results**

A total of 22 (56.4%) of patients had an elevation of at least 1 of the 5 inflammatory markers. Eighteen (18) patients had an elevated MP, TNFR, or ANF, and 9 (50%) of these did not have an elevated ESR or CRP. Fourteen (14) patients showed elevations of CRP and/or ESR. Of these 14, 8 also had an elevated MP, AT, or TNFR.

**Conclusions**

Over half (56.4%) of the intractable pain patients who appeared medically stabilized and were tested showed elevated inflammatory markers. This indicates that symptomatic analgesia is helpful but does not eliminate an inflammatory, likely progressive, disease state. This study suggests that multiple inflammatory markers should simultaneously be tested to best detect unresolved inflammation in pain patients.

## Long-acting opioids in geriatric and long-term care patients

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### Purpose

To systematically review current knowledge on LAOs for chronic pain in geriatric and LTC patients. Pain management in geriatric and long-term care (LTC) patients is challenging. Safety and efficacy data in younger adult populations may not be adequate for clinicians to assess the risks and benefits of therapy for older adults. Safe and effective use of long-acting opioids (LAOs) in geriatric and LTC patients requires an understanding of the literature in these populations.

### Method

Eligible articles were indexed on PubMed with a full abstract, published between May 31, 2003 and June 1, 2013 in the English language, describing a human clinical trial which included a population of patients  $\geq 65$  years of age who received an approved long-acting opioid for chronic pain of cancer or noncancer origin. Hand-search included relevant articles concerning pharmacokinetics, safety, efficacy, or pharmacoeconomics, and excluded articles which were opinion, reviews, guidelines, animal studies, or concerned acute pain or unapproved drugs. Reference lists of relevant articles were not searched. Articles were analyzed by level of evidence, outcome measures, enrollment, demographics, pain etiology, opioid molecule and formulation.

### Results

The search returned 108 hits of which 93 were deemed relevant. There are few efficacy data on opioids in older adults. Physiologic changes with aging and comorbidities increase the susceptibility of older adults to adverse events including respiratory depression, nausea, constipation, and psychomotor impairment. Polypharmacy increases the risk of pharmacodynamic and pharmacokinetic drug interactions. Currently, there are insufficient data to recommend LAOs over short-acting opioids (SAOs) for chronic pain. However, LAOs may benefit geriatric and LTC patients with fewer pain-related sleep interruptions and benefit LTC caregivers with less-frequent medication administration. Slower onset of effect with LAOs vs SAOs may produce less intense subjective effects (eg, euphoria) and less cognitive-psychomotor impairment. Difficulties administering oral medication because of cognitive impairment, dysphagia, and pill phobia may be addressed with transdermal LAOs. Crush-resistant LAOs may prevent cognitively-impaired patients and misguided LTC caregivers from crushing LAO tablets contrary to label warnings.

### Conclusions

Opioids may be appropriate for selected geriatric and LTC patients with moderate to severe chronic pain. Though LAOs are not recommended over SAOs, older patients may find benefit from LAO features, including less-frequent dosing, slow onset of effect, and transdermal or crush-resistant formulations.

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## Opioid risk assessment among pharmacy students

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### Purpose

The use of opioids to manage moderate to severe pain is a proven therapy in current medical practice. One of the pitfalls of opioid therapy is the risk of abuse, addiction, misuse and diversion among patients and nonpatients. In addition, due to access and availability issues, healthcare providers also are at risk for these consequences. The Opioid Risk Tool (ORT) has been utilized to assess this risk among chronic pain patients. The ORT incorporates several questions with weighted scoring relating to the following: family and personal history of substance abuse, age, gender, history of preadolescent sexual abuse, and psychological disease to categorize respondents into low, moderate and high-risk groups.

To date, the ORT has not been used to assess risk in health professionals or students in their professional training years. This study assessed the opioid risk among students enrolled in their last 4 professional years of pharmacy school, of a 6-year program.

### Method

A survey was conducted among pharmacy students at the school. Participation by students was voluntary, and the results remained anonymous and were kept confidential. The study was reviewed and approved by the Rutgers IRB.

### Results

After administering the ORT, the first professional year students (n = 163) had 133 at low risk (82%), 16 at moderate risk (9.5%), and 14 at high risk (8.5%). The second professional year students (n = 107) had 74 at low risk (69%), 20 at moderate risk (19%), and 13 at high risk (12%). Pharmacy students in their third professional years (n = 200) had 163 at low risk (81.5%), 29 at moderate risk (14.5%), and 8 at high risk (4%). Finally, students in their last year of pharmacy school (n = 181) had 140 at low risk (77%), 23 at moderate risk (13%), and 18 at high risk (10%).

### Conclusions

These data mirror the results found in the chronic pain population. Since the stress of pain may lead to moderate to high risk, these data suggests about 20% of this professional group is at significant risk of abuse if they develop severe pain and use opioids. Healthcare professionals need education and should be given tools such as the ORT to assess their own level of opioid risk for future awareness and professional actions, if needed.

## A randomized controlled trial of an online pain self-management program for people with arthritis pain

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### Purpose

One of every 5 adults in the United States (46.4 million people) is affected by arthritis. Healthy People 2010 objective #2-8 was to "Increase the number of people with arthritis pain receiving arthritis education" (US Department of Health and Human Services, 2000). Self-management is a critical component in helping arthritis sufferers learn how to identify, avoid, and manage their pain but clinicians face significant time pressure, leaving little time for patient-provider education and collaboration. Internet-based programs significantly improve knowledge, social support, and clinical outcomes among people with chronic diseases (see review by Murray, et al, 2005); however, in 2002 most existing websites did not offer site users a tailored interactive experience. Some profess "cures" but only offer information and advice of questionable scientific validity, and few sites had been empirically tested to see how much they helped people with arthritis pain attain improved outcomes in self-management and symptom reduction. We developed and tested an interactive, online pain self-management program for adults who suffer from pain associated with osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and other arthritic conditions (eg, psoriatic arthritis) using principles from Social Cognitive Theory (Bandura, 1977, 1997).

### Method

The study was a parallel group design with 2 conditions: (1) An experimental group asked to use the website for a minimum of 8 sessions during a 1 month intervention period, and a minimum of 5 times during a 6-month follow-up period; and (2) A control group that was not exposed to the website. Assessments were conducted at baseline, 1 month, 3 months, and 6 months.

The hypotheses were that participants exposed to the painACTION intervention would report:

(1) Increased positive cognitions (eg, pain self-efficacy and pain awareness), reduced negative cognitions (ie, pain catastrophizing); (2) Increased frequency of self-management behaviors (ie, exercise, cognitive symptom management, communication with physicians); and (3) Reduced pain and improved functioning.

The 228 adult participants in the study had reliable Internet access and e-mail; a self-reported doctor diagnosis of arthritis such as osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis (AS), or other arthritic conditions (eg, psoriatic arthritis); and a self-reported pain level of 4 or more in the past week on the 0 to 10 Numeric Rating Scale (McCaffery & Beebe, 1993) .

Participants were recruited via flyers and online postings, screened and consented, then randomized. A total of 113 participants received the intervention: access to the online intervention and a suggested curriculum for use 2 times a week for 4 weeks followed by 5 additional monthly booster sessions. The painACTION program includes articles, lessons, and interactive tools to facilitate learning pain self-management skills. The control group included 115 participants. All participants received payment for completing each assessment.

### Results

Generalized linear mixed models (GLMM) were run to test whether experimental website participants, as compared to control participants, had a significantly greater mean change over time on the following primary outcomes:

COGNITIONS: Arthritis Self-efficacy Scale (Lorig, et al, 1989); Pain Catastrophizing Scale (PCS; Sullivan, et al, 1995); Pain Awareness Questionnaire (Berman, et al, 2009); SELF MANAGEMENT BEHAVIORS: Exercise Behaviors (Lorig, et al, 1996); Cognitive Symptom Management (Lorig, et al, 1996); Communication with Physicians (Lorig, et al, 1996); and PAIN (LEVEL, FUNCTIONING): Brief Pain Inventory (BPI; Cleeland, 1991). We also looked at the following Secondary Outcomes: AFFECT: Depression Anxiety Stress Scales-Short Form (DASS-21; Lovibond & Lovibond, 1995); COPING: Chronic Pain Coping Inventory-42 (CPCI-42; Jensen, et al, 1995); QUALITY OF LIFE: Patient Global Impression of Change (PGIC; Guy, 1976), The Arthritis Impact Measurement Scale-2-SF (Guillemin, et al, 1997).

Participants exposed to painACTION demonstrated significantly:

- (1) Increased pain self-efficacy at 1-month and 6-month follow-ups
- (2) Reduced pain catastrophizing at 6-month follow-up
- (3) Increased relaxation coping at 3-month follow-up
- (4) Higher average patient perception of global change at 1-month, 3-month, and 6-month follow-ups.

### **Conclusions**

These improvements in participants' pain self-efficacy, pain catastrophizing, coping through relaxation, and quality of life indicate that painACTION can be an important element of a comprehensive disease management approach. Further research is needed to determine which clinical groups may be most effectively treated by an online intervention and to better understand why some dimensions changed after exposure to the treatment while others did not. In closing, healthcare providers who recommend patients to painACTION may help meet the public health need for arthritis education.



## Efficacy and safety of naloxegol in patients with opioid-induced constipation: results from 2 identical phase 3, prospective, randomized, multicenter, double-blind, placebo-controlled trials

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### Purpose

Opioid-induced constipation (OIC) is a common and often debilitating adverse effect of opioid analgesics. OIC results from the binding of opioid analgesics at  $\mu$ -opioid receptors in the gastrointestinal (GI) tract and occurs in 40%-90% of patients undergoing pharmacotherapy. OIC has a major impact on the quality of life of patients taking these medications and can lead to the development of fecal impaction and bowel obstruction or perforation. Often constipation persists despite the use of laxatives or the adoption of lifestyle and diet modifications, and patients may self-titrate their dosage of opioid analgesic medication in an attempt to alleviate OIC. Naloxegol is a PEGylated derivative of the opioid antagonist naloxone. PEGylation confers P-glycoprotein transporter substrate properties and decreases its ability to cross the blood-brain barrier. Naloxegol is an investigational, orally active, peripherally acting,  $\mu$ -opioid receptor antagonist. The objective of these 2 identical 12-week, randomized, multicenter, double-blind, placebo-controlled studies (KODIAC-04, NCT01309841; KODIAC-05, NCT01323790) was to evaluate the efficacy and safety of 2 doses of naloxegol in patients with OIC taking opioids for noncancer pain.

### Method

Outpatients with noncancer pain and OIC taking 30-1000 morphine equivalents/day for pain were randomized to once-daily naloxegol 12.5 or 25 mg or placebo. Patients were required to have active OIC symptoms at screening and confirmed OIC during the 2-week period before randomization (<3 spontaneous bowel movements [SBMs]/week with  $\geq 1$  symptom of hard or lumpy stools, straining, or sensation of incomplete evacuation or anorectal obstruction in  $\geq 25\%$  of bowel movements during the 4 weeks prescreening). The primary endpoint was percentage of responders over 12 weeks (intent-to-treat [ITT] population; defined as having  $\geq 3$  SBMs/week with  $\geq 1$  SBM/week increase over baseline for  $\geq 9$  of 12 weeks and  $\geq 3$  of the last 4 weeks). Key secondary efficacy endpoints were percentage of responders (weeks 1-12) in the laxative-inadequate-response (LIR) population (defined as having taken  $\geq 1$  laxative class for  $\geq 4$  days before screening and ratings of moderate to very severe on  $\geq 1$  of the 4 stool symptom domains in the baseline laxative response questionnaire [2-week recall] at screening); time to first postdose SBM (ITT population); mean number of days/week with  $\geq 1$  SBM (ITT population). Changes from baseline pain scores, daily opioid use, and modified Himmelsbach Opioid Withdrawal Scale scores (weeks 1-12) were assessed. Adverse events (AEs) were monitored throughout the study. Multiplicity testing mandated a critical  $P < .025$  for  $\geq 1$  of the doses vs placebo in the ITT population for primary and key secondary endpoints. Statistical analysis applied the Bonferroni-Holm procedure over dose groups, with fixed sequence testing within groups.

### Results

In KODIAC-04, 1750 patients were enrolled, 652 were randomized, and 524 (80.4%) completed the study. In KODIAC-05, 1969 patients were enrolled, 700 were randomized, and 537 (76.7%) completed the study. Before database lock and unblinding, 15 patients (KODIAC-04,  $n = 11$ ; KODIAC-05,  $n = 4$ ) were found to have been randomized and participating in the program multiple times at different centers within the program and were excluded from the ITT set before unblinding. There were significantly more responders with the 25-mg dose (KODIAC-04: 44.4%,  $P = .001$ ; KODIAC-05: 39.7%,  $P = .021$ ) vs placebo (KODIAC-04, 29.4%; KODIAC-05, 29.3%). The responder rate was significantly increased vs placebo with the 12.5-mg dose in KODIAC-04 (40.8%,  $P = .015$ ) but

not KODIAC-05 (34.9%,  $P = .202$ ). Similar results were observed vs placebo (KODIAC-04, 28.8%; KODIAC-05, 31.4%) in the LIR population for the 25-mg dose (KODIAC-04: 48.7%,  $P = .002$ ; KODIAC-05: 46.8 %,  $P = .014$ ) and with the 12.5-mg dose in KODIAC-04 (42.6%,  $P = .028$ ) but not KODIAC-05 (42.4%,  $P = .074$ ). Median times to first postdose laxation for placebo, naloxegol 12.5 mg, and naloxegol 25 mg were 35.8, 20.4, and 5.9 hours, respectively, for KODIAC-04 (both naloxegol doses vs placebo,  $P < .001$ ) and 37.2, 19.3, and 12.0 hours for KODIAC-05 (naloxegol 25 mg vs placebo,  $P < .001$ ). Mean change from baseline in the number of days/week with  $\geq 1$  SBM for naloxegol vs placebo was significantly increased with the 25-mg dose (KODIAC-04,  $P < .001$ ; KODIAC-05,  $P < .001$ ) and with the 12.5-mg dose in KODIAC-04 ( $P < .001$ ). Mean daily pain scores, total daily opioid doses, and clinically relevant opioid withdrawals were similar across treatment groups. AEs and discontinuations due to AEs were more frequent with the 25-mg dose. The number of serious AEs was generally similar across treatment groups. GI-related AEs (abdominal pain, diarrhea, nausea, flatulence, vomiting) were the most commonly reported treatment-emergent AEs. There were no notable imbalances in major cardiovascular events across treatment groups.

## Conclusions

In patients with OIC, treatment with naloxegol significantly increased the percentage of responders and improved stool frequency relative to placebo. The onset of action was rapid, with greater efficacy for 25 mg vs 12.5 mg of naloxegol, and similar response was observed in patients with LIR with OIC. Opioid-mediated analgesia or daily opioid use was unaffected by naloxegol treatment. Naloxegol was generally well tolerated and safe, with the majority of AEs being GI-related in nature. Naloxegol is a viable option for treatment of patients with chronic pain who experience OIC.

## Naloxegol efficacy in subpopulations of patients with opioid-induced constipation: results from 2 prospective randomized controlled trials

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### Purpose

Opioid-induced constipation (OIC) is a common and often debilitating adverse effect of opioid analgesics. The actions of opioid analgesics at  $\mu$ -opioid receptors located in the gastrointestinal (GI) tract cause OIC, a condition that occurs in 40% to 90% of patients treated with these agents. OIC is associated with the development of GI-related complications and affects quality of life. In addition, OIC may indirectly impact the efficacy of opioid analgesic therapy in some patients by interfering with adherence to the opioid dosing regimen in an attempt to manage the discomfort associated with OIC. In this patient population, the degree of constipation experienced not only may be related to the type and dose of opioid analgesic medication being used but also may be affected by concomitant medications that can exacerbate constipation (eg, those with anticholinergic activity). Naloxegol is an investigational, orally active, peripherally acting  $\mu$ -opioid receptor antagonist in development for the treatment of OIC. The objective of this analysis was to examine the consistency of the treatment effect of the 25-mg dose of naloxegol vs placebo across various prespecified subgroups of patients with OIC and noncancer pain. With the exception of the laxative inadequate responder (LIR) subgroup, the studies were not designed or powered to assess the treatment effect within any particular subgroup.

### Method

Data were pooled from 2 identical phase 3, randomized, double-blind, 12-week studies (KODIAC-04 [NCT01309841]; KODIAC-05 [NCT01323790]) evaluating efficacy of oral naloxegol in outpatients with noncancer pain and OIC. The primary endpoint was the percentage of responders over 12 weeks ( $\geq 3$  spontaneous bowel movements [SBMs] per week with  $\geq 1$  SBM/week increase over baseline for  $\geq 9$  of the 12 weeks and  $\geq 3$  of the last 4 weeks). Pooled response rates to naloxegol 25 mg/d vs placebo were analyzed in prespecified subpopulations of patients (age [ $<50$ , 50-64, or  $\geq 65$  years], sex, race, geographic region [North America or Europe], body mass index [BMI  $<30$  or  $\geq 30$  kg/m<sup>2</sup>], laxative response [LIR (self-reported moderate, severe, or very severe symptoms in  $\geq 1$  of 4 stool symptom domains [incomplete bowel movement, hard stools, straining, or false alarms] of the Baseline Laxative Response Status Questionnaire in patients taking  $\geq 1$  laxative class for  $\geq 4$  days before screening), non-LIR, or 2X LIR (inadequate response to  $\geq 2$  laxative classes)], daily opioid morphine-equivalent dose [low,  $<200$  morphine equivalent units (MEU)/d or high,  $\geq 200$  MEU/d], opioid type [weak or strong], and strong anticholinergic use [yes or no]). The high-opioid-dose definition was based on American Pain Society recommendations (Chou R, et al. *J Pain* .2009;10:113-130). Strong anticholinergics were defined according to the Anticholinergic Burden Scale (score 3) and comprised a wide range of commonly used medications (eg, antidepressants, antihistamines, antipsychotics, and muscle relaxants; Boustani M, et al. *Aging Health* 2008;4:311-320). Exploratory analyses measured consistency of treatment effect across subgroups (Forest plots).

### Results

Pooled analysis of the 2 studies demonstrated statistically significant improvements for naloxegol (n = 446, 41.9%) compared with placebo (n = 446, 29.4%) for the 25-mg group in the overall population (P  $< .001$ ). In patients in subgroups by age, sex, race, study region, BMI, laxative response, daily opioid dose in MEU, type of opioid, or use of a strong anticholinergic, treatment response favored naloxegol as evidenced by relative risk values  $>1$  vs placebo.

Forest plots of the respective subgroup data will be presented. The treatment effect for naloxegol was consistent across all subgroups analyzed, with the confidence intervals for the relative risk (naloxegol/placebo) overlapping with those in the overall population. Results in most subgroups were dose-ordered (higher response rate with increasing dose), with a numerically higher response rate observed in the naloxegol 25-mg group compared with placebo in every subgroup assessed.

## **Conclusions**

The direction of the treatment effect of naloxegol 25 mg was consistent across all patient subgroups analyzed, providing convincing evidence to support the efficacy of naloxegol 25 mg in a broad population of OIC patients with noncancer pain. Naloxegol 25 mg is a viable treatment option for a broad range of patients with chronic pain who experience OIC.

## Implementation of a pilot chronic pain rehabilitation program

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### Purpose

Patients seen at the West Palm Beach Veterans Affairs Medical Center (VAMC) Pain Management Clinic are referred by their primary care physicians and upon assessment, may be further referred for interventional pain procedures, pharmacologic optimization, physical medicine and rehabilitation (PM&R), or to a pain psychologist. An interdisciplinary rehabilitation-focused approach will allow for patients to be assessed by all of the above disciplines in order to help increase patient functionality, quality of life (QOL), and potentially decrease or limit opioid medication use. The West Palm Beach VAMCs Pain Clinic, though multidisciplinary in its nature, lacks an integrated, rehabilitation-focused approach to pain management. The purpose of this project was to implement a pilot outpatient chronic pain rehabilitation program at the West Palm Beach VAMC that would allow patients to receive an interdisciplinary approach to pain management and rehabilitation with a focus on improvement in QOL and functional restoration as well as the potential to reduce or limit opioid medication use. Additionally, the program was designed to meet CARF standards.

### Method

Prior to establishing the program, a review of the workflow process was conducted and administrative documents were prepared. Patients with chronic nonmalignant pain, no active substance abuse, and stable medical/psychological condition were considered for participation in this program. Potential participants were initially evaluated individually by a PM&R physician, pain psychologist, physical therapist, and clinical pharmacy specialist in pain management. An interdisciplinary meeting took place following the individual evaluations to establish patient-specific goals and a plan of care for each patient. Once enrolled, patients completed evidence-based cognitive behavioral therapy sessions, participated in physical therapy, were seen for optimization of pain medications, and were scheduled for pain procedures, as needed. Discharge criteria included achieving goals or maximum benefit from the program, no longer willing or able to participate, displaying aberrant behaviors, substance abuse, a decline in medical or psychological status, more than 2 consecutive "no-show" appointments, or not complying with recommendations. The primary outcome measurements were the Pain Outcomes Questionnaire-Short Form (POQ-SF) and the POQ-Pain Treatment Satisfaction Score; secondary outcome measurements were pain scores and medication use. Outcomes data were collected and assessed throughout the project via retrospective chart review and comparisons to baseline values were made, as applicable. Both formal and informal methods of communication among the interdisciplinary team members occurred throughout the project. Statistical analyses of outcomes data were evaluated. This project was approved by the West Palm Beach VAMC residency project committee; IRB approval was not required as this project was part of a quality improvement process.

### Results

A total of 6 participants completed the program. Each patient completed 10 evidence-based therapy sessions with a pain psychologist (one session weekly for 10 weeks) unless predetermined that the number of sessions would be less (eg, patient who had completed similar program in the past). Physical therapy took place 2-3 times per week for 8 weeks, follow-up with a clinical pharmacy specialist in pain management generally occurred on a monthly or as needed basis, and follow-up with a PM&R physician or scheduling of interventional procedures was completed as needed. The average age of patients was approximately 54 years and the majority of participants were male (83%). The average length of time that patients had pain was approximately 16 years. The median of the average pain

scores reported by patients prior to program initiation and after program completion was 7/10. Pain score reduction was based on the self-reported average pain score at initiation and completion. While only some patients reported reduced pain scores, all patients reported improved functioning as assessed by the POQ-SF. The POQ-SF assesses pain level as well as the patient's perception of the impact of their pain in 5 domains: completion of activities of daily living, mobility, sense of vitality, emotional functioning, and pain-related fear of activity. All participants completed the POQ-Pain Treatment Satisfaction questionnaire and rated their satisfaction level as 10/10 in all 5 areas (ie, overall care received; staff warmth, respect, kindness, willingness to listen; skills/competence of staff; ease of getting appointments, hours of treatment, etc; whether treatment would be recommended to someone they know who has a pain problem). No patients were discharged from the program due to a change in medical or psychological status, substance abuse/aberrant behaviors, more than 2 consecutive "no-show" appointments, or due to inability to comply with recommendations.

## **Conclusions**

Although the sample size was small, the results of this project indicate that the interdisciplinary team approach to managing chronic pain has improved functionality and QOL for these participants. Patient-centered care is promoted via the application of the rehabilitation approach and inclusion of the patient in goal-setting as well as participation in the team meetings. Communication among team members allows for an integrated approach. Patients completing this program have indicated satisfaction and would recommend this program to others.

## **Reference**

Clark ME, Gironde RJ, Young RW. Development and validation of the Pain Outcomes Questionnaire-VA. *J Rehabil Res Dev.* 2003;40(5):381-396.

## Feasibility and satisfaction of pain medication safety education via an online intervention

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### Purpose

The number of prescriptions filled for opioid pain medication has increased dramatically in recent years: From 1997 to 2007, the milligram per person use of prescription opioids in the US increased over 400% (Manchikanti, et al, 2010). While opioid medications have great potential for easing suffering and improving quality of life, they also have potential for abuse. Abuse of opioids is a rapidly growing problem: nearly one-third of people aged 12 and over who used drugs for the first time in 2009 began by using a prescription drug nonmedically (NSDUH, 2010). Moreover, 70% of people who abused prescription pain relievers got them from friends or relatives (NSDUH, 2010). Consequently, there is an urgent need for education to help patients safely manage their prescription opioid medication.

### Method

#### Design

The 2 primary goals of the study were to (1) learn more about how chronic pain patients store and dispose of opioid pain medication and (2) test the feasibility of the Web-based Pain Medication Safety Program, an intervention designed to increase safe management of opioid pain medication. A secondary goal was to discover whether the intervention was an effective way to increase self-efficacy and behaviors related to safe management of opioid pain medication.

The study used a randomized, controlled design that compared the intervention to a waitlist control condition. Feasibility was measured with lesson completion rates and satisfaction with the intervention (experimental group only). Participants were also asked open-ended questions about how they stored and disposed of medication, and what would motivate them to dispose of unused prescription opioid medication according to FDA guidelines. The hypotheses related to efficacy were that, as compared to the control group, people in the experimental group would demonstrate (1) increased self-efficacy for how to safely manage medications and (2) increased behaviors associated with safely managing medication.

#### Participants

One hundred and forty people completed the baseline assessment. Sixty-two percent were female. The most common types of chronic pain reported were back pain (74%); arthritis pain (40%), and headache (23%).

#### Procedure

Participants completed the Web-based Pain Medication Safety Program which consisted of 11 "click through" lessons. Lessons addressed issues such as how to store and dispose of medication safely. Each lesson took about ten minutes to complete, for a total intervention of about 150 minutes.

#### Results

Results suggest that it is feasible to deliver pain medication safety education via an online intervention. Almost two-thirds (65%) of participants in the experimental group completed at least 9 of the 11 lessons. No differences were noted between participants who did and did not complete the lessons.

In general, people were satisfied with the intervention. For example, of participants who answered questions about satisfaction, the majority found the lessons very easy to understand (88%) and well organized (100%). The majority of participants (76%) reported that they learned things they didn't already know, and the majority (82%) had shared the information with a friend or family member.

In terms of efficacy, there were no significant differences between the experimental and control group.

Results of a psychometric evaluation of new outcome measures used in the field trial will be reported. The measures are Self-efficacy for Managing Opioid Medications and Behaviors Associated with Managing Opioid Medications. Construct validity of each measure was evaluated by employing a promax-rotated exploratory factor analysis (EFA). Internal consistency (Cronbach's alpha) and test-retest reliability (Pearson correlation) was also examined.

Finally, results of the qualitative analysis revealed themes relating to how people store and dispose of opioid pain medication.

## **Conclusions**

Results suggest that the Internet is a feasible delivery mechanism for an intervention designed to increase awareness of how to safely manage prescription opioid pain medication. Results of our qualitative analysis provide valuable insight into how people store and dispose of opioid pain medication. Themes related to what would motivate people to dispose of opioid medications according to FDA guidelines may be particularly useful for informing public health messaging.



## No evidence of analgesic interference or CNS opioid withdrawal for TD-1211 in a phase 2b study in opioid-induced constipation

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### Purpose

Opioid-induced constipation (OIC) is a common and debilitating consequence of long-term opioid use. TD-1211 is an investigational, peripherally selective, multivalent inhibitor of the mu-opioid receptor designed with the goal of alleviating gastrointestinal side effects of opioid therapy without affecting analgesia. A 5-week, double-blind, parallel-group study in 217 chronic noncancer pain OIC patients evaluated the safety and efficacy of 3 oral doses of TD-1211 compared to placebo.

### Method

Patients randomized to TD-1211 received 5 mg for the first 4 days of dosing, and on Day 5, remained at 5 mg or were dose escalated to 10 mg or 15 mg for the remainder of the treatment period (Weeks 2-5). Patients randomized to placebo received placebo for all 5 weeks. Throughout the study, patients were required to stop laxatives and bowel movement regimens, except protocol-permitted rescue bisacodyl use. The primary efficacy endpoint was the change from baseline in weekly average complete spontaneous bowel movements (CSBMs) over treatment weeks 2-5. Additional assessments on daily pain score, opioid dose, and central opioid withdrawal are reported here.

### Results

For the primary endpoint, the increase from baseline for placebo-treated patients was 0.8 CSBMs/wk vs 1.5 ( $P = .04$ ), 2.6 ( $P = .001$ ), 2.5 ( $P = .0003$ ) for TD-1211 5 mg, 10 mg, and 15 mg patients, respectively. The mean average daily pain score (0-10 VAS with 10 as worst imaginable pain) was 5.9-6.1 across treatment groups at baseline, and the change from baseline at Week 5 was -0.7, 0.1, and -0.7 for the 5 mg, 10 mg, and 15 mg TD-1211 treatment groups, respectively, compared to -0.5 for placebo. The mean and median baseline daily opioid doses for the study were 145 and 89 oral morphine equivalent units (MEUs), respectively, and the mean change from baseline at Week 5 was -6, -8.9, and -4.3 MEUs for the 5 mg, 10 mg, and 15 mg TD-1211 treatment groups, respectively, compared with + 4.8 MEUs for placebo. On the Clinician Opiate Withdrawal Scale, with a maximum possible score of 48, the maximum score reported during treatment was 6 for both treatment groups (2 TD-1211 patients, 3 placebo patients), indicating no evidence of CNS withdrawal. The most common adverse events reported for TD-1211 were GI-related; these were generally associated with treatment initiation, resolved within a few days, and were mild to moderate.

### Conclusions

Treatment of OIC patients with TD-1211 for 5 weeks improved CSBM frequency and was not associated with impaired analgesia or centrally-mediated opioid withdrawal, based on the Clinician Opioid Withdrawal Score, daily opioid use, or daily pain scores. The data from this phase 2b study support progression of TD-1211 into phase 3 development for treatment of OIC.

**TD-1211 demonstrates a durable increase in bowel movement frequency and return toward normal bowel function in a 5-week Ph2b opioid-induced constipation study**

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**Purpose**

TD-1211 is an investigational, peripherally selective, mu-opioid receptor antagonist designed to alleviate gastrointestinal side effects of opioid therapy without affecting analgesia. 3 oral doses of TD-1211 were evaluated in a 5-week, double-blind, placebo controlled, parallel-group study conducted in 217 chronic noncancer pain opioid induced constipation (OIC) patients.

**Method**

Patients randomized to TD-1211 received 5 mg for the first 4 days of dosing, and on Day 5, remained at 5 mg or were dose escalated to 10 mg or 15 mg for the remainder of the treatment period (Weeks 2 -5). Patients randomized to placebo received placebo for all 5 weeks. Throughout the study, patients were required to stop laxatives and bowel movement (BM) regimens, except protocol-permitted rescue bisacodyl use. Electronic diaries collected frequency, timing, and symptoms of BMs; use of laxatives and opioids; daily pain scores; and satisfaction / quality of life metrics. Safety and efficacy results, including the primary and key secondary endpoints, have been previously reported. Additional pre-specified week-by-week analyses are reported here.

**Results**

For each week during Weeks 2-5, the mean complete spontaneous bowel movements (CSBMs)/week for 10 and 15 mg TD-1211 patients ranged between 2.5 to 3.3 and 2.5 to 3.9, respectively, vs 0.9 to 1.2 weekly for placebo patients over the same period. The mean spontaneous bowel movements (SBMs)/week for 10 and 15 mg TD-1211 patients ranged weekly between 4.1 to 4.9 and 4.6 to 5.2, respectively, for Weeks 2-5, vs 2.6 to 3.3 for placebo patients. In an exploratory analysis, the mean number of days/week with at least 1 SBM for 10 and 15 mg TD-1211 patients ranged weekly between 3.3 to 3.8 and 3.6 to 3.9, respectively, for Weeks 2-5, vs 2.4 to 2.8 for placebo patients. For each week during Weeks 2-5 of treatment, 51%-53% of 15 mg TD-1211 patients reported  $\geq 5$  SBMs/week compared to 14%-29% of placebo patients, indicating a return toward normal bowel function for treated patients. TD-1211 was generally well tolerated, with overall treatment emergent adverse events (TEAEs) similar between TD-1211 and placebo and gastrointestinal TEAEs predominant.

**Conclusions**

At the 2 highest doses examined, TD-1211 provided a sustained response in CSBM and SBM frequency that was observed for the 5-week duration of therapy in OIC patients. The CSBM and SBM frequencies reported for the 2 highest TD-1211 doses indicated a return toward normal bowel function. The data from this phase 2b study support progression of TD-1211 into phase 3 development for treatment of OIC.

**Dose conversion when switching from traditional opioids to tapentadol extended-release (ER)**

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**Purpose**

To review treatment efficacy/effectiveness, safety, and tolerability in clinical trials that converted subjects from traditional opioids to tapentadol ER.

**Method**

Two open-label phase 3b trials enrolled subjects with chronic, severe osteoarthritis or chronic low back pain who had responded (pain score  $\leq 5$  of 10) to traditional WHO Step III opioids but reported opioid-related adverse events; all subjects were rotated to open-label tapentadol ER. A third study evaluated cancer pain control with double-blind tapentadol ER, morphine SR, or placebo; approximately 85% were taking an opioid at baseline. The fourth was a prospective, observational study among 3134 subjects who received tapentadol ER for severe pain in routine clinical practice; 42% were taking traditional WHO Step III opioids before switching to tapentadol ER. In the 2 open-label phase 3b trials, subjects were converted from morphine equivalent doses (MED)  $\leq 100$ , 101-160, or  $> 160$ -300 mg/d to tapentadol ER 50, 100, and 150 mg BID, respectively. In the cancer pain study, dose conversion was based upon the ratio oxycodone 2 mg:morphine 3 mg:tapentadol ER 10 mg.

**Results**

In phase 3b trials in strong opioid responders, tapentadol ER effectiveness was at least comparable to, or largely improved, with improved tolerability; two-thirds of patients did not require further titration. In the cancer pain study,  $>85\%$  of subjects achieved pain control within 1 week after converting to tapentadol ER, which was generally well tolerated. In the prospective, observational study, tapentadol ER was well tolerated and 67% of subjects who switched from traditional WHO Step III opioids to tapentadol ER achieved  $\geq 50\%$  reduction in pain.

**Conclusions**

Findings from studies in subjects with chronic pain provide important information about the safe conversion from traditional opioid analgesics to tapentadol ER.

## Family medicine physicians' confidence, comfort, experiences and beliefs towards opioid analgesic prescribing for patients with chronic nonmalignant pain

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### Purpose

The prevalence of chronic nonmalignant pain is widespread resulting in a substantial proportion of adult primary care appointments involving patients with chronic pain complaints. While opioid medications are a primary treatment modality for the management of severe chronic pain, physicians often face significant obstacles (eg, abuse potential, inadequate medical training) in prescribing opioids for the management of chronic nonmalignant pain. To our knowledge, attitudes and experiences towards opioid analgesic prescribing for the treatment of chronic nonmalignant pain has not been examined among a diverse sample of family medicine physicians practicing in the United States. The purpose of the present study was to explore family medicine physicians' current practices, confidence, comfort, experiences, beliefs, and level of concern about negative outcomes when prescribing opioid analgesics for chronic nonmalignant pain management.

### Method

This study was part of the larger Council of Academic Family Medicine (CAFM) Educational Research Alliance (CERA) omnibus survey. CERA administers an annual survey of active family physician members of CAFM organizations practicing in the United States. Data for this study were collected between November, 2012 and January, 2013. A total of 1099 family physicians were sent an electronic invitation, with automated reminders, and link to participate in an Internet-based survey. This project was approved by the Institutional Review Board of the American Academy of Family Physicians. Respondents completed survey items addressing their (1) sociodemographic and practice characteristics, (2) current opioid prescribing practices, (3) experiences and beliefs toward prescribing opioid analgesics for chronic nonmalignant pain management, (4) level of concern about negative opioid-related outcomes, and (5) confidence and comfort when prescribing opioid analgesics. Data analyses were conducted using the Statistical Package for the Social Sciences (SPSS +) 20.0 software (SPSS Inc, Chicago, IL, USA). Descriptive statistics (frequencies, percentages, means, and standard deviations [SD]) and bivariate correlation coefficients were computed.

### Results

Overall a total of 581 family physicians completed the survey (response rate = 52.9%) with 491 responding to the chronic pain management questions. Males comprised the majority of the sample (n = 284; 57.8%) with 84.1% (n = 413) identifying themselves as non-Hispanic white. Almost all respondents reported prescribing opioids in their current practice (n = 476, 96.9%). The majority of respondents reported being "somewhat" or "strongly" confident (88.4%) and "somewhat" or "strongly" comfortable (76.2%) in their prescribing of opioid analgesics for patients with chronic nonmalignant pain. The majority (80.9%) of respondents did not find it satisfying to prescribe opioids to patients with chronic pain. Furthermore nearly two-thirds of family physicians were concerned about negative patient outcomes (65.2%) and noncompliance (63.8%). Family physicians who were comfortable in their opioid prescribing skills were more likely to report (1) satisfaction in prescribing opioids to chronic pain patients ( $\rho = .494, P < .00$ ), (2) that patients function better with opioids ( $\rho = .345, P < .00$ ), and (3) that patients experience substantial pain relief with opioids ( $\rho = .272, P < .001$ ). Overall, family physicians who were confident in their opioid prescribing skills (1) were more likely to identify pain management as high priority ( $\rho = -.287, P < .00$ ), (2) found greater satisfaction in prescribing opioids ( $\rho = -.283, P < .00$ ), and (3) were less likely to be concerned about getting into trouble with regulatory authorities ( $\rho = -.260, P < .00$ ).

## Conclusions

The majority of family physicians, in this study, prescribed opioid analgesics to patients with chronic nonmalignant pain. There was a strong inverse relationship between confidence regarding opioid prescription and concern about negative consequences (eg, likelihood of patient addiction and overdose). Similarly, comfort level was tied to increased satisfaction with the overall process of opioid prescription. Our findings underscore the need for continued education and training in chronic pain management-including sensible opioid prescribing-throughout family medicine training. Importantly, these findings should encourage further investigation into the underlying causes of this dissatisfaction.

## Pediatric opioid use and safety: a study in the Kaiser Permanente health system

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### Purpose

Little is known about the demographic, clinical or drug utilization characteristics of pediatric patients prescribed opioids for the treatment of pain. Of commonly used opioids, only fentanyl is currently approved for pain treatment in pediatric patients in the United States. However, both clinical observations and data from administrative claims databases suggest that use of other opioids occurs in this pediatric population. Our study objective was to describe the demographics, clinical characteristics, medical events, and drug utilization patterns of pediatric patients prescribed opioids under real-world clinical conditions in a large, integrated health system.

### Method

We identified Kaiser Permanente Northwest patients 16 years of age and under with one or more incident prescriptions for immediate release (IR) or extended-release (ER) single-entity oxycodone, oxycodone/acetaminophen combination products, or hydrocodone combination products. Patients were identified using health plan and electronic medical records in the period from 1998 through 2010. Data included information on patient demographics, inpatient and outpatient diagnoses, and dispenses of medications. Patients taking more than one of the opioids of interest were assigned to a medication category based on the first dispense they had within a medication window, unless they were dispensed oxycodone ER in the window. In the latter case, they were assigned to the oxycodone ER group. Adverse medical events that occurred within 90 days of an opioid prescription were captured. Descriptive statistics; including percentages, means, medians, and ranges; were calculated to evaluate the distributions of the following, stratified by opioid treatment:

1. Demographics, including age category, sex, and race
2. Clinical characteristics, including diagnoses of events such as cancer, arthritis, depression, anxiety, and neuropathy
3. Adverse medical events occurring after the opioid prescription
4. Drug utilization measures, including prior opioid use, use following an inpatient admission, and duration of prescription

### Results

This study included data on 22,964 patients with 24,741 treatment episodes (patients could be included more than once if they had a sufficient gap between periods of opioid treatment). There were 1250 episodes of treatment with IR oxycodone, 94 for ER oxycodone, 2114 for oxycodone/acetaminophen, and 21,228 for hydrocodone. Of these, 91% of treatment episodes for ER oxycodone were in older adolescents (age 12-16). The majority of users of IR oxycodone (70%), oxycodone/acetaminophen (97%) and hydrocodone (86%) were also in this older age category. Opioid use was fairly balanced across males and females in all of the opioids evaluated. For those with race recorded in the medical record, between 88% (IR oxycodone) and 93% (ER oxycodone) of patients prescribed opioids were white, consistent with the health plan's underlying population.

Comorbidities, concomitant medication use, and utilization characteristics varied by opioid type. For example, of pediatric patients who received ER oxycodone, the most frequent comorbidities were pain (19%), depression (10%), anxiety (7%), cardiac disease (5%), diabetes (5%), and cancer (5%). These were also the most frequent comorbidities

in patients prescribed hydrocodone, though at lower rates: depression (6%), pain (5%), anxiety (4%), cardiac disease (2%), and diabetes (1%).

Most patients in this study received opioid prescriptions for <30 days, including 46% of those prescribed ER oxycodone, 87% of those prescribed oxycodone IR, 93% prescribed oxycodone/acetaminophen, and 93% prescribed hydrocodone. Headache was the most frequent medical event diagnosed in the medical records within 90 days after a prescription, occurring in >3% of patients in all treatment groups. Nausea/vomiting also occurred in >3% of patients in the ER oxycodone and IR oxycodone groups. The proportion of patients with these and other adverse medical events varied by treatment, though duration of use and patient profiles also varied by treatment, complicating interpretation of treatment-specific data.

## **Conclusions**

The data from this study suggest that pediatric opioid use is rare, based on data from large healthcare system based in the northwestern United States. Patients using the various opioids of interest were observed to have different underlying clinical characteristics, demographics, and prescription utilization patterns. In general, opioid use in children is of short duration and is more common in older adolescents (age 12-16) than in younger children. Observed safety events in these pediatric patients were similar to those that have been seen in adult patients taking opioids in other studies.

## Long-term pain management with prescription opioid treatment

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### Purpose

Chronic noncancer pain (CNCP) as well as pain associated with malignant disease are significant public health issues. All recent FDA approved opioid analgesics indicated for long-term use must demonstrate analgesic efficacy in randomized, placebo-controlled trials (RCTs) that are 3 months in duration. However, the suitability and effectiveness of opioid analgesic therapy for the long-term management of moderate to severe CNCP is the subject of ongoing debate. Additional information is needed to provide a more comprehensive assessment of this important public health issue. Single-arm open-label (OL) and open-label extension (OLE) studies represent sources of such information. These studies can be used to assess the effectiveness of long-term opioid treatment of CNCP by measuring longitudinal changes in pain from a pre-therapy baseline to 3-months treatment and beyond. Patients who continue in long-term studies may be representative of patients who continue opioid analgesic therapy in the real world. The objective is to evaluate the effects of extended-release (ER) opioids in moderate to severe chronic pain in patients on long-term analgesic therapy.

### Method

Data from ten CNCP open-label multinational studies of ER opioids conducted between 1998 and 2008 with exposures ranging from 6 months to 3 years were evaluated to assess maintenance of pain control. The opioid medications being utilized in this analysis included: buprenorphine transdermal patch (BTDS, a partial  $\mu$ -opioid receptor agonist), ER oxycodone (a full  $\mu$ -agonist), and a combination of ER oxycodone/naloxone (a full  $\mu$ -agonist in combination with a full  $\mu$ -antagonist). For each study, the patients' Average Pain Scores (APS) at the study visits were summarized by calculating summary statistics (n, mean, SD, minimum, and maximum) and 95% confidence intervals.

### Results

In 2 open-label BTDS longitudinal studies conducted in Japan in CNCP patients, decreases of 46% and 50% in mean APS were observed after 12 weeks of treatment. These decreases were sustained through week 52. Also, in 4 open-label extension studies following RCTs of BTDS in CNCP patients conducted in the US, the mean reduction in APS, compared to baseline pain scores (5.1 to 6.7), ranged from 31% to 49% at 52 weeks. In a registry study conducted in the US over 3 years, patients who received ER oxycodone had a 25% reduction in mean APS, from a baseline value of 5.9 to 4.4, at week 12. This observed reduction in pain remained stable through 52 weeks. Finally, similar results were observed in 3 European ER oxycodone/naloxone extension studies (up to 52 weeks) in patients with CNCP.

### Conclusions

Ten studies in CNCP using 3 different ER opioid therapies involving 2750 patients demonstrated maintenance of pain control that began in the initial weeks of treatment and were sustained through 52 weeks. In most cases, this reduction represented a shift in pain level from moderate/severe to mild. These data support the use of ER opioids in the appropriate patients for the long-term management of moderate to severe chronic noncancer pain.



## The long-term analgesic efficacy of opioid therapy in chronic noncancer pain patients: a literature review of randomized controlled, open-label, and epidemiologic studies

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### Purpose

Chronic noncancer pain (CNCP) is one of the most common reasons for seeking medical attention in the United States (US). Patients suffering from CNCP experience reduced quality of life and socio-economic status. Appropriate medical treatment for CNCP includes a variety of options, including opioid analgesic therapies. All FDA-approved opioid analgesics must demonstrate analgesic efficacy in randomized, placebo-controlled trials (RCTs) that are 3 months in duration. However, the analgesic effectiveness of opioid analgesics beyond 3 months of use has been questioned. Additional information is needed to provide a more comprehensive assessment of this important public health issue. Single-arm open-label (OL), open-label extension (OLE), and epidemiology studies, many of which are  $\geq 6$  months, represent a source of such information. These studies can be used to assess the effectiveness of long-term opioid treatment of CNCP by measuring longitudinal changes in pain and functional outcomes from a pre-therapy baseline to 3-months treatment and beyond. Only a subset of patients in RCTs elect to continue into OLE studies; however, in real-world clinical practice only 2% to 20% of patients who start opioid analgesic therapy continue for 6 months or more. Patients who continue in long-term studies may reflect patients who elect to continue opioid analgesic therapy in the real world. The objective of this presentation is to provide an up-to-date review of the literature and summarize changes in pain and function over time as reported in RCTs, OL, OLE, and epidemiologic studies of long-term opioid analgesic therapy among CNCP patients.

### Method

We conducted a literature search of published studies of long-term opioid analgesic therapy  $\geq 6$  months in duration in CNCP patients. Studies were identified using search terms "opioid," "long-term," and/or "therapy" in MedLine, EMBASE, Biosis Previews, and PubMed through February 2013. Additional articles were identified through consensus statements, clinical guidelines, literature reviews, or meta-analyses. Only original, full-text, English-language articles reporting on epidemiologic (cohort or cross-sectional) and clinical (RCT, OL, OLE) studies were included. For this literature review, 4 key outcomes were extracted for each study, where available:

1. Person-time exposed to opioid therapy was either collected directly from study reports or calculated based on the number of subjects and the mean person-time on study.
2. Reported changes from baseline to end of study in "pain right now," "average pain," "current pain," or "usual pain" as measured on the Brief Pain Inventory (BPI), 5-point or 11-point numeric rating scale, or 100-mm visual analogue scale were obtained. Percent changes in pain scores from baseline to end of study were stratified by duration (6 to < 12 months, and  $\geq 12$  months), study type (RCT, OL, OLE, epidemiology), and study drug. For OLE studies, changes in pain score and functional status from both the beginning and end of the preceding RCT phase were obtained where available.
3. Changes in pain scores at 3-month intervals compared to pain at baseline
4. Changes in the physical and mental components of the SF-12 or SF-36 from baseline to the end of study, as a measure of functional status.

## Results

Two hundred fifty 5 articles representing 257 studies on long-term opioid therapy were identified. Of these, 82 were not original studies, 2 were published in a language other than English, 43 did not evaluate a chronic noncancer pain (CNCP) population, 63 were less than 6 months in duration, and 7 did not evaluate analgesic effectiveness. After exclusions, there were 60 studies included in the current report: 8 RCTs, 26 OL trials, 12 OLE studies, 10 cohort studies, and 4 cross-sectional studies. The 46 RCTs, OL studies, and OLE studies represented 10,131 patients and 8,463 person-years of opioid treatment experience. The 14 epidemiology studies represented 5,415 patients and 4,441 person-years of opioid treatment experience.

Forty-six studies had data for percent change in pain scores from study baseline to end of study. Of these, 18 were 6 to <12 months in duration and 28 were  $\geq 12$  months in duration. Among studies 6 to <12 months long, 15 (83%) reported an improvement in pain of  $\geq 25\%$  from baseline. Among studies  $\geq 12$  months long, 23 (82%) reported an improvement in pain of  $\geq 25\%$  from baseline. There were 6 RCTs, 14 OL, and 8 OLE studies that reported pain scores over 3-month intervals. For all of these studies, a large decrease in reported pain occurred from baseline to 3 months; thereafter, reported pain decrease was generally maintained through 6 and 12 months measures, with a few studies demonstrating a maintenance of pain scores out to 36 months.

Ten studies reported change in mental component scores from study baseline to end of study. Of these, 2 (20%) demonstrated a  $\geq 25\%$  improvement in mental component score. Twelve studies presented data for percent change in physical component scores from study baseline to end of study. Of these, 2 (17%) demonstrated a  $\geq 25\%$  improvement in physical component score.

## Conclusions

A large number of studies demonstrated that reductions in reported pain from study baseline to 3 months were maintained over the long term in patients who continued in studies beyond 3 months. Such patients may be reflective of the small proportion of patients who continue on opioids in real-world clinical practice. Over 80% of studies showed a  $\geq 25\%$  reduction in pain compared to baseline. Although mental component and physical scores generally did not improve substantially from baseline, only a few studies reported functional status. Results from these studies  $\geq 6$  months in duration support the long-term analgesic effectiveness of opioid therapy.

## The prevalence of gastrointestinal complications of constipation in opioid-treated patients: a population study

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### Purpose

Constipation is a commonly reported side effect of opioid therapy, but the reported prevalence varies greatly depending on the study population and the method for ascertaining whether patients have constipation. Prevalence estimates ranging from 1% to over 65% have been reported in the medical literature. Though constipation is generally seen as a tolerability issue and treated with over the counter laxatives, it can be associated with more serious gastrointestinal (GI) complications. The frequency with which these complications occur has not been well characterized in either opioid-treated or nonopioid-treated patients.

The objectives of this study were:

- To describe the medical comorbidities, demographics, and drug utilization characteristics of patients with and without these diagnosed constipation, stratified by whether or not those patients are receiving opioids.
- To estimate the frequency of complications associated with constipation in opioid-treated and nonopioid-treated patients.
- To compare the risk of complications associated with constipation in opioid-treated and nonopioid treated patients.
- Within opioid-treated patients, to compare the risk of complications based on opioid dose, constipation diagnosis, duration of treatment, and use of ER vs IR opioids.

### Method

This was a retrospective cohort study using healthcare claims data from commercially insured and Medicare patients in the Marketscan research database. This database includes in- and out-patient diagnosis and prescription data on over 60 million patients from throughout the United States. The outcomes of interest for this study included diagnoses of constipation, intestinal obstruction, GI prolapse or perforation, hemorrhoids, rectocele, fecal impaction, anal fissure, diverticulosis, toxic megacolon, and other GI complications that may be associated with constipation.

We calculated descriptive statistics to characterize patients' demographics; history of selected GI- and non-GI comorbidities, prior or concomitant pharmacotherapy, and history of GI surgical procedures. All descriptive analyses were stratified based on presence of opioid treatment and constipation diagnosis. Cumulative incidence was calculated for each of the GI complications of interest. Analyses were stratified by drug treatment, age and sex for all groups, and by dose in morphine equivalents and duration of opioid prescription for opioid-treated patients. Relative risks for GI complications were calculated for opioid-treated patients compared with nonopioid treated, and multivariate regression was used to adjust for differences in patient populations.

### Results

This study included data on 7.3 million opioid-treated and 4.3 million nonopioid-treated patients from the US. The mean age for commercially insured patients was 42, and for Medicare patients was 75. Opioid-treated patients had a higher prevalence of comorbidities and pharmacotherapy at baseline than nonopioid-treated.

Due to the nature of claims data, the prevalence of diagnosed constipation was relatively low in both opioid-treated and nonopioid-treated patients. Patients who were diagnosed with constipation, GI complications, or both were older and had more comorbidities than those without these diagnoses, regardless of opioid treatment. With the exception of hemorrhoids and diverticulosis, GI complications were uncommon, occurring in <1% of patients, but occurred more often in those with diagnosed constipation. For example, in commercially insured patients, 10.8% of opioid-treated patients with a constipation diagnosis and 1.6% of those without experienced intestinal obstruction; in nonopioid-treated patients the corresponding estimates were 7.8% and 0.6%, respectively. Some outcomes were more common in opioid-treated patients and others in nonopioid-treated patients; in all cases, GI complications were substantially more common in those with a diagnosis of constipation than in those without.

In opioid-treated patients, GI complications were more common in patients treated for  $\geq 90$  days than in those treated for <90 days, however these patients also had a higher prevalence of pre-existing GI comorbidity at baseline. For example, impaired gastric emptying was present in 0.3% of those with  $\geq 90$  days opioid prescription, compared to 0.1% of those with <90 days. There was no clear relationship between complications and opioid dose. Patients who developed complications were more likely to have pre-existing GI comorbidities (such as IBS) than those who did not; these comorbidities were more common in opioid-treated patients compared to nonopioid treated patients. Many, but not all, of the complications were more common in older than in younger patients.

## **Conclusions**

These data suggest that the incidence of most GI complications is low in the general population, and is higher among patients with diagnosed constipation. Diagnosed constipation itself is infrequent. Opioid-treated patients have a higher incidence of GI complications than nonopioid-treated patients, but are also older, sicker and on polypharmacy. Further modeling to adjust for these risks is needed to assess the relationships between drug treatment and GI complications. However, patients with diagnosed constipation have higher prevalence of GI complications, suggesting constipation is more than a tolerability issue, and needs to be prevented or treated to avoid more serious problems.

## Epidemiology of opioid-induced constipation (OIC) among chronic opioid users with noncancer pain

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### Purpose

Opioid analgesics have been increasingly used for management of noncancer pain in recent years. Opioid-induced constipation (OIC) is a frequent and potentially debilitating side effect of opioid therapy. Estimates of OIC incidence in the literature differ by study design, population enrolled, and definitions used. Some studies examined the incidence of constipation among opioid users using prospective approach, such as survey data. However, few studies have examined the incidence of OIC in patients with noncancer pain, particularly in real-world settings. The objective of this study was to identify the incidence of and risk factors for OIC in chronic opioid users with noncancer pain in a US managed care population.

### Method

This retrospective database analysis was conducted using 1) Truven Health MarketScan<sup>®</sup> Commercial Claims and Encounters Database and 2) Medicare Supplemental and Coordination of Benefits Database from January 1, 2007 through December 31, 2011. The study included adult patients who had at least 12 months of insurance enrollment before and after initiating chronic (<sup>3</sup>90 days) opioid use, and excluded patients who had a diagnosis of cancer or drug abuse/dependence during the study period, or constipation or bowel obstruction within 90 days prior to initiation of the study opioid. OIC was identified by ICD-9 codes for constipation (564.0) or bowel obstruction (560.x) within a follow up period of 12 months of initiating chronic opioid therapy. The incidence of OIC was calculated in elderly (<sup>3</sup>65 years), nonelderly, and long-term care (LTC) populations. Demographics, comorbidities, and opioid use patterns were compared between patients who developed OIC and those who did not. Logistic regression models were used to identify characteristics associated with increased risk of constipation.

### Results

Over 24 million patients were identified as initiating opioid therapy during the study period. Of these, 13,808 nonelderly and 2958 elderly patients met inclusion criteria. Four hundred and one nonelderly patients (2.9%) and 194 elderly patients (6.6%) developed OIC during the follow-up period. Among the 566 patients initiating opioids in LTC facilities, 85 (15.0%) developed OIC within the follow-up period. Among the nonelderly patients, the mean age was 48.6 years (SD 10.4), with 50.0% male. Among the elderly patients, the mean age was 78.7 years (SD 8.1), with 30.1% male. The LTC patients had a mean age of 80.7 years (SD 11.6) with 23.0% male. Overall, compared to patients without constipation, patients with OIC were older, more likely to be female, and had more comorbid conditions, including depression, Parkinson's disease, and paralysis. Morphine-equivalent daily opioid dose and duration of opioid use were not significantly different between OIC and non-OIC groups. The logistic model showed that patients who were elderly (odds ratio [OR] = 1.71,  $P < .001$ ), who had higher Charlson comorbidity score (OR = 1.19,  $P < .001$ ), depression (OR = 1.53,  $P < .001$ ), or Parkinson's disease (OR = 4.22,  $P < .001$ ), or who were hospitalized at least once in the 12 months prior to initiating opioids (OR = 1.41,  $P = .002$ ) were significantly more likely to develop OIC, while male patients were less likely to develop OIC (OR = 0.74,  $P = .001$ ). Patients who developed nausea/vomiting after initiating opioids were over 4 times more likely to develop concomitant OIC compared to patients who did not (OR = 4.21,  $P < .001$ ).

## Conclusions

The incidence of OIC (ranging from 2.9% to 15% by study cohorts) was highest in LTC patients, followed by elderly and nonelderly populations. The calculated incidence rates from this study may be conservative estimates as the OIC cases were based on medical claims with ICD-9 codes and does not reflect cases that were not captured or coded in the database. Age, Charlson comorbidity score, depression, Parkinson's disease and prior hospitalization, but not opioid dose or duration, contributed significantly to the risk of OIC among users of chronic opioids for noncancer pain.

## Economic burden of opioid-induced constipation (OIC) among chronic opioid users with noncancer pain

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### Purpose

Opioid-induced constipation (OIC) is a potentially debilitating side effect of opioid therapy, which may result in increased healthcare resource utilization. There are very limited data about the economic burden of OIC among chronic opioid users. Even fewer studies have attempted to quantify the potential impact of constipation on healthcare costs in patients treated with opioids for noncancer pain using recent real-world administrative data. The objective of our study was to estimate the economic burden associated with OIC among chronic opioid users with noncancer pain in a US managed care population.

### Method

This retrospective database analysis was conducted using 1) Truven Health MarketScan<sup>®</sup> Commercial Claims and Encounters Database and 2) Medicare Supplemental and Coordination of Benefits Database from January 1, 2007 to December 31, 2011. The study included adult patients who had  $\geq 12$  months of insurance enrollment before and after initiating chronic ( $\geq 90$  days) opioid use, and excluded patients who had a diagnosis of cancer or drug abuse/dependence during study period, or had constipation/bowel obstruction within 90 days prior to initiation of the study opioid. OIC was identified by any primary or secondary ICD-9 diagnosis codes for constipation (564.0) or bowel obstruction (560.x) within 12 months of initiating chronic opioid therapy. Differences in total cost and cost components, such as inpatient, emergency room, physician office visits, and prescription drugs were calculated between OIC patients and their propensity score-matched non-OIC group during a 12-month follow-up period. Cost data were compared between OIC and non-OIC groups using a nonparametric test (Wilcoxon Rank-Sum test) because cost data are often heavily skewed. Generalized linear model (GLM) was performed to estimate the impact of OIC on total cost, adjusting for covariates.

### Results

A total of 13,808 nonelderly (mean age:  $48.6 \pm 10.4$ , male: 50.0%) and 2958 elderly patients (mean age:  $78.7 \pm 8.1$ , male: 30.1%) met study criteria. One hundred ninety-four elderly patients (6.6%) and 401 nonelderly patients (2.9%) developed OIC during the follow-up period. There were 566 (mean age:  $80.7 \pm 11.6$ , male: 22.9%) patients who initiated opioid therapy in long-term care (LTC) facilities, and 85 (15.0%) of them developed OIC. After matching by key covariates, OIC patients had significantly higher total costs than non-OIC patients in all 3 study cohorts (nonelderly cohort:  $\$23,631 \pm \$67,209$  vs  $\$12,652 \pm \$19,717$ ,  $P < .001$ ; elderly cohort:  $\$16,923 \pm \$38,191$  vs  $\$11,117 \pm \$19,525$ ,  $P = .009$ ; LTC cohort:  $\$16,000 \pm \$22,897$  vs  $\$14,437 \pm \$25,690$ ,  $P = .050$ ). Among the nonelderly patients, those with OIC had higher inpatient costs (OIC vs non-OIC:  $\$7,169 \pm \$33,487$  vs  $\$1,992 \pm \$8,525$ ,  $P < .001$ ), outpatient costs ( $\$10,230 \pm \$33,572$  vs  $\$4,790 \pm \$9,285$ ,  $P = .029$ ), and ER costs ( $\$654 \pm \$2,156$  vs  $\$313 \pm \$915$ ,  $P < .001$ ) compared to matched non-OIC patients, respectively. Similarly, elderly patients with OIC had higher inpatient costs (OIC vs non-OIC:  $\$4,044 \pm \$17,998$  vs  $\$1,664 \pm \$7,776$ ,  $P < .001$ ) and ER costs ( $\$750 \pm \$2,123$  vs  $\$275 \pm \$609$ ,  $P = .004$ ) compared to their matched non-OIC counterparts, respectively. Significantly higher proportion of OIC subjects used prescription laxatives compared to non-OIC patients. In the nonelderly cohort, more OIC patients used prescription laxatives compared to their matched non-OIC patients (8.8% vs 0.8%,  $P < .001$ ). In the elderly or LTC cohorts, similar proportions of patients had laxative prescriptions between OIC and their matched non-OIC patients (elderly: 3.7% vs 2.6%,  $P = .56$ ; LTC: 2.5% vs 1.3%,  $P = .56$ ). GLM

analyses showed that compared to non-OIC patients, OIC patients incurred 89% ( $P < .001$ ) higher total costs in the nonelderly, 52% ( $P < .001$ ) higher total costs in the elderly and similar total costs in the LTC cohort ( $P = .42$ ).

### **Conclusions**

The economic burden of OIC is substantial, with significantly increased inpatient, outpatient and ER costs among the nonelderly population and increased inpatient/ER costs among the elderly population. Although the use of prescription laxatives were higher among OIC patients compared to non-OIC patients, the overall use of prescription laxatives seems substantially low in the 3 cohorts. Future research should evaluate if use of prescription laxatives for treatment of OIC can reduce use of other healthcare resources. Additionally, the economic burden of OIC should be considered when evaluating the cost-effectiveness of pain treatments.



## Abuse potential of chewed or intact oxycodone/naloxone (OXN) tablets in methadone-stabilized, opioid-dependent subjects when administered orally

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### Purpose

Opioid analgesics are an important component of modern pain management; however their abuse and misuse have created a serious and growing public health problem. Opioid products are frequently used for nonmedical purposes by both recreational and opioid-dependent drug users due to their potential to produce euphoria and related reinforcing effects. Taking opioids orally represents the most convenient route for abuse. Abusers often tamper with dosage forms, including by crushing or chewing prior to oral ingestion so that a larger amount of the drug becomes systemically available more quickly. Controlled-release opioid products are particularly likely to be abused via tampering because they contain higher amounts of opioid and because tampering may reduce or eliminate the intact dosage form's controlled-release properties.

OXN, a twice-daily oral controlled-release formulation of oxycodone hydrochloride and naloxone hydrochloride (2/1 ratio), is under development in the US for management of moderate to severe chronic pain. Naloxone is a potent mu receptor antagonist included for its abuse-deterrent properties and potential to decrease opioid gastrointestinal side effects. When intact OXN is administered orally, naloxone is unlikely to affect oxycodone analgesia due to naloxone's low oral bioavailability ( $\leq 2\%$ ). If OXN is chewed prior to swallowing, the resulting immediate-release profile of systemic naloxone exposure may be sufficient to reduce drug-liking opioid agonist effects or even precipitate opioid withdrawal responses in physically-dependent opioid abusers.

This study was designed to characterize the abuse potential of chewed OXN as compared to intact OXN, oxycodone alone, and placebo, following oral administration in methadone-dependent subjects.

### Method

This was a single-center, double-blind, triple-dummy, randomized 4-way crossover study to evaluate the abuse potential, safety and pharmacokinetics (PK) of chewed and intact OXN tablets (oxycodone HCl/naloxone HCl ratio: 2/1 by weight), administered orally. Subjects (21 males, 12 females, aged 23-55 years) were opioid-dependent individuals maintained on a relatively low, stable daily dose of methadone (20-50 mg/day). The study consisted of 4 phases: screening, qualification, treatment, and follow-up. Qualified subjects were to receive OXN 60/30 mg intact, OXN 60/30 mg chewed, oxycodone hydrochloride API 60 mg solution, and placebo in a randomly assigned treatment sequence. Successive treatments were separated by 48h. The timing of daily methadone doses corresponded to 20h prior to, and again 4h after, each study treatment. Pharmacodynamic (PD) and PK assessments were conducted up to 12 or 24h postdose. PD assessments included visual analog scale (VAS) of 'At the Moment Drug Liking,' 'Overall Drug Liking,' 'Take Drug Again,' 'High,' 'Good Effects,' 'Bad Effects,' 'Feeling Sick Effects,' and Alertness/Drowsiness. Both Drug Liking scales were bipolar (0 = Strong Disliking, 50 = Neutral, 100 = Strong Liking). Withdrawal was evaluated by subjective and objective opioid withdrawal scales (SOWS, OOWS). Pupillary responses were measured. Safety evaluations included physical examination, 12-lead electrocardiogram, continuous cardiac monitoring, vital signs, clinical laboratory, medication history, and adverse events. Plasma concentrations of oxycodone, naloxone or methadone were determined and PK parameters were derived. Descriptive statistics, 95% confidence intervals and *P* values for treatments and treatment differences for appropriate PD values or derived endpoints (minimum effect [ $E_{min}$ ], maximum effect [ $E_{max}$ ], time-averaged effect) were computed.

## Results

Mean 'High' VAS  $E_{max}$  was greater for oxycodone (77.1) than for OXN-chewed (27.7), OXN-intact (20.6), or placebo (20.6) ( $P < .001$ ). Mean 'At the Moment Drug Liking' VAS  $E_{max}$  was greater for oxycodone (77.4) than for OXN-chewed (54.6), OXN-intact (54.7), or placebo (54.4); values for the latter 3 treatments were all near 50, the neutral point on the bipolar scale. Mean 'At the Moment Drug Liking'  $E_{min}$  was lower for OXN chewed (28.6) than for oxycodone (48.6), OXN-intact (44.3), and placebo (42.1), demonstrating that OXN-chewed not only lowers drug liking, but also produces actual disliking. A similar pattern was observed for 'Overall Drug Liking' VAS. The negative effects of OXN-chewed were also evident on the 'Bad Effects' and 'Feeling Sick' scales. Mean SOWS scores were slightly higher following OXN chewed compared to other treatments. There were no differences in OOWS scores among the 4 treatments. Pupillometry demonstrated characteristic brisk miosis following oxycodone treatment; OXN-chewed and OXN-intact showed smaller decreases with a delayed time course.

Mean oxycodone  $C_{max}$  was greater following oxycodone (143 ng/mL) and OXN-chewed (131 ng/mL) than following OXN-intact (72.0 ng/mL), while mean  $AUC_t$  was similar for the active 3 treatments. Median  $T_{max}$  was shortest following oxycodone (1.08h) and longer following OXN-chewed (2.07h) and OXN-intact (3.05h). Mean naloxone  $C_{max}$  and  $AUC_t$  were greater following OXN-chewed (0.352 ng/mL, 1.80 ng\*h/mL) than following OXN-intact (0.131 ng/mL, 1.56 ng\*h/mL), with higher mean concentrations for OXN-chewed until 6h postdose. Methadone concentrations were similar for all 4 treatments.

Following oxycodone alone, PD responses corresponded with systemic oxycodone concentrations. OXN-chewed produced similar oxycodone systemic concentrations, but PD responses were reduced or reversed during the period of higher systemic naloxone concentrations.

Most common TEAEs observed included euphoric mood, somnolence, pruritus, and fatigue. Overall, the highest incidence of TEAEs was observed for oxycodone, followed by OXN-chewed, OXN-intact, and placebo.

## Conclusions

This study was conducted to characterize OXN abuse potential in methadone-maintained, opioid-dependent subjects after oral administration of intact and chewed tablets. PD results for OXN-intact were similar to placebo. When the controlled-release properties of OXN were partially defeated through chewing, peak oxycodone concentrations were increased compared to OXN-intact, however positive drug liking effects were reduced, negative effects were increased, and subjects were more likely to report overall disliking, compared to oxycodone alone. These results demonstrate that in methadone-maintained, opioid-dependent subjects, OXN, administered intact or chewed orally, has significantly lower abuse potential than oxycodone API and similar abuse potential to placebo.

## Pain management outcomes: a comparison of American and Chinese hospitalized postoperative patients

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### Purpose

Postoperative pain management has posed a pervasive clinical problem in medical practice. Inadequate management of postoperative pain can lead to negative physiologic and psychological consequences, including chronic pain. Improving quality of pain management has been a focus for more than 20 years in America, but few changes demonstrated. Pain management hasn't become a priority for professionals in China yet, and patients and professionals are likely to use pain medicine conservatively. Evidence of ethnic differences in pain perception may also influence patient outcomes in pain management. Differences in patient outcomes of pain management between Chinese and American patients continue to be a persistent question. The purpose of this study is to investigate the differences in patient outcomes and methods of pain management in postoperative patients between a Chinese and an American large teaching hospital.

### Method

A descriptive comparative survey assessed outcomes of pain management using the Revised American Pain Society Pain Outcome Questionnaire (APS-POQ-R), including pain severity and interference in sleep, activity and mood, adverse effects and perception of care. Present pain, average pain and pain management goal were also measured using numeric rating scale (NRS). Demographic information included type of surgery and analgesics ordered and administered were collected from the medical record. A convenience sample of 244 adult inpatients on the first postoperative day was recruited from a 803-bed hospital in North Carolina, United States. Subsequently, 286 patients with similar surgeries were recruited from a 1860-bed hospital in Beijing, China. To assure comparable data, the final sample included 231 patients in US and 248 patients in China who had anticipated intermediate and major postoperative pain.

### Results

Demographic and surgical characteristics of patients were comparable: aged  $51.13 \pm 15.572$  years old in US and  $51.98 \pm 14.979$  in China, 61.8% (N = 143) of the patients in US and 56.5% (N = 140) in China were female. Surgery type was similar in 2 countries: the majority was nonendoscopic and located in abdomen/pelvic. Most of the patients in US used PCA (N = 138, 59.7%) and non-PCA (N = 92, 39.8%) treatments, while about half patients in China didn't use any medicine at all (n = 128, 51.6%) and 33.1% (N = 82) patients used PCA. 31.6% (N = 12) of the patients using non-PCA treatments used meperidine intramuscular route for pain in China while none in US. In subgroup using PCA, patients in US consumed a little higher parenteral morphine equianalgesic dose (0.55 mg) per kg weight than that in China (0.43 mg). Out of expectation, patients in US had experienced higher level of pain, interference of pain and side effect of treatments, but with better perception of pain care (8.02 vs 6.36). But the amounts of differences were very limited. Difference in mean of the least (3.45 vs 2.68) and worst (8.00 vs 6.04) pain level were less than 30%, which was considered minimum clinical meaning, while difference in mean of the present pain (4.33 vs 2.57), average pain (5.93 vs 3.68), affective interference (3.23 vs 1.51) and side effects of pain treatment (3.44 vs 1.85) were higher than 30%. The pain management goal in US patients was a little higher than that in China (3.14 vs 2.30). Compared with the goal level of pain management, only the least pain level is clinically comparable in both countries.

## Conclusions

Patients in US were experiencing a slightly higher pain level on average and more affective interference than that in China. Patients in US had used more pain medicine and suffered more adverse effects than those in China. Difference in perception of pain may be the best explanation. Patients reported differences between the actual pain and the goal of pain management in both countries. With increasing population diversity, continuing research is needed to better understand differences in pain management outcomes between the 2 populations and how patients respond to pain and manage pain expectations.

## Psychometric evaluation of the revised American Pain Society Patient Outcome Questionnaire (APS-POQ-R) in postoperative patients

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### Purpose

Poor postoperative pain management is a pervasive problem in the clinical environment. Valid and reliable measurement is essential for quality improvement. The Revised American Pain Society Patient Outcome Questionnaire (APS-POQ-R) which measures patient pain outcomes, yet the psychometric characteristics have not been verified for surgical patients. The purpose of this study is to evaluate validity and reliability of APS-POQ-R in postoperative patients and to explore the relationship between pain severity and other pain management outcomes.

### Method

Between January 2012 and May 2012, a convenience sample of 244 adult patients on their first postoperative day was recruited from 5 units in a teaching hospital in North Carolina, United States. The patient outcomes were measured using APS-POQ-R as well as average pain during the first 24 hours after surgery. The demographic and surgical information were collected from the medical record or self-reported by patients.

### Results

Overall Cronbach's alpha for the whole questionnaire was 0.770. 5 subscales were verified by factor analysis with Equamax rotation: pain severity and sleep interference, affective, adverse effects, activity interference and perception of care, explaining 61.41% of the variance. Internal consistency reliability was acceptable (0.647 to 0.797) except for perception of pain care (0.510), which may be because of the homogenous sample. Stepwise regression showed that average and worst pain predicted 18.6% of the variance of activity interference. Time in severe pain and average pain accounted up to 28.9% of the sleep interference and 16.8% of affective interference. 17.9% of the patient satisfaction was explained by degree of pain relief and least pain.

### Conclusions

This study verified acceptable reliability and validity of APS-POQ-R in a postoperative sample, which implies that universal measurement of pain management quality in medical and surgical patients is reasonable. The pain severity items in the APS-POQ-R, the least, worst pain level, and time in severe pain are very important predictors of other pain outcomes. It is recommended that average pain level as another important predictor of the patient outcomes be added to the questionnaire.

## The impact on pain interference of Butrans® (buprenorphine) Transdermal Delivery System in patients with moderate-to-severe chronic low back pain

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### Purpose

Among patients with chronic low back pain (CLBP), Buprenorphine Transdermal System (BTDS) has been shown to reduce pain severity and improve functionality for many activities of daily living (ADLs). What remains unknown is the degree to which BTDS reduces the direct impact of pain interference on patients' functionality. Using data from a clinical trial of CLBP patients, this posthoc analysis examined the impact of BTDS on 1) pain severity and interference generally, and 2) interference of pain in the ability to perform specific ADLs.

### Method

Data were from a multicenter, double-blind, randomized, placebo-controlled, 12-week trial of BTDS (10 or 20 mcg/hr) among opioid-naïve patients with moderate-to-severe CLBP. At several assessments, patients completed the Brief Pain Inventory short-form (BPI), an 11-item survey. The BPI yields scales for pain Severity and Interference, and includes items regarding pain interference with specific ADLs such as social interactions, sleeping, walking, and working. Analysis of covariance (ANCOVA) models tested the impact of treatment arm on Severity and Interference at 12-weeks for each BPI item, while controlling for baseline values. Logistic regression models predicted the odds ratio (OR) of BTDS patients being able to perform specific ADLs as compared to placebo patients, controlling for baseline ability.

### Results

BTDS patients showed significantly less pain Severity and Interference than placebo patients, with scores approximately 1 point lower on all items (range: 0.83 to 1.14 on a 0-10 scale), all multiplicity-adjusted  $P$ s < .001. ORs indicated that BTDS patients were approximately twice as likely to be able to walk, work, and sleep without pain interference than placebo patients (ORs range: 1.83-2.27), all multiplicity-adjusted  $P$ s < .05.

### Conclusions

Patients with moderate-to-severe CLBP who received 12 weeks of BTDS treatment showed greater reductions of Pain Severity and Interference and were twice more likely to be able to engage in several Activities of Daily Living without pain interference than patients receiving placebo.

## The impact of Butrans<sup>®</sup> (buprenorphine) Transdermal Delivery System (BTDS) treatment on depressed and nondepressed moderate-to-severe chronic pain patient

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### Purpose

Some researchers have suggested that depressed patients with chronic pain are less responsive to pain treatment with opioids than nondepressed patients. However, examination of evidence for this claim reveals that poorer outcomes for depressed patients might not necessarily stem from poorer treatment response, but rather might be a function of poorer pre-treatment outcomes. The posthoc subgroups analysis presented here examined pre-treatment values on several patient-reported outcomes, including pain severity and interference, quality of life, sleep problems and quality of sleep, and functional disability between depressed and nondepressed chronic low-back pain (CLBP) patients, as well as whether the impact of Buprenorphine Transdermal Delivery System (BTDS) treatment on these outcomes differed between depressed and nondepressed patients.

### Method

Data were collected from a multicenter, double-blind, randomized, placebo-controlled trial of BTDS at doses of 10 or 20 mcg/hr in opioid-naïve patients with moderate-to-severe CLBP. Following screening (baseline) and open-label run-in periods, patients were randomly assigned to BTDS or placebo for 12 weeks. At multiple assessments, patients completed several self-reported measures of pain severity and interferences (Average Pain over the last 24-hours; Brief Pain Inventory [BPI]), quality of life (SF-36v2 Health Survey [SF-36v2]), sleep quality (Medical Outcomes Study Sleep Scale), and functional disability (Oswestry Disability Index). Baseline depression status (depressed/not depressed) was classified using a cut-point score of 52 (based on 0-100 scoring) on the SF-36v2 mental health (MH). Independent-samples t-tests compared differences in mean baseline outcomes scores between depressed and nondepressed patients. Analysis of covariance models predicting week 12 scores included treatment arm, depression status, and the treatment arm x depression status interaction as fixed factors and pre-treatment scores as covariates.

### Results

Of the 541 patients entering the trial at baseline, 143 (26.4%) were classified as depressed by their baseline SF-36v2 MH score. Depressed and nondepressed patients did not differ in baseline Average Pain, although BPI scores showed statistically significantly greater pain severity and interference for depressed patients. Depressed patients also showed statistically significantly worse quality of life, sleep quality, and functioning at baseline. At study endpoint (week 12), nearly all outcomes showed a statistically significant treatment effect, supporting efficacy of BTDS relative to placebo across both depressed and nondepressed groups. No significant main effect of depression status was observed for most posttreatment outcomes, which would indicate no added effect of depression from that observed at baseline. Finally, no statistically significant interaction effects were observed for any outcomes, indicating a failure to detect any differences in the magnitude of the treatment effect of BTDS relative to placebo between depressed and nondepressed patients.

### Conclusions

At baseline, CLBP depressed patients scored worse than nondepressed patients in pain interference, quality of life, sleep problems, and functional disability. Following treatment, no statistically significant interaction between treatment and depression status was detected, which fails to support the hypothesis that depressed patients show poorer

treatment response. Findings should be interpreted cautiously. While the cut-point of 52 on the SF-36 MH scale for depression screening has been validated in several studies, none included chronic pain patients, and like any screening tools for depression this cut-point may misclassify patients. Further, this analysis may lack sufficient statistical power to detect true effects.



## Diclofenac submicron particle capsules reduce opioid rescue medication use in a phase 3 study in patients with acute pain following elective surgery

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### Purpose

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to provide relief of mild-to-moderate acute pain. NSAIDs are also used as part of multidisciplinary approaches in postsurgical pain management. Diclofenac submicron particle capsules developed using SoluMatrix™ technology are under investigation as a treatment in patients with acute pain and osteoarthritis pain. Lower-dose diclofenac submicron particle capsules with enhanced absorption properties have demonstrated comparable peak plasma levels and lower overall systemic exposure compared with currently available oral diclofenac potassium. The lower-dose submicron particle capsule drug product could help address the recommendation of the US Food and Drug Administration encouraging physicians to prescribe NSAIDs at “the lowest effective dose for the shortest duration consistent with individual patient treatment goals.” A phase 3 study in patients with postsurgical pain quantitatively evaluated the analgesic potential of diclofenac submicron particle capsules. In this study, patients could elect to receive analgesic (rescue) medication consisting of an opioid and acetaminophen for intolerable pain. We report data on the use of opioid-containing rescue medication in this study.

### Method

This multicenter, double-blind, placebo-controlled phase 3 study randomized 428 adults, aged 18 to 65, following bunionectomy surgery under regional anesthesia. Patients experiencing moderate-to-severe pain (pain intensity rating of  $\geq 40$  mm on a 100-mm Visual Analog Scale), received diclofenac submicron particle capsules (35 or 18 mg 3 times daily [TID]), celecoxib (400 mg loading dose then 200 mg twice daily [BID]), or placebo. Following the first hour after study drug administration, patients were permitted to receive hydrocodone/acetaminophen 10 mg/325 mg every 4 to 6 hours or oxycodone/acetaminophen 7.5 mg/325 mg every 6 hours as needed as rescue medication for additional pain control. The primary endpoint was the overall (summed) pain intensity difference over 0 to 48 hours. Secondary endpoints included proportion of patients using rescue medication and time to first use of rescue medication.

### Results

As previously presented, diclofenac submicron particle capsules 35 mg TID (524.0;  $P < .001$ ), 18 mg TID (393.2;  $P = .010$ ), and celecoxib 200 mg BID (390.2;  $P = .011$ ) use led to greater mean overall (summed) pain intensity difference compared with placebo (77.1). Fewer patients in the diclofenac submicron particle capsules 35 mg TID (88/107, 82.2%;  $P = .002$ ), 18 mg TID (93/109, 85.3%;  $P = .005$ ), and celecoxib 200 mg BID (90/106, 84.9%;  $P = .006$ ) treatment groups required opioid-containing rescue medication compared with placebo (103/106, 97.2%). Patients in the diclofenac submicron particle capsules 35 mg TID ( $5.9 \pm 0.8$  hours; hazard ratio [HR] 0.6;  $P < .001$ ), 18 mg TID ( $9.1 \pm 1.6$  hours; HR 0.7;  $P = .003$ ), and celecoxib 200 mg BID ( $4.9 \pm 0.7$  hours; HR 0.7;  $P = .013$ ) treatment groups received opiate-containing analgesia at later times following study entry compared with placebo ( $2.7 \pm 0.5$  hours). Adverse events were generally comparable across treatment groups and the most frequent nonprocedure-related adverse events were nausea (127/428, 29.7%), headache (55/428, 12.9%), dizziness (50/428, 11.7%), and vomiting (48/428, 11.2%).

## **Conclusions**

As expected in this population of patients with severe pain following bunionectomy, opioid-containing rescue medication use was common. Lower-dose diclofenac submicron particle capsules reduced overall pain intensity and were associated with reduced opioid rescue medication use compared with placebo in patients with acute pain following elective surgery.

## Impact of an electronic pain and risk assessment on documentation and clinical workflow

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### Purpose

The Pain Assessment Interview Network—Clinical Advisory System (painCAS™) developed by Inflexxion, is a systematic and tested computer-administered assessment of pain patients. painCAS includes comprehensive pain assessments and incorporates validated opioid risk assessment tools and produces dashboard-like provider and patient reports. Additionally, painCAS offers decision support resources to providers to aid in treatment planning during the patient's clinical visit. painCAS will integrate with clinical Electronic Medical Record (EMR) systems and allow for standardization and complete documentation of all assessments, risk stratification, and treatment decisions. An important value of painCAS, will be its ability to identify patients at increased risk of aberrant drug related behavior and continually assess and track the risk of aberrant drug-related behavior and patient treatments.

Given the FDA's desire to implement a REMS for long-acting and extended-release opioids, there will undoubtedly be the need for standardization of the assessment and re-assessment process, as well as the use of validated tools to screen, track, and document patients for risk. Through the unique combination of such valuable clinical capabilities, painCAS will facilitate achieving many aspects of an opioid REMS, and improve the balance between risk of opioid abuse and misuse, and therapeutic benefits of long-acting and extended-release opioids. The goal of the study proposed here is to examine the challenges and benefits of integrating the painCAS into treatment facilities and to understand how the program can best be implemented in a variety of pain treatment settings and its impact on the administration and standardization of patient assessments.

### Method

Two specialty pain treatment settings utilized a beta version of painCAS instead of paper-pencil versions of the SOAPP-R and COMM. Clinicians (N = 7) and administrative staff (N = 8) from these 2 study sites consented to participate in the study. During the intervention phase, all new patients belonging to consented clinicians, who were beginning opioid treatment were asked to complete the painCAS Beta assessments. Administrative staff, downloaded assessment reports from the painCAS Beta system and attached them to the EMR. Chart reviews were conducted at baseline and postintervention to measure change in risk assessment documentation. Clinicians and administrative staff participated in 60 minute semi-structured interviews over the telephone at baseline and postintervention. The baseline interviews included questions about existing workflow and patient assessment processes. At postintervention interviews focused on the extent to which, if any, integration of the painCAS Beta improved efficiency in clinical workflow. Responses to the interview questions included Likert-type scales (ie, not at all helpful to very helpful), multiple choice, and opened responses.

### Results

In total 105 charts were included in the baseline and post intervention chart reviews, 66 charts were included in the baseline chart review and 39 were reviewed during the post intervention chart review. Significant increases were observed in the documentation of opioid risk assessments between the baseline chart review and the postintervention chart review, the patient charts included documentation of a risk assessment (SOAPP or other) 79.5% of the time with painCAS Beta was in use, whereas at the baseline time point, the charts included documentation of a risk assessment 40.9% of the time ( $X^2 = 14.8$ ,  $df = 1$ ,  $P < .001$ ). For the follow up clinical visits, documentation of the COMM was present in the charts 43.6% of the time when painCAS Beta was in use, whereas it was only present 4.5% of the time

when painCAS Beta was not in use ( $\chi^2 = 24.24$ ,  $df = 1$ ,  $P < .001$ ). Integration of painCAS Beta into the clinical setting was rated by participants as very easy (33%); easy enough (25%), somewhat difficult (33%) and very difficult (8%). Clinicians indicated that painCAS Beta improved workflow to some extent and was somewhat or a lot better than the process they normally use (75%). Suggested improvements to the painCAS Beta system included: 1) improve the process for administering the assessment in the clinic; 2) work with clinics to improve the ease of access to the assessment report in the EMR; and 3) improve the assessment tracking system so it is more efficient and streamlined. Feedback on what currently works well in the painCAS Beta system included: 1) accessibility to painCAS Beta; 2) the electronic format that allowed patients to complete the assessment before their appointment; and 3) automatically calculated the assessment score that generated an electronic assessment report.

## **Conclusions**

painCAS Beta significantly improved the likelihood that risk assessments were documented in the EMR. Perceptions of painCAS Beta by clinicians and administrative staff suggest that specific benefits are achieved by using painCAS Beta, including ease of use, automation of scoring, and immediate incorporation of risk assessments into the EMR. Barriers to implementation of the painCAS Beta included difficulty changing the clinical workflow and patient lack of computer skills/access. Thus, incorporating painCAS Beta into existing clinical workflows was a challenge, although some time saving benefits and other benefits were noted.

**Targeted Penetration Matrix (TPM<sup>®</sup>) transdermal system delivers opioid molecules systemically without treatment limiting skin irritation**

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**Purpose**

Transdermal systems are widely used in pain management to systemically deliver opioids such as fentanyl and buprenorphine. However, it has been challenging for researchers to develop transdermal systems capable of delivering oxycodone and oxymorphone. Achieving therapeutic systemic concentrations of these molecules has been difficult due in part to their inability to easily permeate through the skin. Furthermore, delivering systemic levels of these molecules is confounded due to treatment limiting skin irritation that can result from topical application of some opioids.

TPM<sup>®</sup> is vitamin E based technology that utilizes the unique chemical structure of TPM<sup>®</sup> to increase the absorption of drugs into, or through, the skin with the ability to target local or systemic delivery. TPM<sup>®</sup> does not adversely disrupt the surface of the skin as common penetration enhancers do, and is able to enhance drug solubility in the patch to increase drug load and maximize transdermal delivery. The ability of TPM<sup>®</sup> to deliver analgesic molecules, oxycodone and oxymorphone, is reviewed here.

**Method**

Two phase I studies are reviewed to assess patches containing the TPM<sup>®</sup> transdermal system. Primary endpoints were the characterization of the pharmacokinetic profiles. Secondary objectives were to evaluate the safety and tolerability of patches with a focus on measurements related to skin irritation.

**Oxycodone**—A phase 1 open-label single application study of oxycodone was performed. The study involved a single 3-day application of 3 separate TPM<sup>®</sup> oxycodone patch treatments to the upper side of the torso. All subjects received naltrexone to block the pharmacodynamic effects of oxycodone. Forty-four healthy subjects were enrolled into the study, received Investigational Product and were included in the Intent to Treat (ITT) and Safety Populations. Forty one subjects completed the study as planned and are included in the Pharmacokinetic Population.

**Oxymorphone**—A single center, single dose, open-label pilot phase I study of TPM oxymorphone was performed. Subjects that passed the pre-dose assessments and tolerated the naltrexone challenge received a single application of the oxymorphone patch, applied to the torso for 3 days. This was followed by a wash out period of 4 days during which blood samples were collected for PK analysis. A maximum of 12 healthy male subjects were planned for enrollment in this study. Eleven subjects received the oxymorphone patch, completed the study as planned and are included in the PK Population.

**Results**

**Oxycodone:** following a single 72 hour application of oxycodone, distinct absorption, plateau and (following removal of the delivery system at 72 hours) elimination phases were observed over the 144 hour pharmacokinetic sampling period. The shape of the plasma profiles for the 3 treatment groups was similar. A lag was observed prior to detectable oxycodone levels, then a rapid absorption of oxycodone. Following removal of the patch, an elimination phase was demonstrated.

Forty one subjects received their allocated dose for the full 72 hour application time. Single 3 day patch application of oxycodone at the studied doses were well tolerated and had a comparable safety profile. No significant differences were observed between the treatments in terms of incidence, type, severity, relationship or frequency of treatment emergent adverse events (TEAEs). Review of laboratory parameters, vital signs, physical examination, ECGs, sedation and CNS depression scores, and skin irritation scores suggests no trends or shifts over time following administration of Investigational Product.

Oxymorphone: following the application of a single TPM<sup>®</sup> oxymorphone patch, applied to the upper side of the torso for 72 hours, oxymorphone levels were detected systemically. PK parameters were calculated from blood samples collected and the plasma levels demonstrated relatively constant levels of oxymorphone delivery during the dosing interval. On removal of the patch, an elimination phase was demonstrated.

The majority of treatment emergent adverse events (TEAEs) were mild in severity. The safety and tolerability data collected in this study indicate that a single 3 day patch application of oxymorphone was safe and well tolerated by healthy subjects.

### **Conclusions**

Patches containing TPM<sup>®</sup> successfully delivered the opioid molecules oxycodone and oxymorphone in a sustained manner over a 72-hour period. Treatment limiting skin irritation was not observed with patches containing TPM<sup>®</sup>, suggesting TPM<sup>®</sup> to be a clinically viable transdermal system for the delivery of oxycodone and oxymorphone.

**TPM<sup>®</sup> (Targeted Penetration Matrix)—a novel vitamin E based transdermal drug delivery platform**

Paul Gavin, Sally Kinrade, Mahmoud El-Tamimy  
*Phosphagenics Ltd, Clayton, Australia*

**Purpose**

Transdermal systems are widely used in pain management to deliver opioids such as fentanyl and buprenorphine and are known to improve patient compliance and convenience while providing consistent analgesia. Despite these benefits transdermal systems are often associated with application site reactions, some of which are severe enough to warrant the discontinuation of therapy. These adverse events are typically due to the composition of the patch and components added to enhance patch performance, which disrupt the surface of the skin. Additionally, the transdermal delivery of other widely used opioids such as oxycodone and oxymorphone has been limited due to the challenges faced with skin permeation of these large drug molecules while keeping skin irritation to a minimum while attempting to deliver them.

Vitamin E is widely used in pain management as a treatment for application site reactions resulting from the use of transdermal systems. New applications of vitamin E derivatives are being studied as transdermal systems capable of delivering large analgesic molecules without treatment limiting skin irritation. Targeted Penetration Matrix or TPM<sup>®</sup> is one of the first of these vitamin E based transdermal drug delivery platforms under development. TPM<sup>®</sup>, its structure, application, and proposed mechanisms of action related to transdermal and dermal drug delivery and potential clinical benefits are reviewed.

**Method**

Data on file at Phosphagenics Ltd were reviewed and compiled here within.

**Design**—TPM<sup>®</sup> is a patented dermal/transdermal delivery technology, comprised of a multicomponent, multifunction system facilitating the delivery large analgesic molecules in a less irritating manner. It is a noninvasive, Vitamin E based technology that utilizes the unique chemical structure of TPM<sup>®</sup> to increase the absorption of drugs into-or through-the skin with the ability to deliver locally or systemically. TPM<sup>®</sup> does not disrupt the surface of the skin as currently available patches do; it has enhanced solubility allowing for the passage of drug through the skin.

**Applications**—Potential TPM<sup>®</sup> formulations offer treatment versatility, with options including gel, patch or spray forms, with various dosage units available to suit specific indications.

**Proposed Mechanisms**—TPM has 2 hypothesized mechanisms of action. TPM<sup>®</sup> alters the packing of lipids, decreasing the barrier quality of the "mortar" within the strata corneum to allow increased absorption and deeper penetration. TPM<sup>®</sup> also forms vesicles in the presence of low-to-mid concentrations of organic solvents that are miscible with water, which are then absorbed by the skin.

**Results**

TPM<sup>®</sup> is a mixture of mono- and di-alpha-tocopheryl phosphate. Vitamin E is an oil with poor solubility in water, the addition of a phosphate group makes the TPM<sup>®</sup> molecules amphiphilic, and increases their solubility in water. This is important because the skin has both oil and water domains.

Two core applications of TPM<sup>®</sup> are under development. These include transdermal system applications (ie, Matrix patches), and topical gels and creams.

Matrix Patch-TPM<sup>®</sup> is being applied to matrix patch design leveraging its ability to act as a chemical penetration enhancer in the strata corneum. TPM is able to disturb the packing of lipids, increasing the fluidity of the lipids within the stratum corneum and reducing its barrier qualities. This increased fluidity allows greater dermal absorption of active pharmaceutical ingredients (APIs) formulated with TPM, and deeper penetration to the cells of the viable epidermis and beyond into the systemic circulation.

Topical Gels-TPM<sup>®</sup> assembles into nanostructures (vesicles) in the presence of low-to-mid concentrations of organic solvent that is miscible with water (ie, alcohol). TPM<sup>®</sup> vesicles are ultra-deformable and allow for increased absorption into, or through, the skin and can range in size from approximately 50-500 nanometers. TPM<sup>®</sup> vesicles are able to entrap APIs with high efficiency and carry the entrapped cargo into the skin during absorption.

Unique to TPM<sup>®</sup> is that it can be modulated to optimize compatibility with molecules of varying size or chemistry. It can also be modulated to target drug delivery, with molecules preferentially retained in the skin or delivered deeper into systemic circulation. TPM<sup>®</sup> is also capable of soothing the skin and reducing irritation that may be caused by the actives it delivers.

## **Conclusions**

TPM<sup>®</sup> encompasses a combination of large molecule capability, lack of skin surface disruption, anti-irritant properties, potential application to other administration routes, and targeted delivery capability. TPM<sup>®</sup> presents opportunities for utilization across an array of pain products, including opioids, NSAIDS, and topical local analgesics. In particular, large opioid molecules delivered into and through the skin without the need to significantly disrupt the skin to achieve penetration is promising with TPM<sup>®</sup>. The unique properties of TPM<sup>®</sup> address the treatment limiting factors associated with currently available transdermal systems.



**Bridging from conventional marketed immediate release formulations to new tamper-resistant alternatives**

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**Purpose**

Many solid immediate release (IR) dosage forms containing opioids can be abused by snorting of crushed product or preparation of solutions for subsequent injection. Tamper-resistant IR formulations (TRF-IR) aim to prevent intentional abuse by crushing and dissolving.

Grünenthal (GRT) has developed a TRF technology (INTAC®) for extended-release formulations, already available as marketed products. The technology has now been expanded for IR formulations using also a high molecular weight polymer as excipient. A switch from a conventional immediate release formulation to TRF product alternatives generally requires bridging bioequivalence studies.

**Method**

A GRT-TRF IR formulation (Test) was investigated in an open, randomized, cross-over, relative bioavailability trial against the reference marketed IR formulation of an analgesic product. Single oral doses were administered to healthy male subjects under fasted conditions. Serum drug concentrations were determined by a validated LC-MS/MS method. Noncompartmental PK analysis was performed and the usual 80.00%-125.00% confidence interval acceptance criteria for bioequivalence were used for comparing Test to the reference.

**Results**

The 90% confidence intervals for  $C_{max}$  and AUC<sub>0-t</sub> of Test were 89.74%-117.32% and 94.24%-109.97%, respectively.

The data demonstrate that GRT-TRF-IR tablets have comparable in-vivo performance to standard immediate release formulations.

**Conclusions**

TRF-IR tablets may enable physicians to simply switch patients from conventional to reformulated TRF products.

## Trypsin-Labile Opioid Prodrugs for Extended-Release of Oxycodone and Hydromorphone

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### Purpose

Every year in the United States prescription opioid abuse is responsible for tens of thousands of deaths and tens of billions of dollars in increased health care costs. Our goal was to develop trypsin-labile opioid prodrugs of oxycodone and hydromorphone that provided an extended-release profile following oral ingestion but were inactive following parenteral (IV) administration

### Method

Signature Therapeutics's prodrugs of oxycodone and hydromorphone were designed to release opioid via a two-step process including: 1) bioactivation by trypsin, followed by 2) a cyclization release reaction. Key molecular components include a chemically robust N-substituted carbamate functionality that covalently attaches the active opioid to a diamine linker, which is terminally substituted with a N-acylated L-arginine (amino acid) moiety. Upon oral dosing and exposure to trypsin, the amino acid moiety is cleaved by enzymatic hydrolysis, exposing a nucleophilic terminal amine. The otherwise stable carbamate linkage undergoes an intramolecular attack from the exposed nucleophilic terminal amine, resulting in liberation of the opioid at a controlled rate. This controlled cyclization rate allows for a non-formulation approach for delivering opioids in an extended-release manner. We measured the *in vitro* rate of appearance of opioid following exposure to trypsin, as well as the time-course of systemic opioid in rats and dogs following oral and intravenous administration. We also measured the ability of the opioid prodrug to cross into the central nervous system and the activity at the  $\mu$ -opioid receptor.

### Results

Following *in vitro* exposure to trypsin, cleavage of the amino acid component for both the oxycodone and hydromorphone prodrugs was rapid ( $t_{1/2} < 5$  min). However, the *in vitro* half-life for the subsequent intramolecular cyclization reaction, forming cyclic urea and releasing the opioid moiety was  $\sim 3$  hours for both the oxycodone and hydromorphone prodrugs, under physiological conditions. Following oral administration of the opioids prodrug to rats, the oxycodone and hydromorphone concentrations peaked approximately 2 hours after administration. Following intravenous administration of the opioid prodrugs to rats, systemic conversion to parent opioid was extremely low ( $< 0.01\%$ ). The oxycodone prodrug had 15% the potency of oxycodone at the  $\mu$ -opioid receptor, and 1.2% the penetration across the blood brain barrier (rat), resulting in  $< 0.2\%$  central activity of the opioid activity of intravenous oxycodone. The hydromorphone prodrug had  $< 0.1\%$  of the potency of hydromorphone at the  $\mu$ -opioid receptor, and  $< 2\%$  of the penetration across the blood brain barrier (rat), resulting in potency  $< < 0.01\%$  of the opioid activity of intravenous hydromorphone.

### Conclusions

We have created trypsin-labile, extended-release prodrugs of oxycodone and hydromorphone that release the parent opioid following oral administration. The extended-release profile is intrinsic to the molecular structure and thus cannot be overcome by physical methods (eg, chewing). Minimal conversion of the prodrug to the active opioid occurs following parenteral (IV) administration, and the prodrugs have almost no ability to reach and activate the  $\mu$ -opioid receptor within the central nervous system.

## Trypsin-Labile Opioid Prodrug for Immediate-Release Hydrocodone

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### Purpose

Every year in the United States prescription opioid abuse is responsible for tens of thousands of deaths and tens of billions of dollars in increased health care costs. Our goal was to create a trypsin-labile opioid prodrug of hydrocodone that provided an immediate-release profile following oral ingestion but was inactive following parenteral (IV) administration.

### Method

Signature Therapeutics's prodrug of hydrocodone was designed to release hydrocodone via a two-step process including: 1) bioactivation by trypsin, followed by 2) a rapid cyclization-release reaction. Key molecular components include a chemically robust, N-substituted carbamate functionality that covalently attaches the hydrocodone to a cyclic diamine linker, which is terminally substituted with a N-acylated L-arginine (amino acid). Upon oral dosing and exposure to trypsin, the amino acid component is cleaved by enzymatic hydrolysis, exposing a conformationally-restrained nucleophilic terminal amine. The otherwise stable carbamate linkage undergoes intramolecular attack from the exposed nucleophilic terminal amine, resulting in liberation of hydrocodone at a controlled rate. Steric manipulation of the diamine linker has been optimized for rapid cyclization, resulting in immediate-release of hydrocodone following trypsin digest. We measured the *in vitro* rate of appearance of opioid following exposure to trypsin, as well as the time course of systemic opioid in rats and dogs following oral and intravenous administration. We also measured the ability of the hydrocodone prodrug to cross into the central nervous system (rat) and the activity at the  $\mu$ -opioid receptor.

### Results

Following *in vitro* exposure to trypsin, cleavage of the amino acid component of the hydrocodone prodrug was rapid ( $t_{1/2} < 5$  min). The *in vitro* half-life for the subsequent intramolecular attack, forming cyclic urea and releasing the opioid moiety, was less than 5 minutes under physiological conditions. Following oral administration of the hydrocodone prodrug to dogs, the hydrocodone concentration peaked ~30 minutes after oral administration. Following intravenous administration of the hydrocodone prodrug to rats and dogs, less than 0.1% of the prodrug was converted to the parent opioid. The hydrocodone prodrug had 7% the potency of hydrocodone at the  $\mu$ -opioid receptor, and 1.1% the penetration across the blood brain barrier (rat), resulting in  $< 0.1\%$  of the opioid activity of intravenous hydrocodone.

### Conclusions

We have created a trypsin-labile, immediate-release prodrug of hydrocodone that releases the parent opioid following oral administration. Minimal conversion of the hydrocodone prodrug to hydrocodone occurs following parenteral (IV) administration. The hydrocodone prodrug has minimal ability to reach and activate the  $\mu$ -opioid receptor within the central nervous system.

**Abuse Resistance of Trypsin-Labile Extended-Release Opioid Prodrugs**

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**Purpose**

We have synthesized extended-release prodrugs oxycodone and hydromorphone. The intent of these opioid prodrugs is to not only provide the expected time course of opioid delivery following oral ingestion, but to preclude extraction of active opioid for parenteral administration using commonly available "kitchen chemistry." We subjected our opioid prodrugs to Tier 1 (physical manipulations such as crushing and grinding) and Tier 2 (simple extraction procedures using "usable or ingestible" solvents).

**Method**

We tested our oxycodone and hydromorphone prodrugs for tamper resistance to extraction with 190 proof Everclear, olive oil, vinegar, vodka, baking soda, Coca-Cola<sup>®</sup> and water. The tests were conducted for 15 minutes and 1 hour, at room temperature and in boiling solutions.

**Results**

Our oxycodone prodrug was subjected to various "kitchen chemistry" conditions and did not release any substantial oxycodone in any of the tests. Our hydromorphone prodrug did not release any measurable hydromorphone in any of the tests except for boiling for 1 hour in baking soda, or Coca Cola<sup>®</sup>, which resulted in release of less than 2% of the hydromorphone.

**Conclusions**

Our extended-release prodrugs of oxycodone and hydromorphone are not amenable to Tier 1 and Tier 2 tampering and abuse using standard crushing and extracting techniques.

## Pharmacokinetics of a Trypsin-Labile Extended-Release Hydromorphone Prodrug in Healthy Volunteers

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### Purpose

We have created a trypsin-labile extended-release prodrug of hydromorphone. The first study in man addressed four questions: 1) is the drug safe, 2) does the prodrug convert to hydromorphone and is that conversion dose-proportional, 3) does the prodrug introduce additional variability in systemic hydromorphone concentrations, and 4) does food affect the bioavailability of hydromorphone following oral ingestion of a trypsin-labile extended-release hydromorphone prodrug?

### Method

Following institutional approval and written informed consent, we recruited 51 subjects for a randomized, blinded dose escalation study comparing the pharmacokinetics of an orally administered hydromorphone solution (12 subjects, 0.5 to 24 mg hydromorphone) with an orally administered solution of hydromorphone prodrug (39 subjects, 1 to 48 mg hydromorphone prodrug). In the dose escalation study, all subjects received naltrexone to block opioid drug effects. In the food effect study, following institutional approval and written informed consent 12 additional subjects received 16 mg of oral hydromorphone prodrug solution in each of two sessions. Subjects were randomly assigned to no breakfast or a standard high fat breakfast 30 minutes before drug administration. Pharmacokinetics were determined by venous blood samples drawn at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 60, and 72 hours after drug administration. The food effect subjects did not receive naltrexone to allow for opioid drug effect on gastrointestinal motility.

### Results

Plasma hydromorphone levels following oral administration of hydromorphone in solution peaked in less than one hour of administration. Plasma hydromorphone levels following oral administration of hydromorphone prodrug in solution peaked 3-4 hours after drug administration. Estimation of the relative bioavailability of hydromorphone from the prodrug vs from hydromorphone suggests a ratio of oral hydromorphone prodrug to oral hydromorphone of 2.8:1. Plasma hydromorphone concentration increased linearly with dose in both groups. The inter-subject variability in plasma concentration following administration of oral hydromorphone in solution was greater than the intersubject variability of hydromorphone following administration of hydromorphone prodrug. Food did not significantly affect the pharmacokinetics of the oral hydromorphone prodrug. There were no serious adverse events.

### Conclusions

The pharmacokinetics of the trypsin-labile extended-release hydromorphone prodrug in man were accurately predicted by prior animal studies. The molecular mechanism of hydromorphone release produced a peak concentration of hydromorphone 3-4 hours after drug administration. Since the construction of the prodrug and therefore opioid delivery, is a function of covalent chemistry, it cannot be defeated by physical manipulation (e.g., chewing). The pharmacokinetics are linear with respect to dose, have lower intersubject variability than oral hydromorphone solution, and do not demonstrate a significant food effect. These findings support further clinical development of our trypsin-labile extended-release hydromorphone prodrug.