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Abuse-Deterrent Properties of Oxycodone DETERx®: An extended-release formulation for chronic pain management

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Purpose

Prescription opioids play an important role in the management of chronic pain. Extended-release (ER) opioid products have several advantages including the convenience of less frequent dosing, decreased fluctuations in plasma levels, more consistent analgesia over the dosing period, and less night-time awakening due to pain. However, as ER opioids contain large quantities of active, they are more prone to intentional abuse and misuse. Abusers crush these formulations to get an immediate bolus of the opioid. On the other hand, legitimate patients who cannot swallow large pills/capsules tend to crush or chew them not knowing such manipulation could cause release of a fatal dose of opioid.

In order to reduce abuse and misuse, abuse-deterrent (AD) products are being developed. FDA has recently issued guidance on AD opioids outlining the studies that should be conducted to demonstrate that a formulation has AD properties.

Oxycodone DETERx (Xtampza ER™, Collegium Pharmaceutical, Inc. [Canton, MA]) is an ER, AD analgesic designed to retain its ER properties following common tampering methods such as crushing and chewing. The objective of this work was to evaluate the AD characteristics of oxycodone DETERx as they relate to Category 1 (in vitro manipulation) and Category 2 (Pharmacokinetic) premarketing studies outlined in the FDA Guidance. OxyContin® OP, a marketed ER oxycodone product was used as comparator in the in vitro studies.

Method

Based on literature search, 11 different crushing utensils such as a coffee grinder, hammer, pill crusher that are commonly available and used by abusers were identified and applied to oxycodone DETERx and OxyContin OP. The crushed product and the intact product (control) were tested by dissolution (n=6) for both Oxycodone DETERx and OxyContin OP. Crushed and intact Oxycodone DETERx microspheres were analyzed for particle size by Laser Diffraction and observed by microscopy.

Identified crushing methods were also tested by an independent laboratory for verification. The optimized technique was then used for the PSR technique to prepare samples for the clinical pharmacokinetic (PK) study.

In a PK study, 44 subjects were enrolled into an open-label, active-controlled, single-dose, cross-over, naltrexone-blocked study. Subjects were randomized to receive oxycodone DETERx 40 mg intact, crushed, or chewed in the fed state and oxycodone IR solution, 40 mg in fasted state. Primary PK endpoints included Cmax, AUC0-t, AUCinf and Tmax. Abuse quotient (AQ), a measure of rate of rise in blood concentration due to manipulation was calculated by using Cmax and Tmax (AQ=Cmax/Tmax). Safety was assessed by clinical laboratory values, vital signs, oxygen saturation, and physical exam. The study was approved by an IRB; each subject provided informed consent before any study-related procedure/assessment was conducted.

Results

Crushing of oxycodone DETERx had only a minor impact on dissolution compared to the commercial product. The most effective PSR technique had a 19% increase in release at 2 hours for oxycodone DETERx whereas for OxyContin OP, a 61% increase was observed. Physical manipulation of oxycodone DETERx capsule contents (by crushing or chewing) did not significantly alter Cmax, AUClast, or AUCinf relative to the intact capsules. The ratios of Cmax and AUCinf least square mean (LSM) values for crushed vs. intact oxycodone DETERx were 92.48% (90% CI: 85.96 – 99.51%) and 97.82% (90% CI: 92.66 – 103.27%), respectively. The ratios of Cmax and AUCinf LSM values for chewed versus intact oxycodone DETERx were 89.74% (90% CI: 83.22 – 96.78%) and 101.45% (90% CI: 95.94 – 107.27%), respectively. Both crushed and chewed oxycodone DETERx were bioequivalent to the intact formulation (within 80-125% [FDA BE criterion]. Tmax for intact, crushed, and chewed treatments of oxycodone DETERx were similar (median values were 4.0, 4.5, and 4.5 hr respectively). All oxycodone DETERx (intact, crushed or chewed) Cmax values were substantially lower than for the oxycodone IR solution. When mean AOs were compared, crushed, chewed, and intact treatments of...
oxycodone DETERx (14.43, 13.96, and 19.70 respectively) were much smaller than oxycodone IR (167.81) indicating oxycodone DETERx does not result in a PK profile sought after by recreational drug abusers in order to achieve the desired euphoria.

Conclusions

In vitro studies demonstrated that crushed microspheres of oxycodone DETERx retained the ER properties whereas crushed OxyContin OP demonstrated significant release of drug by multiple crushing techniques. The PK study showed that crushing or chewing oxycodone DETERx does not compromise the ER mechanism; intact and manipulated treatments were bioequivalent. The oxycodone DETERx formulation was tested in a manner consistent with FDA Draft Guidance Category 1 and 2 requirements, and may have abuse-deterrent characteristics not currently available in other marketed products.

In vitro studies characterizing oxycodone DETERx®: An abuse-deterrent, extended–release formulation

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Purpose

Extended-release (ER) opioids offer several clinical advantages such as decreased fluctuations in plasma levels and more consistent analgesia over the dosing period, in addition to the convenience of less frequent dosing, which facilitates medication adherence. Unfortunately, the non-medical use (ie, abuse) of prescription opioids has become a significant public health concern in the United States. For ER opioids, dosage forms are typically manipulated to accelerate the release of drug and make them more amenable to abuse via oral, nasal or intravenous routes.

Oxycodone DETERx® (Xtampza ER™, Collegium Pharmaceutical, Inc., [Canton, MA]) is a multiparticulate, ER, abuse-deterrent formulation, designed to retain its time-release mechanism following common tampering methods such as crushing, chewing, and preparation for IV injection. The formulation was developed to be administered as an intact capsule, but has the potential to be administered by sprinkling or by feeding tube, benefiting patients with dysphagia or difficulty swallowing, but who still need around-the-clock opioid analgesia for an extended period of time.

The objective of the studies presented here was to evaluate the abuse-deterrent properties of oxycodone DETERx by soaking oxycodone DETERx capsule contents (microspheres) in commonly available beverages, by pretreating the capsules and crushing the contents, by syringing the intact microspheres, and by melting the microspheres prior to attempted syringing. These studies represent a subset of the laboratory based manipulation studies conducted on oxycodone DETERx capsules during development.

Method

In the soaking study, 1 oxycodone DETERx 40 mg capsule was opened and the contents were added to 30 mL of the beverages (commonly available beverages including soda, an energy drink and 40% ethanol) in a glass beaker. Contents of the beaker were mixed and soaked for 10 minutes. Soaked samples were tested using a standard dissolution method. A control that was not in contact with any beverage was also tested. Dissolution profiles were compared using the FDA recommended f2 similarity factor where f2 > 50 indicates similarity. The impact of 3 different household utensils applied to oxycodone DETERx 40 mg capsule contents following 2 pre-treatments (heating and freezing) was evaluated using laser diffraction particle size determination and dissolution. Two methods preparing oxycodone DETERx microspheres for direct injection were evaluated using various sized needles: suspending the microspheres in water and melting the microspheres. Studies on suspended microspheres were conducted on both intact and crushed microspheres. Studies on different size needles including a 27 gauge (G) needle (typically used for IV injection), and a 22G needle (typically used for venipuncture or intramuscular injection), were tested. Additionally, a large gauge (18G) needle was also tested to evaluate an extreme scenario. The efficiency of these methods was determined by weighing the amount of material that was expelled from the syringe.

Results

Soaking oxycodone DETERx microspheres in 7 different beverages did not change the release profile; all dissolution profiles had f2 similarity factors that were >50 when compared with the control sample. The material that resulted from heating of DETERx microspheres prior to crushing did not easily reduce to smaller particles, instead, it resulted in a larger median particle size and slower dissolution after crushing with for all 3 household tools when compared with the respective control samples in which household tools were applied without pre-treatment. The results for crushing with all 3 household tools following freezing of capsules were similar to the respective control samples in which household tools were applied without pre-treatment. No significant increase in the dissolution of oxycodone DETERx was found. Suspending oxycodone DETERx microspheres in water in order to inject them through a hypodermic needle was ineffective, even when the microspheres were crushed before suspending them. Only the 18G needle was large enough to pass a measurable quantity of microspheres. Melting oxycodone DETERx microspheres in order to inject them via a hypodermic needle was not feasible. In all cases, due to the high melting point of the formulation, the melt congealed either when drawn up into the syringe or when attempting to expel the molten material.

Conclusions

The dissolution profile of oxycodone DETERx microspheres did not change following exposure to variety of different
beverages. Pre-treating by heating or freezing did not increase the effectiveness of crushing with household tools compared to the same methods applied without pretreatment, and the microspheres maintained extended-release properties. Direct injection of the oxycodone DETERx microspheres was not effective when suspended in water or melted. These results, which are part of the comprehensive program of in vitro and in vivo studies conducted on oxycodone DETERx, demonstrate the resistance of the formulation to several common manipulations for abuse.

Evaluation of the durability of pain relief of oxycodone DETERx: An extended-release, abuse-deterrent formulation throughout its 12-hour dosing interval

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Purpose

Chronic pain is a widespread and growing problem for which many patients do not receive adequate treatment. In many cases, pain is undertreated due to concerns about abuse and tampering with many of the currently available treatment options. For example, deaths in the U. S. from prescription opioid overdose have grown from approximately 4,000 in 1999 to approximately 16,000 in 2012. Although prescription opioids remain the primary treatment for chronic pain, growing public health concerns regarding the abuse and misuse of these analgesics has, at times, resulted in reduced patient access to safe and effective treatments.

In response to widespread prescription opioid abuse, the U. S. government and a number of state legislatures have introduced, and in some cases have enacted, legislation and regulations intended to encourage the development of abuse-deterrent forms of pain medications. The FDA has stated that addressing prescription drug abuse is a priority and the development of abuse-deterrent opioids is a key part of that strategy.

A Phase III trial in patients with chronic low back pain was completed using a novel 12-hour, B. I. D, oxycodone, extended-release (ER), microsphere-in-capsule analgesic containing the DETERx® drug delivery technology (Xtampza ER™, Collegium Pharmaceutical, Inc. [Canton, MA]). Oxycodone DETERx (herein “DETERx”) is an abuse-deterrent formulation (ADF) that provides ER drug delivery. It has been hypothesized that this new single-entity, ER, abuse-deterrent oxycodone provides effective pain relief over the entire dosing interval for patients with moderate-to-severe pain who require daily, long-term opioid treatment.

Method

This study is a post-hoc analysis of DETERx use and rescue medication (acetaminophen [APAP]) use by frequency and distribution of use following the morning and evening dose of 12 hour, B. I. D DETERx. Data from a Phase III, randomized withdrawal, double-blind, placebo-controlled, enriched-enrollment, parallel-group, multicenter, 12-week clinical study in opioid-experienced and opioid naïve subjects with moderate-to-severe chronic low back pain was evaluated. Subjects went through a Screening Phase (up to 21 days), Titration Phase (up to 6 weeks), and were randomized into a 12-week Double-blind Maintenance Phase. Both opioid naïve and opioid experienced subjects were titrated to a stable dose (minimum dose 40 mg/day, maximum dose 160 mg/day) of DETERx prior to randomization. Subjects were allowed to take APAP as rescue medication, up to 2000 mg per day during the Titration and Double-blind Maintenance Phases, including for headache and fever. Dosing with DETERx and rescue medication use was captured daily using an electronic diary. Subjects provided informed consent before any study-related procedures or assessments were conducted; the study was approved by Quorum IRB (Seattle, WA). Subjects (n = 193) who were randomized to receive DETERx during the 12-week maintenance period were included in this analysis.

Results

389 subjects were randomized; 193 randomized to DETERx. Majority of DETERx treated subjects (n=122, 63.2%) completed the Double-blind Maintenance Phase. The mean (±SD) age of the subjects randomized to receive DETERx was 49.2 ±13.31 years. Majority of these subjects were white (74.1%) and female (53.3%). During the Double-blind Maintenance Phase, total number of days exposed to DETERx was 12,084 days, with a total mean (±SD) and median DETERx exposure per subject of 62.61±30.57 days and 82 days, respectively. The mean (±SD) and median total daily dose of DETERx at randomization was 77.82±41.24 mg and 60 mg, respectively. Average (±SD) time between morning and evening dose of DETERx was 11.58±1.34 hours. Average (±SD) time between evening and the following morning dose was 13.24 ±3.29 hours.

Rescue medication was used on 1,379 days (11.4%). During the Double-blind Maintenance Phase, mean (±SD) and median dose/day of rescue medication was 0.15±0.3 dose/day and 0.1 dose/day, respectively, with a range of 0 to 2 dose/day. The mean (±SD) and median amount of dose/day of rescue medication was 144.63±288.72 mg/day and 10.87 mg/day, respectively, (range: 0 to 1714.29 mg/day).

No rescue medication was used following the morning or evening dose of DETERx during 85.37% and 82.74% of the DETERx dosing days, respectively. Distribution of rescue medication use showed that 15.5%, 40.38%, and 21.38% of all doses between 0-12 hours were taken between 0-4, 4-8, 8-12 hours, respectively, after the morning dose. Distribution of rescue medication use after evening dose was 13.06%, 5.13%, and 4.56% for the 4-hour intervals 0-4, 4-8, and 8-12, respectively. The majority (77.25%) of rescue medication use occurred after the morning dose, with majority of after morning rescue medication use within the first 8 hours. Use of rescue medication at the end of DETERx dosing interval
(8-12 hours) was minimal (~26%) compared with the first 8 hours (~74%).

**Conclusions**

Evaluation of rescue medication use during the 12-hour dosing interval of DETERx identified patterns of use that suggest DETERx has durability of effect over the full dosing interval. Patterns included limited overall and per day use of rescue medication and no increase in use at end of 12-hour dosing interval. In addition, patterns of rescue medication suggest that subjects did not experience an end-of-dose failure between hours 8 and 12. This 12-hour, BID, formulation of oxycodone may provide an effective option for patients with chronic pain who require daily, around-the-clock relief from pain.

**Sprinkle administration of oxycodone DETERx®: An abuse-deterrent, extended-release formulation**

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**Purpose**

Chronic pain and dysphagia (CPD) affects approximately 11 million patients in the US creating a significant unmet medical need for patients who need analgesia, but who cannot swallow solid, oral dosage forms. Extended-release (ER) analgesics are recommended for patients with CPD due to the prolonged, more consistent plasma concentrations of drug compared with short-acting agents, thereby decreasing the need for more frequent dosing. Physicians or patients have to alter medications by crushing, breaking, dissolving, or chewing to make them easier to swallow. Such manipulation of currently marketed, ER opioid analgesics alter the pharmacokinetic (PK) properties of these formulations. A bolus release of an opioid analgesic may result in a potentially fatal overdose or exacerbation of serious adverse events such as respiratory depression.

Oxycodone DETERx (Xtampza ER™, Collegium Pharmaceutical, Inc., [Canton, MA]) is a microsphere-in-capsule formulation designed to protect the opioid analgesic from physical and chemical manipulation that would result in an immediate-release formulation. The microsphere-in-capule formulation is designed to enable patients with difficulty swallowing (dysphagia) to open the capsule and sprinkle the capsule contents onto soft food without the need for concern about dose dumping if a patient inadvertently chews some of the microspheres or to administer the capsule contents via enteral tube; both modes of administration maintain the ER properties of the formulation.

The primary objective of this study was to assess the safety and PK profile of oxycodone DETERx administered by sprinkling the capsule contents (microspheres) onto applesauce compared with administration of the intact formulation.

**Method**

In this open-label, randomized, single-dose, naltrexone-blocked, crossover study, oxycodone DETERx was administered either as an intact capsule or by opening the capsule and sprinkling the entire contents onto applesauce to health volunteer subjects in the fed state. Blood samples were collected at predetermined time points up to 36 hours post dose. Plasma samples were analyzed for oxycodone using a validated liquid chromatography - mass spectrometry/mass spectrometry (LC-MS/MS) method. Primary key PK endpoints included maximum observed plasma concentration (Cmax), time to reach maximum plasma concentration (Tmax), area under the plasma concentration-time curves (AUC0-t, AUCINF), T1/2, and abuse quotient (AQ = Cmax/Tmax). Treatment-emergent adverse events (AEs) were assessed in each treatment period. Other safety parameters included vital signs, oxygen saturation, physical examinations, and hematologic, biochemical, and urinalysis clinical laboratory values. The study was approved by an institutional review board; each subject provided written informed consent prior to any study-related procedures or assessments being conducted.

**Results**

Forty-three (43) subjects completed the study. The mean (±SD) values of Cmax for oxycodone DETERx intact and the sprinkled treatments were similar. Cmax (±SD) was similar for both sprinkled and intact administration (48.1± 12.0 and 55.3 ±13.6 ng/mL, respectively). The ratios of Cmax, AUC0-t, and AUCINF least square mean (LSM) values for sprinkled versus intact oxycodone DETERx were 87.27% (90% confidence interval (CI): 81.21 – 93.78%), 98.36% (90% CI: 93.06-103.96), and 98.43% (90% CI: 93.21 – 103.95%), respectively. Sprinkled-to-intact comparison had identical values for Tmax (4.50h, 4.50h, respectively) and had comparable values for t1/2 (±SD) (5.82±0.89h, 5.68±0.84h respectively). AQ (±SD) values were similar between the sprinkled and intact administration (11.8±3.74ng/mL/h, 14.4 ±6.46ng/mL/h, respectively). The frequency of AEs was comparable between both treatments—whether intact or sprinkled. No deaths or other serious AEs occurred and no subjects discontinued from the study due to an AE. No clinically significant changes in clinical laboratory values were noted during the study. There were no clinically significant findings or trends noted for vital signs, blood oxygen saturation, or physical examination.

**Conclusions**

Oxycodone DETERx sprinkled vs. intact treatments were bioequivalent and had identical values for Tmax. Oxycodone DETERx was demonstrated to be safe and generally well-tolerated, whether ingested as an intact capsule or sprinkled onto applesauce. These results of this study demonstrate that oxycodone DETERx can be administered as an intact capsule or by opening the capsule and sprinkling the contents onto applesauce, thus offering a flexible dosing option to both physicians and patients in the treatment of CPD.
Oral and intranasal human abuse potential of oxycodone DETERx®: An abuse-deterrent, extended-release formulation

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Purpose

The misuse and abuse of opioid medications, including oxycodone, is a public health crisis that has become a national epidemic over the past decade. Abusers frequently tamper with extended-release (ER) formulations due to the relatively high drug load and attempt to subvert the ER mechanism to access the entire drug load at once. Many conventional ER formulations are susceptible to tampering techniques such as breaking, crushing, or chewing. Crushing and administering intranasally (IN) or chewing ER formulations is done to circumvent the ER mechanism and, thereby, achieve high plasma concentrations, which maximize the euphoric effects. To mitigate these risks associated with abuse, abuse-deterrent (AD) formulations of opioid analgesics are being developed.

Oxycodone DETERx® (Xtampza ER™, Collegium Pharmaceutical, Inc, [Canton, MA], herein “DETERx”) is an ER, AD, microsphere-in-capsule formulation, designed to retain its ER properties following common tampering methods such as crushing, chewing, and preparation for IV injection.

The IN and oral human abuse potential of DETERx was assessed in two different studies. In study 1, abuse potential of intranasally administered crushed oxycodone DETERx 40 mg was evaluated and compared with intact oxycodone DETERx 40 mg following oral administration (PO) and crushed immediate-release (IR) oxycodone 40 mg following IN administration. In study 2, the oral abuse potential of intact and chewed oxycodone DETERx 40 mg was compared with crushed IR oxycodone 40 mg.

The purpose of these studies was to assess the pharmacokinetics (PK) and human abuse potential of DETERx administered IN and PO.

Method

For both studies, institutional review board approval was obtained prior to start of the study; each subject provided written informed consent prior to any study-related procedures or assessments being conducted. Study 1 (IN) was a randomized, double-blind, active- and placebo-controlled, double-dummy, single-dose, cross-over study. Subjects were non-dependent, non-tolerant to opioids with a history of recreational insufflation of opioids. After successfully completing the Drug Discrimination Phase, subjects entered into the Double-blind Treatment Phase to receive crushed DETERx 40mg dosed IN, intact DETERx 40mg dosed PO, crushed IR oxycodone 40mg dosed IN, and placebo. Primary endpoint: at the moment Drug Liking, measured at pre-defined time points up to 24 hours post-dose using a bipolar visual analogue scale (VAS). Secondary endpoints: Drug Effects Questionnaire (DEQ), Overall (Global) Drug Liking (ODL), Addiction Research Center Inventory-Morphine Benzedrine Group (ARCI-MBG), Take Drug Again (TDA), Price Value Assessment Questionnaire (PVAQ), Pupillometry, Ease of Snorting.

Study 2 (oral) was a randomized, double-blind, active- and placebo-controlled, triple-dummy, single-dose, cross-over study. Subjects had a history of recreational opioid use and were nondependent, nontolerant to opioids. After successfully completing the Drug Discrimination Phase, subjects entered into Double-blind Treatment Phase to receive intact DETERx 40mg, chewed DETERx 40mg, crushed IR oxycodone 40mg, and placebo. Primary endpoint: at the moment Drug Liking measured at pre-defined time points up to 24 hours post-dose using a bipolar VAS. Secondary measures: DEQ feeling high, any drug effects, good effects, bad effects, feel sick, nausea, sleepy, and dizzy.

Safety endpoints: vital signs, oxygen saturation, physical examinations, clinical laboratory values, urinalysis, nasal effects.

Results

Study 1: 36 subjects completed the study. For the primary endpoint (Drug Liking maximum effect [E max]), crushed DETERx IN was significantly lower compared with IR oxycodone IN (p < 0.0001). Least square mean (LSM) E max for Drug Liking was significantly lower for crushed DETERx IN than for DETERx PO (p < 0.0001). For positive effects such as Any Drug Effects, Good Drug Effects, and High, the differences in LSM E max between IR oxycodone IN and DETERx IN and the differences between IR oxycodone IN and DETERx PO were statistically significant for each of the effects-higher for IR oxycodone IN. For nasal effects assessment, subjects reported the highest levels of irritation, burning, and facial pain with DETERx IN at earlier time points. Other than nasal AEs associated with DETERx IN, the safety profile was consistent with an opioid.

Study 2: 38 subjects completed the study. LSM E max for Drug Liking was significantly lower for chewed DETERx (p < 0.0001) than crushed IR oxycodone. The differences in E max between chewed DETERx and crushed IR oxycodone were significant for Any Drug Effects, High, Good Drug Effects, Bad Drug Effects, Sick, Sleepy, Dizzy, Overall (Global) Drug Liking, and ARCI/MBG. Chewed and intact Oxycodone DETERx showed no difference in Drug Liking (p = 0.4264). Oxycodone DETERx was well tolerated by subjects; the safety profile was consistent with an opioid containing drug.

Conclusions

Study 1 demonstrated that likability of oxycodone DETERx IN was significantly lower than that of IR oxycodone IN or DETERx PO. Study 2 showed that drug liking for intact and chewed oxycodone DETERx was lower than for crushed IR oxycodone. These data indicate that chewing oxycodone DETERx does not compromise the integrity of the DETERx formulation. Combined, these data suggest that oxycodone
DETERx administered either by crushing and administering IN or chewing will not be attractive to abusers.

**A Phase 2 randomized, double-blind, placebo-controlled study to evaluate naldemedine for the treatment of opioid-induced constipation in patients with chronic non-cancer pain**

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**Purpose**

Opioid analgesics play an important role in the management of chronic non-cancer pain. One of the most common side effects of opioid therapy is opioid-induced constipation (OIC). Naldemedine (S-297995) is a novel peripherally-acting mu-opioid receptor antagonist (PAMORA) being developed for the treatment of OIC.

**Method**

This study evaluated oral naldemedine 0.1, 0.2, or 0.4 mg once daily for 4 weeks in patients with chronic non-cancer pain who had OIC. Eligibility criteria included: chronic opioid therapy for ≥3 months, <3 spontaneous bowel movements (SBM) per week during the screening period. The primary efficacy endpoint was change from baseline in frequency of SBM per week to the last 2 weeks of treatment period. Primary efficacy analysis was done using covariance model with frequency of SBM per week at baseline as a covariate. A secondary efficacy endpoint was the proportion of SBM responder over the last 2 weeks of treatment period (patients with ≥3 SBM per week and increase of ≥1 SBM per week from baseline). Safety assessments included adverse events, laboratory tests, Clinical Opiate Withdrawal Scale (COWS) questionnaire and 11-point Numerical Rating Scale (NRS) pain questionnaire. (ClinicalTrials.gov identifier NCT01443403).

**Results**

A total of 244 patients were randomized 1:1:1:1 to naldemedine 0.1, 0.2, 0.4 mg or placebo (PBO) groups. Baseline patient characteristics were generally balanced. A statistically significant improvement in the primary efficacy endpoint was observed for both 0.2 and 0.4 mg: the least-squares mean change in the frequency of SBM per week from baseline to the last 2 weeks of treatment period was 1.42 for PBO group, and 1.98 (p=0.35 vs PBO), 3.37 (p=0.0014 vs PBO) and 3.64 (p=0.0003 vs PBO) for the naldemedine 0.1, 0.2 and 0.4 mg groups, respectively. The proportion of SBM responder was 39.3% for PBO, and 52.5% (p=0.15 vs PBO), 71.2% (p=0.0005 vs PBO) and 66.7% (p=0.003 vs PBO) for naldemedine 0.1, 0.2 and 0.4 mg groups, respectively. Gastrointestinal (GI) disorders including abdominal pain, diarrhea, flatulence and nausea were the most common treatment-emergent adverse events (TEAEs). The incidences of all TEAEs and GI-related TEAEs were 50.8% and 13.1% in the placebo group, 41.0% and 21.3% in the 0.1 mg group, 50.0% and 25.0% in the 0.2 mg group, 55.7% and 34.4% in the 0.4 mg group, respectively. Most TEAEs were mild to moderate in severity; 1.6%, 4.9%, 3.3% and 8.2% patients in PBO, 0.1, 0.2 and 0.4 mg groups, respectively, had a severe TEAE. No clinically meaningful changes from baseline in NRS pain scores or COWS scores were observed in any of the naldemedine groups.

**Conclusions**

Naldemedine given orally at 0.2 and 0.4 mg once daily demonstrated efficacy in treating OIC in patients with chronic non-cancer pain. Naldemedine was generally well tolerated at all doses. The most frequent AEs were GI-related, which is expected due to the mechanism of action of naldemedine. Based on the overall efficacy and safety profile, 0.2 mg was selected for Phase 3 clinical trials.

**Lumbar Spine Surgeries and its Long Term Effects in Patients with Chronic Pain**

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**Purpose**

The purpose of this clinical study is to determine long term benefits of lumbar spine surgery in the management of chronic pain. 42 patients who have undergone lumbar spinal fusion or laminectomy surgeries, were interviewed and a detailed questionnaire was given to assess their pain level and sleep pattern and other chosen parameters. The efficacy of spine surgery in providing quality of pain control and improvement in ADL in these patients were assessed.
Method

42 patients were interviewed after informed verbal consent. The parameters questioned included

- Change in VAS pain score before and after surgery. Patients were asked to rate their pain score before and after surgery on a scale of 0-10.
- Change in requirement for pain medications. Patients were asked about change in average number of pain pills taken before and after surgery.
- Improvement in activities of daily living. Patients were asked to rate the improvement in activities of daily living before and after surgery.
- Change in sleep pattern before and after surgery. Patients were asked about the number of hours they sleep on an average before and after surgery.
- Patient satisfaction or dissatisfaction with spinal surgery. Patients were asked to rate from 0-6 whether they were completely unhappy (0) vs very satisfied (6) with surgery based on their outcome and experience.

Results

On assessing the improvement in VAS score before and after, the questionnaire reveals on an average there was 19% improvement in the overall pain score. 16 out of 42 patients either had no improvement on the VAS score or worsening of their pain that led to increase in their VAS score. 5 out of 42 patients had more than 50% improvement in their pain score after their surgery.

21 out of 42 patients showed either no improvement or worsening of their requirement for pain pill intake. 5 patients out of 42 showed 50% or greater reduction in their pain pill requirement.

26 out of 42 patients reported no improvement or worsening in their activities of daily living. 26% of the patients questioned admitted to moderate improvement or better in their activities of daily living.

31 out of 42 patients showed negative change in their sleep pattern. The sleep patterns after surgery showed deterioration in quality of sleep in many patients overall.

The final question about the overall improvement in pain with the surgery revealed that 25% of the patients who had back surgery were satisfied enough with the surgery, that they would either make the same choice to have surgery or will recommend back surgery for their friends or family. 22 out of 42 patients were very dissatisfied with the surgery that they regret making their decision to have surgery.

Conclusions

With the evidence of poor outcomes after spine surgeries, more studies need to be performed to evaluate the efficacy. Minimally invasive surgeries have reduced the morbidity and mortality following spinal fusion surgeries. Still the results of lumbar fusions for spinal stenosis and lumbar disc degenerations diseases are mediocre at best. Use of alternate modes of therapy such as pain management and physical therapy may reduce the need for surgery and may improve outcomes. Comprehensive spine centers that have multispecialty team members that include surgeons, physical therapist, interventional pain doctors and psychologists provide better outcomes in patients with back pain.

Pharmacokinetic evaluation of subcutaneously administered ZYN001 in male Sprague-Dawley rats

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Purpose

The antinociceptive and antihyperalgesic properties of delta-9-tetrahydrocannabinol (THC), a cannabinoid and the primary component in Cannabis sativa, have been extensively reported. However, the currently approved THC-containing medications, which are orally administered, have been associated with psychotropic effects, such as catalepsy, deficits in motor performance, and hypothermia. In some patients, these side effects may limit the therapeutic use of THC for analgesia.

ZYN001 is a synthetic pro-drug of THC that is formulated for delivery via a transdermal patch. ZYN001 is produced synthetically and is not derived or extracted from botanicals. The pro-drug technology facilitates the transport of THC, which is naturally hydrophobic, across the stratum corneum and into the systemic circulation. Chemically, ZYN001 is the D-(-)-glyceric acid ester of THC, but unlike THC, ZYN001 can be absorbed into the skin transdermally. After crossing the stratum corneum, ZYN001 is hydrolyzed back to THC and glyceric acid by esterases in the skin. The transdermal patch is a non-invasive, non-oral dosage form that may be able to achieve sustained, consistent plasma levels of THC while avoiding the common psychoactive adverse events associated with high plasma levels of THC.

The objective of this study was to evaluate the in vivo pharmacokinetics of ZYN001, specifically to confirm in vivo that ZYN001 is hydrolyzed to THC. As the rat is the usual rodent model used for evaluating various classes of chemicals, and there were no gender differences expected in neurological function, only male rats were used.

Method

A total of 3 male experimentally naïve Sprague-Dawley rats were included in this study. During the acclimation period, animals were observed daily with respect to general health and any signs of disease. They were housed individually in cages and maintained under controlled conditions before testing and during the testing period. Rats were given a single subcutaneous bolus injection of ZYN001 at a dose of 1 mg/kg. Dose volumes were individualized by body weight. Plasma samples were analyzed by liquid chromatography-tandem mass spectrometry. Plasma concentrations of ZYN001;
THC; its main active metabolite, 11-hydroxy-delta-9-tetrahydrocannabinol (THC-OH); and its main inactive metabolite, 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH), were measured, and total THC equivalents (ZYN001 + THC + metabolites) were calculated. Blood samples were obtained at baseline and at 0.08, 0.25, 1.17, 3, 6, 12, 24, 31.30, 47.50, 56, 72, and 96 hours postdose. Immediately after the samples were harvested, plasma was separated, and 50 μL of plasma was extracted with solvent to precipitate the proteins. Samples were centrifuged (10,000 g x 3 minutes), supernatant was removed, and the samples were evaporated to dryness under nitrogen gas. Samples were reconstituted with acetonitrile and analyzed.

Results

Plasma concentrations of ZYN001 ranged from 26.4 ng/mL at 0.08 hours postdose to 17.4 ng/mL at 72 hours postdose; they peaked at 6 hours postdose (45.8 ng/mL). Values for THC ranged from 159.6 at 0.08 hours postdose to 93.3 ng/mL at 72 hours postdose, peaking at 0.25 hours postdose (162.9 ng/mL). Concentrations of THC-OH were 1.4 ng/mL at 0.08 hours postdose, and they decreased in roughly linear fashion to 0.1 ng/mL at 72 hours postdose. For THC-COOH, concentrations were 4.1 ng/mL at 0.08 hours postdose and 1.9 ng/mL at 72 hours postdose, with a peak of 25.9 ng/mL at 6 hours postdose.

Conclusions

After subcutaneous dosing, ZYN001 was rapidly converted to THC, with low levels of its main metabolites, THC-OH and THC-COOH, observed over the course of the study period. Since THC-OH is a potent psychoactive metabolite that crosses the blood-brain barrier more easily than THC, low levels in plasma may reduce the likelihood that patients will experience treatment-emergent psychotropic effects.

Characterizing downstream healthcare resource utilization and costs based on prior utilization patterns of immediate release hydrocodone

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Purpose

According to a 2011 Institute of Medicine of the National Academies report, there are approximately 100 million adults (about 44% of all adults) in the United States (U. S.) who experience chronic pain, and the worldwide prevalence ranges from 10% to 55%. Opioids are often used to manage chronic pain, and immediate-release (IR) hydrocodone is among the most widely prescribed opioid analgesics in the U. S. A recent report found that almost half of the new patients prescribed opioids for more than 30 days in the first year continued to use them for three or more years, with about half of these patients prescribed only IR opioids. Moreover, higher comorbidity levels and poor health among high utilizers of IR hydrocodone suggest that these patients may have higher healthcare resource utilization (HRU) and costs than low utilizers of IR hydrocodone. The objectives of the current study are to assess downstream HRU and costs among IR hydrocodone patients by days’ supply and average pills/month in the prior six months in a diverse U. S. population, including commercially insured, Medicare and Medicaid patients.

Method

A retrospective analysis using healthcare claims from Truven MarketScan® commercial, Medicare supplemental, and Medicaid multistate databases was performed. Patients prescribed IR hydrocodone during the 6-month baseline (7/2011-12/2011), and with continuous insurance enrollment during baseline and the 12-month follow-up (2012) were selected. IR hydrocodone prescription information during the baseline period, including number of days’ supply (<60 vs. ≥60 days) and average number of pills/month (≤60 vs. >60 pills/month) of IR hydrocodone were assessed to classify patients. Days’ supply was defined as the longest period of consecutive days with supply during the baseline period. A maximum gap of 30 days between the end of one prescription and the pick-up of the next prescription was allowed to reflect real world behavior. Average number of pills/month was calculated as the total number of IR hydrocodone pills prescribed during the baseline period divided by six months. Initial cut points for the ≥60 days’ supply and >60 pills/month subpopulations were defined a priori to identify patients that received a minimum of two full months of therapy (at least one monthly refill) or more than two pills per day on average, respectively. HRU and per-patient-per-month (PPPM) costs (2014 US dollars) were assessed at follow-up. Descriptive analyses and multivariate regressions were conducted to compare HRU and costs at follow-up by days’ supply and average pills/month of IR hydrocodone at baseline. Adjusted odds ratios (ORs) for HRU and predicted adjusted PPPM all-cause total costs by baseline days’ supply and average pills/month for IR hydrocodone were reported.

Results

1,698,845 commercial, 264,038 Medicare, and 151,063 Medicaid IR hydrocodone patients were identified. During follow-up, commercial patients with prior ≥60 days’ supply were more likely to have an inpatient admission (13.2% vs. 7.5%), outpatient hospital visit (69.1% vs. 57.0%), office visit (97.6% vs. 91.0%), emergency room (ER) visit (28.1% vs. 21.4%), and had higher PPPM total costs ($1,494 vs. $842) than the <60 days’ supply subgroup (all p<0.05). Trends were similar for the Medicare and Medicaid samples, except for Medicare patients with baseline ≥60 days’ supply, where no differences were found with office visits. Opioid pharmacy costs were less than 0.6%, 0.4%, and 0.7% of overall costs among IR hydrocodone patients, respectively.
costs for commercial, Medicare, and Medicaid, respectively, representing a small proportion of total costs. After adjusting for confounding factors, among commercial patients the adjusted odds ratio for baseline ≥60 days’ supply of IR hydrocodone vs. baseline <60 days’ supply was 1.62, 1.33, 2.58 and 1.48 (all p-values < 0.05) for at least one inpatient admission, outpatient hospital visit, office visit, and ER visit, respectively. Trends were similar with pills/month subgroups (<60 vs. >60 pills/month at baseline) and across all plan types, but were not statistically significant in all subgroups by plan type. Adjusted PPPM all-cause total costs were higher among patients with baseline ≥ 60 days’ supply of IR hydrocodone as compared to patients with < 60 days’ supply in the commercial ($1,245 vs. $851), Medicare ($1,954 vs. $1,596), as well as Medicaid ($1,372 vs. $1,206) samples (all p<0.05). When assessed by baseline pills/month, the predicted adjusted PPPM costs were significantly higher among patients with > 60 pills/month as compared to patients with ≤ 60 pills/month in the commercial ($1,250 vs. $864), Medicare ($1,959 vs. $1,617), as well as Medicaid ($1,376 vs. $1,225) samples (all p<0.05).

Conclusions
High utilizers (≥60 days’ supply or >60 pills/month) of IR hydrocodone during baseline had higher PPPM all-cause total costs in the following year across all insurance types compared with low utilizers (<60 days’ supply or ≤60 pills/month). Total all-cause costs were dominated by non-pharmacy, direct medical expenditures. Opioid pharmacy costs represented only a small fraction of overall pharmacy costs. Utilization patterns of IR hydrocodone may help to predict future costs, providing an opportunity to flag patients in order to implement interventions to improve their quality of care.

Opioid treatment patterns following prescription of immediate-release hydrocodone
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Purpose
Opioid medication is widely prescribed for the management of chronic pain, with nearly 10 million insured Americans estimated to have received long-term opioid therapy in 2013 alone. Immediate-release (IR) hydrocodone is the most widely prescribed opioid analgesics in the United States (U. S.). Little is known about how it is being used in terms of duration of therapy and treatment patterns, including utilization of extended-release/long-acting (ER/LA) opioids among patients on IR hydrocodone. A better understanding of how IR hydrocodone and ER/LA opioids are used to manage pain is needed. The objective of the current study is to assess downstream length of opioid therapy and utilization patterns of ER/LA opioids among IR hydrocodone patients.

Method
Retrospective analysis using healthcare claims from Truven MarketScan® commercial, Medicare supplemental, and Medicaid multistate databases was performed. Patients prescribed IR hydrocodone during the 6-month baseline (7/2011-12/2011), and with continuous enrollment during baseline and the 12-month follow-up (7/2012-7/2013) were selected. Patients meeting the selection criteria were classified into four subgroups based on opioid utilization patterns: i) IR hydrocodone and ER/LA opioid use during baseline (concomitant users); ii) Only IR hydrocodone at baseline and conversion to an ER/LA opioid during follow-up within 60 days of the last day of IR hydrocodone use (converters); iii) only IR hydrocodone at baseline and initiation of an ER/LA opioid during follow-up more than 60 days after the last day of IR hydrocodone use (new starts); and iv) Only IR hydrocodone at baseline and follow-up (non-users of ER/LA opioids). Downstream length of therapy, defined as number of days supplied with opioids, and downstream utilization of ER/LA opioids during follow-up were examined by average pills/month (≤60 vs. >60 pills/month) and days’ supply (<60 vs. ≥ 60 days’ supply) of IR hydrocodone during baseline. Initial cut points for the ≥60 days’ supply and >60 pills/month subpopulations were defined a priori to identify patients that received a minimum of two full months of therapy (at least one monthly refill) or more than two pills per day on average, respectively. Chi-square tests and ANOVA were used for categorical and continuous variables, respectively to evaluate differences by pills/month and days’ supply of IR hydrocodone in the baseline period.

Results
At baseline, 1,743,933 commercial, 277,096 Medicare, and 157,922 Medicaid patients prescribed IR hydrocodone were identified. During follow-up, 1.7%, 2.9% and 2.8% of patients initiated (i.e. converters or new starts) ER/LA opioids for commercial, Medicare and Medicaid groups, respectively. Downstream initiation of ER/LA opioids was significantly higher among commercial patients prescribed IR hydrocodone for > 60 pills/month than with ≤ 60 pills/month (7.8 vs. 1.2%, respectively, p<0.05) at baseline. Among commercially-insured converters or new starts length of ER/LA therapy during follow-up was significantly longer among patients with baseline IR hydrocodone > 60 pills/month than with ≤ 60 pills/month (103.6 vs. 70.2 days for converters; 82.6 vs. 69.1 days for new starts, respectively, p<0.05). Similarly, among commercially-insured concomitant users, downstream length of ER/LA opioid therapy was significantly longer among patients with >60 pills/month in baseline (229.5 days) than with ≤60 pills/month (147.8 days). All results were consistent when examined by levels of days’ supply. Among non-users of ER/LA opioids, there was a substantial difference in downstream length of IR hydrocodone therapy during follow-up among non-users. Nearly 90% of non-users...
of ER/LA opioids averaged ≤60 pills/month of IR hydrocodone during baseline, and had downstream average length of IR hydrocodone therapy of 18.3, 38.0, and 35.0 days respectively for commercial, Medicare, and Medicaid, whereas downstream average length of IR hydrocodone therapy was 247.0, 231.4, and 268.1 days respectively for non-users of ER/LA opioids with >60 pills/month during baseline. Similarly, non-users of ER/LA opioids with prior <60 days’ supply of IR hydrocodone had downstream average length of IR hydrocodone therapy of 12.5, 25.9, and 23.7 days during follow-up, as compared to 240.1, 224.4, and 242.3 days respectively for commercial, Medicare and Medicaid non-users of ER/LA opioids with ≥60 days’ supply in the baseline period.

Conclusions
A majority of the population prescribed IR hydrocodone was not prescribed opioid therapy beyond two months on average in the one-year follow-up period. A small subset of patients prescribed IR hydrocodone had increased pills/month or days’ supply of IR hydrocodone in the baseline period and continued to be high utilizers in the following year, averaging nearly eight months of prescribed opioid use. This knowledge can help policy makers and physicians target small subsets of patients to improve care.

Utility of MDDScore in the detection of comorbid major depressive disorder (MDD) in patients with chronic intractable pain
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Purpose
The presence of comorbid MDD has a direct impact on chronic pain, being associated with increases in pain intensity, comorbidities and the frequency of suicide. Both chronic intractable pain and MDD are disorders, with diagnosis often based upon generally subjective complaints. As such, traditional diagnostic paradigms have failed to adequately identify true MDD from the demoralization or depressed mood states commonly associated in patients with Chronic Intractable Pain (CIP). MDDScore is a multi-analyte proteomic blood test for MDD, which monitors the inflammatory, metabolic, neurotrophic and HPA axis pathways altered in MDD. MDDScore has been shown to segregate MDD patients from non-MDD subjects in multiple prospective studies with 93% overall accuracy. The MDDScore test was applied to CIP patients to aid in determination of treatment for comorbid MDD as opposed to general mood change.

Method
The study groups analyzed included: (a) patients (n=93) diagnosed with CIP from the Veract Intractable Pain Clinic, and (b) healthy non-CIP subjects (n=86). Each study group participant had a blood sample drawn for quantitation by immunoassay of 9 serum biomarkers (Alpha-1 Antitrypsin (A1AT), Apolipoprotein C3 (ApoC3), Brain Derived Neurotrophic Factor (BDNF), Cortisol, Epidermal Growth Factor (EGF), Myeloperoxidase (MPO), Prolactin (PRL), Resistin (RETN), and soluble TNF Receptor II (sTNFR2). MDDScores were calculated using a proprietary algorithm and patients were scored from 1-9. MDDScores of ≥5 are indicative of a high probability of MDD. In a recent prospective study, 93.7% of well characterized MDD patients had an MDDScore ≥ 5; in contrast 91.9% of healthy normal subjects had scores of <5 (Bilello et al. J. Clinical Psychiatry 76: 199, 2015).

Results
Our results indicate that the MDDScore test was able to segregate CIP patients into two groups based upon MDDScores. Approximately half of the CIP patients (53.2%) had MDDScores ≥ 5 (mean 8.39; median 9) indicative of unipolar depression. The CIP patients with MDDScores < 5 had a mean of 1.68 and a median score of 1. The non-CIP subjects had a mean MDDScore of 1.97 with a median score of 1. Hypermapping of the inflammatory, metabolic, neurotrophic, and HPA axis pathways indicated that the largest difference between both the CIP populations and non-CIP subjects resides in the inflammatory and the stress (HPA axis) pathways. Analysis of box whisker plots indicates that the CIP patients had significantly lower serum levels of cortisol than normal subjects (mean CIP 9.8 vs 13.4 μg/dL for normal, p = 0.002) with a broader and lower distribution of values (CIP 1.9-36.9, median 7.8 μg/dL vs normal 2.9-37.3 median 12.9 μg/dL). CIP patients with MDDScores of ≥ 5 were statistically significantly different from both non-CIP subjects and CIP patients with MDDScores < 5 (p = <0.0001). A1AT, MPO, and sTNFR2 are biomarkers of chronic inflammation and their serum levels were all statistically different from non-CIP subjects. Since the MDDScore test is gender-specific, we were able to compare biomarker expression in male and female CIP patients. By way of example, prolactin concentration was statistically significantly different from non-CIP subjects in male but not female CIP patients. While differences in specific panel biomarker levels were noted between CIP and non-CIP subjects, these individual biomarker measurements alone are not enough for delineation between the presence or absence of comorbid MDD. The application of the MDDScore proprietary algorithm, and the resultant MDDScores, has been shown to allow for the segregation of the CIP patients into these two sub-populations.

Conclusions
This study indicates that it is possible for pain specialists to use this multi-analyte blood test to identify CIP patients with an MDDScore ≥5, who have an increased risk of comorbid MDD. Furthermore, MDDScore can identify residual chronic inflammation and changes in specific hormones and may provide a path to differential treatment of CIP patients with...
Do conventional pharmacokinetic endpoints for bioequivalence correlate with abuse potential pharmacodynamic endpoints: An exploratory analysis of ALO-02 (Extended Release Oxycodone with Sequestered Naltrexone) abuse potential studies

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Purpose

Prescription opioids are important medications for managing pain; however, the epidemic of opioid abuse in the US is a well-recognized problem. Abuse deterrent opioid (ADO) formulations have been developed to help address this problem. ALO-02 is a novel agonist/antagonist ADO formulation, consisting of a capsule containing pellets of extended-release (ER) oxycodone that surrounds sequestered naltrexone. The antagonist, naltrexone, is not released until the dosage form is manipulated.

FDA has published guidance (1) on the studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties, this guidance groups studies in four categories. Category 2 (Pharmacokinetic [PK] Studies) corresponds to systemic drug exposure studies comparing ADO and non-ADO formulations using bioequivalence methods. Clinical abuse potential (CAP) studies correspond to Category 3 studies and are performed to assess the abuse potential of ADO formulations. Positive subjective measures (PSM) such as “drug liking” are commonly compared in CAP studies. Previous work has indicated that PK alone may not adequately predict abuse deterrence (2). The objective of this work is to explore the relationship between the conventional bioequivalence and CAP endpoints for ALO-02.

Method

PK endpoints and “drug liking” VAS parameters from ALO-02 intranasal (3), oral (4) and intravenous (5) CAP studies that evaluated crushed ALO-02 and crushed oxycodone immediate release (IR) formulations in non-dependent recreational opioid users were investigated. Observations from 89 subjects who completed the studies (n=28 for the intranasal, n=32 for the oral and n=29 for intravenous study) were analysed.

For each study, oxycodone PK endpoints were related to “drug liking” VAS parameters for both the oxycodone IR and ALO-02 arms. The relationships evaluated were: (i) maximum plasma oxycodone concentration (Cmax) vs maximum response in “drug liking” (Emax), (ii) area under the plasma oxycodone concentration/time curve 0 to 2 hours (AUC0-2) vs the area under the response/time curve 0 to 2 hours (AUE0-2) and (iii) area under the plasma oxycodone concentration/time curve 0 to infinity (AUCinf) vs the area under the response/time curve 0 to 8 hours (AUE0-8).

A Spearman’s rank correlation coefficient was calculated for each relationship in each study to numerically evaluate the statistical dependence between both endpoints. Graphical analysis was used to determine if nonlinear relationships between PK parameters and “drug liking” VAS parameters for both the oxycodone IR and ALO-02 arms were present. (1) FDA Guidance for Industry: Abuse-Deterrent Opioids - Evaluation and Labeling. April, 2015. (2) Shram M. Use of PK-PD Modeling to Evaluate the Impact of Formulation on a Subject’s Drug Experience: Can we predict Abuse Potential. 77th Annual Meeting - College on Problems of Drug Dependence, Jun 13-18, 2015.

Results

The correlation between ALO-02 and oxycodone IR PK parameters and the “drug liking” parameters was small (correlation coefficients ranged between -0.247 and 0.265), and were not statistically significant (p>0.050). Further graphical exploration of the data indicated more evidence of a non-linear relation between oxycodone PK parameters and “drug liking” parameters for oxycodone IR (Emax vs Cmax & AUC0-2 vs AUE0-2 relationship) than for ALO-02. However, this was not the case for AUCinf vs AUE0-8, where a relationship between the endpoints was not evident.

Further work is merited such as incorporating the full time course data, the integrated predictors of agonist and antagonist interactions (e.g. pupillometry), the associated rate of onset of the PD response, and/or other potential covariates into the analysis.


Conclusions

In general, establishing a correlation between PK endpoints and “drug liking” parameters was limited by (i) the high degree of variability in the data, (ii) the non-normal distribution of data and (iii) “drug liking” data being bounded between 0 and 100.
Standard bioequivalence endpoints have only limited predictive ability in characterising the relationship with PSM such as “drug liking” of ADO formulations. Therefore, this work suggests that assessment of ADO formulations in Category 3 studies cannot be replaced by Category 2 studies alone.

Ultra-fast targeted screening of 35 drugs of abuse in urine at 9 seconds per sample using SALLE extraction and laser diode thermal desorption mass spectrometry (LDTD-MS/MS)

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Purpose

Immunoassays are most often used to screen different classes of drugs in urine samples. To reduce the number of screening assays, laboratories have opted to adopt a different detection method using mass spectrometry. The screened drugs have different polarities and they require a long LC chromatographic method in order to separate them. To increase sample analysis throughput, the Laser Diode Thermal Desorption Mass Spectrometry (LDTD-MS/MS) method using fast B-glucuronide digest and generic Salt Assisted Liquid-Liquid Extraction (SALLE) is evaluated.

Laser Diode Thermal Desorption Mass Spectrometry (LDTD-MS/MS) offers specificity combined with an ultrafast analysis for an unrivaled screening method. To develop this application, we focused on performing fast and simple extraction methods using a SALLE procedure. 35 drugs of abuse from different classes (opioids, benzodiazepines, amphetamines, barbiturates, cocaine, PCP, etc.) are analyzed simultaneously, with quantitative screening results generated in less than 9 seconds per sample.

Method

The following drugs were spiked in urine at 50%, 100% and 200% of the required concentration according to the initial cutoff test suggested by SAMSHA. Non-listed drugs were added in the screening method using the cutoffs reported by toxicology laboratories such as Quest Laboratories and Redwood labs. The following drugs were screened using positive ion mode: nordiazepam, 7-aminoflunitrazepam, diazepam, 7-aminoclonazepam, oxazepam, estazolam, temazepam, alprazolam, lorazepam, α-OH-alprazolam, 2-OH-ethylfluorazepam, α-OH-midazolam, α-OH-triazolam, chloridiazepoxide, clonazepam, flunitrazepam, amphetamine, methamphetamine, BZE, cotine, dextromethorphan, MDMA, MDEA, MDA, methadone, EDDP, codeine, morphine, oxycodone and PCP. The following drugs were screened using negative ion mode: butabital, secobarbital, phenobarbital, amobarbital/antobarbital and butabarbital.

Samples were extracted using a generic sample preparation, namely salt-assisted liquid-liquid extraction (SALLE). 10 μL of urine sample was mixed with 3 μL of purified B-glucuronide (IMCSzyme) and 4 μL of internal standard solution diluted in a rapid hydrolysis buffer. A fast digestion was performed at 55°C for 15 minutes. 75 μL NaCl (saturated solution in water) and 300 μL of acetonitrile were added. After sample mixing by vortex and phase separation, 2 μL of upper layer is spotted in a LazWell™ pre-coated plate with EDTA. Analysis is performed by LDTD-MS/MS after solvent evaporation.

Results

The LDTD-MS/MS was operated in MRM mode to provide rapid measurement of all drugs that desorbed simultaneously. Specific transitions were monitored for each drug to quantitate calibrator levels. Ionization was performed in positive mode for group one and negative mode for the second group. Analysis included spiked drugs in urine, potentially interfering drugs and real samples. All compounds give good linear responses around the cutoff level. Potential “cross reactivity” is evaluated by monitoring all transitions while desorbing individual drugs spiked at 1000 ng/mL. Cross reactivity between Codeine/Hydrocodone, Morphine/Hydromorphone and Amobarbital/Pentobarbital is observed since they have the same elemental composition and fragmentation pattern. Drug concentrations in real patient samples were also evaluated in LC-MS/MS with a long gradient to separate each drug class. For each drug in real samples, correlation of the data generated by LDTD-MS/MS and LC-MS/MS shows less than 10% of false positives and no false negatives. The benzodiazepine and opioids requires a B-glucuronide enzyme treatment for drug detection.

Conclusions

The LDTD technology combined with generic sample preparation (SALLE) allows for robust drug screening in urine samples with quantitation levels close to the cutoff level recommended by SAMSHA. Sample-to-sample run time of 9 seconds is achieved with the capability to simultaneously analyze 30 drugs in positive MRM mode and 5 drugs in negative MRM mode.

Neurophysiological and clinical effects of laparoscopic retroperitoneal triple neurectomy in patients with refractory postherniorrhaphy neuropathic inguinodynia

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Purpose

Refractory neuropathic inguinodynia following inguinal herniorrhaphy constitutes a severe, debilitating complication. The risk of developing chronic postherniorrhaphy inguinal pain (CPIP) with impact on activities of daily life is...
approximately 6-8%, which given the high frequency of inguinal hernia repair (> 20 million/year worldwide) translates into immense human suffering and a vast socioeconomic burden. Operative remediation of CPIP reduces pain and ameliorates health-related function in selected patients that are refractory to conservative and interventional measures. In the absence of recurrence or meshoma, laparoscopic retropitoneal triple neurectomy (LRTN) has emerged as an effective treatment for neuropathic inguinodynia, comprising advantages such as direct access to the inguinal nerves proximal to the mesh material and any possible aberrant distal branches, and more consistent neuroanatomy within the retropitoneum. The main objectives of this study were to (1) comprehensively evaluate the neurosensory and clinical effects of LRTN, and (2) examine factors that might guide patient selection and influence treatment effect.

**Method**

This single-center, prospective cohort study presents a detailed microlongitudinal quantitative sensory testing (QST) and clinical evaluation of the effects of LRTN in 10 adult CPIP patients with unilateral neuropathic inguinodynia. All patients had undergone systematic behavioral, pharmacologic and interventional treatments by a pain specialist. Moreover, occult hernia recurrence, meshoma, and differential diagnoses of CPIP had been excluded by imaging techniques. Serial assessments of sensory function were performed in four areas on the affected side and one area on the contralateral side, through a well-established QST protocol at three time points: preoperative (preop), directly postoperative (postop), and late postop. Dermatomal mapping was conducted prior to the sensory testing, to acquire a neurosensory overview of the groin region and identify the areas with maximum pain. The contralateral unaffected groin was used as comparison site. Clinical effects of LRTN were assessed through validated measures of pain, health-related function and sleep over the course of a six-month follow-up period. Bivariate correlations examined relationships between neurophysiological, clinical and demographic variables.

**Results**

Mean duration of CPIP was 2.6 ± 1.9 years. The postoperative QST assessments were done 160.9 ± 61.0 min after extubation (direct) and 27.9 ± 23.8 days after surgery (late). QST revealed marked group-level increases of thresholds for mechanical detection, mechanical pain detection, pressure detection, pressure pain detection, thermal detection and thermal pain detection in the two areas with maximum pain prior to surgery for the direct (p < .01) and late postop (p < .05) assessments compared to baseline. Prior to surgery all patients exhibited pronounced pressure allodynia; LRTN abrogated this somatosensory abnormality in 90% of patients. There was a significant increase of the cold pain detection threshold on the contralateral, unaffected side between baseline and the late postop assessment, indicative of decreased central sensitization. Wind-up phenomena were eliminated by the surgery. LRTN provided robust and significant group-level improvements of all clinical measures at the 3- and 6-month follow-up time points. Pain and functional impairment was completely eliminated in 2 patients, whereas 2 patients experienced only limited benefit. Significant, strong positive correlations (r > 0.80) were found between change of corrected heat pain threshold (preop compared to late postop) and improvements of pain visual analog scale (VAS), SF-36 bodily pain and activity assessment scale scores. Preop duration of CPIP showed a strong negative correlation to improvement of McGill pain questionnaire score.

**Conclusions**

LRTN may produce immediate, profound and consistent positive effects across multiple mechanical and thermal QST variables, and marked group-level improvements of pain, health-related function and sleep quality in selected CPIP patients. Dynamic change of heat pain threshold might predict pain and functional status. The direct abrogation of wind-up pain indicates that persistent noxious peripheral input may be required to maintain peripheral and central sensitization in a majority of CPIP cases. For future studies, it is imperative to focus on timing of intervention and factors that guide patient selection and predict treatment effect.

**Evaluation of the relative intranasal abuse potential of a hydrocodone extended-release tablet formulated with abuse-deterrence technology in nondependent, recreational opioid users**

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**Purpose**

The misuse and abuse of opioids pose serious public health and safety risks. A new, single-agent hydrocodone bitartrate extended-release (ER) tablet was formulated with a CIMA® Abuse-Deterrence Technology (ADT) to provide resistance against rapid release of hydrocodone when tablets are manipulated or taken with alcohol, potentially reducing abuse liability when misused or abused. This study characterizes the relative abuse potential of manipulated (milled) intranasal hydrocodone ER in healthy, nondependent adults with a history of recreational and intranasal opioid use.

**Method**

Healthy subjects aged 18-55 years who were able to tolerate a 45-mg intranasal dose of hydrocodone active pharmaceutical ingredient (API) powder (surrogate for immediate-release hydrocodone) and discriminate the effects of hydrocodone from placebo were randomized into a double-blind, 5-period,
crossover treatment phase to assess abuse potential. Subjects received each of the following separated by a ≥7 day washout period: intranasal milled hydrocodone ER 45 mg, intranasal hydrocodone API 45 mg, intact oral hydrocodone ER 45 mg, intranasal milled Zohydro ER 45 mg (commercially available hydrocodone ER capsule at the time the study was conducted), and placebo. Drug liking and other abuse-related measures were assessed through 48 hours after administration of study drug. Coprimary pharmacodynamic endpoints included maximum effect (E_{max}) for “at the moment” drug liking and E_{max} for end-of-day/next-day Overall Drug Liking (drug liking over a full 24-hour period after study medication administration), both scored on a 100-point bipolar visual analog scale (VAS; 0=strong liking, 50=neutral, 100=strong liking). Secondary pharmacodynamic measures included area under the effect curve (AUEC) for “at the moment” drug liking, E_{max} for Take Drug Again VAS and Price Value Assessment Questionnaire, E_{max} and AUEC for select subscales of the Addiction Research Center Inventory and Subject-Rated Assessment of Intranasal Irritation, and VAS score for ease of snorting. Minimum effect (E_{min}; minimum pupil diameter) and AUEC for pupillometry were also assessed to determine the physiologic effect of the treatments.

Results

Of 45 subjects enrolled, 34 were evaluable for pharmacodynamic assessments. E_{max} of “at this moment” drug liking was significantly (P<0.004) lower for hydrocodone ER vs. hydrocodone API and Zohydro ER (72.8 vs. 80.2 and 83.2, respectively) and significantly (P<0.001) higher vs. oral hydrocodone ER (57.3) and placebo (58.6). E_{max} of end-of-day/next-day Overall Drug Liking VAS was also significantly (P<0.004) lower for hydrocodone ER vs. hydrocodone API and Zohydro ER (68.5 vs. 77.1 and 79.8, respectively) and significantly (P<0.001) higher vs. oral hydrocodone ER (57.8) and placebo (57.7). Findings for secondary pharmacodynamic measures were generally consistent with findings for the coprimary pharmacodynamic measures. Mean E_{min} for pupil diameter measurements were significantly (P<0.001) lower for all 3 intranasal hydrocodone treatments vs. placebo, validating the physiologic effect of intranasal hydrocodone. Intranasal adverse events were modest, ranging from “no problem” to mild effects at most, and were unlikely to be clinically relevant. The majority of adverse events were mild in severity and resolved. The overall incidence of adverse events was lowest with placebo (18%), slightly higher with intact oral hydrocodone ER (24%), similar with intranasal hydrocodone API (53%) and intranasal hydrocodone ER (52%), and highest with intranasal Zohydro ER (61%).

Conclusions

Abuse potential after intranasal administration of hydrocodone ER formulated with CIMA® ADT was significantly lower compared with intranasal hydrocodone API. Abuse potential of intranasal hydrocodone ER was also significantly lower compared with the non-abuse-deterrent opioid formulation of hydrocodone ER (Zohydro ER). When administered as intended (intact orally), hydrocodone ER liking scores were similar to placebo. These findings, along with results from a previous study assessing abuse potential with oral administration, suggest that hydrocodone ER formulated with CIMA® ADT has significantly lower abuse potential when administered through the 2 most common routes of hydrocodone abuse (oral and intranasal).

Effect of food on the steady-state pharmacokinetics of a hydrocodone extended-release tablet formulated with abuse-deterrence technology in healthy volunteers

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Purpose

Hydrocodone bitartrate extended-release (ER) tablet employs CIMA® Abuse-Deterrence Technology (ADT), a platform that provides controlled release of hydrocodone over an extended period, resistance against rapid release of hydrocodone when tablets are comminuted, and resistance against dose dumping when tablets are taken with alcohol. A previous study demonstrated that area under the plasma concentration-time curve (AUC) following administration of a single 90-mg dose of hydrocodone ER was similar in the fed and fasted states; however, maximum observed plasma concentration (C_{max}) was 40% higher when hydrocodone ER was administered with food. In order to understand what the effect of food may be under therapeutic dosing conditions, the current study assessed the effects of a high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800-1000 calories) meal (as defined in the US Food and Drug Administration food effect guidance, December 2002) on the steady-state pharmacokinetics (PK) of hydrocodone ER following administration of twice-daily 90-mg doses, the highest anticipated dosing regimen.

Method

This single-center, open-label, crossover study randomized healthy subjects aged 18-45 years to two 12-day treatment periods in which hydrocodone ER was administered in the fed and fasted states. Subjects received naltrexone HCl 50 mg throughout the study to block opioid receptors and minimize opioid-related adverse events (AEs). On day 1, subjects received a single 90-mg dose of hydrocodone ER. Subjects were then titrated to a 90-mg twice daily dose of hydrocodone ER according to the following schedule: 45-mg dose twice daily on days 2/3; 60-mg dose twice daily on days 4/5; and 90-mg dose twice daily on days 6 through the morning of day 11. There was a minimum 14-day washout between the last dose in one period and the first dose in the second...
period. Serial PK sampling was performed on days 1 (single dose) and 11 (steady state). Two-sided 90% confidence intervals (CIs) for the geometric least squares (LS) mean ratio between the fed and fasted states for AUC and C$_{\text{max}}$ were calculated. Bioequivalence criteria were applied to detect if there were differences in AUC and C$_{\text{max}}$ between the fed and fasted states. The fed state was considered bioequivalent to the fasted state if the 90% CI of the geometric LS mean ratio fell completely within the limits of 0.8 to 1.25 for both AUC and C$_{\text{max}}$ at steady state. Safety was assessed throughout the study.

Results

Forty-three subjects met entry criteria and were randomized; 30 subjects completed the study. Following administration of a single 90-mg dose of hydrocodone ER, AUC$_{0-12}$ (AUC from time 0 to 12 hours after administration of study drug) (fed/fasted ratio [90% CI]: 1.24 [1.19, 1.30]) and C$_{\text{max}}$ (fed/fasted ratio [90% CI]: 1.34 [1.28, 1.40]) were higher when hydrocodone ER was administered with food. Following multiple-dose administration, geometric LS mean hydrocodone C$_{\text{max}}$ (fed: 126.6 ng/mL; fasted: 111.3 ng/mL) and AUC$_{r}$ (AUC over 1 dosing interval) (fed: 1288.7 ng*h/mL; fasted: 1165.0 ng*h/mL) were only slightly higher when administered in the fed vs. fasted state. The CIs for the geometric LS mean ratio between fed and fasted for C$_{\text{max}}$ (ratio [90% CI]: 1.14 [1.07, 1.21]) and AUC$_{r}$ (ratio [90% CI]: 1.11 [1.04, 1.17]) met bioequivalence criteria (ie, 0.8, 1.25). Following administration of the first 90-mg dose of hydrocodone ER, hydrocodone t$_{\text{max}}$ (time to C$_{\text{max}}$) occurred 3 hours sooner in the fed (median: 6 hours) vs. fasted state (median: 9 hours). At steady state, the t$_{\text{max}}$ was comparable between fed and fasted states (median: 6.0 hours). Administration of single and multiple doses of hydrocodone ER titrated to 90 mg twice daily in the fed and fasted states was generally well tolerated; the most common AEs overall were headache (27.9%), infrequent bowel movements (25.6%), and nausea (25.8%). Nine (20.9%) subjects were discontinued because of AEs; consistent with the protocol requirement that any subject experiencing emesis at any time following administration of study drug in either period be withdrawn from the study, the most common AE leading to discontinuation was vomiting (fed state, n=7; fasted state, n=1).

Conclusions

Administration of a single 90-mg dose of hydrocodone ER in the fed state resulted in an earlier t$_{\text{max}}$ and higher C$_{\text{max}}$ (34%) and AUC$_{0-12}$ (24%) of hydrocodone compared with the fasted state. At steady state, the effect of food was less pronounced, with C$_{\text{max}}$ and AUC$_{r}$ increasing by 14% and 11%, respectively, compared with administration in the fasted state. The CIs for the ratios of geometric means on these outcomes met the criteria for bioequivalence following multiple-dose administration. t$_{\text{max}}$ was comparable between fed and fasted states. The extended-release characteristics of hydrocodone ER were maintained when administered with food.

Treatment of breakthrough pain in cancer: Efficacy and acceptability of low versus high doses of fentanyl pectin nasal spray

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Purpose

Many patients with cancer experience acute episodes of severe pain, known as breakthrough cancer pain (BTPc). Optimal treatment of BTPc would be provided by medications with pharmacokinetic profiles correlating with the pattern of breakthrough pain: sudden onset, short time to maximum severity, and short duration of pain. Therefore, transmucosal formulations of fentanyl have been developed, and are the only medications approved for treatment of BTPc. Among these, Fentanyl Pectin Nasal Spray (FPNS; Lazanda$^{(8)}$), available in 100 – 800 μg dosages, is the only nasal spray which allows direct absorption of fentanyl from the nasal mucosa, potentially permitting rapid pain relief.

Unless a ceiling dose is reached, patients report an increase in pain relief with increasing doses of analgesics; however, the incidence of opioid-induced adverse events generally exhibits a dose-related increase. Therefore, we evaluated the effectiveness, acceptability, and safety of different FPNS dosages in treatment of BTPc.

Method

In two multicenter, double-blind, crossover Phase 3 studies, patients with cancer were taking ≥60 mg/day oral morphine (or equivalent) for their background pain, and 100-, 200-, 400-, or 800-μg FPNS or matching placebo for acute episodes of BTPc. The primary efficacy endpoint was patient-averaged summed pain intensity difference at 30 min post-dose (SPID$_{30}$). Secondary endpoints included SPID at 5, 10, 15, 45, and 60 min post-dose, and patient acceptability scores: overall satisfaction, speed of relief, reliability, ease of use, and overall convenience of the nasal spray. Post-hoc analyses of FPNS efficacy and safety were performed for patients divided into the placebo group and FPNS groups: All FPNS (combined FPNS dosages), 100, 200, 400, or 800 μg. Statistical significance for the difference from placebo was set at p<0.05.

Results

There were 152 patients in the efficacy population (100-μg, n=24; 200-μg, n=25, 400-μg, n=54, 800-μg, n=49). Mean baseline pain intensity (0 – 10 scale) was similar between All FPNS and placebo (7.3 and 7.0, respectively), and between individual FPNS groups (from 7.3 to 7.6). At 5-to-60 min post-dose, patients receiving 800 μg FPNS reported higher pain intensity than patients receiving lower dosages.

For the primary efficacy endpoint, compared with placebo, SPID$_{30}$ was significantly larger for All FPNS vs. placebo (8.5 vs. 4.5; p<0.0001), and for 100 – 800 μg FPNS groups vs.
placebo (6.6 – 10.2 vs. 4.5; all p<0.05). SPID_{30} for patients receiving 800 μg FPNS was smaller than for patients receiving 100 – 400 μg FPNS (6.6 vs. 10.2 – 6.6, respectively). SPID values at all other dose time points were significantly larger for all FPNS, and 100 – 200 μg FPNS, than for placebo (all p<0.05). SPID values were significantly larger for 800-μg group vs. placebo at 45- and 60-min post-dose (all p<0.05).

Patient-averaged mean acceptability scores for the overall satisfaction, speed of relief, and tolerability of the nasal spray at 30-min and/or 60-min post-dose were significantly greater for all FPNS vs. placebo, with no significant differences among individual dosages of FPNS. After the last treated episode of BTPc, on average 73.5% of all patients were satisfied or very satisfied with the ease of use or overall convenience of the nasal spray.

Overall, 50.7% of patients receiving FPNS reported adverse events (AEs). AEs were typical of fentanyl, mostly mild-to-moderate in severity, and did not increase in frequency or severity with increasing FPNS dosage.

Conclusions

FPNS was efficacious and accepted across all dosages by patients experiencing BTPc, and lower dosages were at least as effective as higher dosages. No new AEs or safety signals were observed compared with those reported for other fentanyl formulations, and higher dosages of FPNS did not affect its safety and tolerability. This study suggests that FPNS matches the pattern of acute, short-lived breakthrough pain and provides rapid and effective analgesia, with a potential for range of dosages for treatment of BTPc.

Decreased pain following use of a topical analgesic: Interim results from the optimizing patient experience and response to topical analgesics (OPERA) observational study

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Purpose

As many as 40% of patients treated for chronic pain do not attain adequate analgesia, which can lead to physical and social dysfunction and diminished quality of life. Unfortunately, most pain therapies, including opioids and NSAIDs, are associated with adverse effects and the addition of further systemic medications to control pain increases the risk of drug-drug interactions and side effects. Because of lower systemic exposure observed with topical analgesic therapies, there may be a benefit from reduced side effects, lower risk of drug-drug interactions, and improved tolerability. Therefore, evaluation of opioid-sparing treatments including topical compounded formulations is critical to identification of safer and more effective approaches to the treatment of pain.

OPERa is an ongoing observational survey study (IRB-approved, informed consent, 16 sites) of patients ages 18-64 who experience chronic neuropathic or musculoskeletal pain and who have been prescribed a topical analgesic (Flurbiprofen 20%, Amitriptyline 5%, Magnesium Chloride 10%, Gabapentin 6%, Bupivacaine 2% or other pain-relieving transdermal cream). Most of the patients had been prescribed opioids or other oral analgesics, or were taking over-the-counter medications for chronic pain. The purpose of the pre-planned interim analysis of the OPERA study was to: 1) Evaluate the efficacy of the topical analgesic in reducing pain in patients experiencing either neuropathic or musculoskeletal pain, using the Brief Pain Inventory (BPI) Short Form, 2) Assess changes in the percentage of patient-reported primary pain complaints/symptoms, 3) Assess patient satisfaction with the topical analgesic, and 4) Identify any adverse effects.

Method

Following IRB approval and patient consent, data were collected beginning in 2014 via paper survey forms completed by study participants from 16 physicians who treat patients with chronic pain. Physician specialties included anesthesiology, family practice, obstetrics/gynecology, orthopedic surgery, pain management, physical medicine and rehabilitation. Observation Study Design: Survey 1 (at first patient visit before use of topical analgesic) included questions regarding primary pain complaint/symptoms and location, the BPI Short Form, and current medication usage. Data collected at Survey 2 (at second patient visit—approximately 45 days since starting use of topical analgesic, same questions as Survey 3 described below) were not used for this interim analysis. Survey 3 (at third patient visit—approximately 90 days since starting use of the topical analgesic) included all Survey 1 questions, and questions related to use of the topical analgesic. All surveys included queries on side effects. Completed forms were collected and entered into Microsoft Excel. Survey 1 records were matched with Survey 3 records using a unique patient identifier. The first 100 records were used, with 22 removed due to incomplete/misaligned data, leaving a total of 78 paired records for analysis. Data were transferred from Excel into the Statistics Package for the Social Sciences for statistical analysis. Descriptive statistics were run for all questions. Statistically significant differences between Survey 1 and Survey 3 results were calculated using the McNemar test for binomial data and the Wilcoxon Signed Ranks test for scale data. Cohen’s d was calculated as appropriate. Alpha was set at .05.

Results

78 adult patients (51 female, 27 male) with a mean age of 41.1±11.7 years at Survey 1 and a mean of 105±43 days between Survey 1 and 3 were included in this analysis. From Survey 1 to 3, there were statistically significant decreases in the percentage of patients reporting pain associated with arthritis (P=.027), neuropathy or radiculopathy (P=.002) and “other” pain (P=.035). There was a statistically significant 22.3% decrease in the proportion of patients who reported
non-everyday kinds of pain on the day of Survey 1 (84%) compared to the day of Survey 3 (65%), \( P = .013 \). A 23.9% statistically significant decrease was found in the overall BPI Severity Score from 4.6 to 3.5 on the 10-point scale \( (P < .001) \), with a medium Effect Size (Cohen’s \( d = .55 \)). Mean ratings for 3 of the 4 BPI Severity Score components decreased \( (P \leq .002) \). There was a statistically significant 35.4% decrease in the overall BPI Interference Score from 4.8 to 3.1 \( (P < .001) \) on the 10-point scale, with a medium to large Effect Size (Cohen’s \( d = .67 \)). Mean ratings for each of 7 BPI Interference Score components core decreased \( (P \leq .003) \). Fewer patients reported taking oral pain medications at Survey 3 as compared to Survey 1 for each of OTC \( (P < .001) \), prescription anti-inflammatory \( (P = .041) \), and opioid medications \( (P = .001) \). Reported use was reduced by about half for each: OTC \( (48.5\%) \); prescription anti-inflammatory \( (47.6\%) \); and opioid medications \( (56.1\%) \). Overall patient satisfaction with topical analgesics was high: 93% were either satisfied or very satisfied \( (61\% \) were very satisfied), and 95% found the topical analgesic use to be convenient. 89% preferred the topical analgesic to oral pain medications. 97.4% (75) of patients reported no side effects, 1 reported rash, and 1 reported an “other” side effect. Neither of the 2 side effects reported was a serious adverse event.

Conclusions

Results from this interim analysis suggest that the topical analgesics used in this study may reduce BPI Severity and Interference scores for adult patients with neuropathic and musculoskeletal pain, reduce the number of primary pain complaints for arthritis and neuropathy or radiculopathy, and reduce the use of oral OTC, anti-inflammatory and opioid analgesics. Patient satisfaction with topical analgesics was high. Topical analgesics were safe and well-tolerated. Results from the interim analysis justify continuation of the OPERA trial. Note: Results will be updated in the poster, incorporating data from a larger pool of patients completing Surveys 1 to 3.

Evaluating the impact of medication therapy management for chronic pain on depression and opioid aberrant behavior

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Purpose

Chronic pain affects more Americans than diabetes, heart disease, and cancer combined at 100 million according to the American Academy of Pain Medicine. Aberrant behaviors in patients using long-term opioids for the treatment of chronic pain are a concern to clinicians treating these patients. Guidelines developed by the American Pain Society and American College of Physicians recommend routine and frequent monitoring of pain and problematic medication behaviors. Prior studies suggest pharmacists are well poised to provide medication therapy management (MTM) services to patients with chronic pain on opioid therapy. The St. Louis University Family Medicine Residency (SLUFM) Pain Service is a pharmacist-led, multiprofessional team that provides MTM services to patients with chronic pain referred by their primary care provider. Primary service philosophy is functional improvement, reduction in confounding comorbidities, adjuvant analgesic maximization, multi-modal therapy inclusion, and reduction in opioid burden.

Method

This was a one-year retrospective longitudinal chart review. Inclusion criteria: adult patients with chronic pain referred to the SLUFM clinic, ambulatory, able to provide consent, and with at least two follow-up visits were included in evaluation. At each visit patients completed the Brief Pain Inventory (BPI), Patient Health Questionnaire (PHQ-9), and Current Opioid Misuse Measure (COMM) instruments. In this study we looked at changes in PHQ-9 and COMM scores from baseline to last visit within the defined study timeframe to evaluate the impact of a pharmacist-led, multiprofessional team providing MTM services to patients with chronic pain. Data was analyzed using IBM SPSS Statistics for Mac, Version 21.0. Armonk, NY: IBM Corp.

Results

A total of 163 unique patients were seen by the SLUFM pain service with 110 returning for 2 or more office visits during the study period. The mean age was 49.8 years and 54.8% of patients were female. Ethnicities of patients included in the study were: Caucasian (76.5%), African American (15.1%), Hispanic (3%), Asian (0.6%) and unknown (0.6%). Primary pain diagnosis included: chronic low back pain (44.6%), osteoarthritis (13.3%), cervicalgia (9.6%), fibromyalgia (7.8%), headache/migraine (4.8%), neuropathic pain – all etiologies (4.2%), rheumatoid arthritis (2.4%), and other (13.2%). Binominal analyses were conducted to evaluate the impact of the pharmacist-led clinic toward improving depression scores (PHQ-9) and opioid misuse measure calculated risk (COMM). Two-sided T-tests with a predetermined alpha of 0.05 were conducted. The PHQ-9 baseline scores range from 0 to 27. A decrease in total scores would indicate a reduction in depressive symptoms. In the sample, the baseline mean PHQ-9 score was 9.476 (SD 6.41). The endpoint mean PHQ-9 mean score at the completion of our 1-year study was 8.157 (SD 7.72). At the end of the study, the mean COMM score was 7.00 resulting in a mean reduction of -1.163 (\( p = .001 \)). The baseline mean COMM score was 8.18 (5.6) resulting in a mean decrease in PHQ-9 score of -1.38 (\( p = .029 \)). The baseline mean COMM score was 8.157 (SD 7.72). At the end of the study, the mean COMM score was 7.00 resulting in a mean reduction of -1.163 (\( p = .001 \)). A COMM score of 9 and above is positive for opioid abuse or misuse and is concerning when managing chronic pain.

Conclusions

Long-term opioid therapy is problematic because of its potential for abuse and/or misuse compounded by the fact that patients may experience depressive symptoms impacting their
quality of life. Pharmacists play a vital role in managing the medication regimens of their patients, which includes assessing aberrant behaviors and adjusting treatment with a goal of reducing opioid burden. Based upon the study results, the population at SLFUM lowered both their COMM and PHQ-9 scores over time. Clinicians working with chronic pain management may consider implementing pharmacist-led pain management clinics to potentially reduce opioid aberrant behaviors and depressive symptoms in their patient populations.

**Self-administered electrical stimulation of the knee for relief of osteoarthritis pain**

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**Purpose**

Demonstrate the objective efficacy of a proprietary, OTC electrotherapy device designed for relief of osteoarthritis of the knee. The Acuknee (FDA and Health Canada cleared) system delivers electrotherapy along known acupuncture points and meridians in a simple, easy to use, reproducible, thirty-minute daily treatment. The principle purpose of this investigation was to determine the durability and extent of treatment effects as shown by the highly validated KOOS score (knee osteoarthritis outcome score).

**Method**

Patients were recruited (n= 45) from Utah Orthopedics (Ogden, Utah) and the Acuknee.com website. Patient recruitment was limited to uncomplicated mild, moderate and severe osteoarthritis without coexisting morbidities. Patients with unrepaired meniscal tears, unrepaired torn ligaments, osteochondral defects, implanted cardiac pacemakers or narcotic usage were excluded. Patients were instructed with a standardized instruction sheet. KOOS data was obtained at time 0 and then at 2, 4 and 8 weeks of a daily, thirty minute, self-administered treatment. Data was tabulated and presented as individual plot lines for the three categories. Patients were not compensated for their participation.

**Results**

Results will be presented in graphic format for mild, moderate and severe osteoarthritis of the knee as defined by KOOS score at study entry. X-ray, MRI or physical findings were not used to classify extent of osteoarthritis. KOOS scores improved from 67 to 92, 48 to 88, and 31 to 67 for mild moderate and severe osteoarthritis, respectively. Improvement was further shown to be durable after 8 weeks with maintenance therapy. Long term durable pain relief is not generally obtainable with conventional TENS therapy which utilizes a Melzack and Wall Gate Theory mechanism. We believe our mechanism of action is by way of suppression of interleukin-1 as demonstrated by many lines of Chinese and other electrotherapy interventions. We further see dramatic enhancement of the effect of intraarticular platelet rich plasma when combined with Acuknee pretreatment, presumably by creating a more permissive biological environment by way of suppression of interleukin-1.

**Conclusions**

The Acuknee System provided dramatic and durable improvement in uncomplicated osteoarthritis at eight weeks following a single, thirty minute, daily self-administered treatment. Durable, long term relief of knee osteoarthritis symptoms with short duration electrotherapy has heretofore not been presented in the medical literature. The device was well accepted and found to be easy to use by study participants. The Acuknee System provides a viable, low-cost, side effect free treatment for uncomplicated osteoarthritis and may slow or stop the progression of OA. Preliminary follow-on data shows treatment with PRP combined with Acuknee provides further enhanced durable effects.

**The Impact of a standardized online chronic pain assessments on medical record documentation**

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**Purpose**

The study is an empirical demonstration of the impact on pain-related documentation of using the Pain Assessment Interview Network - Clinical Advisory System (PainCAS™), a systematic computer-administered assessment of pain patients intended to replace existing paper and pencil pain assessments at participating treatment facilities. The primary objective was to test pain-related documentation between a treatment-as-usual condition and a PainCAS condition during which patients and providers were exposed to the opportunity to use the PainCAS. It was expected that chart elements related to a comprehensive pain evaluation would be documented significantly more often in the PainCAS condition as compared with the treatment-as-usual condition.

**Method**

The primary study objective was an empirical demonstration of the impact of using the PainCAS to replace existing paper and pencil pain assessments at participating treatment facilities on documentation of pain-related elements in the medical chart. The study involved tracking documentation for 209 medical records at three pain treatment centers. Five clinicians were consented, and charts of patients managed by the consented clinicians were included in the chart reviews. Three pain clinic sites participated: (1) Newton-Wellesley...
Hospital Ambulatory Center’s Pain Service, (2) Brigham and Women’s Hospital Pain Management Center, and (3) the University of Mississippi Medical Center’s Family Medicine Department. Changes in documentation were determined by chart reviews in the treatment-as-usual and PainCAS conditions at three pain treatment facilities. Chart reviews of participating providers were carried out for visits that occurred prior to and following introduction of PainCAS at the participating clinics. Onsite Research Assistants (RAs) reviewed the charts (electronic medical records) for elements that should be documented in the chart of a patient with a chronic pain condition using a checklist of presence or absence of the chart element.

Results
Significant differences were found between conditions in the percent of charts containing elements reflecting opioid risk assessment documentation (i.e., presence of SOAPP or SOAPP-R, SOAP or SOAPP-R score, COMM, COMM score, formal risk assessment using any assessment method, documentation of opioid risk stratification, and documentation of a monitoring plan regarding opioid use). Greater levels of chart documentation were also observed for the PainCAS condition for a number of other individual chart elements (e.g., pain description, pain frequency and duration, pain severity, impact of pain, and current workers’ compensation and/or disability status), than in the pre-PainCAS chart condition. Charts in the PainCAS condition had also revealed a higher percentage of documentation of use of herbal supplements, non-pharmacological approaches, interventional treatments, complementary and alternative treatment, seeking other healthcare providers, self-treatment, history of adverse effects with pain medications, and having specific, desired treatment outcomes. Charts in the PainCAS group had a greater percentage than the pre-PainCAS condition of documentation relating to psychological symptoms such as depression, anxiety, irritability, concentration problems, social isolation, fatigue, and forgetfulness. Significant findings were also observed for documentation related to the presence/absence of formal mental health treatment/counseling, support system evaluation, and overall opinion of personal health. There were significantly more charts in the PainCAS condition that included reports on past or present history of alcohol abuse, smoking, prescription drug abuse, family past or present history of substance use, and aberrant medication related behaviors compared with the pre-PainCAS condition. Finally, charts in the PainCAS condition were also more likely to include substance use/abuse related litigation and pain related litigation than in the control condition.

Conclusions
Overall, significant differences in favor of the electronic pain assessment (PainCAS) condition were observed with increased presence of documented risk assessment and other pain-relevant documentation. While some variables encompassing medical and psychological history were present in the records of both groups, many more variables regarding opioid risk assessment were found among charts following introduction of the computerized PainCAS software when introduced into the clinical flow. These results supporting the impact of the PainCAS assessment, has implications for improving quality of care.

The Impact of a standardized online chronic pain assessment on patient-provider communication
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Purpose
The study is an empirical demonstration of the impact on the patient-provider encounter of using the Pain Assessment Interview Network - Clinical Advisory System (PainCAS™), a systematic computer-administered assessment of pain patients intended to replace existing paper and pencil pain assessments at participating treatment facilities. The PainCAS collects information from the patient prior to their initial or follow-up visit and summarizes that information for both patient and provider in a readily digestible output that highlights areas that should be explored further. While no individual visit requires complete coverage of all topics, we hypothesized that the patient having completed the PainCAS and the provider having access to PainCAS reports would tend to stimulate more clinically relevant topics covered during any given visit. This was measured by post-visit interviews with patients who were asked to endorse topics covered during the clinical encounter they had just experienced. Specifically, we expected patients in the PainCAS condition to report higher levels of communication with their healthcare providers relevant to topics including pain-related concerns, aberrant drug-related behaviors, and substance use than in the treatment-as-usual condition.

Method
An interview study was conducted at Newton-Wellesley Hospital Ambulatory Service’s Pain Center and the Brigham and Women’s Hospital Pain Management Center. Clinicians at both study sites were consented, as well as patients. Consented patients belong to either a treatment-as-usual condition or the PainCAS condition. Consented patients in the PainCAS condition received PainCAS assessments to complete prior to their clinic visit. After the clinic visit, patients completed a post-visit live interview with an onsite researcher. Control patient participants did not receive a PainCAS assessment prior to their clinic visit, but they did participate in the post-visit live interview with an onsite researcher. During the post-visit live interview patients were asked a variety of questions related to four topics that might be discussed in a pain-related medical visit: pain related, psychosocial, substance use history, and medication safety/treatment monitoring. If a particular topic was discussed, the
Results

An independent samples t-test was conducted to evaluate the impact of a PainCAS assessment on post-visit interviews of dialogue related to pain-related topics that might be considered important to cover in a chronic pain clinical encounter. Examination of the sum of relevant topics covered indicated that individuals in the PainCAS condition were significantly more likely to report having discussed their substance use history with their provider than patients in the control (no-PainCAS) condition (t=-2.26, p=0.0256). There were no statistically significant differences between control and PainCAS subjects for pain related, psychosocial, and medication safety/treatment monitoring for baseline post-visit interview pain indicators. Chi-Squares tests of independence on each item for all four topics were evaluated. Results indicated that individuals in the PainCAS condition were significantly more likely to report having discussed being on workers’ compensation and/or disability with their provider than patients in the control (no-PainCAS) condition ($\chi^2 = 5.148$, p=0.023). Individuals in the PainCAS condition were significantly more likely to report having discussed involvement with the legal system/law suits related to their pain with their provider than patients in the control (no-PainCAS) condition ($\chi^2 = 4.448$, p=0.035). Individuals in the PainCAS condition were significantly more likely to report having discussed any past or current substance abuse in their family with their provider than patients in the control (no-PainCAS) condition ($\chi^2 = 7.638$, p=0.006). Individuals in the PainCAS condition were significantly more likely to report having discussed taking pain medications differently from how they were prescribed with their provider than patients in the control (no-PainCAS) condition ($\chi^2 = 14.101$, p<0.001). Individuals in the PainCAS condition were significantly more likely to report having discussed talking about compensation and/or disability, involvement with the legal system/law suits related to their pain, drug/alcohol use history, family history of substance abuse, and taking pain medications differently from how they were prescribed. These results have implications for improving quality of care.

Conclusions

We examined the question of whether a well-designed, comprehensive electronic pain assessment (i.e., PainCAS) that collects clinically relevant information and delivers summary reports to patients and provider would impact patient-provider communication. Results suggest the PainCAS increases the likelihood that certain, possibly difficult-to-discuss, topics are discussed during the medical encounter. Specifically, greater dialogue/communication was observed with respect to being on workers’ compensation and/or disability, involvement with the legal system/law suits related to their pain, drug/alcohol use history, family history of substance abuse, and taking pain medications differently from how they were prescribed. These results have implications for improving quality of care.

An Empirical evaluation of the assumptions underlying the relationship between volume and abuse for select ER and IR prescription opioid medications using the NAVIPPRO® ASI-MV® System

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Purpose

To address the significant problem of prescription opioid abuse in the U.S., the FDA issued new post-marketing requirements (PMRs) to manufacturers of extended-release (ER) and long-acting (LA) prescription opioids. The PMR notification mandated a revised labeling requirement to indicate that immediate-release opioid options be demonstrated as adequate before prescribing ER/LA products. Results reported by the FDA and other entities suggest that prescription-adjusted prevalence of abuse is generally higher for ER products as compared to IR products. While prescription availability is a key factor to consider when evaluating prescription opioid abuse, also important is consideration of how prescription volume (a.k.a. exposure) has been accounted for in these studies, as it directly affects the estimated relative abuse prevalence of products (e.g., ER products are more highly abused than IR products). To date, the amount of prescription volume has been assumed to have a direct, proportional relationship with prescription opioid abuse. The purpose of this study was to (1) determine the observed (empirical) relationship between prescription volume and prescription opioid abuse and (2) estimate and contrast the levels of abuse across prescription opioid products after adjusting for the empirically-derived effect of prescription volume.

Method

This was a cross-sectional, observational surveillance study design which examined past 30-day abuse from approximately 3,460 adult prescription opioid abusers using data collected via the Addiction Severity Index-Multimedia Version (ASI-MV®), a data source of the NAVIPPRO® surveillance system, during the 4th Quarter of 2014. The ASI-MV® is a standard computerized clinical interview for evaluation and triage in substance abuse treatment settings which contains questions about past 30-day abuse of illegal substances and product-specific prescription medications. Prescription volume data were obtained from IMS Health, representing over 99% of retail stores in the United States. Using these data, a series of mixed effects logistic regression models were employed to determine the relationship between 3-digit ZIP code level prescription volume and self-report abuse of select IR and ER prescription opioid products. Prescription-adjusted probabilities of abuse for the opioid products were estimated from the final model. Issues pertaining to comparing IR and ER opioid products with varying amounts of prescription volume dispensed were also examined.
Results

Results revealed product-specific, curvilinear (quadratic) relationships between the amount of prescription volume and abuse, with a relatively strong and positive relationship at low levels of volume but weaker in areas with higher levels of volume. After accounting for the curvilinear relationship, the prescription-adjusted probabilities of abuse for the select IR and ER opioid products differed substantially from previously reported estimates which assumed a direct proportional relationship between prescription volume and abuse. Specifically, ER opioid products did not always have higher levels of abuse as compared to IR opioid products. With respect to the varying amounts of volume dispensed across ER and IR products, treating prescription volume as a product-specific covariate requires an actual value be set to an amount of volume. Setting the amount of volume to a value within the shared range of all products led to reasonably expected standard errors (relatively reliable estimates). However, setting volume to a value outside the observed range for a given product resulted in large standard errors (relatively unreliable estimates).

Conclusions

Current assumptions about the relationship between prescribed availability and abuse may present an incomplete picture of a complex, multilayered phenomenon. A statistical modeling approach in which the association between prescription volume and abuse is empirically derived as opposed to an assumed proportional relationship may have certain advantages when estimating and contrasting abuse across prescription opioids products. Prescription-adjusted relative prevalence of abuse for products which have little to no shared range of volume should be justified by the research question and interpreted with caution.

Do state characteristics predict a state passing and implementing medical marijuana or marijuana legalization policy?
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Purpose

Increasingly, marijuana has become a popular alternative to chronic pain medications, such as prescription opioids. As of July 2015, 23 states and DC have passed medical marijuana laws (MMLs) which allow for persons with approved medical conditions to receive set amounts of marijuana for medical treatment. Although states vary in their medical marijuana policies, across the board, chronic pain has been included as an approved condition. Of the 23 states with MMLs, five have passed marijuana legalization laws allowing for the possession and recreational use of marijuana among persons 21 or older. But passage of marijuana laws is only the first step; states must also implement the laws once they are passed. Implementation of recreational marijuana laws can legally offer access to marijuana-as-medication to people who do not have regular access to physicians who write medical marijuana prescriptions.

The majority of research on marijuana policy looks for a relationship where policy affects rates of use and perception of risk. Given that national opinion on marijuana policy has changed vastly in the past 40 years, we test the reverse of most marijuana policy hypotheses. We propose that past month marijuana use in the years before medical marijuana or marijuana legalization laws pass and/or perception of risk for using marijuana lend to state-wide cultural acceptance of MMLs and marijuana legalization laws, leading these laws to be implemented faster in certain states.

Method

Epidemiological data for this study come from the annual National Survey on Drug Use and Health (NSDUH), which conducts in-person surveys of the civilian, non-institutionalized population in the United States aged 12 years or older. The data used in the current analysis were collected during calendar years 2002 through 2012. When analyses include state-level data, NSDUH combines two-year annual averages to ensure confidentiality of participants. The two-year pairs included in this analysis span 2002-2003 through 2011-2012. Data for this study were taken from the NSDUH state area estimation tables. State estimates are based on a small area estimation methodology in which state-level NSDUH data are combined with county and census block group/tract-level data from the state. NSDUH measures for this study include past month marijuana use and perceived risk of smoking marijuana once per month.

Marijuana policy passage and implementation years by state were found on the state-level government websites, which linked to official government documents on each policy. In this study, we utilize by state: the year a MML passed vote and the year it was implemented, and the year a recreational marijuana law passed vote and the year it was implemented.

Graphical and multi-level random effects models were used to identify the trends of marijuana use over time.

Results

Our findings indicate the overall percentage of past month marijuana use increased between 2002-2003 to 2011-2012 from 6.5% to 7.3%. Interestingly, the overall perception of “great risk” with using marijuana once a month decreased starting around 2007-2008. Among states with no MMLs, past month use of marijuana was lower, ranging from 6.2% to 6%. However, in states with MMLs, use was consistently higher in each year compared to those states with no medical marijuana laws. The percentages increased from 7.9% in 2002-2003 to 9.6% in 2011-2012. In addition, states, with MMLs exhibited a greater decline in perceived risk of marijuana use over time compared with states that do not have MMLs. We found that states that passed, but did not implement MMLs exhibited about the same level of use compared to those states that had a MMLs and had implemented
the law. The effect began to diverge in 2010-2011, where states with implementation exhibited slightly lower rates of use compared to those without implementation. Further, in the year prior to legalization, states were approximately 0.5 of a percentage point higher on past month use compared to states that did not legalize in the next year.

Conclusions
The findings suggest that states with MMLs had higher marijuana use rates in the year prior to legalization compared to states that did not legalize. Further, we found that the perceived risk of marijuana in states with MMLs was lower than in states without. These findings together indicate that the culture in a state around marijuana permissiveness may in fact lead to faster implementation of marijuana policy. Clinicians should be aware of the status of medical medicalization in their state. Public use of and opinion toward marijuana may impact clinician’s ability to eventually prescribe marijuana as pain treatment.

Incidence of inappropriate urine drug analysis in patients receiving controlled substances in the urban primary care setting
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Purpose
Opioid therapy plays a substantial role in chronic pain management where non-opioid and other adjuvant therapy has failed. Physicians in the primary care setting must be cautious of diversion and aberrant behavior. Urine drug analysis has become a popular tool for screening patients to determine non-adherence, misuse, and/or abuse of prescribed controlled substances; the utility of performing these still remains controversial. The purpose of this study is to elucidate the rate of inappropriate urine drug screens in patients prescribed controlled substances in the urban primary care setting.

Method
The Institutional Review Board approved this study. The electronic medical record identified patients who received a drug of abuse screening (DOA). Patients included encompass the following: 18 years and older, diagnosis of chronic pain, at least one DOA, and current prescription(s) for controlled substances in an urban primary care setting. Patients were excluded if incarcerated, enrolled in another research protocol, or did not receive a controlled substance 6 months prior to the DOA. Data collected includes: age, gender, controlled substances prescribed, DOA results, number of patients discharged, and patients screened. The primary endpoint is to assess the rate of inappropriate DOAs. Secondary endpoints included: rate of patients discharged due to an inappropriate DOA or multiple providers, rate of controlled substances prescribed, and illicit substances or non-prescribed controlled substances in DOAs, correlation of inappropriate DOAs to controlled substances prescribed, correlation between strength of medication prescribed and total daily dose of short acting pain medication, and rates of inappropriate DOA. Data was analyzed using descriptive statistics.

Results
In the historical time period between April 1, 2014 to August 1, 2014, 4,078 patients were evaluated for controlled substance refills. Of the patients screened 1,165 patients had a DOA performed prior to receiving their prescription for a controlled substance. It was discovered the 61.3% of the DOAs obtained were deemed inappropriate. The reasons for inappropriate DOAs were; negative for prescribed substance (62%), positive for non-prescribed substance (19%), positive for THC (13%) and positive for cocaine (6%). During the controlled substance refill clinic review process via the Florida prescription drug monitoring program, 27 patients using multiple providers were identified.

Conclusions
The high incidence of negative DOA results reported in this study may be due to the following: timing of the patients last controlled substance dose, patient tampering with the urine sample, or limitations in the sensitivity and/or threshold of the immunoassay. Clinical decision making should not be based off DOA results alone but in the context of additional patient characteristics including: the frequency of missed appointments or follow-ups. past history of aberrant behavior (i.e., criminal history/substance abuse), and scoring on the opioid risk assessment tool

Abuse prevalence and patterns for immediate-release hydrocodone combination products
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Purpose
Prescription opioid abuse is a significant public health problem in the United States. While the problem is multi-faceted, one contributing aspect is overprescribing of these medications (CDC, 2012). In describing this epidemic, the Centers for Disease Control (CDC) estimated that current prescription volume for hydrocodone combination products is sufficient for approximately a one-month supply for everyone in the U.S. (CDC, 2012). Hydrocodone combination products are also one of the most common drugs involved in prescription overdose deaths (CDC, 2015). Yet there is a perception that the abuse risk is greater for extended-release/long-acting (ER/LA) opioids than for immediate-release (IR) opioid formulations with a number of national strategies intended to reduce opioid abuse specifically focused on ER/LA opioid formulations. In October 2014, the Drug Enforcement Administration
(DEA) decision to reschedule hydrocodone IR combination products from schedule III to schedule II was implemented resulting in certain restrictions in prescribing and dispensing of these opioid medications (DOJ, 2014). While rescheduling is expected to result in lower abuse and diversion of hydrocodone combination products, it is important to understand and characterize the pattern of abuse of these products to be able to examine the impact of this change. This analysis aimed to evaluate abuse of hydrocodone combination products including the overall prevalence of abuse using various denominators, abuse via different routes of administration, and abuser characteristics among a high-risk population of individuals assessed for substance abuse treatment problems relative to comparator opioid compounds (immediate-release and extended-release, ADF and Non-ADF) currently on the market.

Method

Data were examined during an approximate two-year period from January 1, 2012 through September 30, 2014 from a sample of 151,704 adults assessed for substance abuse problems and treatment planning at centers in the U. S. using the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO) surveillance system. Individuals were assessed using the Addiction Severity Index-Multimedia Version (ASI-MV), a standardized clinical interview that collects self-reported data on past 30-day use of illegal substances and prescription medications from adults during treatment admission and planning. Estimates of relative abuse prevalence for hydrocodone combination products and other opioid compounds were calculated as the proportion of abuse via any route of administration (ROA) reported within the past 30 days among the study sample, per prescriptions dispensed, as well as per morphine equivalent milligrams dispensed. Route of administration (ROA) patterns (i.e., proportion of abuse via oral route, snorting, injection) and characteristics (e.g., abuse severity, illicit drug use) of abusers of hydrocodone combination products were also examined.

Results

Within this adult treatment population, prevalence of past 30-day abuse of hydrocodone combination products per 100 assessments was greater than abuse for IR oxycodone products (combination and non-combination) and all ER/LA opioids. Per 100,000 prescriptions dispensed, abuse of hydrocodone combination products was lowest among the opioid compound categories reviewed. However, abuse estimates considering the total weight in milligrams dispensed and opioid compound strength (measured in morphine equivalents), indicate a level of hydrocodone combination product abuse similar to all ER/LA opioids and abuse deterrent formulations (ADF) of ER/LA opioids. ROA patterns for hydrocodone combination products indicate that 23.1% of those who abuse these products report snorting and 1.1% reported injection. While the percentage of alternate routes of administration (i.e., snorting, injection) among abusers of hydrocodone combination products was low compared to other prescription opioids, the total absolute number who report snorting hydrocodone combination products is comparable to that reported for other prescription opioids typically reported with high levels of snorting (all non-ADF ER/LA opioids and oxycodone IR single-entity products). Drug problem severity scores as well as the high percentage of reported use of illicit drugs (79.9%) among those who abuse only hydrocodone products including the use of heroin, suggest that individuals who abuse only hydrocodone IR combination products indicate a level of severity in their drug abuse behavior that can be classified as having “considerable” or “extreme” problems (49.1%).

Conclusions

Examination of the level of abuse of hydrocodone combination products within a high-risk population of adults within a substance abuse treatment context indicates abuse of hydrocodone combination products impacts a large number of prescription opioid abusers who demonstrate a level of severity in abuse behavior. In absolute numbers, oral abuse of hydrocodone combination products is higher while snorting is similar to other prescription opioids. Evaluating the abuse burden of hydrocodone should include not only adjustment for drug exposure (prescriptions dispensed), but also the amount of active pharmaceutical ingredient available to better inform strategies to reduce abuse risk of these products.

Patterns of abuse of hydrocodone combination products: results from an Internet survey of recreational drug users

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Purpose

To better understand the potential impact that a new hydrocodone combination product (HCP) may have on the overall landscape of prescription opioid abuse, the abuse patterns of hydrocodone combination products were examined and characterized among a sample of individuals on a drug related discussion forum using an Internet-based survey. Of particular interest was to examine the characteristics of abuse among individuals who report use of hydrocodone combination products to determine whether and if these opioid products may serve as a gateway drug for abuse of other prescription opioids known to be associated with increased addiction severity. Specifically, we sought to understand the progression of abuse, routes of administration, and reasons and motivation for abuse of hydrocodone combination products.

Method

A web-based survey on medical and non-medical use of hydrocodone combination products was administered to individuals ages 18 and older who visited drug related discussion
forums such as the harm reduction website Bluelight.org or individuals who were directed to the website by their peers for the purpose of taking the survey. This online community represents a sentinel population of individuals at high risk for abuse. Participants were recruited between December 2014 and March 2015 and the survey was administered and analyzed for U. S. participants. Factors related to abuse of hydrocodone combination products such as demographic characteristics, history of abuse, specific routes of administration and knowledge and opinions of hydrocodone combination products were examined. Non-medical use (abuse and misuse) was defined as using the product when it was not prescribed to the individual or used in a manner not prescribed. Knowledge and opinions of the recent rescheduling of hydrocodone combination products from schedule III to schedule II were also assessed.

Results

The survey sample included 304 adults. Approximately 94% (n=285) of respondents indicated either medical or non-medical use of a prescription opioid at one point in their lifetime, while nearly 6% (n=17) of respondents indicated use of only a prescription opioid for medical reasons and use as prescribed. More than 50% of first time opioid users reported non-medical use and first time users of hydrocodone combination products (HCP) were very young in age (17% were between 10 to 13 years). Nearly 60% of lifetime hydrocodone combination products users indicated their first lifetime HCP use was non-medical, and were primarily between 14 and 18 years old at first use. Most first time and lifetime HCP users swallowed the product whole and obtained it from a family member or friend. Among the lifetime HCP users (n=288), approximately 60% (n=175) were former HCP users who moved on to more potent prescription opioids to get a better quality high (n=28). Among lifetime HCP users, swallowed whole was selected as the preferred route of administration (58.6%), while 41.4% of individuals progressed to experiment with and prefer illicit routes such as chewing, drinking in solution and snorting. An equal number of first lifetime HCP users compared with first lifetime oxycodone combination product (OCP) users and other opioid users (other than HCP and OCPs) used 10 or more prescription opioids in their lifetime. Nearly the entire survey sample population (97.2%) was aware of the risks associated with the acetaminophen in hydrocodone combination products, and the majority attempted to avoid the risks by limiting the amount used orally. Similarly, the majority (73.0%) of respondents were aware of the rescheduling of hydrocodone combination products from schedule III to schedule II, and reported the rescheduling would not have an impact on their use of hydrocodone combination products or other opioid products.

Conclusions

An evaluation of the data from this Internet survey indicated that at current levels, abuse of hydrocodone combination products impacts a large number of prescription opioid abusers who demonstrate a level of progression and severity in their abuse behavior. This level of abuse and misuse of hydrocodone combination products may indicate these products serve as a gateway drug as individuals start to progress to greater levels of substance abuse behaviors especially given the reported ages at which these behaviors began among the current survey sample.

Comparison of systemic and cerebrospinal fluid disposition of nasally and sublingually delivered fentanyl

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Purpose

Breakthrough cancer pain (BTPc)-characterized by rapidity of onset, short duration, and high pain intensity-demands a fast-acting medication for effective pain relief. Fentanyl, a potent μ-opioid receptor agonist is approved, in various delivery and dosage forms, for the treatment of BTPc. However, no study has been conducted to understand the disposition of fentanyl at its putative site of action, the central nervous system (CNS). This study aims to do this by determining the concentrations of fentanyl in the cerebrospinal fluid (CSF)-the approximate surrogate of brain interstitial fluid concentrations-as it relates to the route of administration-intranasal (IN) vs. sublingual (SL). Furthermore, absolute systemic bioavailability of both IN and SL fentanyl is determined by the comparison of fentanyl area-under the plasma concentration curve (AUC) between IN or SL vs. that of intravenous dose.

Method

Thirteen healthy subjects were randomized to receive one of the two crossover dosing sequences on Day 1 and Day 3: IN and SL fentanyl (single 200-μg dose) or vice versa; all received a 2-minute IV infusion on Day 5 (100-μg fentanyl). Naltrexone was dosed orally to block the opioid effects of fentanyl during each administration. Blood samples were collected prior to and at 5, 10, 15, 20, 30, 45, 60 minutes and 1.5, 2, 3, 4, 6, 8, 12, 24 hours post IN and SL administration, and 2, 5, 10, 20, 30, 60 minutes and 2, 3, 4, 6, 8, 12, and 24 hours post IV administration. CSF samples were collected via a spinal catheter-implanted on Day 1 under lidocaine anesthesia at pre-dose and 5, 10, 20, 30, 45, 60 minutes and 2, 3, 4, and 6 hours post intranasal and sublingual administrations. This catheter was removed after the 6-hour CSF sample collection on Day 3. Vital signs and adverse events were monitored throughout the study.

Blood and CSF samples were analyzed to quantitate fentanyl concentrations. To derive area under the concentration-time curve (AUC), fentanyl concentration-time data were analyzed using a pharmacokinetic-model-independent method. Maximum plasma concentration (Cmax) values were directly obtained from the observed concentration data. Absolute systemic bioavailability was calculated based on the dose-normalized AUC from the non-IV route (IN or SL)
and 60% higher AUC 0-2h (mean±SD; 766±370 vs. 574±220 pg·h/mL; p=0.0386) compared with SL spray, IN fentanyl exhibited ~40% higher Cmax (mean±SD; 659±413 vs. 413±152 pg/mL; p=0.0386) and 60% higher AUC0-2h (mean±SD; 766±370 vs. 574±220 pg·h/mL; p=0.0430). The absolute systemic bioavailability (mean±SD) was 68%±22 (IN) and 54%±13 (SL). CSF pharmacokinetics: compared with SL delivery, IN fentanyl displayed 40-55% higher concentrations (mean±SD) at 0.75 hours post-dose (447±230 vs. 303±85 pg/mL; p=0.0255), 1.0 hour post-dose (429±213 vs. 327±159; p=0.0034), and 2.0 hours post-dose (368±153 vs. 294±148; p=0.0355). These resulted in ~50% higher CSF AUC0-2h (mean±SD; 118±63 vs. 80±26 pg·h/mL; p=0.0195). All treatments were well tolerated, with headache as the main adverse event arising from the lumbar catheterization.

Conclusions
Compared with SL fentanyl, IN fentanyl demonstrated a more rapid rate of entrance to the site of action for analgesia. Moreover, bioavailability in both the central and peripheral compartments assessed by the first 2-hour post dose concentrations was significantly superior for the nasal route of administration. These results suggest that the pharmacokinetic properties of IN fentanyl not only match the pattern of breakthrough pain but also may explain a lower median effective dose (400 μg for intranasal vs. 800 μg for sublingual) for the treatment of BTPc in phase 3 studies.

Trends in abuse, diversion, and fatalities in multiple surveillance systems four years after introduction of reformulated OxyContin
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Purpose
In August 2010, Purdue Pharma introduced reformulated OxyContin, which was intended to deter abuse through routes that require tampering, such as snorting or injecting. This study examines changes in abuse, diversion, and fatalities in multiple surveillance systems up to 4 years after reformulation. In addition to examining abuse via any route, changes in rates of abuse through oral and non-oral routes were estimated.

Method
Quarterly data from five on-going surveillance systems were examined: 1) Intentional abuse exposures in the RADARS® System Poison Center (PC) program and 2) National Poison Data System (NPDS); 3) assessment of individuals in substance abuse treatment through the NAVIPPRO ASI-MV system; 4) reports by law enforcement officials participating in the RADARS System Drug Diversion program; and 5) fatalities involving OxyContin reported to Purdue’s Pharmacovigilance Department. The rates of abuse, diversion, and death for OxyContin and comparator opioids in the 4 years after reformulation (January 2011 to December 2014) were compared to the average rate in the year prior to reformulation (July 2009 to June 2010). Rates were estimated adjusted by population and number of prescriptions.

Results
Population-adjusted rates of intentional abuse exposures for OxyContin reported in the RADARS PC program and NPDS declined steadily in the four-year post-reformulation period relative to the one-year period prior to reformulation. For each of these systems, rates declined approximately 20% in the first quarter in the post-reformulation period (1Q2011), to more than a 70% decline by the end of the 4-year follow-up (4Q2014). On average, intentional abuse exposures declined 54% in the NPDS in the four years after reformulation compared to the year prior to reformulation, with similar declines in the RADARS program. Among opioid abusers assessed in the NAVIPPRO system, rates of abuse of reformulated OxyContin were 39% lower by the end of the 4-year follow-up relative to average rate in the one-year pre-reformulation period. In each of these surveillance systems, reductions in rates of abuse were observed for both oral and non-oral routes of administration although the magnitude of decline was larger for abuse through non-oral routes. OxyContin drug diversion rates declined more than 80% in the fourth year after compared to the year before reformulation. Fatalities reported to Purdue’s Pharmacovigilance Department decreased after reformulation – in 2014, the numbers of fatal cases with date of death information declined by 79.5%, while fatalities indicating overdose declined by 81.8% compared to the year prior to reformulation. Prescription-adjusted rates of OxyContin in each of these surveillance systems also decreased through the post-reformation follow-up period relative to pre-reformation rates, although the magnitude of decreases were somewhat smaller in magnitude than population-adjusted estimates. In general, a decline in measures of abuse and diversion of OxyContin across multiple studies/populations was observed soon after reformulation and was larger for OxyContin than for comparator opioids.

Conclusions
These findings suggest that declines in abuse, diversion, and fatalities involving OxyContin have persisted up to four years post-reformulation and declines were larger for routes that required tampering, consistent with the design of the reformulation.
Extreme work requirement of EG-001, an abuse-deterrent extended-release morphine product, as demonstrated with the ALERRTSM visual analog scales
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Purpose
EG-001 (Egalet Corporation, Wayne, PA) is a new abuse-deterrent, extended-release (ER) morphine sulfate formulation designed to resist physical and chemical manipulations. It is manufactured using a proprietary technology (GuardianTM Technology, Egalet Corporation, Wayne, PA) that combines a polymer-based formulation with plastic injection molding, which results in an extreme hardness of the tablets that is expected to offer substantial resistance to physical and chemical manipulation. Recently, the US Food and Drug Administration finalized guidance on the evaluation and labeling of abuse-deterrent opioids, including a recommendation of performing laboratory-based manipulation studies designed to determine the relative difficulty of compromising potential abuse-deterrent properties of a formulation. The goal of this study was to measure the work (combination of time, individual effort, and resources) involved in the manipulation of EG-001 relative to marketed comparators using a newly developed instrument, “Assessing Labor, Effort and Resources Required for Tampering” (ALERRTSM), composed of a set of visual analog scales (VASs) intended to allow trained technicians to evaluate the labor needed to manipulate products using various pre-defined tools.

Method
The study was conducted at an independent laboratory (DrugScan, Horsham, PA) by 4 trained technicians with 2 EG-001 tablets (60 and 100 mg) and 2 comparator tablets: morphine ER 60 mg (MS Contin®, Purdue Pharma, LP, Stamford, CT) and morphine sulfate immediate release (IR) 30 mg under standardized conditions utilizing 10 household tools commonly used for manipulating opioid products. The tools and methods ranged from simple (crushing with spoons) to complex (electrical grinding with a coffee grinder). Work was measured using the ALERRTSM VASs, with scores ranging from 0 (very easy) to 100 (extremely difficult); the outcome of each manipulation was defined descriptively using terms including, but not limited to, “completely powdered” and “remains intact”.

Results
Results from the study clearly differentiated the work required in manipulating EG-001 tablets relative to morphine ER and IR tablets. Across all household tools, mean and median work ratings for EG-001 100 mg tablets were consistently high, with mean (SD) and median (range) values of 90.1 (11.4) and 96.5 (65-100), respectively; similar ratings were reported for EG-001 60 mg tablets, demonstrating that the product is “extremely difficult” to manipulate. In contrast, mean (SD) and median (range) ratings for morphine ER tablets were 10.1 (11.9) and 4 (0-51), respectively, and 5.3 (5.6) and 3 (0-23) for morphine IR tablets, respectively, denoting that these products are “very easy” to manipulate. In some cases, the work ratings for the EG-001 tablets were as much as 10-fold higher than the comparator tablets. The outcome of these manipulations was that EG-001 tablets generally remained intact while the comparators were defeated completely or substantially and were reduced to a powder.

Conclusions
The work required and the levels of effort needed to manipulate EG-001 tablets were significantly greater than that needed to manipulate morphine ER and IR tablets. In none of the cases were the manipulations of Egalet-001 tablets able to produce a pulverized material, whereas this could be achieved with many of the test tools with limited effort for both the IR and ER comparators. The relative hardness of EG-001 tablets, level of effort to manipulate, and limited reduction in particle size after extreme work are expected to offer substantial resistance to abuse.

EG-002, a novel proprietary abuse-deterrent, extended-release formulation of oxycodone, demonstrates strong abuse-deterrent potential based on the results from a category 1 in vitro physical manipulation study
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Purpose
Manipulation of extended-release (ER) opioid formulations by way of crushing, grinding, or chewing has the potential to reduce the particle size of the tablet and increase the speed of opioid release. Recently, the US Food and Drug Administration finalized guidance on the evaluation and labeling of abuse-deterrent opioid formulations that includes a recommendation for laboratory-based manipulation studies (Category 1) designed to determine the relative difficulty of compromising the potential abuse-deterrent properties of a formulation. EG-002 (Egalet Corporation, Wayne, PA) is a new ER formulation of oxycodone using novel proprietary technology (GuardianTM Technology, Egalet Corporation, Wayne, PA) that combines a polymer-based formulation and plastic injection molding to manufacture tablets designed to have robust abuse-deterrent properties. The formulation is designed with properties to resist physical manipulation through the extreme hardness of the outer shell component. This study evaluated the ability of EG-002 to withstand a
variety of methods of physical manipulation in comparison with controlled-release (CR) oxycodone (OxyContin®; Purdue Pharma LP, Stamford, CT), an approved abuse-deterrent formulation of oxycodone.

Method

A laboratory study conducted by DrugScan, Inc. (Horsham, PA), compared EG-002 and CR oxycodone for crushability using common household tools and the impact of heat or cold on ease of manipulation. The physical characteristics of the particles resulting from manipulation were determined using photographs taken with a high-resolution camera and by particle size distribution using sieves with different pore sizes. The 2 primary study endpoints were based on the crushability of EG-002 in comparison with an abuse-deterrent CR oxycodone product. The first endpoint used the same amount of time and/or effort needed to grind the comparator, and the second endpoint used up to 5 times the time and/or effort used on the comparator.

Results

EG-002 was not easily crushed to a powder, with many of the manipulations resulting in flaking or breakdown into large and small solid chunks. Manipulation with a food grater, foot file, spice grinder, and coffee grinder produced some powder and some chunks of EG-002 and CR oxycodone. The time and/or effort of manipulations needed to produce powder or chunks of EG-002 was up to 5 times greater than that needed to produce similar characteristics for CR oxycodone. When EG-002 was physically manipulated with extreme force, the formulation components cominged. The hardened nature of the core retarded grinding to a fine powder with mechanical tools or milling to a fine powder using electrical tools. In contrast, CR oxycodone tablets could be ground down to a fine powder using electrical tools. A mean of 12.6% (by weight) of the ground EG-002 core particles had diameters <500 microns (used as a cutoff for particle size that can be snorted). In contrast, a mean of 74.2% of the ground intact CR oxycodone tablet had diameters <500 microns. The percentage of the intact EG-002 tablet weight recovered after grinding (93.8%) was not enhanced by heat stressing (microwave and oven) the tablets before grinding, whereas freezing the tablets before grinding diminished recovery to approximately 72.6%.

Conclusions

Overall, EG-002 tablets, compared with CR oxycodone, required up to 5 times more physical manipulation in time/effort to defeat these products. When EG-002 tablets were subjected to equivalent effort, the particle size reduction outcome was far less successful than with CR oxycodone (ie, larger chunks and less powder). It seems likely that the difficulty and level of effort required to manipulate EG-002 will offer substantial deterrence to methods of abuse requiring small particles, such as nasal insufflation.

Randomized controlled trial of minimally invasive sacroiliac joint fusion using triangular titanium implants vs. non-surgical management for sacroiliac joint dysfunction: 12-month outcomes

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Purpose

Background - Sacroiliac (SI) joint dysfunction is a prevalent and underdiagnosed cause of chronic, unremitting lower back pain.

Objective - To concurrently compare outcomes after surgical and non-surgical treatment for chronic SI joint dysfunction.

Method

Design - Prospective, multicenter randomized clinical trial (INSITE, registered on ClinicalTrials.gov [NCT01681004]). Setting - outpatient clinics for patients with chronic spinal pain.

148 subjects (19 clinical sites) with SI joint dysfunction were randomly assigned to minimally invasive surgical (MIS) fusion of the sacroiliac (SI) joint with triangular titanium implants (iFuse Implant System, SI-BONE, Inc.) (N=102) or non-surgical management (pain medications, physical therapy, SI joint steroid injections and/or radiofrequency ablation of the SI joint) (NSM, n=46). Pain (VAS, 0-100), disability (Osweyry Disability Index, ODI, 0-100) and quality of life (SF-36 and EuroQol-5D) scores were collected at baseline and at 1, 3, 6 and 12 months. The primary endpoint (overall treatment success) was a composite of pain relief (≥20 point drop) and lack of severe adverse events related to surgery at 6 months. Success rates were compared using Bayesian methods. Crossover from non-surgical to surgical care was allowed after the 6-month study visit was complete.

Results

Subjects (mean age 51, 70% women) were highly debilitated at baseline (mean SI joint VAS pain score 82, mean ODI score 57). The duration of pain prior to enrollment averaged 6.4 years (range 0.5-40.7 years). By 6 months, success rates were higher in the surgical group (81.4% vs. 26.1%, posterior probability of superiority >0.9999). In the SI joint fusion group, mean SI joint pain improved from 82.3 at baseline to 30.4 at 6-month follow-up (52.0 point improvement, p<0.0001) and 28.3 at 12-month follow-up (54.2 point improvement, p<0.0001). In the NSM group, mean SI joint pain improved from 82.2 at baseline to 70.3 at 6 months (mean improvement of 12.2 points, p=.001). The improvement in SI joint pain after SI joint fusion exceeded that of NSM by a mean of 38.2 points (p<.0001, repeated measures analysis of variance). Clinically important (≥15 point) ODI improvement at 6-months occurred in 72.5% of the SI joint fusion group vs. 13% of the NSM group (p<0.0001). At 12 months, improvements in SI joint pain and ODI were sustained in the surgical group. As of
June 2015, 35 of 44 (79.5%) who were still participating crossed over to surgical treatment; all crossovers underwent SI joint fusion using the study device and all crossovers were after the 6-month visit. Subjects who crossed over had improvements in pain, disability and quality of life similar to those in the original surgical group. Adverse events were slightly more common in the surgical group at 6 months (1.3 vs. 1.1 events per subject, p=0.3063).

Conclusions
This level 1 study showed that MIS SI joint fusion using triangular titanium implants was more effective than non-surgical management at one-year in relieving pain, improving function and improving quality of life in patients with SI joint dysfunction due to degenerative sacroiliitis or SI joint disruptions. Pain, disability and quality of life also improved after crossover from non-surgical to surgical treatment.

Chronic pain and non-medical use of opioids, benzodiazepines, and pregabalin in the United Kingdom
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Purpose
To investigate the relationship between chronic pain and use of illicit drugs and non-medical use of prescription drugs in a web-based Survey of Non-Medical Use of Prescription Drugs (NMURx) in the UK. A secondary aim was to compare data on the prevalence of illicit drug use collected from the NMURx and the Crime Survey for England and Wales (CSEW).

Method
The NMURx deploys a web-based survey biannually via a survey administration company. Respondents age 16 years and older living in the UK are eligible. We analyzed the July 2014 dataset for whether the individual had experienced chronic pain (“pain lasting for at least 3 months that either occurs constantly or flares up frequently”); prevalence of illicit drug use; and prevalence of non-medical use of prescription drugs (“use without a doctor’s prescription or for any reason other than recommended by a doctor”). Data on lifetime non-medical use of prescription drugs was studied for opioids, benzodiazepines, and pregabalin/gabapentin. Fisher’s exact test was used to determine statistical significance with an alpha level of ≤0.05. For the secondary aim, respondents from the NMURx were restricted to those aged 16 to 59 years residing in England or Wales (n=1,594) to allow comparison with the CSEW. CSEW is an annual household survey in England and Wales used to monitor illicit drug use and is considered a representative population sample. The 2013/14 CSEW included 34,906 respondents aged 16 to 59 years. Lifetime and last year prevalence of illicit drug use was compared for the NMURx and the CSEW between the whole group (16-59 years) and in young adults (16-24 years).

Results
Of the 2,499 eligible respondents from the NMURx, the mean ± SD age was 48.0 ± 15.6 years and 49.9% were male. 693 (30.8%) respondents reported lifetime use of an illicit drug and 984 (39.4%) reported lifetime non-medical use of any prescription drug. Chronic pain was reported by 1132 (45.3%) respondents. Lifetime use of illicit drugs and non-medical use of any prescription drug were more common in those with chronic pain (illicit drugs: 31.5% and prescription drugs 45.1%) compared to those without chronic pain (illicit drugs 24.6% and prescription drugs 34.6%), and both were significant at p<0.0001. Reported non-medical use of opioids, benzodiazepines, and pregabalin/gabapentin were all more common in those with chronic pain (44.8% reporting opioids, 3% benzodiazepines, and 1.1% pregabalin/gabapentin) than those without chronic pain (33.7% reporting opioids, 1.7% benzodiazepines, and 0.1% pregabalin/gabapentin); all p-values <0.005.

Of the 1,594 respondents eligible from the NMURx for the secondary aim, the mean ± SD age was 40.9 ± 11.5 years, 47.2% were male. Prevalence of use of illicit drugs in the NMURx and CSEW were similar. Lifetime use of illicit drug: NMURx 32.6%, CSEW 35.6%. Use of illicit drug in the last year: NMURx 8.6%, CSEW 8.8%. For young adults, lifetime use of illicit drug: NMURx 31.4%, CSEW 36.3%. Use of illicit drug in the last year use: NMURx 15.0%, CSEW 18.9%. For lifetime use, cannabis was the most common in each data source (23.7% and 29.9%), amphetamine was the second (9.7% and 11.1%) and any cocaine was the third (8.2% and 9.5%).

Conclusions
This study suggests that use of illicit drugs and non-medical use of prescription drugs are more common in those with chronic pain. Further work is required to understand the reasons for this association, which is important given the high prevalence of chronic pain in Europe and North America. The prevalence of illicit drug use was similar in the NMURx and the CSEW. Comparability of these findings suggests that using a web-based survey to obtain UK data on drug use comparable to a well-established, representative household survey may be feasible.

Does the impact of OIC differ by type of chronic pain?
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Purpose

Opioid analgesics are commonly used to treat moderate-to-severe pain. Patients with chronic noncancer pain who are treated with opioids have a reported prevalence of opioid-induced constipation (OIC) ranging from 40%–80%. Although OIC has been shown to be highly burdensome and to cause considerable symptoms, as well as to interfere with pain management, the impact of OIC on different types of chronic pain is not known. There is an interdependent relationship between back pain and constipation in which constipation and trying to have a bowel movement (BM) can intensify back pain symptoms, while back injuries causing back pain can interfere with the autonomic nerves responsible for intestinal action. To compound this interdependence, the addition of opioids can intensify constipation. The purpose of this analysis was to examine the impact of OIC on patients with different types of chronic pain with a focus on patients with chronic back pain to better understand the patient experience when chronic low back pain and OIC co-occur.

Method

Patients aged 18–85 years receiving daily opioids for ≥4 weeks for chronic noncancer pain who reported OIC were recruited into a 24-week prospective longitudinal study of OIC burden. Patients were recruited from a variety of healthcare settings in the United States, Canada, the United Kingdom, and Germany. Patients completed web-based surveys at Baseline and Weeks 2, 4, 6, 8, 12, 16 and 24 to assess OIC symptoms (Patient Assessment of Constipation-Symptom [PAC-SYM]), laxative use, level of pain, health-related quality of life (HRQL) (Patient Assessment of Constipation-Quality of Life [PAC-QOL]), productivity (Work Productivity and Activity Index-Specific Health Problem [WPAI-SHP]), and perceived satisfaction with laxative treatments (Benefit, Satisfaction, and Willingness to Continue questionnaire [BSW]). Patients were further asked about the frequency of their constipation symptoms and the amount of bother of each reported symptom. Patients were divided into three groups based on their self-reported chronic pain condition: back pain only (BP), back pain + other pain (BPOP), and other pain only (OP). Comparisons of OIC symptoms, HRQL, productivity, laxative use, and benefit, satisfaction, and willingness to continue with laxatives were made among these three groups. Descriptive statistics were used to describe the cohorts and impact. Chi-square tests with Bonferroni and ANOVA with Scheffé s post-hoc adjustment for pairwise comparisons were used to compare the chronic pain groups. Statistical significance represents adjusted p values < 0.01.

Results

Of 489 eligible OIC patients, 89 (18.2%) had BP, 286 (58.5%) BPOP and 114 (23.3%) OP. There were no differences in gender or age among the chronic pain groups (gender: 45%, 38%, 33% male; mean age: 51.8, 52.9, 52.3 years respectively). BP patients were significantly less likely to be white (68.5% vs 87.1% and 92.1%) and had the shortest duration of chronic pain and opioid use (6.2 and 4.1 years vs 11.5 and 7.3 and 8.3 and 6.1 years respectively). BP patients were significantly more likely to be employed full-time (33.7% vs 15.7% and 15.8%) and less likely to be on work disability (21.3% vs 38.1% and 34.2%). Of BP patients, 53% reported that constipation moderately (or greater) interfered with their pain management (vs 52.4% and 29.2%). Several OIC symptoms were reported to occur with > 25% of BMs more frequently among BP than OP patients: abdominal discomfort, 95.5% vs 80.7%; abdominal pain, 87.6% vs 71.9%; rectal burning 66.3% vs 48.2%; and BMs too hard, 92.1% vs 78.9%. BP patients reported significantly greater bother with their OIC symptoms of abdominal pain, bloating, stomach cramps and painful BMs than OP patients. PAC QOL scores on the psychological discomfort (PD) and worries and concerns (WC) domains indicated statistically significantly greater HRQL impact among BP vs OP (PD: 1.5 vs 1.2; WC: 1.9 vs 1.5, respectively). Activity impairment due to constipation was significantly higher among BP than OP patients (43.6% vs 30.4%). BP patients reported significantly higher rates of no-laxative use than either group (39.3% vs 25.5% and 21.1%, respectively) while OP patients reported the highest rates of sufficient laxative use (52.6% vs 49.7% BPOP vs 36% BP). BP patients were more likely to report little benefit from laxatives (71%) than other groups (56.8% and 43.8%, respectively).

Conclusions

BP patients reported significantly greater OIC symptom frequency, bother and HRQL impact than their OP counterparts. Surprisingly, BP patients have the highest rates of no-laxative use which likely contributes to their notably higher OIC symptom burden. Further exploration is needed on whether better information on effective OIC therapies for patients will provide relief from OIC burden or whether currently available therapies are not acceptable to patients due to tolerability issues or lack of efficacy. Clinician-patient conversation is clearly warranted to better understand what next steps are needed and additional attention given for patients with BP and OIC.

Does the timing of ingestion of NSAID prevent muscle pain and damage following unaccustomed upper limb eccentric exercise?

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Purpose

Athletes often ingest non-steroidal anti-inflammatory drugs (NSAID) prior to, or after unaccustomed exercise to treat or prevent delayed onset muscle soreness (DOMS).
The purpose of this study was to determine the effects of the NSAID meloxicam (M), on symptoms of muscle damage and plasma creatine kinase concentrations [CK] following unaccustomed eccentric exercise.

Method

Forty-five healthy male volunteers consented to participate in a double-blind placebo controlled, parallel group, laboratory based study. The biceps muscles of the subjects’ non-dominant arms were damaged using an eccentric exercise protocol. Subjects were randomly assigned to treatment with either M 15mg immediately before (ME) or 48 hrs after induced injury (ML) or a placebo (P) and monitored for a total of 168 hrs. Main outcome measures included subjective pain rating, arm carrying angle & [CK].

Results

Subjects in all three groups experienced severe pain (2.5 ± 2.2 units; 2.3 ± 2.1 units; 2.4 ± 2.5 units vs. control P<0.001) following the eccentric exercise bout. After 24 hours the difference in elbow joint angle of all three groups had increased significantly from the control arm (7.0 ± 6.5°; 4.3 ± 3.4°; 2.7 ± 2.7°; ME, ML, P vs. control; P < 0.05), possibly as a consequence of elbow flexor muscles shortening. [CK] at 72 hr was higher in ME (2540 ± 4230 U. L-1) compared to ML (671 ± 953 U. L-1) and P (675 ± 1002 U. L-1; P< 0.05 vs. pre exercise control).

Conclusions

The results of this study suggest that i) induced pain following the eccentric protocol was not influenced by either early or late ingestion of M; and ii) skeletal muscle damage was not positively positively affected by ingestion of M. Indeed, it appears that ingestion of M immediately preceding injury may affect muscle cell membrane permeability leading to higher peak [CK]. These findings are likely to have important implications for athletes who ingest NSAIDs before exercising in an attempt to decrease muscle injury and pain.

Classifications of controlled substances: Insights from 23 countries

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Purpose

Every country in the world has established a classification system for controlled substances. Controlled substances are among the most highly abused and therefore highly regulated medications. The types of prescription drugs most commonly abused are opioid pain relievers like Vicodin or OxyContin, stimulants for treating Attention Deficit Hyperactivity Disorder (ADHD) like Adderall, Concerta, or Ritalin, and central nervous system (CNS) depressants for relieving anxiety like Valium or Xanax. The purpose of this study was to describe and compare the classification systems that different countries use for controlled substances. This study examines how drugs are regulated in different countries around the world compared to the United States.

Method

The World Health Organization (WHO) website was used to identify controlled substance regulations and the regulatory authorities responsible for medicines in each country. In addition, worldwide leaders in the pharmaceutical industry were contacted by email and postal mail in order to identify additional information. Information was gathered, sorted, translated into English when necessary, and analyzed. Information from 23 countries were obtained. These countries were grouped into regions based on roughly similar socioeconomic characteristics: North America, Western Europe, the Middle East, and Asia.

Results

Across the 23 countries, the number of schedules within controlled substance guidelines/legislation ranged between 2 and 15. The Netherlands and Belgium had 2 classification systems, while Japan had 15. European classification of controlled substances ranged from 2 schedules (Belgium and the Netherlands) to 10 schedules (Norway). Of the 17 countries, 10 countries had subgroups for the different classifications and 7 countries had no subgroups. The wide range is notable for a classification system attempting to address the same universal problem. In Asia, 3 countries were studied. Australia had 9 different schedules, New Zealand had 3 schedules, and Japan had 15 schedules.

The European Country with the most liberal drug laws is Portugal; in 2001 it was the first European country to officially abolish all criminal penalties for personal possession of drugs. It has 6 classification levels for controlled substances. Interestingly, just after 5 years of decriminalization, illegal drug use among teens in Portugal declined, rates of new HIV infections caused by sharing contaminated needles dropped, while the number of people seeking treatment for drug addiction more than doubled. Following decriminalization, Portugal had the lowest rate of lifetime marijuana use in people over 15 in the E. U. – 10%. The most comparable figure in the United States is in people over 12 with lifetime marijuana use at 39.8%. Proportionally more Americans have used cocaine than Portuguese people have used marijuana.

The U. S. has long championed a hardline drug policy, supporting only international agreements that enforce drug prohibition and imposing on its citizens some of the world’s harshest penalties for drug possession and sales. The U. S. has the highest rates of cocaine and marijuana use in the world. Most of the E. U., including Holland, has less drug use than the U. S. does, despite more liberal drug laws.

Conclusions

The solution of this problem is the creation of a system that provides hurdles to abusers, but does not add additional
barriers for legitimate users. It was found that there are numerous ways to control abusable substances but it is not clear what the best system is. In just this past year, Tramadol has been classified as a controlled substance and all hydrocodone done products are now class 2 narcotic substances. Are tighter regulations to the classification system working? The problem may not be the system but instead the prescribing and dispensing of these medications.

Multi-channel LC-MS/MS forensic methods for high-throughput screening to detect ethanol use
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Purpose
Ethyl glucuronide (EtG) and ethyl sulfate (EtS) are long-term biomarkers for ethanol consumption. Although they are minor metabolites of ethanol, their longer half-lives make them useful for detection of past alcohol use in forensic settings. The assay presents two major challenges to analytical laboratories using liquid chromatography coupled to mass spectrometry (LC-MS). The first is the high polarity of the compounds. This makes them retain poorly on most reversed-phase chromatography columns and elute on or near the chromatographic solvent front. This results in poor peak shape and large matrix effects. Here an ion-pairing reagent was used to retain these compounds on an HPLC column long enough to move them off the solvent front. This enabled better peak shape and less matrix interference.

The second challenge is throughput. Due to the prevalence of alcohol consumption, forensic laboratories need high-throughput LC-MS solutions to keep up with demand and lower per sample analysis cost. Multi-channel LC systems improve system throughput by efficient utilization of the mass spectrometer’s time, making the analytical workflow more cost-efficient. We evaluated performance of a 4-channel LC system. The system was coupled to a Thermo Scientific™ TSQ Endura™ triple quadrupole mass spectrometer.

Method
Equal volumes (25 μL) of urine and internal standard (5,000 and 500 ng/mL of EtG-d5 and EtS-d5, respectively) were mixed and then diluted with 450 μL of water. For analysis, 30 μL were injected into the LC-MS/MS.

Chromatographic separation was performed under gradient conditions. The analytical column was maintained at room temperature. The injection volume was 30 μL. Mobile phases A and B consisted of 5 mM dihexylammoniumacetate (TCI America™) ion-pairing reagent in water and acetonitrile, respectively. The flow rate was 1 mL/minute, and the total run time was four minutes with a data window of one minute. The 4-channel system stagger the injections across the channels and diverts only the one-minute data window during which EtG and EtS are eluting to the mass spectrometer. This increases the utilization time of the mass spectrometer. Two selected-reaction monitoring (SRM) transitions were monitored for EtG, EtS and their deuterated internal standards to provide ion ratio confirmations (IRC). Data were acquired and processed with Thermo Scientific™ TraceFinder™ software.

Intra-assay precision and accuracy were determined by analyzing a calibration curve along with six replicates of quality control (QC) samples. Inter-assay precision and accuracy were determined by analyzing a calibration curve along with six replicates of QC samples on three different days. Matrix effects were evaluated by observing the internal standard signals in 23 different lots of human urine.

Results
A maximum throughput of 50 urine samples per hour was achieved when batches were multiplexed across four channels. Since the data window of the method was one quarter of the total run time, throughput was approximately quadrupled when compared to a conventional single-channel LC-MS system.

Both compounds were linear over a wide dynamic range. EtG was linear from 50 to 50,000 ng/mL, while EtS had a range of 25 to 50,000 ng/mL. This method gave limits of detection in urine of 50 ng/mL for EtG and 25 ng/mL for EtS. Accuracy of the QC samples was within 4% for both compounds. Precision was within 13% for both compounds across all QC samples. The calibration curves collected for EtG and EtS were consistently linear (r² > 0.990, 1/X weighting) whether calibrators were injected into one channel or across all channels.

Conclusions

- The 4-channel LC system produced results for EtG/EtS methods that were consistent with those produced by the conventional single-channel LC system.
- An ion-pairing reagent helps chromatographically separate the compounds from interferences on the solvent front, thereby improving limits of detection.
- The TSQ Endura MS is a robust system that provides accurate results within 5% and good precision all the way down to the LOQ.

Patient knowledge of safe use of ER/LA opioid analgesics following implementation of the class-wide REMS
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Purpose

Extended release (ER) and long-acting (LA) opioid analgesics are approved by the United States (US) Food and Drug Administration (FDA) for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for ER/LA opioid medications on July 09, 2012 with the goal of reducing serious adverse outcomes from the inappropriate prescription, misuse, and abuse of ER/LA opioids. The REMS program consists of educational efforts, including both patient and prescriber education. Patient communication tools created as part of the REMS are a one-page Medication Guide that is provided at the pharmacy each time the drug is dispensed and a one-page Patient Counselling Document (PCD) for use by prescribers when counselling their patients. Other efforts include class-wide safety labeling changes, use of prescription drug monitoring programs, and initiatives by health plans, provider groups, and state/local government.

The purpose of this study was to assess patient knowledge of the safe use of these products following implementation of the REMS and evaluate possible unintended consequences of the REMS on patient satisfaction with their access to pain medicine.

Method

Consenting commercially-insured survey-eligible adults identified from administrative claims in the HealthCore Integrated Research DatabaseSM (HIRD) who filled at least one prescription for an ER/LA opioid analgesic between September 1, 2013 and August 31, 2014 were asked about knowledge concerning the safe use of ER/LA opioid analgesics, receipt and comprehension of the Medication Guide and PCD, perceived access and satisfaction of access to pain medication and patient-reported prescriber behaviors, including appropriate screening and counseling. A Knowledge Assessment Score (KAS), defined as the proportion of questions about key elements of safe use that respondents answered correctly, was developed to assess factors associated with knowledge of safe ER/LA opioid analgesic use.

Results

We surveyed 423 patients who received at least one dispensing of an ER/LA opioid analgesic in the past year. A large majority of respondents reported that they received (99%), read (97%), and understood (98%) the Medication Guide. A smaller proportion of respondents reported that they received (46%), had a healthcare provider who referenced (26%), and understood the PCD (57%). Knowledge of safe use measured through the KAS was high; 74% of respondents had a KAS ≥80%. In multivariable analyses, having read the Medication Guide was the strongest predictor of a KAS ≥80% (OR 7.77, 95% CI 1.41 - 42.68). Other factors predicting high knowledge scores included diagnosis of unspecified abdominal pain (OR 3.24, 95% CI 1.45 - 7.21), self-reported understanding of the PCD (2.48, 95% CI 1.08 - 5.71), having a pain specialist prescribe the ER/LA opioid (3.36, 95% CI 1.29 - 4.31), female gender (2.33, 95% CI 1.32 - 4.12), and having completed a college degree (1.87, 95% CI 1.02 - 3.44). The only general knowledge questions that fewer than 80% of respondents answered correctly concerned storing ER/LA opioid analgesics away from other household medications, the need to read the Medication Guide with each pharmacy dispensing, never splitting or crushing tablets (question asked to oral product users only), and the need to inform a healthcare provider of fever (question asked to patch product users only). In terms of access to pain medicine, 71% of respondents were satisfied with their access to ER/LA opioid analgesics.

Conclusions

Nearly all respondents received, read, and understood the Medication Guide, and key safety messages were well recognized. We saw more moderate use of the PCD. Among important risk messages central to the REMS, safe discontinuation and disposal especially need to be emphasized. Overall, the REMS patient communication tools appear to be effective in conveying key safety messages. The impact of the REMS on the incidence of serious adverse events is currently being evaluated.

Incidence of opioid and heroin overdose among patients using ER/LA opioid analgesics before and after implementation of the class-wide REMS

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Purpose

Extended release (ER) and long-acting (LA) opioid analgesics are approved by the United States (US) Food and Drug Administration (FDA) for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Although these medications are an important therapeutic option for many patients, concerns have arisen in recent years. The National Center for Health Statistics reports that natural and semisynthetic opioid analgesics were involved in about 11,700 drug-poisoning deaths in 2011, up from about 2,700 deaths in 1999. The public health response to this alarming trend has taken a multifaceted approach. The FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for ER/LA opioid medications on July 09, 2012 with the goal of reducing serious adverse outcomes from the inappropriate prescription, misuse, and abuse of ER/LA opioids. The REMS program includes educational efforts, including both patients and prescriber education. Other efforts include class-wide safety labeling changes, use of
prescription drug monitoring programs, and initiatives by health plans, provider groups, and state/local government.

The purpose of this study was to assess the incidence of opioid and heroin overdose among patients prescribed an ER/LA opioid analgesic and to compare the incidence of emergency department (ED) visits and hospitalizations for opioid overdose/poisoning across the REMS pre-implementation period (July 2010 through June 2012), REMS implementation period (July 2012 through June 2013) and REMS active period (July 2013 through August 2014).

**Method**

We conducted a retrospective cohort study using the HealthCore Integrated Research DatabaseSM (HIRD) as well as available deidentified data from US Medicaid. In the main analysis, we included patients who received at least one dispensing of an ER/LA opioid during at least one REMS study period (i.e., pre-implementation period, implementation period, or active period) with at least six months of prior continuous health plan eligibility. Patients were followed from the time of the first ER/LA opioid analgesic dispensing in a REMS period until the end of the REMS period, the end of health plan eligibility or the first instance of a study outcome, with primary analyses limited to opioid-exposed person-time.

The number of opioid and heroin overdose events observed during each REMS period was divided by the total person-time at risk within that REMS period to compute an incidence rate and its associated 95% confidence interval (CI). Unadjusted and adjusted incidence rate ratios (IRR) were then calculated comparing the pre-implementation period to the active period. Analyses were performed separately for Medicaid and commercially-insured patients.

**Results**

Among commercially-insured patients, we identified 80,209 ER/LA opioid analgesic users in the pre-implementation period, 48,654 users in the implementation period and 43,730 users in the active period. The IRR for opioid overdose for the active period versus the pre-implementation period among all users with current exposure was 0.83 (95% CI 0.70 - 0.99) after adjustment for region, Deyo-Charlson comorbidity index, use of benzodiazepines, use of sleep medications, chronic pain, alcohol abuse, anxiety disorder, depressive disorder, bipolar disorder, history of overdose, drug abuse and time since most recent ER/LA opioid exposure. The IRR for heroin overdose during periods of current opioid exposure was 3.70 (95% CI 0.92 - 14.86) after adjustment for history of opioid or other drug addiction. In analysis of new ER/LA opioid users, we did not see the same decrease in the IRR of opioid overdose (adjusted 1.06, 95% CI 0.78 - 1.45).

In the Medicaid population, we identified 3,488 ER/LA opioid analgesic users in the pre-implementation period, 3,746 users in the implementation period and 3,625 users in the active period. The IRR for opioid overdose for the active period versus the pre-implementation period among all users was 0.85 (95% CI 0.59 - 1.20) after adjustment for use of sleep medications, alcohol abuse, bipolar disorder, depressive disorder and history of overdose. Adjustment for age and history of opioid or other drug addiction yielded an IRR of 2.22 (95% CI 0.77 - 6.39) for heroin overdose.

**Conclusions**

The rate of opioid overdose during periods of ER/LA opioid exposure decreased after the REMS became active but not in new users of ER/LA opioid analgesics. There was also a numerical increase in the rate of heroin overdose during ER/LA opioid exposure. Amidst an increasing rate of opioid overdose events in the years prior to REMS implementation, the relatively stable rate of opioid overdose is consistent with a positive impact of the REMS.

**FDA 2015 guidance on abuse-deterrent opioids: Implications for new product development and clinical practice**

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**Purpose**

In April 2015, FDA issued its Guidance for Industry entitled “Abuse-Deterrent Opioids-Evaluation and Labeling”. The Guidance discusses potential test methods and labeling implications for new opioid formulations. Laboratory manipulation and extraction studies (i.e., Category 1) are designed to evaluate the ease with which the potentially abuse-deterrent (AD) properties of a formulation can be defeated or compromised. Pharmacokinetic studies (i.e., Category 2) are proposed to be conducted to understand the in vivo properties of the formulation by comparing the pharmacokinetic profiles of the manipulated formulation with the intact formulation and with manipulated and intact formulations of the comparator drugs through one or more routes of administration. Clinical abuse potential studies (i.e., Category 3) are proposed to provide comparative data on putative AD formulations and standard products in a randomized, double-blind, placebo- and positive-controlled-crossover study conducted in a drug-experienced, recreational user population, and can be used to compare the abuse potential of intact and manipulated test and control products. Finally, postmarket studies (i.e., Category 4) are proposed to determine whether the marketing of a product with AD properties will result in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death in the post-approval setting. The current poster will discuss the design and interpretation of these studies, as well as potential issues and limitations from both a drug development perspective, as well as a clinical perspective.

**Method**

This poster will discuss the methods for assessing the AD properties of new formulations and the implications for
labeling, as well as the impact on public health and patient care. These methods are based on FDA guidance documents as well as our experience using these methods.

Results
Methods for testing the AD properties of new opioid formulations (including in vitro and in vivo methods) have been steadily evolving over the past decade. However, whereas the base of knowledge about testing has increased as more new formulations become available, new questions have also arisen as the number of products has increased. For example, when an AD formulation (ADF) is already on the market, is the correct comparator the original formulation (which may or may not still be on the market) or the marketed ADF? How can one properly conduct hypothesis-driven postmarketing surveillance with a new formulation that may have a very low market share compared to the original formulation that is being marketed as a generic product? 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.

Conclusions
The implications for drug development and regulation are profound and include “abuseterrent” labeling, the potential for differential scheduling of the same drug with differing formulations, and the nature of the risk mitigation strategies required for drug approval. Clearly, no currently available opioid is devoid of abuse potential, but new formulations of these opioids may make the drugs less attractive to at least some abusers. It will be important to clinicians to understand the potential benefits and limitations of new formulations to be able to make informed decisions about their prescribing practices.

Assess genetic variants in mesolimbic dopaminergic pathways using AutoGenomics INFINITI system
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Purpose
More than 116 million people worldwide are struggling with chronic pain and prescription drug dependence. Almost three-fifths of adults 65 and older with pain, as well as fifty percent of cancer patients in the United States said it had lasted for one year or more. Genetic factors play a key role in addiction and pain, but are generally not evaluated in clinical practice. Some people who experience chronic pain are genetically predisposed to certain specific neurochemical deficiencies. Physicians are failing to control pain in roughly 60% of patients taking narcotic pain medication, even as they increase the dosage and potency. In response, there has been an increase in testing genes responsible for pharmacokinetics, such as cytochrome p450 genes to improve patient care. The objective of this study is to evaluate the prevalence of mesolimbic genotypes linked to neurochemical deficiency among patients diagnosed with drug/alcohol addiction, mental depression, and chronic pain patients taking narcotic pain medications.

Method
138 subjects diagnosed with drug/alcohol addiction, mental depression, and chronic pain patients taking narcotic pain medications were genotyped with AutoGenomics Neurological Response panel using multiplexed film-based microarray technology. INFINITI Neurological Response panel targets the following 15 genes/16 mutations or SNPs: 5-HT2A (rs7997012), 5-HTTTLPR (rs25531), COMT (rs4680), DRD2 (rs1800497), DRD1 (rs4532), DRD4 (rs3758653), DAT1 (rs6347), DBH (rs1611115), MTHFR (rs1801133), OPRK1 (rs1051660), GABA (rs211014), OPRM1 (rs1799971, rs9479757), GAL (rs948854), DOR (rs2236861) and ABCB1 (rs1045642). One multiplex PCR yielded 16 target amplicons and followed by one multiplex analyte specific primer extension (ASPE) for signal amplification of 16 W- and/or M-analyte. Resulting ASPE primers were hybridized (via tags of primers) to specific capturing probes addressed on the BioFilmChip to be scanned in the fully automated platform.

Results
Statistical significance was found in the prevalence of 5HT2A (38% vs 27%, p<0.003), COMT (50% vs 37%, p<0.001), OPRM1 (12% vs 22%, p<0.004), DOR (27% vs 14%, p<0.000002), and ABCB1 (54% vs 40%, p<0.0002). No statistically significant genetic variants were found for subjects with no history of illegal/prescription drug addiction, alcoholism, and serious mental disorders.

Conclusions
The study indicates higher prevalence of genetic predisposition in the mesolimbic dopamine pathways among patients with drug/alcohol addiction, mental depression, and chronic pain patients taking narcotic pain medications. By assessing these high prevalent genetic variants along with mutations status of cytochrome p450 genes involved in therapeutics, it may provide information to physicians to improve therapeutic efficacy and reduce adverse events for patients.

Relative bioavailability of axelopran and oxycodone when administered as a fixed-dose combination or as the individual components to healthy subjects
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Purpose
Axelopran is a peripherally-restricted μ-opioid receptor antagonist in development for alleviating gastrointestinal side effects of opioid therapy without impairing analgesia. Fixed-dose combinations of axelopran and opioids may provide analgesia without gastrointestinal side effects while reducing pill burden and enhancing compliance. The objective of this study was to evaluate the relative bioavailability of axelopran and oxycodone administered either as a fixed-dose combination tablet (FDC) or individual tablets administered together and individually.

Method
This was an open-label, randomized, four-period crossover study in 28 healthy subjects. Treatments were 10 mg axelopran and 20 mg oxycodone CR FDC, 10 mg axelopran and 20 mg oxycodone CR as separate tablets (A+O), 10 mg axelopran tablet (A) and 20 mg oxycodone CR (O) tablet. Subjects received 50 mg of oral naltrexone 15 and 3 hours before and 9 and 21 hours after administration of axelopran and/or oxycodone to block the effects of the opiate. Pharmacokinetic samples were collected for 72 hours post dose with a 7-day washout between periods. Relative bioavailability was assessed using the ratio of the least squares geometric mean and 90% confidence intervals (CIs) for $C_{\text{max}}$, $AUC_{0-T}$ and $AUC_{0-\infty}$. Bioequivalence was established if the 90% CI of the ratio of $C_{\text{max}}$, $AUC_{0-T}$ and $AUC_{0-\infty}$ was contained within 80-125% of the reference product.

Results
The ratio of oxycodone $C_{\text{max}}$, $AUC_{0-T}$ and $AUC_{0-\infty}$ administered as the FDC relative to A+O was 102% (95.2-109%), 96.0% (92.7-99.5%), and 96.0% (92.6-99.5%), respectively.

The ratio of oxycodone $C_{\text{max}}$, $AUC_{0-T}$ and $AUC_{0-\infty}$ administered as A+O relative to O was 104% (98.1-111%), 100% (96.5-104%), and 100% (96.4-104%), respectively.

The ratio of axelopran $C_{\text{max}}$, $AUC_{0-T}$ and $AUC_{0-\infty}$ was 84.2% (70.1-101%), 86.0% (80.2-92.2%) and 86.1% (80.3-92.4%), respectively.

The ratio of axelopran $C_{\text{max}}$, $AUC_{0-T}$ and $AUC_{0-\infty}$ was 91.4% (73.8-113%), 103% (93.2-114%) and 103% (93.2-114%), respectively.

Conclusions
Oxycodone bioavailability was bioequivalent between all treatments indicating no interaction of axelopran or the formulation with oxycodone pharmacokinetics. Axelopran was also bioequivalent (AUC) between the FDC and individual treatments. The lower bound of the 90% CI on axelopran $C_{\text{max}}$ was slightly lower than 80%, however, this decrease is unlikely to be clinically relevant. This proof-of-concept study demonstrates bioequivalence on all powered endpoints and the feasibility of co-formulation of axelopran with an opioid.

Pain, insomnia, fibromyalgia and PTSD (Post Traumatic Stress Disorder) - a treatable clinical target
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Purpose
Patients afflicted with PTSD typically present with a myriad of complaints indicative of severe anxiety and depression as well as very problematic insomnia. Typically, if a history of a disturbed sleep cycle is present, fibromyalgia is also present (by 1990 ACR criteria) but only if the diagnosis is sought after. These patients will be diagnostically dissected psychiatrically and treated appropriately but the patient’s overall aches and pains are often disregarded or at best minimally addressed and therapeutically dismissed. Unfortunately, this can contribute to continued disturbed sleep and cyclically contribute to impaired fibrocytic tender point pain and fibrocytic pain amplification.

The treatment course psychiatrically for PTSD can be very challenging. Despite the use of multiple psychiatric medications and/or cognitive therapy patients often experience difficulty achieving desired goals and activities.

Over the past 3+ years, I have seen that if you can improve these patient’s ability to achieve restorative sleep-as documented by their history of increase sleep duration, lessening of sleep awakenings and feeling better rested on awakening and corroborated by and improvement in both the number and tenderness of overall fibrocytic tender points - when this does occur it is not uncommon to see a gradual but significant improvement in these patients response to their psychiatric therapy as well as a dramatic improvement in achieving goals and activities associated with “normalcy”.

Performing an accurate fibrocytic tender point exam is very important as these patients may not always provide an accurate portrayal of their response to their medications.

Method
Patients are screened for fibromyalgia - blood work consisting of ESR, CBC, chem-profile, uric acid, TSH, rheumatoid factor, ANA, and any other relevant testing, ie, thyroid autoantibodies, Lyme disease testing etc. Very important to search for sources of chronic ongoing pain that would corrupt sleep - such as obesity with pes planus and associated chronically painful tarsal sinus syndrome, anserine bursitis, trochanteric bursitis and SI joint strain. After screening, if sleep duration, awakenings and fatigue are less than desirable, concentration and focus less than optimal, additional medication may be necessary. I introduce medication to modulate tenderpoint pain and augment restorative sleep i.e. I prefer the initial combination of tramadol (50-100 mg TID) and tizanidine capsules (4-8 mg QHS). Consideration to the addition of pregabalin, duloxetine or...
milnacipran can be given - if beneficial they can be retained. If pain and sleep are still problematic, with persisting awakenings and fatigue, with concentration and focus remaining suboptimal, additional medication may be necessary.

Non PTSD patients may experience some degree of benefit from the aforementioned regime - typically PTSD patients benefit will be only marginal esp. if pure mu agonists are used alone. Pure narcotic substances may be associated with insufficient clinical response and/or dependency issues. For the PTSD patients I add tapentadol 50 mg PO QHS for 2 nights - observe if benefit is achieved, if not increase the dose to 100 mg - subsequent dose increases as appropriate if necessary.

Results

In greater than 40 patients thus treated over the past three years, typically there was an almost universal increase in the duration of sleep, less awakenings and substantially less fatigue. Subsequently fibrocytic tender point pain is reduced as well as headache and stiffness-energy levels were gradually increased. When measured, the FIQ was typically improved, i.e. from values of less than 25 to values greater than 80 were observed. Both concentration/memory gradually improve as fibrositic pain diminishes. So too is the ability to successfully focus on a goal and accomplish it - this cannot be understated. Being able to hold a job, sustain a personal relationship, and even obtain higher education credits have been observed in varying degrees on a regular basis. The response to concomitant psychiatric therapy also appears to be gradually improved as noted by their psychiatrists - an overall lessening of anxiety and depression is typically observed. By staying with very low doses of tapentadol, only rarely have I encountered any problematic use with concomitant CNS antidepressants and have not seen any serotonin related clinical issues.

Conclusions

Fibromyalgia can be a clinical tool used to assess whether or not there has been an improvement in the sleep status of patients with PTSD. Clinically the use of pure mu agonists tends not to be satisfying, neither symptomatically to the patient nor to the physician in terms of achieving a desired clinical result. Tapentadol offers a combination analgesic effect, offering both mu agonism and nor epinephrine and serotonin reuptake inhibition. This overall method of concomitant pain inhibition and sleep augmentation offers a therapeutic alternative that can offer significant symptomatic and functional relief.

Differences in economic burden by long-term opioid therapy type among chronic non-cancer pain patients

Pamela Landsman-Blumberg1, Nathaniel Katz2, Anna O. D’Souza1, Sham L. Chaudhari1, Kavita Gajria*3, Paul Yeung3 & Richard White4

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Purpose

The economic burden of chronic pain in the United States is high, with estimated annual direct and indirect costs ranging from $560 to $635 billion per year. Opioids are a common pharmaceutical treatment option for patients with chronic non-cancer pain (CNCP), with 14.3% of ambulatory visits for CNCP resulting in an opioid prescription. Little information is available regarding chronic pain (CP)-related healthcare costs and utilization of long-term opioid users with CNCP.

The study purpose was to assess 12-month CP-related healthcare utilization and costs post-opioid initiation among CNCP patients initiating different long-term opioid treatments - monotherapy long-acting formulations of opioids (mono-LAOs), monotherapy short-acting formulations of opioids (mono-SAOs), combination (LAOs with SAOs), and opioid switch (switchers).

Method

A retrospective cohort study using the Truven Health MarketScan® claims databases (2006-2012) was conducted. Patients were defined as having CNCP if ≥ 3 non-diagnostic claims with ICD-9-CM diagnosis codes of the same type of 5 pain categories (low back, neck, osteoarthritis, fibromyalgia, or neuropathic pain) in any position related medical claims, and prescription claims for pain-related medications including opioids, nonsteroidal anti-inflammatory drugs/acetaminophen, muscle relaxants, corticosteroids, antidepressants, anticonvulsants, and benzodiazepines). One-way ANOVA and Kruskal-Wallis tests comparing continuous measures and chi-square and Fisher’s exact tests comparing categorical measures were employed. Differences in CP-related costs across the four opioid user cohorts were assessed using multivariate generalized linear models with log-link function and gamma distribution, controlling for differences in demographic and clinical characteristics. Adjusted costs (2012 USD) were output from the models with 95% confidence intervals for CP-related total, medical, and prescription costs.

Results

A total of 21,203 CNCP patients were included in the final study sample, of which 74% were long-term mono-SAO users, followed by long-term combination (22%), switch (2%), and mono-LAO (2%) users. Patients were 52.7 (SD...
14.7) years of age and 51.2% were female. The most common chronic pain diagnosis was low back pain (89% to 92% across cohorts), with the combination cohort more likely to have ≥ 2 types of CNCP diagnoses (37%) compared to other cohorts (27% to 31%, p<0.001). During pre-index, the mono-LAO cohort had a greater mean Charlson comorbidity index (0.96 vs. 0.81-0.61), greater rate of diagnosed drug abuse/dependence (14.3% vs. 4.2-1.3%), and lower NSAIDS/acetaminophen, muscle relaxant, and corticosteroid use, all p<0.001, than the other opioid cohorts; mono-SAO users had lower antidepressant and anticonvulsant use than the other cohorts. On average, the mean opioid supply post-initiation was 240-285 days. Average daily dose (morphine mg equivalents) was highest in the mono-LAO users (96.4 ± 86.6 mg) compared to the combination (89.8 ± 81.8 mg), switch (64.3 ± 55.4 mg), and mono-SAO (36.2 ± 27.7 mg) users. Compared to mono-LAO users, significantly greater proportions of patients in the three other cohorts had at least one CP-LAO mono-LAO users, significantly greater proportions of patients in the three other cohorts had at least one CP-LAO users with chronic non-cancer pain (CNCP), with 14.3% of ambulatory visits for CNCP resulting in an opioid prescription. It is well-recognized that opioids when combined with alcohol increases the risks of adverse outcomes such as accidents, overdose, and death. Prior research has found that long-term CNCP opioid users are significantly more likely to have been diagnosed with alcoholism and non-opioid drug abuse compared to CNCP patients not using opioids. However, information is lacking on differences between CNCP patients who are long term, opioid users with and without alcohol abuse and/or dependence (AAD). The primary objectives of this study were to compare patient characteristics and outcomes (opioid overdose, accident, injury rates, and health care costs) among CNCP patients on long-term opioid treatment with and without prior diagnosis of AAD.

Purpose

Opioids are a common pharmaceutical treatment option for patients with chronic non-cancer pain (CNCP), with 14.3% of ambulatory visits for CNCP resulting in an opioid prescription. It is well-recognized that opioids when combined with alcohol increases the risks of adverse outcomes such as accidents, overdose, and death. Prior research has found that long-term CNCP opioid users are significantly more likely to have been diagnosed with alcoholism and non-opioid drug abuse compared to CNCP patients not using opioids. However, information is lacking on differences between CNCP patients who are long term, opioid users with and without alcohol abuse and/or dependence (AAD). The primary objectives of this study were to compare patient characteristics and outcomes (opioid overdose, accident, injury rates, and health care costs) among CNCP patients on long-term opioid treatment with and without prior diagnosis of AAD.

Method

A retrospective cohort study using Truven Health MarketScan® claims databases (2006-2012) was conducted. Patients were defined as having CNCP if ≥ 3 non-diagnostic claims with ICD-9-CM diagnosis codes of the same type of 5 pain categories (low back, neck, osteoarthritis, fibromyalgia, or neuropathic pain) in any position on inpatient or outpatient claims. Outcomes were computed during the 12-month post-index period, and included adverse events (opioid overdose, accident and injury episodes identified by E-codes) and all-cause healthcare costs (defined as all payments received by providers of care, including those paid by the insurer and the patient for medical and prescription claims regardless of diagnosis). T-tests and Mann-Whitney tests comparing continuous measures and chi-square and Fisher’s exact tests comparing categorical measures between those with and without AAD diagnoses were employed.

Results

A total of 21,203 CNCP patients with long-term opioid treatment were included in the final study sample, of which 750 (3.5%) had an AAD diagnosis prior to opioid initiation. AAD patients were significantly younger (48.4 ± 11.4 vs. 52.8 ± 14.8 years), less likely to be enrolled in Medicare supplemental plans (4% vs. 17%), and more likely to be male (67% vs. 48%); all p<0.001. There were no differences in type or number of CNCP diagnoses or Charlson comorbidity index. AAD patients had significantly higher rates of depression and anxiety diagnoses, antidepressant and benzodiazepine use, and drug abuse/dependence diagnoses in the

Conclusions

The vast majority of CNCP patients on long-term opioid therapy received SAO monotherapy. Those using monotherapy LAOs were prescribed the highest average daily dose. Compared with the other opioid regimens, patients using monotherapy LAOs had the lowest total costs driven by lower use of medical and non-opioid prescription pain treatments and fewer CP-related ER visits and inpatient stays. Future research confirming these study findings taking into consideration factors such as pain level and duration would further help in determining the optimal long-term opioid regimen for CNCP patients in terms of both clinical and economic outcomes.

Differences in outcomes by alcohol abuse or dependence diagnosis among long term opioid users with chronic non-cancer pain

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pre-index period. During the 12-months post-opioid initiation, rates of opiate overdose (1.2% vs 0.2%, p<0.001), accident (7.3% vs. 2.8%, p<0.001), and injury (46.1% vs. 36.8%, p<0.001), were significantly greater in the AAD cohort. While prescription costs were similar between the 2 groups ($3,562 vs. $3,312, p=0.212), patients with AAD had significantly higher all-cause medical costs ($28,429 vs. $22,082, p<0.001) and therefore significantly higher all-cause total healthcare costs ($31,991 vs. $25,395, p<0.001). Both inpatient and outpatient components of medical costs were significantly higher for the AAD cohort versus the non-AAD cohort.

Conclusions

In the first-year post-opioid initiation, the proportion of CNCP patients with long-term opioid use and diagnosed alcohol abuse or dependence was 5 times greater for opioid overdoses, 2.3 times greater for accidents, and 1.2 times greater for injuries compared to those without diagnosed alcohol abuse or dependence. Opioid overdose rates found in this study suggest that an estimated 2,000 overdoses per year could occur in patients with alcohol abuse or dependence among the approximately 5 million long-term opioid users in the US.

Characteristics and dosing patterns in patients using long-acting opioids long-term for non-cancer chronic pain treatment

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Purpose

Short-acting and long-acting formulations of opioids (SAOs and LAOs) play an important role in the management of chronic non-cancer pain (CNCP). While SAOs are ideal for addressing short-term pain relief, LAO formulations provide extended pain relief through steady and sustained peak plasma concentrations reducing the need for more frequent dosing. LAOs are recommended for those patients requiring around-the-clock pain relief for extended period of time. There is limited information on the patterns of use of different LAO formulations. The primary objective of this study was to describe LAO opioid dosing patterns and compare demographic and clinical characteristics across average opioid daily dose categories among commercially insured and Medicare supplemental enrollees using LAOs alone or in combination with SAOs.

Method

A retrospective cohort study using Truven Health MarketScan® claims databases (2006-2012) was conducted. Patients were defined as having CNCP if they had ≥ 3 non-diagnostic claims with ICD-9-CM diagnosis codes of the same type from 5 pain categories (low back, neck, osteoarthritis, fibromyalgia, or neuropathic pain) in any position listed on inpatient or outpatient claims, with each claim between 1 month and 1 year apart. Patients using LAOs on a long-term basis either alone or in combination with another opioid for their pain were the target population. Long-term opioid use was defined as ≥90 days’ continuous supply of any class 2 or 3 LAO within the first 12 months following the first pain diagnosis and first index opioid. All patients were required to have continuous enrollment 12 months prior to the initial pain diagnosis (pre-index) and 12 months after opioid start. Patients were classified into average daily opioid dose groups using milligram morphine equivalent dosing (mg MED) of the total opioid dose (LAO monotherapy or combination of LAO+SAO). Descriptive statistics were used to characterize the study sample during the pre-index period. T-tests (for binary categories of average daily dose) and one-way ANOVAs were used to compare continuous measures and chi-square and Fisher’s exact tests were used to compare categorical measures across the average daily opioid dose groups.

Results

A total of 5,002 patients were included in the final sample, of which 92% received combination therapy and 8% were treated with LAO monotherapy. The average age of the study cohort was 53.0 (SD=15.1) years with 49% being male. The majority (66%) received an average MED of 20 to 99 mg/day and 20% had MED of ≥120 mg/day. Of the total mono LAO patients, 30% had average daily doses ≥120 mg/day MED compared to combination users which was 20%. Patients with higher average opioid daily doses (≥ 120 mg MED) were more likely to be male, < 64 years of age, have lower comorbidity burden (Charlson Comorbidity Index), and more likely to have diagnosed drug abuse/dependence during the pre-index period than those receiving <120 mg MED; the number of chronic pain diagnoses between the groups was comparable. SAO use accounted for approximately 13% of the total opioid daily dose in combination users. Furthermore, in ~9% of combination users, SAO supplementation increased their average daily dose to ≥120 mg MED. Despite the availability of high dose-strength formulations for LAOs, a vast majority of the patients used lower dose-strengths instead of higher dose-strengths that were equivalent to the total average daily dose requirements of the patient.

Conclusions

Most CNCP patients on long-term opioid treatment were prescribed combination therapy. Dose ranges varied widely with majority of the patients receiving MED doses between 20-99 mg/day; a small proportion received MED ≥120 mg/day. These dosing patterns demonstrate the need for wide dose range availability for a single opioid entity, which can help customize therapy based on individual patient needs. The availability of abuse-deterrent LAO formulations that may minimize abuse risk can also provide value in long-term CNCP management.
Outcomes from long-term opioid and concomitant alcohol use in chronic non-cancer pain patients: An electronic medical record data analysis of an integrated health plan population

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Purpose

Although an effective treatment option for patients with chronic non-cancer pain (CNCP), opioids have high abuse and addiction potential with long-term use. Concurrent use of alcohol further increases risk of adverse events such as accidents, overdose, and death posing a significant public health burden. A major concern of combining alcohol and opioids is the pharmacokinetic consequence of drug dumping-the unintended rapid release of opioid in a short period of time that increases both their dangers and potential for abuse, particularly for long-acting formulations of opioids (LAOs). There is limited information on the prevalence of use of alcohol and opioid treatment in CNCP and its impact on health care resource use and costs. The purpose of this study was to assess the prevalence of concomitant alcohol use with opioid treatment including type of opioid treatment among CNCP patients. Further resource use and outcomes between alcohol users and non-users was investigated.

Method

A retrospective cohort study was conducted using electronic medical record (EMR) data (Jan 2009 to Aug 2014) from an Integrated Health Plan (IHP). Study index was the date of the first opioid medication order. Long-term opioid CNCP users were patients aged ≥18 years having ≥10 opioid medication orders and ≥1 pain diagnosis (occurring on/before the index order) of any of five pain types (back, neck, osteoarthritis, fibromyalgia, neuropathy, pain not elsewhere classified). Alcohol users for the study timeframe (1-year pre-index and 1-year follow-up period) were identified based on responses to the question ‘Do you drink alcohol?’ Patients were categorized based on the pattern of their opioid use- monotherapy short-acting opioids formulations (mono-SAO), and any LAO use (including monotherapy LAO, combination LAO with SAO, and opioid switchers from SAO to LAO or vice-versa). Demographic and clinical characteristics were assessed during the 1-year pre-index, and used to characterize the population at baseline. Outcomes computed during the 1-year follow-up period included average daily dose in morphine equivalents (MED), adverse outcomes (opioid overdose, suicide and self-inflicted injury, accident, and injury), all-cause and pain-related (defined as records with a primary diagnosis of any of the five pain diagnosis) health resource use, and costs. These outcomes were compared between alcohol users and non-users for the total sample and within the mono-SAO and any-LAO subgroups. Comparisons were made using t-tests for continuous measures and chi-square and Fisher’s exact tests for categorical measures.

Results

A total of 1,643 long-term opioid CNCP users met the study criteria, of which the majority (82%) was treated with mono SAOs. Nearly half (45%) reported drinking alcohol - these rates were comparable between mono-SAO and any-LAO users. A total of 144 alcohol users reported amount of use, of which 86% were then categorized as light drinkers and 14% as moderate to heavy drinkers. Alcohol users were significantly younger (49 vs. 55 years, p<0.001) and more likely to be male (51.3% vs. 35.8%, p<0.001) than non-alcohol users. At baseline, a significantly higher proportion of alcohol users had low back and neck pain, and lower comorbidity burden (Charlson comorbidity index) than those who reported no alcohol use (p<0.05). Comorbidities such as sleep disorders/insomnia (15.9% vs. 11.5%, p<0.010) and drug abuse/dependence (19.2% vs. 15.1%, p<0.031) at baseline were also higher among the alcohol users than non-users; this difference was found mainly in the mono-SAO group with no difference in the any-LAO cohort. During the 1-year follow-up period, mean daily MED was 38.6 mg (SD=21.8) in the mono-SAO group and 106.0 mg (SD=116.2) in the any-LAO group; MED was comparable between alcohol users and non-users. Within the any-LAO group, the rate of accidents and injuries was higher among the alcohol users than non-users, with significance for the rate of injuries (49.6% vs. 37.4%, p=0.034). The proportion of patients who were hospitalized was also significantly higher for those who reported alcohol use than those who reported no alcohol use (60.0% vs. 45.4%, p=0.010) within the any-LAO group. These outcomes were similar between alcohol users and non-users in the mono-SAO group.

Conclusions

The observed opioid use patterns indicate that both SAOs and LAOs play an important role in the management of CNCP. Alcohol is known to have additive effects with opioids, yet we observed almost half of long-term opioid users report at least some alcohol use. The results show higher adverse outcomes such as injuries and hospitalizations among alcohol users than non-users in the any-LAO group further highlighting the risk of LAO and alcohol use. Opioid formulations that can minimize this increased risk may be of value in helping address this public health concern.

Respiratory evaluation of subcutaneously administered ZYN001 in male Sprague-Dawley rats

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Purpose

ZYN001 is a synthetic pro-drug of Δ9-tetrahydrocannabinol (THC), a cannabinoid and the primary component in Cannabis sativa, formulated for delivery via a transdermal patch that contains ZYN001 and is intended for application to the
upper arm, back, or thigh. The drug substance is produced synthetically and is not derived or extracted from botanicals. The excipients in the patch have been classified as Generally Recognized As Safe and have been used in transdermal products previously approved by the FDA.

The pro-drug formulation is an enabling technology designed to facilitate the transport of THC, which is naturally hydrophobic, across the stratum corneum and into the systemic circulation. The transdermal patch is a non-invasive, non-oral dosage form that may be able to achieve sustained, consistent THC plasma levels with an improved adverse effect profile. Chemically, ZYN001 is the D-(-)-glyceric acid ester of THC, but unlike THC, ZYN001 can be absorbed into the skin transdermally. After crossing the stratum corneum, ZYN001 is hydrolyzed back to THC and glyceric acid under physiological conditions.

The objective of this study was to evaluate the potential effects of ZYN001 on respiratory function. As the rat is the usual rodent model used for evaluating the toxicity of various classes of chemicals, and there were no gender differences expected in pulmonary function, only male rats were used.

Method

A total of 32 male experimentally naïve Sprague-Dawley rats (weight, 205-241 g) were included in this study. During an 11 to 18-day acclimation period, animals were observed daily with respect to general health and any signs of disease. They were individually housed in whole body plethysmograph respiratory monitoring chambers ≥1.5 hours predose, temporarily removed for dosing, and returned immediately postdose so pulmonary monitoring could continue for ≥ 4 hours. Rats within ±20% of the mean weight were randomly assigned to receive a single subcutaneous bolus injection of vehicle (sesame oil filtered through a 0.2 μm nylon syringe filter) or ZYN001 at doses of 50 mg/kg, 100 mg/kg, or 200 mg/kg. Dose volumes were individualized by body weight because the dosing formulation was released as a single concentration of 220 mg/mL. The vehicle dosing preparation was prepared twice, up to three days before dosing, and was stored refrigerated (2-8°C) until acquired for dosing. A 25 g needle was used to inject study drugs into the scapular region on the back of each animal. Assessments of respiratory effects and body weight, and respiratory function (respiratory rate, tidal volume, minute volume, inspiration time, expiration time, peak inspiratory flow, peak expiratory flow, end inspiratory pause, and end expiratory pause).

Results

All animals survived to study termination. Predose, one-hour postdose, and end of monitoring clinical observations were all “normal.” There were no clinical signs of toxicity noted in any rat on this study. Body weights were consistent with expectations for the age and gender of the animals in this study. Rats demonstrated a normal pattern of acclimation to the whole-body plethysmograph chamber, and there was no physiologically relevant respiratory depression at ZYN001 doses up to 200 mg/kg. The effects of ZYN001 on tidal volume were within the upper range of normal and were not considered to be adverse. There were no physiologically meaningful changes in group mean minute volumes before or after dose administrations of up to 200 mg/kg ZYN001. No consistent alterations in air exchange were observed during the monitoring periods, but ZYN001 changed the topography of breathing by causing a substantial increase in end expiratory pause. The effect was most likely a compensatory response to known central nervous system and peripheral cannabinoid-related interactions and does not represent an adverse pharmacological effect on pulmonary function.

Conclusions

All respiratory dynamics parameters (respiratory rates, tidal volumes, minute volumes) were within normative values for the strain, age, gender, and bodyweights of the rats assessed in the present study. At the highest tested dose of 200 mg/kg, ZYN001 changed the topography of breathing by eliciting an increase in end expiratory pause. Published literature suggests that this effect is a compensatory response to known central nervous system and peripheral cannabinoid-related interactions that does not represent an adverse pharmacological effect on pulmonary function. This finding marks an important distinction from opioids, with which respiratory depression is a common, potentially dangerous side effect.

Novel extended release formulation of hydrocodone bitartrate (ZX007) resists physical manipulation and extraction of hydrocodone

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Purpose

A twice-daily, single-entity, extended-release hydrocodone bitartrate tablet (ZX007) is being developed using INTELLITAB™ technology. INTELLITAB technology is designed to resist both physical manipulation and extraction with typical household solvents. Studies presented here were undertaken using the methods available to opioid abusers to manipulate a controlled release product as well as ways in which a patient may alter the formulation (unintentionally or intentionally) that change the rate of drug released over time. The studies were performed to evaluate the dissolution performance of the formulation when exposed to alcohol, the resistance of the formulation to crushing and cutting, the ability of the formulation after manipulation to allow drug extraction and syringing and the controlled release performance of the formulation after crushing and grinding.

Method

Several in vitro studies were conducted. In the first series of studies, the ability of the formulation to resist crushing in a hardness tester between two spoons, between two metal...
plates, in a standard pill crusher, and using a mortar and pestle was tested. The second series of studies were the extraction studies performed using the results from the grinding studies and exposing the contents to household solvents typically available to abusers such as cold or boiling water, sodium hydroxide, sodium chloride/ hydrochloric acid, ethanol (40% in water), methanol, nail varnish remover (acetone solution) or isopropyl alcohol. The mixtures were left for 30 minutes and for up to 20 hr under static and agitated conditions. Any supernatant formed was aspirated and drug content assessed by an HPLC method. Attempts to expel reconstituted debris through syringe needles were also made.

The third series of studies measured the rate of drug release in water and 40% ethanol/water using standard dissolution apparatus. The drug liberation rate from tablets subject to crushing and grinding was also determined at neutral pH, in pH 1.2 and in the presence of alcohol (40% in water).

Results

The ZX007 tablets demonstrated resistance to being crushed in a pharmaceutical hardness tester, between two spoons or between wide metal plates. Crushing in a standard pill crus her resulted in some surface fracture but tablets were not reduced to a particle size suitable for insufflation. Tablets resisted initial attempts at breakage using a pestle but, after repeated impact (greater than 20 strokes) were reduced to large fragments with diameters of greater than 2 mm. Extended grinding of this material resulted in semi-uniform particles with up to 50% of the particles being of greater than 500 micron.

Extraction utilizing the addition of 1 or 5 mL of cold or boiling water, low pH, high pH media, alcohol, methanol, nail varnish remover or isopropyl alcohol resulted in a dark coloured solid with no supernatant or aqueous extraction solution being formed; viscous gel formed immediately on addition of the liquids and were stable, with no supernatant forming for over 20 hours whether static or vigorously agitated. The viscous gel could only be drawn up into needle free syringes with difficulty and could not be expelled through 27 or 23 gauge needles. In experiments where 10 mL of water was added to crushed and ground tablets, hard gels again formed with no particle settling, distinct aqueous extract or supernatant.

The results from the dissolution experiments showed that the intact and crushed and ground tablets exhibited a reduced rate of drug release in alcoholic compared to non-alcoholic media. The release rate in neutral pH was similar to that of the intact tablet and while in pH 1.2 initial release rates increased controlled released was maintained for over 8 hours.

Conclusions

The ZX007 in vitro data demonstrates that the formulation resists manipulation, prevents extraction in a wide range of solvents and maintains controlled release after extended attempts at crushing and grinding. These results provide support for the continued evaluation of the formulation in human abuse liability studies.

Treatment of chronic pain with a novel wearable transcutaneous electrical nerve stimulator

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Purpose

One third of American adults suffer from chronic pain. In addition to the direct experience of pain, many have poor overall health, low quality sleep, anxiety, depression and other co-morbid medical conditions. Pharmacotherapy may have substantial side effects and many patients do not achieve satisfactory results. Therefore, there is an urgent need for non-pharmacological pain relief options.

Transcutaneous electrical nerve stimulation (TENS) provides pain relief by up regulating the descending pain inhibition system through activation of Ab sensory fibers. When electrical stimulation is delivered at high frequencies (80 – 100 Hz), the analgesia is mediated by enkephalins, which are endogenous opioids that act through δ-opioid receptors located in the dorsal horn of the spinal cord and elsewhere in the central nervous system. The descending pain inhibition system has diffuse projections extending beyond the segmental distribution of the stimulated nerves. As a result, localized stimulation can evoke a widespread analgesia.

Conventional TENS devices are not ideal for chronic pain because they are not wearable, have limited technical specifications, present awkward electrode and user interfaces, and lack automation. Many patients with chronic pain have constant or at least daily pain, and most have difficulty sleeping. Therefore, devices that cannot be worn while the patient is active or overnight have limited utility. The objective of this study was to evaluate the efficacy of a novel wearable high frequency TENS device for the management of common forms of chronic pain.

Method

This study was a retrospective analysis of data collected from 130 chronic pain sufferers during a product usage test conducted between May and July 2015. The participants consented to having their de-identified data shared for subsequent analyses. Participants were at least 40 years of age, had pain involving the lower back, legs or feet, experienced pain for most days during the past 3 months or longer. All participants self-administered an FDA cleared high-frequency TENS device at home (Quell; NeuroMetrix Inc., Waltham, MA, USA). This device is always placed at on the upper calf and may be worn continuously, including during sleep. It has high electrical power (100 V, 100 mA) and automatically regulates the stimulation intensity to optimize therapy.

The study was designed to reflect real world usage. Participants were not given special instruction on the device
and were not asked to alter their analgesic medications or other pain treatments. Prior to obtaining the device, the participants completed an online questionnaire covering demographics, medical history and pain, which was assessed with the Brief Pain Inventory (BPI-SF). Thirty days after receiving the device, subjects were requested to complete an online follow-up questionnaire. This questionnaire included a self-rated change in chronic pain and overall health using a 5-point patient global impression of change (PGIC) scale. Participants also reported changes in their analgesic consumption and completed the BPI-SF.

Results

The usage database consisted of baseline and 30-day clinical questionnaires from 94 subjects with chronic pain. The mean age was 55.7 ± 7.6 years and 46.8% were female. The subjects reported a mean of 3 anatomical pain sites among feet (43.6%), legs (58.5%), lower back (85.1%), hands (34.0%), arms (30.9%), and neck (47.9%). The five most commonly reported medical conditions were arthritis (60.6%), diabetes (40.4%), sciatica (27.7%), fibromyalgia (25.5%), and neuropathy (22.3%). At baseline, 4.3% of subjects had mild pain (BPI-SF average pain 0-3), 56.4% had moderate pain (4-6), and 39.4% had severe pain (7-10). The mean BPI-SF pain interference rating was 6.3 and the mean BPI-SF pain relief rating was 43.1%.

On the 30-day follow up questionnaire, device usage was reported as several times a day for 25.5% of the subjects, 1-2 times a day for 42.6%, and less than daily for 31.9%. On the PGIC scale, the percentage of subjects reporting an improvement in their chronic pain and overall health was 80.9%. Among the remaining subjects, 17.0% reported no change and 2.1% a worsening. Increasing device usage was associated with higher PGIC ratings (chi-square and Wilks’ G², p<0.05).

A reduction in pain medication use was reported by 67.0% of subjects (25.5% reported substantial decrease). At 30-day follow up, there was a statistically significant improvement in all BPI-SF items but average pain. The BPI-SF pain relief item increased from 43.1% to 57.2%. In a multiple linear regression analysis, baseline BPI-SF pain relief, change in BPI-SF pain relief, and pain medication use were independent positive predictors of PGIC and together explained over 40% of its variance (R²=42.6).

Conclusions

About 80% of chronic pain sufferers reported improvement in their pain and overall health (PGIC) after using a wearable, high frequency, fixed location, TENS device for 30 days. PGIC was positively correlated to device usage, suggesting dose dependence. Over 40% of the PGIC variance was accounted for by the baseline assessment of pain relief, the 30-day change in pain relief, and the change in pain mediation use. In this study, the wearable TENS device may have delivered its benefit by decreasing the need for pain medications and enhancing the effectiveness of the subject’s overall pain treatment program.


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Purpose

The analysis of natural and synthetic opioid drugs continues to be an important area of analytical research. Typical methods to detect these drugs often require enzymatic hydrolysis prior to analysis. However, incomplete hydrolysis can result in inaccurate measurement. The method presented herein directly analyzes glucuronide metabolites, eliminating uncertainty associated with enzymatic hydrolysis. The presented work details a technique for analysis of 26 opioid drugs and their metabolites in urine using mixed-mode solid phase extraction (SPE) followed by reversed-phase UPLC/MS/MS.

Method

Urine samples (100 μL) were pretreated with equal parts 4% H3PO4 and internal standard solution (dissolved in water). After conditioning mixed-mode SPE plates, pretreated urine samples were loaded onto the sorbent bed. After washing each well with water and MeOH, samples were eluted with 60:40 ACN:MeOH containing 5% NH4OH. Sample eluates were then evaporated to dryness, reconstituted in starting mobile phase and injected onto the LC/MS/MS system.

Results

All analytes eluted in less than 5.5 minutes, and baseline separation was achieved for all isobaric compounds. All compounds demonstrated excellent linearity, accuracy and precision from 5-500 ng/mL. All calibration points fell within 10% of their target values, and %CVs were under 15%. Intraday imprecision for quality control samples at 7.5, 75, 250 and 400 ng/mL were all under 10% CV with only one exception (morphine @ 7.5 ng/mL; %CV = 10.1%), and all QC samples deviated by less than 15% from target values. When compared to a simple dilution method, mixed-mode SPE resulted in significantly reduced matrix effects and improved linearity, accuracy and precision.

Authentic urine samples, which had been previously analyzed by enzymatic hydrolysis, were also analyzed. Comparison of the two methods revealed good agreement for oxycodone and hydromorphone, which do not undergo glucuronidation. However, the method described here resulted in significantly higher calculated concentrations for total oxymorphone and hydromorphone, in agreement with previous reports of incomplete or inconsistent hydrolysis of their glucuronide metabolites, and emphasizing the importance of direct analysis of these metabolites.
Conclusions

The direct analysis of glucuronide metabolites enables direct quantification of these key metabolites, eliminating the risk of poor quantification due to incomplete hydrolysis. Sample preparation with mixed-mode SPE further improved method performance, by reducing matrix effects and improving linearity, accuracy and analytical precision for all analytes.

For research use only. Not for use in diagnostic procedures.

Screening for drugs in urine using high-resolution MS/MS spectra and simplified high-performance screening software
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Purpose

Screening for drugs can be a daunting task. Immunoassays are easy but are not specific and are prone to interferences. Many laboratories are now using liquid chromatography coupled to triple quadrupole mass spectrometers (LC-MS/MS) to test for a fixed set of “the usual suspects.” However, some are realizing that the net must be cast wider in order to determine the compounds present in a given sample. Forensic toxicologists need an economical solution to screen for a virtually unlimited number of compounds in urine. Here we evaluated a method for screening using approximately 300 compounds in human urine using a dilute-and-shoot approach with a high-resolution accurate mass (HRAM) mass spectrometer and simple screening software.

Method

Samples were processed by simple dilution. Briefly, an aliquot of centrifuged urine was spiked with stable-labeled internal standard and diluted 30-fold before an aliquot was subjected to gradient HPLC chromatography. No hydrolysis was performed. The internal standard used was tolbutamide-d9. This compound was used for its versatility because it ionizes in both positive and negative mode. Limits of detection were determined by spiking compounds of interest into pooled blank urine in the range of 1 to 500 ng/mL. The total run time was 10 minutes.

Compounds were detected on a Thermo Scientific™ Q Exactive Focus benchtop Orbitrap mass spectrometer. Data were acquired in full scan - data dependent MS² mode. In this mode, both positive and negative high resolution full scan data at resolution of 70k were collected and then MS² spectra at a resolution of 17.5k were triggered for compounds in the inclusion list.

To test this method, 300 compounds, both positively and negatively ionized, including drugs of abuse, therapeutic drugs and environmental toxins were selected for evaluation. Spiking solutions of 8-10 compounds each were prepared and used to make test mixes at concentration of 500, 100, 50, 10, 5 and 1 ng/mL in pooled donor urine.

Test mixes were processed and analyzed using procedure above. Additionally, positive donor samples from a collaborator laboratory were processed and analyzed.

Data was processed using Thermo Scientific™ ToxFinder™ software.

Results

ToxFinder software uses a database that contains compound related information and tolerances for identification. It also utilizes proprietary spectral libraries including forensic toxicology libraries containing drugs of abuse, therapeutic drugs and environmental toxins and food safety and environmental libraries containing pesticides, mycotoxins, veterinary drugs and PFCs. Both of these features are combined into a processing method. In this study, the primary method identified compounds based on retention time, accurate m/z, and spectral library matching. The LOD/cutoff for each compound was determined to be the lowest spiked concentration in which peaks were identified by ToxFinder software. If even greater identification confidence is required, isotopic pattern matching can also be added to the method parameters.

Using the primary data processing method, the vast majority of compounds analyzed had detection limits at or below 10 ng/mL. When the additional requirement of isotopic pattern matching was employed, the limits of detection were, not unexpectedly, slightly higher. This is to be expected because of the naturally lower abundance of isotopic ions.

Conclusions

- We successfully evaluated urine screening method for about 300 compounds, both positively and negatively ionized, including drugs of abuse, therapeutic drugs and environmental toxins.
- Collected data demonstrated good method sensitivity and specificity in diluted urine samples.
- ToxFinder software’s simple user interface enabled quick method development and rapid data review.
- The Q Exactive Focus mass spectrometer and ToxFinder software together provide high confidence in data output by combining the power of an Orbitrap mass analyzer with the comprehensive identification workflow of the software.

Evaluation of the tolerability of switching patients on chronic full opioid agonist therapy to BEMA™ Buprenorphine
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Purpose

To determine whether patients with chronic pain receiving 80 to 220 mg oral morphine sulfate equivalent (MSE) of an around-the-clock (ATC) full opioid agonist could be safely transitioned to BEMA® Buprenorphine at approximately 50% of their oral MSE dose without inducing opioid withdrawal or sacrificing analgesic efficacy.

Method

This was a randomized, double-blind, double-dummy, active-controlled, 2-period crossover Phase 2 study in patients 18 to 60 years old receiving ATC full opioid agonist therapy (either morphine sulfate or oxycodone) and confirmed to be opioid dependent by naloxone challenge. Study doses were substituted at the time of the regular dose schedule for each patient. The primary endpoint was the proportion of subjects with a maximum Clinical Opiate Withdrawal Scale (COWS) score ≥13 (significant withdrawal) or were rescued due to withdrawal symptoms.

Randomized patients were stratified into 2 groups based on their original ATC MSE dose. MSE dose group 1 was composed of patients requiring between 80 and 160 mg MSE per day, and MSE dose group 2 was composed of patients requiring between 161 and 220 mg MSE per day of either morphine sulfate or oxycodone HC1 ATC for ≥28 days. BEMA Buprenorphine doses of 300 and 450 mcg were chosen for the 2 dose groups based on 50% of the calculated dose from a 100:1 morphine to buprenorphine conversion ratio. The 50% dose adjustment represents the recommended starting dose for opioid rotation. A 50% dose of the full agonist was used as the control group.

Results

35 subjects (31 on 80-160 mg and 4 on 161-220 mg oral morphine sulfate equivalent per day) completed both periods of the study and were evaluable for opioid withdrawal status.

Of the 35 subjects completing both study periods, significant withdrawal was experienced by 1 subject on BEMA Buprenorphine and 2 subjects on the full agonist. In addition, the mean maximum COWS scores were similar between BEMA Buprenorphine and full agonist treatments (mean [SD] 4.6 [3.15] and 5.3 [4.42], respectively; \( P = 0.79 \)) and there was no significant difference in pain ratings between the 2 treatments in MSE dose group 1.

The most frequent adverse events with BEMA Buprenorphine were headache (19%), vomiting (13%), nausea, diarrhea, and drug withdrawal syndrome (each 9%); with full opioid agonist treatment the most frequent adverse events were headache (16%), drug withdrawal syndrome (13%), and nausea (6%).

In summary, in subjects receiving ATC full mu opioid agonist doses of 80 to 220 mg MSE, administration of 300 or 450 μg doses of BEMA buprenorphine buccal film 8 to 12 hours after the last full agonist dose was not associated with a higher incidence of opioid withdrawal or adverse events compared to the 50% full agonist opioid dose.

Conclusions

The results demonstrate that in this study, chronic pain patients treated with around the clock full mu opioid agonist therapy can be switched to BEMA Buprenorphine (partial mu agonist), without the need for an opioid taper, at approximately 50% of the full agonist dose without an increased risk of experiencing opioid withdrawal or loss of pain control.

1.8% Lidocaine patch (ZTlido™): Review of a new formulation

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Purpose

Lidocaine is an amide local anesthetic that has been widely utilized in a variety of topical formulations. Lidocaine blocks neuronal voltage gated sodium channels to prevent depolarization and inhibit the propagation of nerve impulses.

A 5% lidocaine patch was approved by the FDA and is indicated for the relief of pain associated with post-herpetic neuralgia (PHN). The penetration of lidocaine into intact skin after application of the 5% lidocaine patch is sufficient to produce an analgesic effect, but less than the amount necessary to produce a complete sensory block. An evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology determined that based upon class I evidence, topical lidocaine is effective in reducing the pain of PHN. In addition, a 1999 publication in the journal PAIN (Galer) concluded that the topical lidocaine patch relieved PHN more effective that a vehicle topical patch.

SCILEX Pharmaceuticals recently submitted a New Drug Application with the FDA for ZTlido™ (1.8% lidocaine patch) for pain associated with postherpetic neuralgia (PHN) based upon positive pharmacokinetic (PK) and dermal safety studies. The purpose of this presentation is to review the studies and the development of ZTlido™.

Method

ZTlido™ (pronounced Z-T-lido), is a branded, fourth-generation cutaneous lidocaine formulated as a 1.8% patch named after SCILEX’s proprietary anhydrous Zero H2O Transdermal Lidocaine system. SCILEX believes that ZTlido™ may offer significant advantages over the 5% lidocaine patch and its generic equivalents, including more efficient delivery of lidocaine, superior adhesion, improved manufacturing efficiency and less residual drug left in the patch after normal use. Less residual drug may reduce toxicity from unintentional exposure following removal of the patch. Also, the thinness of the patch makes it pliable and, given the improved adhesion, allows for the patch to be placed on contoured parts of the body.
Results

ZTlido: Novel and Proprietary Technology:

Although hydrogel patches (the 5% lidocaine patch and generics) are multi-layered with high water content, ZTlido™ is an anhydrous single layered patch. ZTlido™ uses a proprietary drug delivery technology that contains only 36 mg of lidocaine per patch, with an efficient single layer formulation that is thinner compared to the 5% lidocaine hydrogel patch—which contains 700 mg of lidocaine in a multiple layer hydrogel system, including a rate-controlling membrane. Given the hydrogel patch delivery system, the 5% lidocaine patch is compounded with 700 mg of lidocaine to achieve the same amount of drug delivery as ZTlido's 36 mg patch.

A 1996 study by Rowbotham (PAIN) indicated minimal systemic absorption of lidocaine from the 5% patch. A bioequivalence study with pharmacokinetic endpoints confirmed bioequivalence between ZTlido™ and the 5% lidocaine patch, and therefore, indicates the same overall safety and efficacy. This study was performed in 56 healthy volunteers in which area under the curve (AUC) and maximum plasma concentration observed (Cmax) were measured. The results demonstrated that for AUC and Cmax the 90% confidence interval of the ratio of geometric means was within 80% to 125%, indicating that the two treatments can be considered bioequivalent (according to the guidelines of the Food and Drug Administration’s Center for Drug Evaluation and Research (FDA-CDER)). In addition, dermal safety studies demonstrated that ZTlido™ had a safety profile consistent with that established for the 5% lidocaine patch.

Conclusions

ZTlido™ is a next-generation branded lidocaine patch formulation for relieving the pain of PHN. A clinical study confirmed bioequivalence between ZTlido™ and the lidocaine 5% transdermal patch. As a single layered anhydrous patch, ZTlido™ 1.8% contains only 36 mg of lidocaine and may offer significant advantages over the 5% lidocaine patch (with 700 mg lidocaine) and its generic equivalents including more efficient delivery of lidocaine, superior adhesion, improved manufacturing efficiency and less residual drug left in the patch after normal use.

A review of the clinical data on ZTlido™ (lidocaine patch 1.8%)

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Purpose

SCILEX Pharmaceuticals recently submitted a New Drug Application with the FDA for ZTlido™ (lidocaine patch 1.8%) for pain associated with PHN based upon positive pharmacokinetic (PK) and dermal safety studies. An earlier abstract outlined the attributes and putative benefits of a newer formulation of a 1.8% cutaneous lidocaine patch ZTlido™. Here, we will highlight some key clinical data regarding this formulation.

Method

A comparative pharmacokinetic (PK) study demonstrated bioequivalence between ZTlido™ 1.8% and the 5% lidocaine patch, indicating comparable safety and efficacy between the two products. This study also evaluated the effects of heat and exercise on the PK of ZTlido™ and, qualitatively, showed that these conditions have minimal effect on product performance.

A study to evaluate the adhesion of ZTlido™ demonstrated significantly improved adhesion compared to the 5% lidocaine patch. The study was completed in 41 patients who were randomized to receive both ZTlido™ and the 5% lidocaine patch. Adhesion scoring was rated 0-4, with 0 being >90% adherence (essentially no lifting off of the skin) and 4 when the patch completely detached from the skin. The mean adhesion score for ZTlido™ was 1.1 versus 2.2 for the 5% lidocaine patch (SD 1.4 and 1.5 respectively), suggesting superior adhesion for ZTlido™[SCI-LIDO-DERM-001]. The superior adhesion may result in improved patient compliance as the patch is less prone to inadvertent detachment and will require less reinforcement during the 12-hour treatment period.

By weight, ZTlido™ is a lighter product as it is constructed with 2 grams of adhesive tape versus 14 grams with the 5% lidocaine patch. In addition, ZTlido™ is thinner at 0.0315 inches versus 0.0675 inches for the 5% patch.

Results

SCILEX completed additional clinical studies to evaluate the dermal safety of ZTlido™ which suggested that ZTlido™ has a safety profile consistent with that established for the 5% lidocaine patch. In a photoallergy study, there was no evidence of photosensitization to ZTlido™. Also, there was no evidence of significant dermal irritation with ZTlido™. In a phototoxicity study, there was no indication of phototoxicity present among the subjects in the study. In a study that examined sensitization, cumulative irritation and adhesion, there was no sensitization to ZTlido™ during the study. Although the mean cumulative irritation was higher with ZTlido™ than the 5% lidocaine patch, the observed irritation was not considered clinically significant.

There were a limited number of treatment-related adverse events in the studies that were rated as severe, moderate and mild. No serious adverse events were reported.

Conclusions

ZTlido™ is a next-generation, branded lidocaine patch 1.8% whose data demonstrate:

- Bioequivalence consistent with the lidocaine 5% patch
- Dermal safety profile consistent with the lidocaine 5% patch
- Photoallergy, phototoxicity and sensitization/irritation studies were completed.
Phase 3 study of hydrocodone extended-release tablets formulated with an abuse-deterrence technology platform for moderate to severe pain: Efficacy and safety in patients with chronic low back pain

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Purpose
The US Food and Drug Administration identified a need for abuse-deterrent formulations of opioids as a high public priority. The efficacy and safety of a new hydrocodone extended-release (ER) tablet formulated with a CIMA® Abuse-Deterrence Technology (ADT) platform was assessed in this phase 3 study.

Method
This 12-week, randomized, double-blind, placebo-controlled, randomized-withdrawal study included patients aged 18-80 years with a ≥3-month history of moderate to severe chronic low back pain. Study patients were given open-label treatment with hydrocodone ER in increasing doses until they identified their analgesic dose (i.e., stable pain relief without unacceptable adverse events [AEs]). Those achieving an analgesic dose were randomized to double-blind treatment with hydrocodone ER every 12 hours at the identified dose (30-90 mg) or matching placebo. The primary efficacy measure was mean change from baseline to week 12 in weekly average of daily worst pain intensity (WPI) scores. Secondary efficacy measures included change from baseline to week 12 in average pain intensity (API) scores and proportion of patients discontinuing the study owing to loss of efficacy. Safety was measured using adverse events (AEs).

Results
Three hundred seventy-one patients achieved an analgesic dose of hydrocodone ER during open-label titration and were randomized to double-blind treatment. The change from baseline to week 12 in weekly average of daily WPI scores was significantly greater with placebo vs. hydrocodone ER: least squares (LS) mean change (standard error [SE]) 0.74 (0.15) vs. 0.11 (0.14); P<0.001. Change from baseline to week 12 in API scores was also significantly higher with placebo vs. hydrocodone ER: LS mean change (SE) 0.55 (0.14) vs. -0.03 (0.12); P<0.001. The proportion of patients discontinuing the study owing to loss of efficacy was lower with hydrocodone ER (23%) vs. with placebo (30%): hazard ratio (95% confidence interval) 0.68 (0.45, 1.01); P=0.059. Constipation (14%) and nausea (10%) were the most common AEs during treatment with hydrocodone ER.

Conclusions
Hydrocodone ER was significantly more effective than placebo in alleviating chronic low back pain, with a safety profile consistent with that of hydrocodone and other opioids. Further, hydrocodone ER is formulated with an ADT platform and has the potential to reduce occurrences of abuse and the adverse consequences of overdose.

Randomized, double-blind, placebo-controlled study assessing risk of diversion and loss of extended-release hydrocodone tablets formulated with abuse-deterrence technology in patients with chronic low back pain

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Purpose
Prescription opioid misuse has been implicated in rising rates of emergency department visits and deaths, underscoring a need for abuse-deterrent formulations of these medications. A single-agent (i.e., acetaminophen- and ibuprofen-free) hydrocodone extended-release (ER) tablet was developed with a CIMA® Abuse-Deterrence Technology platform to maintain extended-release properties despite attempts at abuse through manipulation by crushing or alcohol extraction.

Method
This was a 12-week, phase 3, randomized, double-blind, placebo-controlled, randomized-withdrawal study that assessed abuse characteristics of this hydrocodone ER formulation. Eligible patients aged 18-80 years with a ≥3-month history of moderate to severe chronic low back pain entered an open-label treatment period in which they received increasing doses of hydrocodone ER until identifying their analgesic dose (i.e., stable pain relief without unacceptable adverse events). Patients who successfully identified an analgesic dose were randomized to double-blind treatment with hydrocodone ER every 12 hours at their identified dose (30-90 mg) or matching placebo. Rescue medication (hydrocodone immediate release/acetaminophen 5/325 mg tablets) was allowed with limits. During the first 4 weeks of double-blind treatment, signs and symptoms of opiate withdrawal were measured on the Subjective Opiate Withdrawal Scale (SOWS) and the Clinical Opiate Withdrawal Scale (COWS). Study drug diversion and loss were monitored throughout the study.
Results
A total of 371 patients achieved an analgesic dose and were randomized to double-blind treatment with hydrocodone ER. The majority of patients receiving hydrocodone ER (59%-68%) and placebo (52%-65%) classified their opioid withdrawal symptoms as normal (i.e., no withdrawal) on the SOWS. Similarly, clinicians classified opioid withdrawal symptoms in the majority of patients receiving hydrocodone ER (87%-95%) and placebo (82%-93%) as normal on the COWS. Diversion of study drug and rescue medication occurred at a low rate overall (≤2%); diversion of hydrocodone ER was reported by 6 patients, diversion of rescue medication by 6 patients, and diversion of placebo by 1 patient. Loss of study drug loss also occurred at a low rate (≤4%; 20 patients).

Conclusions
Opioid withdrawal symptoms were predominantly absent or mild after randomized withdrawal of hydrocodone ER, and low rates of study drug diversion and loss support the abuse-deterrence properties of this new hydrocodone ER formulation.

A new role for clinical pharmacists: Managing patient controlled analgesia (PCA) therapy
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Purpose
Patient controlled analgesia (PCA) is a treatment modality allowing on-demand, intermittent opioid delivery upon patient request. Pharmacist-led PCA dosing services have been successfully implemented at other health-systems; however, no direct comparison to physician-dosed PCA therapy has been reported. The objective of this study was to develop and implement a pharmacist-led PCA dosing service and to compare pain control of patients on this service to patients receiving physician-dosed PCA therapy.

Method
Initial service development required a multi-disciplinary approach including health-system approval of the policy and electronic medical record build support. Implementation consisted of multiple steps including identification of a superuser team, guideline development and extensive training of clinical pharmacists. After implementation, an evaluation was conducted examining two groups: patients receiving pharmacist-dosed PCA therapy (November 2014 - present) compared to a historical cohort of patients receiving physician-dosed PCA therapy (June - August 2014). Data collected included patient demographics, opioid use, current PCA regimen, pharmacist interventions, pain scores, vital signs and sedation level using the Richmond Agitation-Sedation Scale (RASS). The primary endpoint of the study was the time to sustained pain goal defined as a pain score of less than 5 for two consecutive assessments. Secondary endpoints included time to first pain score less than 5 with no subsequent pain score of 7 or greater, time to first pain score of less than 5, length of stay, duration of PCA therapy, time to oral conversion, median pain scores and 30-day readmission secondary to uncontrolled pain. Safety endpoints included naloxone, antiemetic and antipruritic administration, need for emergent intervention, number of RASS scores of less than -2 and death. Pharmacist workload was also evaluated.

Results
Data collection and analysis are currently being conducted; preliminary results and conclusions will be presented at the 2015 PAINWeek Conference.

Conclusions
A pharmacist-led PCA dosing service was developed and successfully implemented at a large, tertiary, academic hospital. The steps involved in the development of the service included superuser identification, policy and guideline development, EMR support and pharmacist competency training. The service provides direct patient care in a manner not traditionally performed by pharmacists.

A 24-week extension of a 12-month open-label, safety study evaluating the safety and effectiveness of once-daily, single-entity, hydrocodone in patients with chronic nonmalignant and nonneuropathic pain
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Purpose
Hysingla® ER (HYD) is a once-daily, single-entity hydrocodone bitartrate tablet formulated with abuse-deterrent properties that is under development for treatment of moderate-to-severe chronic pain. This 24-week extension of a long-term, open-label study with a 45-day dose titration period and a 12-month maintenance period characterized the safety, effectiveness, and impact on quality of life (QoL) measures of HYD (20, 40, 60, 80, 120 mg/day) treatment in patients with moderate-to-severe chronic non-malignant and non-neuropathic pain.

Method
A total of 106 opioid-naïve and opioid-experienced patients who completed the 12-month maintenance period participated in the extension portion of the study. Evaluations included adverse events (AEs), aberrant drug behaviors, audiologic and clinical laboratory assessments, ECGs, average daily pain
scores, the Brief Pain Inventory, the Short Form-36, and the MOS-Sleep-revised. Changes in HYD dose levels and the use of concomitant nonstudy short-acting opioid and non-opioid analgesics were also evaluated.

**Results**

Compared to baseline, HYD treatment resulted in improvements in and maintenance of pain relief, sleep, BPI scores, and QoL outcome measures throughout the 76-week maintenance period. The average daily dose of HYD, as well as the average daily doses of nonstudy opioid analgesics and the mostly commonly used nonopioid analgesics, were relatively stable throughout the treatment maintenance. Treatment-emergent AEs occurring in ≥ 5% of patients during the entire treatment duration included dizziness, somnolence, hypertension, insomnia, headache, anxiety, fall, nephrolithiasis, muscle strain, and arthralgia. No study drug abuse or diversion was reported. No apparent safety concerns were revealed from evaluations of audiologic, clinical laboratory, and ECGs assessments.

**Conclusions**

The results of this study suggest that the effectiveness and safety of HYD were maintained for up to 76 weeks of treatment in patients with chronic non-malignant and non-neuropathic pain without the continual need for dose increase.

**Long-term effectiveness and safety of once-daily, single-entity, extended-release hydrocodone in patients of ≥75 years of age with moderate to severe nonmalignant and nonneuropathic pain**

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**Purpose**

Treating chronic pain in extremely old and frail patients (75 years of age or older) is challenging, especially with opioids. In these elderly individuals, increased susceptibility to opioid side effects, physiologic changes associated with aging, a higher incidence of co-morbid disease, and greater likelihood of polypharmacy complicate pain management. HysinglaER (HYD) is a once-daily, single-entity, extended-release formulation of hydrocodone with abuse-deterrent properties approved for the treatment of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The objective of this subanalysis was to determine the effectiveness and safety of HYD for the treatment of moderate-to-severe chronic pain among the elderly (≥75 years) for a 52-week duration.

**Method**

This post hoc analysis evaluated an elderly population (≥75 years) participating in a previously reported open-label study that examined the effectiveness and safety of HYD for the treatment of nonmalignant and nonneuropathic pain over a period of 52 weeks. Elderly patients ≥75 years with moderate-to-severe chronic nonmalignant and nonneuropathic pain received HYD doses ranging from 20 to 120 mg during a 52-week maintenance period following dose titration. Pain levels were recorded using “pain right now” and “pain over the previous 24 hours” scores on an 11-point numerical rating scale. In addition, pain severity and interference were assessed on a 0 to 10 scale using the Brief Pain Inventory-Short Form (BPI-SF). A treatment satisfaction questionnaire was administered to patients at week 4 of the maintenance period (or the end of study/early discontinuation for patients who discontinued study prior to week 4). Safety measures included adverse events, clinical laboratory test results, vital sign measurements, and electrocardiogram findings.

**Results**

Elderly patients (N = 24) presented an expected pattern of increased comorbidity and polypharmacy at baseline. They reported a clinically significant decrease in mean “pain over the last 24 hour” scores of 2.46 points during 52-week maintenance treatment with HYD (exceeding the minimum clinically important difference [MCID] threshold of 2.0), while pain interference was reduced by 2.0 points (exceeding the MCID threshold of 1.0). Furthermore, patients no longer required the use of additional nonopioids for pain control at the end of the study. The dose of HYD administered during the maintenance phase was relatively stable: 55% of patients did not require HYD dose change, while 20% increased their HYD dose by 20 mg, and another 20% decreased their dose. Patients reported a high level of satisfaction with the convenience and ease of use of HYD.

The most frequently observed AEs were gastrointestinal disorders, including constipation (54%), nausea (17%), vomiting (8%), and dry mouth (4%). Overall, 7 of 24 patients (29%) discontinued due to an AE during the titration and maintenance periods. There was no incidence of falls or fractures. There were no deaths. Serious AEs were reported for 5 (21%) patients, and were attributed primarily to the concurrent medical conditions expected in this population.

**Conclusions**

HYD provided clinically significant relief from chronic pain in the elderly population of this long-term study. HYD treatment was generally well tolerated among the elderly patients in this study.
Impact of a pharmacist-led, multi-disciplinary chronic pain service embedded within a large family medicine residency program
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Purpose
Chronic pain affects an estimated 100 million adults in the U.S. As awareness of this public health problem has increased, so too has the incidence of prescription opioid use, misuse, abuse, and unintentional overdose deaths. Increasingly, primary care providers are called upon to manage chronic pain while simultaneously incorporating accepted opioid risk mitigation and monitoring. Here we describe a multi-professional, pharmacist-led, primary care-embedded, chronic disease management service for patients with persistent pain requiring ongoing opioid therapy. The St. Louis University Family Medicine (SLUFM) Residency Pain Management Team practices under the tenets of 1) patient accountability and functionality, 2) non-pharmacologic modality incorporation, 3) non-opioid analgesic maximization, as well as opioid reduction. All patients referred to the SLUFM pain service must be empaneled patients already established with a primary care provider within the residency. The primary objective was to compare the change in total pain severity and total pain interference from baseline to last evaluable office visit. Secondary objectives include comparison of individual indices of the Brief Pain Inventory (BPI), the Patient Health Questionnaire (PHQ)-9, and the Current Opioid Misuse Measure (COMM), which patients are requested to complete at each office visit.

Method
This study was a one year, retrospective, chart review of all patients referred to the SLUFM pain service. Inclusion criteria included > 2 office visits and age > 18 years. General descriptive statistics and paired, two-tailed student’s t-test were performed using a common statistics software platform (IBM SPSS 21.0, Chicago, IL). Participants were also stratified based on age, gender, ethnicity, and numerous categories (e.g. depression, positive COMM screen, and 30% responder status). Correlations of parametric interval data were performed using the Pearson correlation.

Results
Of the 163 unique patients seen by the SLUFM pain service over the one-year study period, 110 meet inclusion criteria. Patients were seen an average of 3.7 (SD 1.7) times and were largely Caucasian (80.0%) and female (55.5%). Patients had a mean age of 50.0 yrs (SD 12.6). Most common chronic pain syndromes included chronic low back pain (44.5%), osteoarthritis (13.6%), fibromyalgia (9.1%), cervicalgia (8.2%), and migraine headache (5.5%). Brief Pain Inventory results were categorized into domains of Pain Severity and Pain Interference, with each containing four to nine Likert style 0-10 pain assessment questions. Severity included pain ratings for “now”, “average”, “least”, “worst”, and “total”. Interference, which refers to the patient’s perception of pain interference on individual components of functionality, included “activity”, “mood”, “walking”, “sleep”, “work”, “enjoyment”, and “relations”. Patient perception of overall pain relief with all modalities considered is also queried. Of these, only total pain interference (-5.98; p = 0.003), pain interference of mood (-0.76; p = 0.023), pain interference of work (-0.75; p = 0.032), pain interference on relationships (-0.68; p = 0.046), pain interference on sleep (-0.89; p = 0.012), and pain interference with enjoyment of life (-1.13; p = 0.002) were considered statistically significant reductions. While all of the pain severity indices appeared to be lower compared to baseline, none were statistically different. Patients also did not perceive a difference in % relief from all modalities between baseline and last visit. Defining a response as 30% improvement, 24 of 110 patients (21.8%) were responders based on the pain severity domain. Interestingly, 85 of 110 (77.2%) patients were considered responders based on 30% reduction of total pain interference scores. Opioid doses were maintained or reduced via wean or opioid rotation in all patients.

Conclusions
A pharmacist-led, multi-disciplinary pain service embedded within a large family medicine residency clinic may positively impact chronic pain patient outcomes in terms of functionality and pain interference with activities of daily living, but not pain severity or self-perceived relief. Further study is warranted to identify the best model for chronic disease management for patients with persistent pain, as well as the preferred outcome measures in which to assess patient improvement.

Psychometric validation of the electronic chronic pain questions in a primary care setting
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Purpose
Chronic pain is a disabling condition that affects a significant number of adults globally. It is associated with increased healthcare resource utilization and loss of productivity worldwide and is often not effectively screened, managed or treated in primary care settings. The electronic Chronic Pain Questions (eCPQ) is a 14-item instrument that was developed for use in clinical practice to capture key patient-reported outcomes in chronic pain (identified through a review of literature, guidelines and consultation with patients and clinicians) with the aim of assisting physicians to efficiently
assess, manage and monitor chronic pain patients in a primary care setting. The eCPQ includes items to identify patients experiencing chronic pain (pain on most days or every day in the past 3 months), to assess the intensity, location and type of pain, and to evaluate levels of pain interference with function, sleep and mood. The eCPQ was fully integrated into the electronic medical record (EMR) of a southeastern Michigan health system. This study evaluates the psychometric properties of the eCPQ in this primary care setting, including its concurrent validity with select ancillary measures, ability to discriminate between known patient groups, and its reproducibility.

Method

All men and women aged > 18 years who arrived to one of two similar primary care clinics, were invited to participate in the study. Clinic staff verbally administered the eCPQ to patients and recorded their answers directly into the EMR prior to patients seeing their physician. The results were available for review by the physician during the subsequent patient-physician consultation. After the visit, patients completed the following questionnaires: Pain Outcomes Questionnaire-Short Form (POQ-SF), the SF-36 (Version 1.0), the Hospital Anxiety and Depression Scale (HADS), the Medical Outcomes Study (MOS) Sleep Problems Index I, and the Fibromyalgia Survey Questionnaire (FSQ). Spearman correlations were performed between eCPQ and ancillary measures. T-tests and chi-square tests were performed to compare outcomes between patients with chronic pain versus no chronic pain. Known-group validity was assessed via two approaches: 1) stratifying patients based on self-reported chronic pain status (yes/no); and 2) grouping patients by pain diagnosis (i.e., EMR ICD-9 codes). ICD-9 diagnosis data were collected for the current visit and for the prior 12 months. Patients were invited to complete the eCPQ online within 3 days of their clinic visit (Time 1) to assess for mode effects (interviewer-administration vs. self-administration). Patients who completed the eCPQ online were invited to complete it a second time 6 to 9 days later (Time 2) to assess for reproducibility of the eCPQ over time. A subset of patients and staff members participated in a qualitative interview to discuss their thoughts on the eCPQ.

Results

Of patients invited, 455 participated (85.2% participation); 395 had analyzable eCPQ data. 70.1% were Caucasian, 68.1% female, and mean age was 43.4 years. 52.4% of participants were employed full or part-time. Slightly over half (n=208, 52.7%) reported to have chronic pain over the past 3 months. No major demographic differences between patients recruited from the two clinical sites were found.

Correlations between the eCPQ and ancillary measures supported concurrent validity. Excellent discrimination between groups was evidenced on the eCPQ when using self-reported chronic pain status. While significant discrimination was noted for the eCPQ items between “pain” and “no pain” patients based on ICD-9 pain diagnosis (current and past), the results were not as robust as the group comparisons based on self-report of chronic pain. Patients with self-reported chronic pain reported significantly (p<0.0001) higher pain ratings (5.7 vs 1.7) on the 0-10 pain rating and greater interference with usual activities, sleep, and mood than those without chronic pain. Similar group discrimination trends were noted for the POQ-SF, SF-36, HADS, MOS Sleep Problems Index I, and FSQ.

Test-retest reliability of the eCPQ from interviewer-administered to the self-administered at the initial web session (Time 1) was excellent (completed by 115 patients) with the Intraclass Correlation Coefficient (ICC) values ranging from 0.70 to 0.86 and Spearman's correlations ranging from 0.64 to 0.86 (p<0.0001). Test-retest reliability of the self-administered eCPQ from Time 1 to Time 2 among 84 patients was also excellent, with ICC values ranging from 0.81 to 0.93 and Spearman's correlations ranging from 0.75 to 0.88 (p<0.0001). Based on the qualitative interviews, patients found the eCPQ easy to answer and understand, and reported that it facilitated more in-depth discussion with their healthcare provider. Staff found the eCPQ to be useful and brief, estimating its administration time to be approximately 1 to 3 minutes.

Conclusions

Correlations between eCPQ and ancillary measures aligned with expectations, thereby supporting concurrent validity. Excellent discrimination between patients with and without chronic pain was demonstrated when using self-reported chronic pain status, as well as ICD-9 chronic pain diagnosis. Additionally, the eCPQ was found to have excellent reproducibility. In all, these findings suggest that the eCPQ has sound measurement properties. Finally, patients and staff found the eCPQ easy to complete and relevant to patient care. All of this suggests that the EMR-based approach would be useful to identify patients with chronic pain and to assess and monitor their symptoms over time.

Evaluation of the in vitro percutaneous absorption of ketoprofen transdermal formulations

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Purpose

The purpose of this study is to characterize the percutaneous absorption of 2 ketoprofen formulations (ketoprofen 10% in PLO and ketoprofen 10% in Lipoderm), when applied to the human cadaver trunk skin, in vitro, using the Franz diffusion cells to dose and culture the skin samples. It has been shown to be a valuable tool in predicting in vivo percutaneous absorption kinetics of topically applied drugs. Ketoprofen is an analgesic, anti-inflammatory agent that belongs to a class of drugs known as nonsteroidal anti-inflammatory drugs, widely used in the management of
chronic musculoskeletal pain. The risk of gastrointestinal complications associated with oral ketoprofen has led to an increase in demand for research and development of ketoprofen formulations for transdermal delivery. Ketoprofen can be incorporated into transdermal bases such as Pluronic Lecithin Organogel (PLO) or Lipoderm for delivery across the skin.

Method

The percutaneous absorption of ketoprofen was evaluated using human cadaver trunk skin from 3 donors. The skin from each donor was cut into small sections to fit on nominal 1 cm² Franz diffusion cells, chambers specially designed to maintain the skin at a temperature and humidity that match in vivo conditions. Within each chamber, the skin section was mounted on a diffusion apparatus so that the dermal layer is immersed in receptor solution while the epidermal surface is exposed to the ambient laboratory condition via the chimney. The receptor solution consisted of 1x-phosphate buffered saline, pH 7.4 ± 0.1, stirred magnetically at approximately 600 revolutions per minute within the receptor compartment. A variable finite dose of each formulation was applied to 3 replicate skin sections per donor, using a positive displacement pipette set to deliver 5 μL formulation/cm². At predetermined time points (0, 4, 8, 12, 24, 32, and 48 hr), the receptor solution within each chamber was removed, replaced with fresh receptor solution, and an aliquot was saved for analysis. After the last receptor sample was collected, each skin section was washed to remove unabsorbed formulation from the skin surface. Skin sections were then split into epidermis and dermis, and extracted overnight at room temperature in 50:50 ethanol:water. Ketoprofen content within the receptor solution and the skin were determined via high-performance liquid chromatography analysis of the extractant sample.

Results

To characterize the percutaneous absorption of ketoprofen, a total of 3 parameters were determined for each chamber, as follows: total absorption, rate of absorption, and skin content. Mean values and standard deviation were calculated for each parameter across the 3 donors and expressed as percentages of the applied dose. Total absorption was calculated as the sum of ketoprofen content within the 7 samples collected over 48 hr for each chamber. Rate of absorption, presented as flux (μg/cm²/hr) of ketoprofen into receptor solution, was determined by dividing the amount of ketoprofen absorbed during a time interval and the length of that interval. Skin content refers to the amount of ketoprofen detected within the dermis and epidermis after 48 hr. The mean total absorption of ketoprofen, when in Lipoderm (14.487% ± 1.905), was higher than when in PLO (5.513% ± 1.623). The higher mean total absorption of ketoprofen, when in Lipoderm, suggests that this base has greater penetration potential in comparison to PLO. When examining rate of absorption for both transdermal formulations, mean flux for ketoprofen was higher at each time point, when in Lipoderm, than when in PLO. The mean percentage of ketoprofen content detected within the receptor solution (total absorption), dermis, and epidermis were also summed to obtain a mean percent permeation of the applied dose through the stratum corneum. Penetration across the stratum corneum was 6.354% for ketoprofen in PLO and 16.048% for ketoprofen in Lipoderm. Though results of this study show that PLO and Lipoderm were capable of facilitating the penetration of ketoprofen through the stratum corneum and into underlying layers of the skin, mean percent permeation was higher for the Lipoderm formulation.

Conclusions

Higher mean total absorption, faster rate of absorption, and greater penetration across the stratum corneum observed with the ketoprofen in Lipoderm formulation suggest that Lipoderm may be a more appropriate base for the transdermal delivery of ketoprofen in comparison to PLO. Ketoprofen 10% in Lipoderm could potentially offer practitioners and pharmacists a viable alternative option for the management of chronic musculoskeletal pain.

Development of a monitoring tool to identify risk factors for opioid induced respiratory depression in surgical patients

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Purpose

Primary pharmacologic intervention for managing pain in surgery patients are opioid analgesics. When opioids are administered there is always a potential risk for opioid induced respiratory depression (OIRD). Identifying patients at risk for OIRD can reduce adverse events, increase patient safety and improve satisfaction. The Joint Commission also recommends patients are screened for respiratory depression risk factors. Multiple risk factors can influence the occurrence of oversedation and respiratory depression caused by opioids. The risk factors fall into two major categories, individual risk and iatrogenic risks. Individual risks are defined as patient-specific factors that predispose a person to unintended opioid induced oversedation and respiratory depression, such as disease states, age and weight. Iatrogenic risks are defined as pain therapy related and nurse practice variables that may predispose a patient to increased risk for unintended oversedation and respiratory depression, such as administering concomitant sedative or administering IV Push opioids. The objectives of this study were to develop and validate a pre-operative OIRD risk index tool to identify high-risk surgical patients base on patient specific factors and to retrospectively determine contributing iatrogenic factors that may contribute to oversedation and/or respiratory depression in patients who receive naloxone.

Method

This was a retrospective, observational, single-center study to determine the presence of established OIRD risk factors in
surgical inpatients. This study looked at 13,976 surgical patients in a two-year period. Patient risk factors include: age, airway obstruction, surgical procedure, cardiac, hepatic, pulmonary and renal dysfunction. The patient population was divided into two groups: post-operative patients who did not receive naloxone versus patients who received naloxone for OIRD. A logistic regression analysis occurred to determine the significant risk factors observed for the patient population. The logistic regression model was fit with naloxone administration as the dependent variable, and the model fit on the entire dataset was determined by first including all the potential predictors thereafter dropping the ones in which the p-value cut off of .15 was not met i.e., backwards selection of adjustment variables. Iatrogenic factors were evaluated in the patients who received naloxone. A multifactorial risk index was developed using this information to determine patients that are at risk for OIRD. The iatrogenic risk factors found in our hospital population will be used to make recommendations on how we monitor and/or treat high risk patients identified from the multifactorial risk index tool.

Results
The final multivariate logistic regression model included BMI, gender, and the following risk factors: Obstructive sleep apnea (OSA), renal dysfunction, hepatic and high risk procedure with a concordance index (c-statistic) of 0.74 which indicates good discrimination of naloxone administration. This model shows no evidence of lack of fit based on the Hosmer and Lemeshow Goodness-of-Fit test with a p-value of 0.16, and where the null hypothesis is the model adequately fits the data. We find the biggest effect size attributable to the hepatic risk factor for naloxone administration (OR: 3.60; 95% CI: 2.40, 5.40). The risk factor for OSA had the next largest effect size (OR: 2.396; 95% CI: 1.473, 3.898), which was then followed by the risk factor for renal dysfunction (OR: 2.396; 95% CI: 1.473, 3.898). The risk factor for surgery showed the smallest effect (OR: 1.617; 95% CI: 1.065, 2.477). Female patients were more likely to receive naloxone relative to males (OR: 1.676; 95% CI: 1.134, 2.477).

The population was divided into four groups: very high, high, moderate, and low risk. 1.6% of the patients were classified as a very high risk with 4.37% of these patients requiring naloxone. While 22% were defined as high risk with 1.85% requiring naloxone, 22.4% were defined as moderate risk with 0.8% requiring naloxone. Lastly, low risk patients comprising the remaining 54% with 0.32% requiring naloxone.

Looking at the iatrogenic risk factors, over 70% of the patients who received naloxone did so on post-op day 0 or day 1. A majority of the patients receiving naloxone (72.8%) were also receiving IV opioids within 12 hours of naloxone administration and over 55% of the patients were also administered a sedative within 12 hours of naloxone administration.

Conclusions
Most post-operative patients receive opioid analgesia, and there is an inherent risk for OIRD. Reduced adverse effects and an increase in patient safety can be obtained by identifying and monitoring patient at high risk for ORID. It is possible to classify surgical patients into four categories based on the presence or absence of five weighted risk factors. The higher the score the more likely the patient will require naloxone. Through identifying these patients, they can be monitored more carefully and/or opioid medications could be altered. This strategy could be useful in providing the patient with safe and effective pain management.

Intranasal human abuse potential of a novel abuse-deterrent formulation of immediate release oxycodone
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Purpose
The introduction of an abuse-deterrent formulation (ADF) of extended-release (ER) oxycodone resulted in significant reductions in reports of intentional misuse and abuse of ER-oxycodone; however, these reductions were associated with a concomitant increase in the abuse of immediate-release (IR) oxycodone. In an effort to address this “balloon effect,” a novel ADF of IR-oxycodone is under development that incorporates barriers to physical and chemical manipulation that increase the hurdles to intentionally misuse the formulation through routes of administration employed by prescription opioid abusers. To evaluate whether these physicochemical properties can reduce drug liking in vivo, a human abuse potential study was performed in nondependent recreational opioid abusers.

Method
This randomized, double-blind, double-dummy, placebo-controlled, 4-way crossover study evaluated the abuse potential and safety of equivalent doses of crushed intranasal Oxycodone ARIR (RoxyBond™, Inspirion Delivery Technologies, LLC) relative to a commercially available IR-oxycodone. Treatments included 30 mg of crushed intranasal Oxycodone ARIR, crushed IR-oxycodone, intact orally administered Oxycodone ARIR, and placebo.

Results
Twenty-nine subjects completed the clinical trial with a 47% reduction in maximum drug liking (P < .0001), a 72% reduction in early drug liking from 0-1 hour (P < .001), and a 59% reduction in early drug liking from 0-2 hours (P < .001) for crushed intranasal Oxycodone ARIR relative to crushed intranasal IR-oxycodone. Secondary endpoints were consistent with the primary endpoint.
Conclusions
Even though both formulations are IR products expected to provide equivalent safety and efficacy profiles when taken as directed, Oxycodone ARIR may have a lower intranasal abuse potential relative to IR-oxycodone.

Human abuse potential of a novel abuse-deterrent formulation of extended release morphine: evaluation of positive and negative drug effects following intranasal administration
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Purpose
Although only a small number of extended release abuse-deterrent products are currently available, epidemiologic evidence suggests that introduction of these products has had a marked impact on reducing misuse and abuse of these formulations. Unfortunately, these data also suggest that as abuse-deterrent formulations enter the market, abusers of prescription opioids migrate to non-abuse-deterrent extended release formulations or to immediate release formulations. An area of different approaches to abuse-deterrence are under investigation but most late stage or marketed formulations employ physiochemical barriers to increase the hurdles required for manipulation or include opioid antagonists or aversive agents to block euphoria or produce untoward adverse effects upon manipulation and illicit administration. To assess whether reductions in drug liking are associated with a reduction in the positive effects or an increase in the negative effects of different formulations, abuse potential studies incorporate a range of subjective drug effect assessments. These data help characterize the abuse potential and unique risks and benefits of each investigational product for both patients and intentional abusers of these powerful pain relievers. An abuse-deterrent formulation of extended release morphine that utilizes physiochemical barriers to resist physical manipulation, retain extended release characteristics even when manipulated, and form a non-syringeable material in aqueous environments to provide barriers to routes of administration commonly employed by abusers of morphine. Here we evaluate 8 subjective assessments collected from study subjects which include: Do you feel any drug effects? Does the drug make you feel sick? Do you have any nausea? Does the drug make you sleepy? Does the drug make you dizzy? The DEQ was administered pre-dose (when applicable) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours post-dose. For each question, subjects marked a vertical line on a 0-100 mm unipolar visual analog scale (VAS) anchored on the left by “none” (score of 0) through “extremely” on the right (score of 100).

Results
The primary variable of interest was met with statistically significant and clinically meaningful reductions in mean maximum drug liking (Emax, 45% reduction; P<.0001) as well as early drug liking from 0-1 hour (AUE0-1, 64% reduction; P=.0005) and 0-2 hours (AUE0-2, 59% reduction; P<.0001) for crushed intranasal Morphine ARER relative to crushed intranasal ER-morphine. Mean maximum effect (Emax) for crushed intranasal Morphine ARER was significantly lower for the ‘positive’ DEQ evaluations any effects (P=.0003), good effects (P=.0004), drug high (P=.0001) for crushed intranasal Morphine ARER compared to crushed intranasal ER-Morphine. Mean effect over time curves and statistical analyses of areas under the effects curves, especially at early time points, were highly consistent with both reductions in the Emax for each question in the DEQ and showed similar trends to the primary variable of interest, maximum drug liking. Mean Emax scores for the ‘negative’ DEQ evaluations sleepy, bad effects, and dizzy were not statistically different between crushed intranasal treatments; however, Emax for sick (P=.0141) and nausea (P=.0141) was significantly lower for crushed intranasal Morphine ARER compared with ER-Morphine. Thus study subjects reported significantly higher scores for sickness and nausea for crushed intranasal ER-Morphine relative to crushed intranasal Morphine ARER even though they liked ER-Morphine significantly more in all other assessments. There were no significant differences in Emax for any of the DEQ assessments when comparing crushed intranasal Morphine ARER and intact oral Morphine ARER suggesting similar abuse potentials despite physical manipulation and intranasal administration. When comparing crushed intranasal ER-Morphine and intact oral Morphine ARER, there were significant differences in any effects (P<.0001), good effects (P<.0001), drug high (P<.0001), bad effects (P=.0443), and sleepy (P=.0054) but no significant differences in sick, nausea, or dizzy.
Conclusions
Evaluation of secondary endpoints provides important information about both the abuse potential and unique risks or benefits of investigational opioids. The data herein suggest that the significant reductions in mean maximum drug liking, and therefore abuse potential, for Morphine ARER are driven primarily by the significant reductions in the positive effects, but not increases in the negative effects of the drug. Negative assessments were reported by subjects in all arms highlighting the importance of continuing to implement universal opioid prescribing precautions including the need to counsel patients about the known side effects and risks associated with opioid therapy.

Abuse deterrent reformulation of controlled release oxycodone is associated with persistently declining rates of abuse and diversion by both oral and non-oratal routes
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Purpose
Increasing prescription opioid use in the United States has had many unintended consequences. Increased availability of these medications increases the population of patients exposed to opioids, even when initially prescribed for appropriate medical indications. A significant proportion of the intended patient population, patients with painful conditions appropriately treated with opioids, has a combination of predisposing factors for addiction. Once these patients with risk factors are exposed, some are likely to progress to abuse and addiction, and as the exposed population increases, so does the number of at-risk patients exposed. Patients may also progress from swallowing their medication as intended to other routes of use. Studies of the “natural history” of prescription opioid abuse behavior suggest that patients may progress from swallowing, to chewing, crushing, snorting, and eventually injecting. Some patients may begin with an appropriate prescription for a painful condition, but venture toward unintended routes of use in an attempt to relieve their pain more quickly. However, once they begin to experience the enhanced psychotropic effects, along with pain control, this may increase their risk of addiction and the likelihood of further progression down this pathway. The most promising benefit of abuse deterrent formulations (ADFs) is to prevent initiation and progression down this spiral to addiction. A commonly abused formulation of oxycodone controlled release (OxyContin) was reformulated to be resistant to crushing and solubilization. The new formulation was introduced in August 2010. In this study, we compare the rates of OxyContin® abuse and diversion before and after the ADF reformulation.

Method
Data from four Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) System Programs were used. The average quarterly rates of diversion and abuse for controlled release oxycodone (OxyContin) were compared one year prior to reformulation to rates in the 4th quarter of 2014. The change in rates were compared to the change in rates for other opioid tablets and capsules during the same time frame. Other opioids included immediate release (IR) oxycodone, IR and extended release (ER) hydrocodone, IR and ER morphine, IR and ER hydromorphone, IR oxymorphone, IR and ER tramadol, and IR and ER tapentadol. Rates were adjusted for population and drug utilization through retail channels using the number of prescriptions dispensed.

Results
Rates of OxyContin abuse and diversion after adjustment for prescriptions dispensed significantly declined every quarter following the introduction of the abuse deterrent formulation. These declines were greater than changes observed for other opioids. In the Poison Center Program, the rate of OxyContin abuse declined by 72.6% from one year prior to reformulation to the 4th quarter of 2014, while other opioids declined by 37.1% (p < 0.001). In the Drug Diversion Program, the rate of diversion for OxyContin declined by 85.7% during the same time frame, while other opioids declined by only 21.6% (p < 0.001). In Opioid Treatment Programs, the rate of OxyContin abuse declined by 79.7%, while the rate for other opioids declined by 30.0% (p < 0.001). In the Survey of Key Informants Patients Program, the rate for OxyContin abuse declined by 58.1% while the rate for other opioids declined by 22.3% (p < 0.001). Abuse through both oral and non-oratal routes of self-administration declined following the reformulation. The geometric mean street price of the new formulation was 23% less than the original formulation.

Conclusions
Reformulation of OxyContin was associated with declining rates of abuse and diversion that were greater than those observed for other opioids. The decreased rates have persisted for 4 years. ADFs have potential to reduce the number of people who progress from oral overuse to other unintended routes of abuse such as snorting and injecting.

Medical Outcomes Associated with Unintended Routes of Prescription Opioid Abuse
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Purpose
Public health risks associated with injection drug abuse are well-documented and include increased risk of drug dependence, overdose, and infectious disease (e.g. HIV and Hepatitis C). For an oral (tablet or capsule) formulation of a drug, unintended routes include all non-oratal routes of
administration such as inhalation and injection. The severity of the immediate clinical outcomes associated with prescription opioid abuse via unintended routes has not been well studied. Poison centers receive large numbers of calls addressing the acute health effects of prescription opioids. We hypothesized that death and major medical outcomes would occur more frequently among prescription opioid abuse exposures reported to poison centers via unintended routes compared to oral ingestion.

Method

Data from the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) System Poison Center Program from 2006 through 2014 were limited to adult (>12 years) intentional abuse cases (an exposed individual) involving any oral prescription opioid product containing hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, or tapentadol and for which the case was followed to a known medical outcome. Analyses were focused on cases classified as Intentional Abuse ("an exposure resulting from the intentional, improper, or incorrect use of a substance where the patient was likely attempting to gain a high, euphoric effect or some other psychotropic effect, including recreational use of a substance for any effect") (National Poison Data System Manual, version 3.1, 2014). The severity of outcome was based upon standardized definitions of death-direct, major effect, moderate effect, minor effect, no effect, and unrelated effect. Percent of subjects with a death or major outcome were compared between exposures via oral ingestion (includes swallowing intact and crushed or chewed then swallowed) and those involving unintended routes (inhalation [includes snorting and smoking], injection, and other/multiple). Cases with unknown routes were excluded. Abuse exposures where multiple routes were reported were considered unintended route cases if any unintended route was reported. Relative risks were calculated for having an outcome of death or major effect (life-threatening or significant disability) given that the exposure involved an unintended route.

Results

There were a total of 25,432 intentional abuse exposures to prescription opioids identified. Of these, 17,837 intentional abuse exposures met the inclusion criteria of a known medical outcome during the period of interest. Of these, 2,321 (13.0%) involved unintended routes, 11,093 (62.2%) reported oral ingestion only, and 4,423 (24.8%) had unknown routes. Among all unintended route cases, 11.7% resulted in death or major medical outcomes compared to 7.2% of oral ingestion. The proportion of cases resulting in death or major medical outcomes was highest for injection followed by inhalation, other/multiple routes, and oral ingestion. These data suggest acute safety risks associated with unintended routes of prescription opioid abuse, in addition to the known long-term public health concerns. Additional interventions are warranted to curb the increasing prescription opioid abuse via unintended routes and, in turn, mitigating both the immediate and long-term associated risks.

Conclusions

Based upon RADARS Poison Center data, unintended routes are associated with more severe medical outcomes than abuse via oral ingestion. The proportion of cases resulting in death or major medical outcomes was highest for injection followed by inhalation, other/multiple routes, and oral ingestion. These data suggest acute safety risks associated with unintended routes of prescription opioid abuse, in addition to the known long-term public health concerns. Additional interventions are warranted to curb the increasing prescription opioid abuse via unintended routes and, in turn, mitigating both the immediate and long-term associated risks.

Screening of 122 drugs of abuse in urine on a triple quadrupole mass spectrometer

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Purpose

Forensic toxicologists face an ever-expanding list of compounds for analysis. Traditionally, compounds are analyzed in standard panels by immunoassay, GC (gas chromatography), GC-MS (GC-mass spectrometry), or LC-UV (liquid chromatography coupled to ultra violet spectrometer), depending on the compounds being targeted. LC-MS (liquid chromatography-mass spectrometry) systems can accommodate a wider variety of compounds on a single platform in a single analytical run, thereby saving time and money. In addition to the standard panels, forensic scientists need to frequently add new designer drugs to the list of targeted compounds. LC-MS also has an advantage over other technologies in the ease by which new compounds can be added to existing methods.

In large panels, scan speeds of triple quadrupole mass spectrometers can limit the number of data points acquired, impacting sensitivity and quantitative performance. Performance can further deteriorate when an analysis involves polarity switching and very narrow peaks.

This poster presents work done using a next-generation triple quadrupole mass spectrometer with fast SRM acquisition speed for quantitation of 122 analytes in a single chromatographic run. Compounds analyzed include opiates, opioids, benzodiazepines, barbiturates, amphetamines, tricyclic antidepressants, illicit compounds, and more.

Method

Samples were processed by enzymatic hydrolysis followed by liquid-liquid extraction (LLE). Briefly, an aliquot of urine was
spiked with internal standard and incubated with β-glucuronidase enzyme. The resulting mixture was extracted using Amtox A™ liquid-liquid extraction tubes (Ameritox Labs, Hilliard, OH). The organic layer was dried and reconstituted before an aliquot was subjected to gradient HPLC separation and subsequent detection on a Thermo Scientific™ TSQ Endura™ triple quadrupole mass spectrometer. The injection volume was 10 μL and the total run time was 15 minutes.

Calibrators and controls were prepared by spiking compounds into blank synthetic urine in the range of 0.5 to 500 ng/mL. The upper calibration range was limited by the concentration of stock solutions used in making the multidrug spiking solutions.

In this method, two selected-reaction monitoring (SRM) transitions were monitored for each of the 122 analytes to obtain ion ratio confirmation (IRC), and one SRM transition was monitored for each of the 84 stable isotope-labeled internal standards used. A total of 328 transitions were monitored in both positive and negative mode. Data were acquired and processed, including performing ion ratio calculations, by Thermo Scientific™ TraceFinder™ software.

Limits of detection, precision, and accuracy were evaluated by processing and analyzing calibrators and replicate controls. Matrix effects were determined by spiking 12 different lots of blank donor urine at 10 ng/mL and comparing results to that of a sample prepared in water.

Results

Limits of quantitation were defined as the lowest concentrations that had back-calculated values within 20%, ion ratios within defined tolerance, calibration curve with R2 values >0.9, and quality controls with %RSD within 20%. Using these criteria, forensic cutoffs were met, and in many cases exceeded, for the compounds tested in this study. Intra-assay precisions for quality control replicates were within 17% across all concentrations and all compounds, and most were within 10%.

Passing matrix effects were defined as a back-calculated concentration of ±50% of nominal. Less than 2% of the results failed for compounds that had stable isotope-labeled analog internal standards, whereas 21% of the results were out of range for compounds without a stable isotope-labeled analog as the internal standard.

Conclusions

• A single analytical LC-MS method was developed for 122 chemically diverse compounds, including both polar and non-polar analytes as well as positively and negatively ionizing compounds. Stable isotope-labeled analog internal standards are crucial to minimize matrix effects.
• The fast scanning speed and polarity switching of the TSQ Endura mass spectrometer enabled the analysis of all 122 compounds plus 84 stable-isotope labeled internal standards (328 total transitions) without a loss of signal intensity.
• A single sample processing scheme was used for all compounds, making the method efficient.

• Forensic toxicological limits of quantitation were met or exceeded.

Change in the rate of diagnosed opioid addiction/dependence among individuals dispensed OxyContin after its reformulation with abuse-deterrent characteristics compared to comparator opioids

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Purpose

Abuse of prescription opioids is a serious public health problem. This study assessed the effect of reformulating OxyContin with abuse-deterrent characteristics in August 2010 on rates of diagnosed opioid addiction/dependence in a commercially insured population. The objective of the study was to assess changes in rates of diagnosed opioid addiction/dependence associated with OxyContin dispensed without concomitant opioids in the year before versus three years after its reformulation as compared to changes in rates associated with comparator opioids dispensed without concomitant opioids. This study time frame was requested by FDA for post marketing requirement studies for OxyContin. The analyses focused on use of single opioid use only so that the effect of that opioid could be isolated without disturbance by other concomitant opioids, but does not take into account other external factors that might have led to changes.

Method

A retrospective cohort study was designed using Truven MarketScan Commercial data. Separate cohorts were created for OxyContin and four comparator opioids: extended-release (ER) morphine, ER oxymorphone, IR hydromorphone and immediate-release (IR) single-entity oxycodone. Changes in rates for the one year before (August 2009-July 2010) vs. three years after (November 2010-October 2013) the introduction of reformulated OxyContin were assessed. Rates per 100 person years of opioid use were calculated for each time period. Person time accumulation began at the date of the initial dispensing of opioid and ended at the occurrence of an event or at the end of a dispensed opioid use episode, whichever came first. The event of interest was diagnoses of opioid addiction/dependence and was defined using ICD-9-CM codes (304.0x or 304.7x). Opioids used by cases diagnosed with opioid addiction/dependence associated with OxyContin dispensed without concomitant opioids in the year before versus three years after its reformulation as compared to changes in rates associated with comparator opioids dispensed without concomitant opioids.
Results
The rate of diagnosed opioid addiction/dependence per 100 person years of OxyContin use among individuals dispensed OxyContin without concomitant opioids decreased by -25% (95% CI -33% to -16%, p<.0001) from the year before to three years after reformulation, from 4.0 to 3.0 per 100 person years of use. For the four opioid comparator groups, the rate of diagnosed addiction/dependence per 100 person years of opioid use for ER morphine increased 21% (95%CI: 4% to 40%, p 0.0154), for ER oxymorphone increased 13% (95% CI -14% to 48%, p=0.3860), for ER hydromorphone increased 31% (95%CI: 12% to 54%, p 0.009) and for IR single-entity oxycodone increased 7% (95%CI: -1% to 16%, p=0.0825) from baseline. The decrease from baseline for OxyContin was significantly greater than changes from baseline for ER morphine (p <0.0001), ER oxymorphone (p=0.0064), IR hydromorphone (<0.001) and IR single-entity oxycodone (<0.001). After the introduction of reformulated OxyContin, the rate of diagnosed opioid addiction/dependence was lower among individuals dispensed OxyContin (3.0 per 100 person-years of use) compared to individuals prescribed comparator opioids (3.2 for ER morphine, 6.0 for ER oxymorphone, 4.9 for IR hydromorphone, and 5.6 for IR oxycodone single-entity per 100 person-years of use).

Conclusions
There was a significant decrease in the rate of diagnosed addiction/dependence per 100 person years of OxyContin use among individuals in this database dispensed OxyContin from the year before to 3 years after reformulation of OxyContin. This decrease was significantly different from the change from baseline for two comparable ER opioids and two IR single-entity comparator opioids.

In vitro and in vivo evaluation of, and fda approved labeling for, the abuse-deterrent properties of hysingla® er, a once-daily, single-entity, hydrocodone bitartrate formulation
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Purpose
Extended-release opioid formulations may be manipulated in attempts to increase the amount or rate of active ingredient absorbed. It is important for extended-release opioid formulations to be formulated to resist intentional abuse and accidental misuse. Rigorous premarketing studies were performed to evaluate the abuse-deterrent properties of Hysingla® ER.

Method
Laboratory-based in vitro studies (Category 1) were designed to simulate abuser manipulations. Hydrocodone/acetaminophen (HCD/APAP) and/or Hysingla® ER tablets were physically manipulated using commonly available household devices ranging from simple tools to mechanized grinders. The effort expended in manipulation was recorded and the release rate and recovery of hydrocodone from HCD/APAP, and from intact or manipulated Hysingla® ER were measured. Preparation for intravenous abuse was assessed through testing many experimental variables.

Two randomized, double-blind, placebo and active-comparator studies in nondependent opioid abusers were conducted to characterize the abuse potential of Hysingla® ER following physical manipulation and administration via the intranasal and oral routes (Category 3). For each study, primary subjective pharmacodynamic (PD) measures included visual analog scores (VAS) for “At This Moment” Drug Liking and Feeling High. Plasma hydrocodone concentrations were measured from blood samples collected and safety was assessed.

Results
In vitro studies demonstrated that Hysingla® ER resists crushing, breaking, and dissolution using a variety of tools and solvents and retains some extended-release properties despite manipulation. In water, it forms a viscous hydrogel that resists passage through a hypodermic needle.

Clinical studies indicated that Hysingla® ER fine and coarse particle size intranasally administered and Hysingla® ER chewed orally was associated with statistically significantly lower mean scores for “At This Moment” Drug Liking and Feeling High compared to hydrocodone powder (P<0.001) or hydrocodone solution (P<0.001), respectively.

Conclusions
In vitro manipulation and extraction studies demonstrated that Hysingla™ ER has properties expected to deter intranasal and intravenous abuse. Clinical studies of abuse potential with support from in vitro studies also indicated that Hysingla™ ER has physicochemical properties expected to reduce intranasal abuse and oral abuse when chewed.

The FDA has approved labeling regarding abuse deterrent properties of Hysingla™ ER. It is recognized that abuse is still possible, via the intravenous, intranasal, and oral routes. Actual abuse-deterrence will be assessed through postmarketing epidemiology studies (Category 4).

Pharmacokinetic profile and sustained 24-hour analgesia following administration of a novel hydrocodone single-entity, once-daily, extended-release tablet [Hysingla™ ER] formulated with abuse-deterrent properties: results of two studies
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Purpose
To review steady-state pharmacokinetic (PK) and analgesic data following once-daily dosing with Hysingla® ER based...
on two studies: Steady-State PK, and a Long-Term Effectiveness and Safety.

Method

**PK study:** Open-label, multiple-dose, two-period, crossover. Twenty-four subjects were dosed with Hysingla® ER 30mg or Vicoprofen for 3 days. Twenty-four hour steady-state PK profiles were obtained on day 3 of each treatment period.

**Long-term study:** Open-label, Hysingla® ER 20 to 120 mg tablets were administered to 922 patients with moderate-to-severe chronic nonmalignant and non-neuropathic pain; 728 patients stabilized on a HYD dose during dose titration and entered the 12-month maintenance period. Short-acting opioid rescue analgesics were permitted. “Pain right now” scores, for evaluation of analgesic effect over the 24-hour dosing interval, were collected twice-daily: immediately prior to HYD dosing (which generally occurred in the morning) and at approximately 8 pm.

Results

**PK study:** Systemic exposure (AUC24,ss) and average plasma concentration (Cavg,ss) of hydrocodone at steady state after once-daily administration of HYD were equivalent to that after every 6-hour administration of Vicoprofen. Mean peak to trough hydrocodone ratio at steady state was reduced from 2.4 (Vicoprofen IR) to 1.6 (HYD ER).

**Long-term study:** HYD administered once-daily produced sustained analgesic effect over the 24-hour dosing interval, with “pain right now” scores ranging from 3.3 to 3.6 on a 0-10 11-point numerical rating scale (NRS). There was limited use of rescue opioid analgesics and a low rate of discontinuation due to lack of therapeutic effect.

Conclusions

Once-daily, single-entity, extended-release HYD provided consistent plasma hydrocodone concentrations (PK study) and sustained analgesia over the 24-hour dosing interval (long-term study).

**Effects of exercise on select biomarkers and associated outcomes in chronic pain conditions: Systematic review**

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**Purpose**

Chronic pain is highly prevalent affecting approximately 116 million people. Persistent difficulty in pain management has resulted to this high prevalence and subsequently, excessive healthcare costs. Current management and research in chronic pain are challenged by lack of consistent and validated biological markers with pain typically assessed using self-reports. Several studies have examined biomarkers to improve our understanding of the underlying mechanisms in chronic pain. Consequently, clinical trials employing exercise, a common intervention in chronic pain, have evaluated biomarkers as biological measures in addition to behavioral chronic pain outcomes.

To date, studies have shown that biomarkers in many pathways (e.g., ion channels, sodium channels, purinergic receptors, glutamate receptors, inflammatory markers, neurotransmitters, and neurotrophins) are associated with chronic pain mechanisms. Genetic markers involved in nociception are thought to be implicated in these mechanisms more than degenerative markers. Nociception is commonly explained through the peripheral pain pathway mechanism. Biomarkers within these pain pathways (e.g., inflammatory markers, neurotransmitters, and molecular receptors detecting metabolites that influence pain) involved in transduction, conduction, transmission, or modulation of pain response have been examined as therapeutic targets in chronic pain clinical trials.

However, it is a question whether biomarkers are useful objective measures in chronic pain. To synthesize the state of knowledge translating the potential utility of biomarkers in chronic pain, this systematic review assessed data from published clinical trials to identify the influence of exercise on biomarkers along the pain pathways and evaluate the association between these biomarkers and pain-related outcomes in chronic musculoskeletal nonmalignant pain conditions.

**Method**

Two authors independently conducted systematic literature searches. Search words included “chronic pain,” “musculoskeletal”, “exercise,” “biomarker,” “genes,” “proteins,” “blood,” “serum,” “plasma,” and various combinations of these words. Databases included PubMed, BioMed Central, Academic Search Premier, CINAHL, Web of Knowledge, Scopus, and Cochrane. Hand searches in bibliographic references were also completed resulting to retrieval of 693 studies. However, only 12 studies met the inclusion criteria (published in English with no limit in publication period, diagnosed with musculoskeletal chronic non-malignant pain condition, employed exercise interventions, and measured biomarkers). Studies using pharmacological interventions, measuring biomarkers outside the pain pathways, or having participants with non-chronic pain comorbidities were excluded.

The Jadad Scale was utilized in this systematic review as a widely known, valid, and reliable instrument for evaluating the methodological quality of pain research trials. This is an 11-item instrument with 2 items having a potential 2-point score with a total maximum score of 13 points. Items included questions regarding randomization, double blinding, control or comparison groups, objectives and outcome measures, inclusion and exclusion criteria, sample size, interventions and adverse effects, withdrawals and dropouts, and statistical analyses. Three authors independently reviewed each study using the Jadad Scale.
Results

Jadad scores ranged from 5-11 out of 13 points for the 12 studies included in this systematic review. Four studies were randomized clinical trials while the rest were case-control clinical studies. No study was double blinded, and all studies had either a control and/or a comparison group, identified their objectives, and reported clearly defined outcome measures. One study did not clarify inclusion/exclusion criteria and only two studies had adequate sample sizes based on power analysis. All studies described their interventions but only one described the method used to assess adverse effects of their intervention, while five studies did not meet criteria in describing participant completion of intervention. All studies reported methods of statistical analyses used.

The 12 studies were published between 2006-2013. One study had more male participants; the rest were predominantly female. Pain conditions included chronic low back pain (2), ankylosing spondylitis (1), knee osteoarthritis (2), fibromyalgia (3), and chronic fatigue syndrome (4). Various exercise interventions included stretching, strength training, squats, aerobics, cycling, pool exercises, and spa-exercise therapy, with duration ranging from 3-4 weeks to 18 months.

Biomarkers most commonly evaluated in the pain pathways post-exercise were inflammatory markers, followed by neurotransmitter-related genes, and metabolite detecting-markers. Anti-inflammatory markers like interleukin (IL)-10 in chronic fatigue syndrome and transforming growth factor (TGF-β1) in ankylosing spondylitis and low back pain were significantly increased post-exercise. Several pro-inflammatory markers were significantly decreased in knee osteoarthritis (IL-6, Tumor Necrosis Factors [TNF]-α) and fibromyalgia (IL-1β, TNF-α, IL-6, IL-8, IL-18, interferon gamma, C-reactive protein). Neurotransmitters like Catechol-O-methyltransferase (COMT) and adrenergics were increased in chronic low back pain, fibromyalgia, and/or chronic fatigue syndrome.

Further, COMT and some inflammatory markers were significantly associated with pain, disability, fatigue, anxiety, and depression after exercise interventions. However, laboratory quality control measures were not consistently reported with varying methodology in the studies reviewed.

Conclusions

A hypoalgesic effect of exercise in some chronic pain conditions was implicated in the studies reviewed with significant decreases in several pro-inflammatory markers, increases in select anti-inflammatory markers, and upregulation of certain neurotransmitters. The potential translational value of biomarkers in chronic pain is evident although it remains a question whether biomarkers can be utilized as objective measures for risk assessment, diagnosis, and evaluation of chronic pain progression. Study replications, adequate sample sizes, and longitudinal research with consistent methodologies are warranted. Advancing genomic science is vital while incorporating a comprehensive biobehavioral perspective in progressing individualized healthcare and improving chronic pain management.

In vitro evaluation of a novel immediate release formulation of oxycodone for the potential for abuse via injection

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Purpose

The introduction of abuse-deterrent formulations of extended release opioids into the market appears to have significantly reduced rates of misuse and abuse of these products but epidemiologic data suggest that abusers of prescription opioids may simply switch to immediate release formulations to circumvent abuse deterrence. A novel abuse-deterrent formulation of immediate release oxycodone, Oxycodone ARIR (abuse resistant immediate release), has been developed to help prevent switching to immediate release opioids. Oxycodone ARIR tablets incorporate a proprietary abuse-deterrent technology that makes tablets difficult to manipulate and resist extraction in widely used solvents. These tablets are difficult to crush and prepare for absorption with most household tools but even if they are manipulated with a coffee grinder, the resulting particles form a coarse powder that alters the intended release profile and rapidly forms a material that resists passage through a needle when subjected to a liquid environment. Taken together, these unique properties are designed to create significant hurdles to commonly used methods of manipulation and routes of administration for abuse, thereby achieving abuse deterrence while avoiding the potential risk of using opioid antagonist or aversive agents. Because in vivo injectability abuse potential studies are not considered safe for study participants, in vitro tests are commonly employed to characterize their abuse-deterrent properties. To evaluate the potential for abuse of Oxycodone ARIR tablets via injection, a comprehensive series of in vitro syringeability and small volume extraction studies were performed.

Method

Syringeability and extractability of Oxycodone ARIR 30 mg tablets (RoxyBond™, Inspirion Delivery Technologies, LLC) relative to commercially available IR-Oxycodone tablets were performed according a prespecified protocol. Briefly, Oxycodone ARIR tablets (n=5) were either left intact, cut with a knife, or ground (crushed) in a coffee grinder for 60 seconds and placed in glass vials containing either 5 or 10 mL water for 1, 5, 10, and 30 minutes with and without agitation (100 RPM). At each time point, attempts were immediately made to draw the mixture into a 10 cc syringe fitted with 27-, 24-, or 18-gauge needle. Difficulty was assessed by the laboratory technician on a scale of 1 (very easy to syringe) to 10 (impossible to syringe). All tests were completed in an iterative fashion whereby the smallest needles were tested first; if passage through the needle was successful the larger needles were not tested. Finally, if any liquid was syringeable, the volume was recorded and analytically tested for oxycodone.
**Results**

Crushed IR-Oxycodone was easily syringed into small needles (27 gauge) and released more than 90% of its oxycodone within 1 minute in these extraction experiments. In contrast, manipulated Oxycodone ARIR tablets (tablets cut with a knife or crushed in a coffee grinder) immediately formed a material that was difficult to syringe and did not produce a meaningful amount of liquid, even through large 18 gauge needles. Subjecting manipulated samples to agitation or adding additional manipulated tablets to the mixture did not increase the oxycodone released or resulted in a completely non-syringeable sample. In some cases, a small amount of liquid was syringeable but contained visible particulate that would not be suitable or safe for intravenous injection. For example, in non-agitated samples, 2 mL from 5 mL experiments and 7 ml from 10 mL experiments was syringeable from both crushed and cut Oxycodone ARIR tablets; however, under these ‘optimal conditions’ for extracting and injecting oxycodone from Oxycodone ARIR tablets, a maximum of 19% of oxycodone was released at room temperature and a maximum of 33% was released at near boiling temperatures (90°C). In general, earlier time points and lower temperatures resulted in less oxycodone release. No dose dumping was observed at any time point under any of the conditions evaluated.

**Conclusions**

The inherent physiochemical properties within Oxycodone ARIR significantly increased the hurdles required to successfully prepare the formulation for injection. Even though tablets are designed to release oxycodone immediately when administered as directed, very low levels of oxycodone were injectable even after very long 30-minute time points under rigorous laboratory conditions. Overall, these data suggest that Oxycodone ARIR has abuse-deterrent properties that may aid in reducing abuse via injection.

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**A case study in the use of mindfulness-based biofeedback treatment on psychological adjustment in chronic pain**

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**Purpose**

The objectives of this case study are two-fold: 1) Examine the utility of a Mindfulness-Based Biofeedback Treatment program that could be delivered as part of a rehabilitation program for individuals with pain; and 2) Examine the benefits and challenges of this Mindfulness-Based Biofeedback Treatment approach in affecting psychological adjustment in persons living with chronic pain.

**Method**

Patient with chronic pain was seen for an intensive outpatient, twice a week, 4-week Mindfulness-Based Biofeedback Treatment program within the Shepherd Pain Institute. Pre and post-intervention data regarding emotional health and pain is compared. Emotional health is assessed using the Beck Depression Inventory II, Beck Anxiety Inventory, Stress Arousal Checklist, Perceived Stress Scale, and Self-Compassion Inventory. Pain intensity is measured using subjective report at the time of first and last intervention.

**Results**

Results of pre- and post-intervention findings on measures of adjustment and pain will be reported. We will examine the ways in which these treatment modalities can be implemented in a rehabilitation setting.

**Conclusions**

Individuals with complex medical diagnoses often experience physical and emotional needs that fluctuate considerably. An integrated treatment approach, such as Mindfulness-Based Biofeedback Treatment, combines mind-body medicine to more thoroughly address combined physical and psychosocial needs.

**Incorporating psychophysiological training via mindfulness-based biofeedback treatment in psychoeducational pain management groups**

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**Purpose**

Patients with chronic pain may experience physical and emotional needs which may fluctuate tremendously. The resulting physiological impact is often inadequately resolved with an exclusively medically-based program. A truly holistic treatment approach responds to the needs for an integrative model which combines mind-body medicine to more thoroughly address combined physical and psychosocial needs.

**Method**

To add Mindfulness-Based Biofeedback Treatment training to a traditional psychoeducational pain group and examine the benefits and challenges in such adaptation.

**Results**

Mindfulness-Based Biofeedback Treatment facilitates effective coping and stress management for patients with pain. The combination of biofeedback and mindfulness meditation allows patients to learn to control physiological processes such as respiration, heart rate, and muscle use while at the same time learning to accept the sometimes unpredictable waxing and waning of pain symptoms. The incorporation of biofeedback and mindfulness based training into group therapy results in education-based interventions...
which are more readily accepted and therefore successfully incorporated into patient care due to their consistency with the medical rehabilitation model requiring active participation in treatment.

Conclusions
A truly holistic treatment approach responds to the necessity for an integrative model which combines mind-body medicine to address both physical and psychological needs. Incorporating the physiology of self-regulation through biofeedback and mindfulness training into group treatment fosters an educational model which achieves this goal.

TRV250: a novel G protein-biased ligand at the delta receptor for the potential treatment of migraine
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Method
Based on data suggesting that G protein coupling without β-arrestin2 engagement at the DOR would reduce seizure liability, we identified TRV250, a novel small molecule G protein-biased ligand targeting the DOR. Rat and mouse models of migraine pain, medication overuse headache, central sensitization, depression, and anxiety suggest potential for the treatment of migraine. Activity in models of migraine, TRV250 shows promise as a potential new class of therapy for treating migraine.

Results
Compared to unbiased agonists AZD2327 and SNC80, TRV250 has potent, full efficacy for G protein coupling (EC50 = 1 nM), but much weaker engagement of β-arrestin2 (EC50 = 126 nM with 30% efficacy vs. unbiased ligands). TRV250 is highly selective for the DOR versus a panel of more than 130 other targets, including the mu and kappa opioid receptors. In rat nitroglycerin-induced hyperalgesia models of migraine, TRV250 showed robust efficacy after both subcutaneous and oral dosing (ED50 = 0.8 and 12 mg/kg, respectively), with consistent exposure-response relationships across dose. Estimated free plasma concentrations at active doses were consistent with predicted delta receptor occupancy. TRV250 was also active in mouse models of migraine, medication overuse headache, and central sensitization, as well as the tail suspension and novelty induced hypophagia tests of depression and anxiety. TRV250 had no observable effect in the mouse rotarod test of neurobehavioral deficit at doses up to 30 mg/kg.

Conclusions
TRV250 shows promise as a potential new class of therapy for the treatment of migraine. Activity in models of migraine, central sensitization, depression, and anxiety suggest potential utility of TRV250 for treating migraine as well as other CNS disorders. TRV250 pharmacology and pharmacokinetic/pharmacodynamics relationships are consistent with selective activation of the delta receptor by TRV250. The broad margin for CNS activity vs. seizure liability differentiates TRV250 from previously published unbiased DOR agonists. Preclinical development to support future clinical trials of TRV250 is underway.

Assessing the percent of days linaclotide improved abdominal symptoms and stool frequency in patients with irritable bowel syndrome with constipation (IBS-C): pooled analysis of 2 Phase 3 trials
Satish Rao1, Lin Chang2, Xinming Hao3, Bernard Lavins*3, Steven Shiff4, Xiaofan Cao4, Mark Currie3 & Jeffrey Johnston3

Purpose
Linaclotide (LIN), a minimally absorbed guanylate cyclase C agonist (GCCA), improved abdominal symptoms and bowel movement (BM) frequency in patients (pts) with IBS-C in 2 Phase 3 trials. This post-hoc analysis determined the % of days pts reported improvements in abdominal symptoms and BMs with LIN or placebo (PBO) treatment.
Method
In 2 Phase 3 trials, pts with IBS-C (Rome II criteria) were randomized to LIN 290 μg qd po or PBO. Using pooled intent-to-treat (ITT) data from the 1st 12 wks of both trials, we determined 1) % of days with ≥30% improvement in either abdominal pain, discomfort, bloating, cramping or fullness (for pts with an average baseline score ≥3 out of 10 for each respective parameter) and 2) % of days with a spontaneous BM (SBM) or a complete SBM (CSBM).

Results
The pooled ITT population included 797 PBO- and 805 LIN-treated pts. During the 2-wk Baseline Period, pts had an SBM on a mean of 24% of days and a CSBM on a mean of 3% of days. Pts in subgroups with an average baseline abdominal symptom score ≥3 experienced ≥30% improvement in the specific abdominal symptom on a significantly greater % of days for LIN vs PBO. LIN treated pts had ≥30% improvement in abdominal pain for 55% of days vs 41% for PBO (p < 0.0001). Results were similar for other abdominal symptoms, with LIN-treated pts achieving ≥30% improvement for ~50% of days during the Treatment Period; PBO pts met the threshold on 33-42% of days. LIN also significantly increased the % of days with SBM/CSBM vs PBO.

Conclusions
LIN improved abdominal symptoms (pain, discomfort, bloating, fullness and cramping) by ≥30% on ~50% of treatment days and significantly increased the % of days with SBM/CSBM. Thus, LIN relieved key IBS-C symptoms and increased the % of days with symptom improvement. These data provide estimates for results of treatment with LIN that clinicians and pts may anticipate.

Knowledge, skills, and attitudes of pain management among pharmacy students
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Purpose
Pain is the most common reason Americans seek healthcare, and it affects more Americans than heart disease and diabetes combined. Analgesics are consistently among the “Top 100 Dispensed Drugs” list. Pharmacists can play in improving safety and efficacy of analgesics. In 2012, the Strategic Planning Summit for Pain and Palliative Care Pharmacy Practice outlined core competencies for pharmacy students and recommended a proposed 5-hour curriculum. To date, these suggestions have not been adopted nationally or systematically. At the University of Maryland School of Pharmacy, first-year pharmacy students receive 15 content hours regarding pain management. Our module covers the pain content recommended by the Summit. Recorded lectures are used in this unit. The purpose of this study is to describe the knowledge, skills, and attitudes related to pain management among pharmacy students at University of Maryland School of Pharmacy before and after the pain module in the curriculum.

Method
A case-based survey was developed to evaluate self-perceived knowledge and attitudes related to 10 domains of pain management, including the importance and frequency that a pharmacist would use this knowledge and skill in practice. This survey was administered before and after the pain module. Surveys also included questions related to study habits and learning preferences. Actual knowledge and skill was determined at the end of the module by a written multiple-choice computer-based examination (ExamSoft) and an Objective Structured Clinical Exam (OSCE). The pain OSCE was designed to measure knowledge-based skills and soft skills such as empathy. The OSCE was piloted with 4th year pharmacy students prior to use. Students were incentivized to complete all surveys with bonus points equivalent to 1% of their course grade. Changes in self-perceived knowledge and attitudes were evaluated with chi-square and Fisher’s exact test. Descriptive statistics were used to analyze exam scores.

Results
150 student pharmacists participated in the pre-course survey and 127 completed the post-course survey. After the pain module more respondents believed selecting non-drug therapy (80.3% vs. 65.77% baseline, p = 0.025) and designing an equianalgesic drug regimen (60.63% vs. 41.61% baseline, p = 0.0113) were essential skills a pharmacist should possess. Moreover, the expected frequency of performing these tasks increased. Students reported that a pharmacist would frequently (e.g. on a daily basis) monitor patients for analgesic drug toxicity (37.5% vs. 22.97% baseline, p = 0.0156) and design equianalgesic regimens (21.43% vs. 9.66% baseline, p = 0.0093). Students perceived knowledge gains in all 10 domains (p < 0.0001). Student (n=156) performance on the written examination (mean = 75%; median = 77.5%) and the OSCE (mean= 69.6%; median of 69.9%; interquartile range 63.4-76.0%) suggested most had reasonable knowledge mastery but most had skill deficits. Specifically, on the OSCE, only 11.5% of students recommended an analgesic regimen that would fully meet the needs of the standardized patient and 12% adequately addressed opioid-related drug related problems. In addition, only 25.6% of students appropriately recommended a combination of nonpharmacologic and pharmacologic approaches. Lastly, while 97.5% responded to the standardized patient's emotional needs and cues, only 39.5% consistently responded in a perceptive and genuine manner.

Conclusions
Pharmacy students' knowledge, skills, and attitudes regarding pain management are improved after a 15-hour lecture-based pain module, but students were not able to consistently apply...
Efficacy and safety of n1539, a novel intravenous formulation of nanocrystal meloxicam, in subjects with moderate to severe pain following dental impaction surgery
Randall J. Mack*1, Stephen A. Cooper2, Wei Du3 & Alex Freyer1
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Purpose
To evaluate the efficacy and safety of single doses of N1539 compared with placebo and active control (ibuprofen), in subjects with acute moderate to severe pain over the first 24 hours following surgical removal of impacted third molars. This study was designed to evaluate a dose range of N1539 (15-60 mg) in an otherwise healthy acute pain population, and characterize the duration of analgesic effect. N1539 is a novel intravenous (IV) formulation of NanoCrystal Colloidal Dispersion™ meloxicam, being developed for the management of acute moderate to severe pain.

Method
This was a randomized, double-blind, double-dummy, placebo-controlled, single center study in subjects who had undergone surgical extraction of >2 third molars, at least one of which was to be a partial or complete mandibular bony extraction. Healthy male and female subjects, aged 18 years or greater were enrolled with written informed consent. Participation consisted of a screening visit, an inpatient period including surgery and 24 hours of evaluation following dosing, and a follow-up phone call 3 to 5 days post-dose. Following oral surgery, subjects who experienced moderate to severe pain within five hours after surgery, were randomly assigned to treatment in two cohorts with placebo, ibuprofen 400 mg, or N1539 15, 30, or 60 mg. Treated subjects received a single study dose under double-dummy conditions (oral and IV active/placebo administration). Efficacy assessments included Pain Intensity (PI) assessed using a 100 mm visual analog scale (VAS), and Pain Relief (PR) assessed using a 5 point scale, at intervals over the 24-hour post-dose period. Time to perceptible and meaningful pain relief were evaluated using the double stopwatch method. Rescue analgesia, hydrocodone/acetaminophen, was available for pain not relieved by the study drug. The primary efficacy endpoint was the Summed Pain Intensity Difference from Hour 0 to Hour 24 (SPID24) after dosing. Safety assessments included clinical laboratory tests, vital signs, ECGs, and monitoring of adverse events (AEs).

Results
N1539 was demonstrated to be safe and effective across the studied dose range. For the primary efficacy analysis, the greatest SPID24 values were seen for the N1539 60 mg group followed by the 30 mg, 15 mg, and ibuprofen groups. Statistically significant differences for SPID24 were seen between each N1539 group compared to placebo (P<0.001), and for the N1539 60 mg and 30 mg dose groups compared to the ibuprofen group (P<0.001 and P=0.002, respectively). Statistically significant PI differences (PIDs) were detected among the groups at every time point in the study, and were apparent as early as 10 minutes post-dose, continuing through the 24-hour evaluation period. PR scores at each time point, as well as summed PR from Hour 0 to Hour 24 (TOTPAR24), were generally greatest in the N1539 60 mg group, followed by the 30 mg, 15 mg, ibuprofen, and placebo groups; statistically significant differences were seen among the groups at every time point during the study. Meaningful pain relief was achieved by 10% of placebo subjects, compared to 92% in the N1539 60 mg group, 86% in the 30 mg group, 76% in the 15 mg group and 78% in the ibuprofen group; the difference between each active treatment and placebo was statistically significant. Approximately 93% of placebo subjects required rescue medication during the study, compared to 28%, 58%, 58%, and 72% in the 60 mg, 30 mg, 15 mg, and ibuprofen groups, respectively. There were no deaths, serious AEs (SAEs), or discontinuations due to AEs reported during this study. The frequency of AEs was low and comparable between treatment groups, with events reported by more than one subject in the study including: nausea, vomiting, and headache.

Conclusions
Overall, N1539 was demonstrated to be safe and effective in comparison to placebo and active control. The N1539 60 mg dose produced the greatest reduction in pain, followed by the 30 mg and 15 mg doses, with statistically significant differences seen between the treatment groups and placebo. The onset of analgesia was rapid, with statistically significant differences in PID and PR detected as early as 10 minutes post-dose, and sustained through Hour 24 in SPID24 and TOTPAR24. Treatment with N1539 was well-tolerated with no deaths, SAEs, or discontinuations due to AEs reported, and a low incidence of AEs.

Efficacy and safety of N1539, a novel intravenous formulation of NanoCrystal meloxicam, in subjects with moderate to severe pain following open abdominal hysterectomy
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Purpose
To evaluate the efficacy and safety of single doses of N1539 compared with placebo and active control (morphine), in subjects with acute moderate to severe pain over the first 24 hours following open abdominal hysterectomy. This study was designed to evaluate a dose range of N1539 (5-60 mg) in an otherwise healthy acute pain population following soft tissue surgery. Additionally, this study allowed for open-label
safety and efficacy assessment of N1539 administered once daily for up to seven doses. N1539 is a novel intravenous (IV) formulation of NanoCrystal Colloidal Dispersion® meloxicam, being developed for the management of acute moderate to severe pain.

Method

This was a multicenter, randomized, double-blind, placebo- and active-controlled study in female subjects, aged 18-65 years in otherwise good health, undergoing open abdominal hysterectomy. Study participation included a screening visit with written informed consent, an inpatient surgery and treatment, and a follow-up visit after hospital discharge. On Postoperative Day 1, qualifying subjects with moderate to severe pain were randomized in two cohorts to receive placebo, morphine 10-15 mg, or N1539 5 mg, 7.5 mg, 15 mg, 30 mg, or 60 mg. All subjects were unblinded after 24 hours, and evaluated as responders or non-responders. Subjects randomized to N1539 who were responders, and those randomized to placebo or morphine who were non-responders, were eligible to receive once daily dosing with N1539 on an open-label basis while IV analgesia was required during hospitalization. Efficacy assessments included Pain Intensity (PI) assessed using a 100 mm visual analog scale (VAS), Pain Relief (PR) assessed using a 5-point scale, rescue analgesia use, and a global evaluation score, at intervals over the 24-hour double-blind phase, and beyond in open-label use. Time to perceptible and meaningful pain relief were evaluated using the double stopwatch method. Rescue analgesia, morphine, was available for pain not relieved by the study drug. The primary efficacy endpoint was the summed PI difference from Hour 0 to 24 (SPID24) and total PR from Hour 0 to 24 (TOTPAR24) after dosing. Safety assessments included clinical laboratory tests, vital signs, ECGs, and monitoring of adverse events (AEs).

Results

This study included 460 evaluable subjects age 25-65 years in the efficacy analysis. The greatest SPID24 scores were seen in the N1539 30 mg and 60 mg groups followed by the 15 mg, 5 mg, 7.5 mg, morphine, and placebo groups, with a statistically significant difference among groups (P<0.001). Statistically significant differences in SPID24 were seen for each N1539 group compared to placebo (P<0.001), and for N1539 60 mg, 30 mg and 15 mg compared with morphine (P<0.003). The greatest TOTPAR24 scores were seen in the N1539 30 mg, 60 mg and 15 mg groups, followed by the 5 mg, 7.5 mg, morphine and placebo groups, with a statistically significant difference among groups (P<0.001). Statistically significant differences in TOTPAR24 were seen for all N1539 doses and morphine compared to placebo (P<0.001), and for the N1539 60 mg, 30 mg, and 15 mg doses compared to morphine (P<0.001). Statistically significant PI differences (PID) from baseline were detected as early as 10 minutes postdose and continued throughout the double-blind phase for all N1539 doses. The majority of subjects in the N1539 60 mg (97.5%), 30 mg (100%), 15 mg (98.3%), 7.5 mg (88.8%), and 5 mg (93.3%) dose groups and the morphine group (96.7%) reported meaningful PR during the double-blind phase, compared to 31.7% in the placebo group. Rescue medication use during the double-blind phase was lower in all N1539 groups - 60 mg (38.8%), 30 mg (36.7%), 15 mg (45.0%), 7.5 mg (62.5%), 5 mg (60.0%) - compared with morphine (76.7%) and placebo (95.0%). No deaths were reported during the study, five subjects experienced SAEs with none assessed as related to treatment, and one subject discontinued due to an AE. AEs were generally similar across groups, the most commonly reported AEs included: ketonuria, anemia, insomnia, nausea, constipation, and flatulence.

Conclusions

This study demonstrated N1539 as an effective treatment for moderate to severe pain following open abdominal hysterectomy. Overall, N1539 30 mg and 60 mg doses produced the greatest reduction in PI (SPID24), and were the only dose groups to maintain a >50% reduction in pain for the entire double-blind phase. Rescue medication use, perceptible and meaningful PR, and global evaluation scores were more favorable in all N1539 groups compared to placebo during the double-blind phase. Treatment with N1539 was well-tolerated with no deaths, no treatment related SAEs, one discontinuation due to an AE, and a low incidence of AEs.

Migraine and nausea: evaluation of patients treated with diclofenac potassium for oral solution

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Purpose

Nausea and vomiting are common symptoms of migraine and major causes of migraine disability. Both symptoms can also interfere with oral drug absorption, thus significantly hindering treatment of migraine. In turn, some treatment options can cause or aggravate nausea. As analyses of migraine treatments in patients who experience nausea are lacking, we evaluated the effectiveness of migraine treatment with diclofenac potassium for oral solution (DPOS; Cambia®, Depomed, Newark, CA) vs. an equivalent placebo in patients with or without nausea at the time of dosing, and, after treatment, we determined nausea symptoms in patients who were nausea-free at dosing.

Method

This was a post-hoc analysis of data pooled from two randomized, placebo-controlled trials of DPOS in patients with acute migraine. Adult migraineurs treated one moderate or severe attack with 50 mg DPOS (dissolved in approximately 2 ounces of water) or matching placebo. The co-primary endpoints
were the percentages of patients who were pain-, photophobia-, phonophobia-, and nausea-free at 2 hours. Subgroups analyzed included patients with nausea or no nausea at time of dosing. P-values for comparisons between DPOS and placebo were from Cochran-Mantel-Haenszel test (center stratified); for comparisons between patient subpopulations with no nausea vs. with nausea at dosing, p-values were from the z-score. The significance level was set to p≤0.05.

Results

The integrated population included 1272 patients-628 dosed with DPOS and 644 dosed with placebo. At dosing, 61.6% of patients reported nausea (DPOS, 62.3%; placebo, 60.9%). Patient demographics were similar between DPOS and placebo, and between patient subpopulations. The mean age was 39.8 years (no nausea, 40.1 years; nausea, 39.6 years) and 89.0% were Caucasian (no nausea, 88.2%; nausea, 89.6%). The only difference between patients with no nausea vs. nausea at dosing was in the proportion of females-overall, 85.4% were female (no nausea, 79.4%; nausea, 89.2%; p<0.001).

Pain-, photophobia-, and phonophobia-free responses at 2 hours after dosing were significantly greater for DPOS than placebo (all p<0.01), and similar for patients with or without nausea at the time of dosing. Pain-free response at 2 hours (no nausea/nausea) was 25.7/24.6% for DPOS and 13.1/9.4% for placebo; photophobia-free response at 2 hours was 54.0/44.8% for DPOS and 42.9/33.4% for placebo; phonophobia-free response at 2 hours was 57.0/50.9% for DPOS and 43.7/36.0% for placebo.

For patients with nausea at dosing, more were nausea free at 2 hours when treated with DPOS vs. treated with placebo (50.1% vs. 35.2%, p<0.001). Furthermore, smaller proportion of patients with no nausea at dosing developed nausea after receiving DPOS compared with placebo (11.8% vs. 17.9%; p=0.048).

Conclusions

The efficacy of DPOS in treatment of acute migraine was not affected by whether or not patients were experiencing nausea at the time of treatment. It also significantly reduced symptoms of nausea in patients who were already nauseated. Furthermore, rates of treatment-emergent nausea were lower with DPOS than with placebo. These results suggest that DPOS is an effective treatment option for acute migraine, including in patients who experience nausea and those who are sensitive to migraine medications that cause nausea.

The 5% lidocaine patch decreases opioid use and postoperative pain in sternotomy patients: Prospective, double blind, placebo controlled study

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Purpose

Post-sternotomy pain (PSP) is one of the major concerns of patients’ discomfort after cardiac surgery. To reduce PSP, we used 5% lidocaine patch at the sternotomy site and evaluated its effect on the PSP.

Method

In a prospective, double blind, placebo controlled manner, the patients receiving sternotomy under general anesthesia were randomly allocated to receive 5% lidocaine patch (L group) or placebo (P group) on each side of the wound at the end of the surgery (44 P group and 62 L group). At 6, 12, 24 and 48 hours after surgery, the degree of the pain was investigated. The dose of rescue opioid use, incidence of nausea/vomiting/sleep disturbance, use of anti-emetics were also evaluated.

Results

Opioid use for postoperative pain control was significantly decreased in L group. And L group reported significantly less pain over all study periods. However, there were no differences in other outcome variables between the groups.

Conclusions

Application of lidocaine patch on each side of the incision site can reduce opioid use and postoperative pain in patients receiving sternotomy.

New pain therapies with low inherent abuse potential; are prodrugs an answer to the opioid abuse epidemic: a review

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Purpose

One potentially important step towards the goal of creating safer opioid analgesics has been the development of opioids that are formulated to deter abuse. The FDA considers the development of these products a high public health priority. The Institute of Medicine estimates that approximately 100 million people suffer from chronic pain in the United States. Prescription opioids are an important component of chronic pain management. However, increased access to opiates has contributed to the current epidemic of drug abuse and diversion leading to significant morbidity and mortality related to opioid abuse. According to recent CDC estimates more than 16,000 deaths every year are attributed to opiate overdose.

Most of the abuse deterrent opioid formulations available and in development are intended to make abuse by manipulation more difficult or less rewarding. Also, the presence of abuse deterrent properties does not mean abuse is not possible, it rather means that the potential of abuse is lower than it
would be without those properties. Some examples include formulations that are harder to crush or chew or those combined with antagonists to prevent manipulation. Although novel and beneficial strategies, these technologies have not yet proven to be successful at deterring the most common form of overuse or abuse: swallowing multiple intact capsules or pills (known as oral overconsumption). Prodrugs and new molecular entities are also a category that the FDA document called “Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling” recognizes as having the potential for abuse deterrent properties.

**Method**

A prodrug is a pharmacologically inert molecule that is metabolized or breaks down chemically or enzymatically in vivo to produce the active ingredient. The active molecule typically is a parent drug (for analgesics, an opioid). The intact prodrug would ideally be inactive and would only be activated after oral administration. There are opioid prodrugs that are not abuse deterrent because they are activated by ubiquitous enzyme systems; an example is codeine which converted to morphine by the cytochrome P450 enzyme CYP-2D6. Codeine gets into the bloodstream and activated whether taken orally, intranasal administration or through intravenous (IV) administration. Prodrugs that are activated by digestive tract specific enzymes could have abuse-deterrent properties. Prodrugs would remain inactive when introduced by non-oral routes (IV, inhalational or nasal) because the digestive tract specific enzymes are not found elsewhere. Also, if the activating system can be saturated, this could limit the potential for abuse and possibly overdose by oral overconsumption.

In making the prodrug, the new chemical attachment can alter the solubility and extractability of the parent drug. If the prodrug is poorly water soluble, it could help with tamper resistance because it could be difficult to extract. Once extracted it would need to be chemically treated to release the parent drug. The cleavage reactions would likely require multiple additional steps including harsh chemical reactions, neutralization, and isolation which may eventually lead to a significant loss of yield.

**Results**

Studies have shown that abusers on average want to spend no more than 10 minutes tampering with the formulations and are deterred when the yield is low. Thus, prodrugs may be inherently tamper-resistant.

Our literature search on abuse-deterrent prodrugs yielded very limited, if any, published articles in this area, especially as related to opioid analgesics. We did find published data showing evidence of reduction in non-oral routes of lisdexamfetamine abuse (intranasal and intravenous) both in the laboratory setting and abuse trends in substance abuse treatment population when Vyvanse<sup>®</sup> was developed to combat the prescription drugamphetamine abuse when it was rampant in the early 2000s.

There are numerous ways that a prodrug approach could contribute toward making an opioid pain reliever with low-abuse potential. It is a technology that could be combined with other abuse-deterrent technologies, such as those with physical barriers, antagonist or aversive formulations, or extended release formulations, creating a new formulation with even greater abuse deterrent properties.

KemPharm is a pharmaceutical company that is taking the prodrug approach to making opioid analgesics with lower potential for abuse than the parent compounds. Their two most advanced compounds are KP201 (benzhydrocodone hydrochloride), a prodrug of hydrocodone that is being developed in combination with acetaminophen (APAP), and KP511, a prodrug formulation of hydromorphone. In (preclinical studies), both compounds have demonstrated significant abuse-deterrent and tamper resistant properties. KP201/APAP is intended to be the first abuse-deterrent version of the most widely prescribed opioid analgesics, immediate-release hydrocodone/acetaminophen combination products, with a planned NDA submission in late 2015. In animal models, KP511, currently in the preclinical stage, has shown significantly reduced intranasal and IV bioavailability, limited oral bioavailability at high supratherapeutic doses, as well as high tamper resistance.

**Conclusions**

Prodrug formulations have great potential for creating abuse-deterrent analgesics. They can be inherently tamper-resistant without the need of special formulations, and, if activated in the digestive tract, they will have little to no bioavailability if administered IV or intranasally. In addition, if this activation system can be saturated, the oral bioavailability at high doses could be limited, possibly conferring some overdose protection. Like all abuse-deterrent analgesics, prodrug formulations will require post-marketing studies to determine whether they result in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death in the post-approval setting.

The Pharmacokinetics, bioavailability, abuse-deterrent and tamper-resistant properties of KP201/APAP, a combination opioid pain reliever containing a hydrocodone-based prodrug, a review

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**Purpose**

Recent CDC reports estimate that there are more than 16,000 deaths/year attributed to overdoses of opiate pain relievers. The FDA considers the development of safer opioid pain relievers that are formulated to deter abuse and are tamper resistant a high public health priority. Prodrugs are one category that the FDA Guidance for Industry recognizes as having the potential to provide these properties.
KP201 (benzhydrocodone) is a prodrug of hydrocodone that is designed to provide the same efficacy for pain relief as immediate-release hydrocodone medications while providing abuse-deterrent and tamper-resistant properties. KP201 uses a technology developed by KemPharm that chemically links hydrocodone with a ligand that is generally recognized as safe, creating a new molecular entity that is poorly water soluble. This prodrug is designed to be metabolized in the digestive system resulting in the release of the active drug-hydrocodone. The release of hydrocodone from KP201 should be negligible if taken by parenteral routes, ie. Intravenous, inhalation, or intranasal. KP201 can be formulated with acetaminophen (APAP) similar to immediate-release hydrocodone/APAP products.

The purpose of these studies was to: 1) Compare the bioavailability of KP201 and KP201/APAP with that of immediate-release hydrocodone bitartrate/APAP (Norco®) after administration of single doses in healthy volunteers under fasted conditions; 2) Investigate the multiple-dose pharmacokinetics (PK) and bioavailability of KP201/APAP in healthy volunteers; 3) Investigate the effect of food on the bioavailability of hydrocodone and APAP from KP201/APAP in healthy volunteers; and 4) Investigate the abuse-deterrent and tamper resistant properties of KP201 and KP201/APAP.

Method

The PK of KP201 and KP201/APAP were studied in 4 trials with healthy human volunteers. Safety and adverse events were monitored in each trial. The trials included:

- The oral bioavailability and PK of hydrocodone and hydromorphone, the major metabolite of hydrocodone, after administration of single doses of KP201 (5 or 10 mg doses) compared to hydrocodone bitartrate/APAP (10 mg/325 mg) (Norco®) in 24 subjects
- The oral bioavailability and PK of hydrocodone, hydromorphone and APAP after administration of single doses of KP201/APAP (6.67 mg/325 mg) compared to hydrocodone/APAP (7.5 mg/325 mg) in 30 subjects
- A single and multiple-dose PK and bioavailability study of KP201/APAP (6.67 mg/325 mg) in 26 subjects. The multiple dosing regimen included 13 doses of 2 tablets of KP201/APAP every 4 hours
- The effects of food on the PK and bioavailability of KP201/APAP (6.67 mg/325 mg) in 30 subjects

Additional studies included:

- The abuse-deterrent properties of KP201 compared with the parent drug (hydrocodone) studied in:
  - Intranasal PK studies in rats
  - IV PK studies in rats

The tamper resistant properties of KP201 were investigated by:

- Extractability studies of KP201

- Studies on the stability of KP201 to hydrolysis (hydrolysis creates the parent drug, hydrocodone)

The activity of the intact prodrug (KP201) at opioid receptors was studied in vitro

Opioid receptor activity of KP201: Receptor binding assays showed that KP201 has insignificant affinity to the enteric μ-opioid receptors.

Results

The PK study of single dose of KP201 revealed:

- The high-dose (10 mg) of KP201 and the Norco® comparator were bioequivalent based on exposure to hydrocodone and hydromorphone
- Release of hydrocodone from KP201 was dose-linear between low-dose and high-dose treatments
- Type, severity and timing of AEs were similar for KP201 and Norco®

The comparator PK and bioequivalence trial of a single dose of KP201/APAP (6.67 mg/325 mg) with Norco® (7.5 mg/325 mg) revealed:

- Bioequivalence was demonstrated between KP201/APAP and Norco® for hydrocodone, hydromorphone, and APAP
- There were no unusual or unexpected AEs related to the study medication
- The single and multiple dose PK and bioavailability study of KP201/APAP revealed:
- The PK of hydrocodone and APAP are linear and predictable after administration of single and multiple doses of KP201/APAP
- There were no unusual or unexpected AEs related to the study medication

Food effects study on PK and bioavailability of KP201/APAP

- When KP201/APAP was administered with a meal, there was no overall change in exposure to hydrocodone or to APAP that would be of clinical significance
- There were no unusual or unexpected AEs related to the study medication

Abuse deterrence studies in rats: Intranasal administration of KP201 in rats resulted in significantly reduced exposure to hydrocodone (AUC 23% of parent drug). In the intravenous PK of KP201 in rats, KP201 was poorly soluble in aqueous media, as a result the amount that could be injected was significantly lower compared to hydrocodone bitartrate and very little hydrocodone appeared in circulation after the injections of KP201.

Tamper Resistance of KP201: Extraction studies yielded only the inactive prodrug. The prodrug was demonstrated to be chemically stable and only hydrolyzes and/or decomposes under harsh conditions.
Conclusions

KP201/APAP is a novel combination pain reliever containing a hydrocodone prodrug that demonstrates abuse-deterrent and tamper resistant properties. Both of the active components of KP201/APAP are bioequivalent to the hydrocodone and APAP components in immediate-release hydrocodone bitartrate/APAP (Norcot®). There was no measurable systemic exposure of the prodrug in any of the studies and no unusual or unexpected AEs related to the study medication. KP201 is poorly water soluble; extraction yields only inactive prodrug; and is chemically stable and only hydrolyzes and/or decomposes under harsh conditions. KP201/APAP can be administered without regard to meals.

Comparison of the effect sizes of ketorolac nasal spray and commonly prescribed oral combination opioids in moderate to severe short-term pain

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Purpose

Successful treatment of moderate to severe short-term pain is a clinical challenge in many medical conditions. Opioids are frequently used for the treatment of moderate to severe short-term pain, but there are concerns about this treatment approach. A recent metaanalysis compared the effectiveness of opioid analgesics for postoperative pain after third molar surgery, an excellent model of moderate to severe short-term pain, but omitted oral tramadol HCl formulations and ketorolac tromethamine nasal spray (Sprix® Nasal Spray; Egalet, Wayne, PA), a nonsteroidal anti-inflammatory product indicated for the short-term (up to 5 days) management of moderate to moderately severe pain requiring analgesia at the opioid level. The objective of this study was to use an effect size analysis of pain relief outcomes to compare the effectiveness in moderate to severe short-term pain of ketorolac nasal spray with oral combination opioid formulations of hydrocodone, oxycodone, and tramadol.

Method

An effect size analysis of 3 randomized, double-blind, placebo-controlled studies in young adults undergoing third molar extraction surgery compared pain relief with ketorolac nasal spray and commonly prescribed combination opioids including hydrocodone/acetaminophen (APAP) 7.5/500 mg, hydrocodone/APAP 10/650 mg, oxycodone/APAP 5/325 mg, oxycodone/ibuprofen 5/400 mg, tramadol HCl/APAP 37.5/325 mg, and tramadol HCl/APAP 75/650 mg. In each study, patients were randomized to receive postoperative pain medications when pain intensity was rated ≥50 mm on a 100-mm visual analog scale. Effect size comparisons were made using total pain relief scores (TOTPAR6 or TOTPAR8; the weighted sum of pain scores through 6 or 8 hours). Pain relief was measured with a 5-point categorical rating scale (0-4; 0=none, 1=a little, 2=some, 3=a lot, 4=complete). The effect size equivalent correlation, r, was determined using an online effect size calculator (http://www.uccs.edu/~lbecker/).

Results

According to established criteria, an effect size r value of 0.20-0.49 represents a small treatment effect, 0.50-0.79 represents a moderate treatment effect, and ≥0.80 represents a large treatment effect compared with placebo. TOTPAR6 data indicated a moderate effect size for ketorolac nasal spray (0.51) and oxycodone/ibuprofen 5/400 mg (0.64) and a small effect size for hydrocodone/APAP 7.5/500 mg (0.24) and oxycodone/APAP 5/325 mg (0.32). TOTPAR8 data indicated small effect sizes for ketorolac nasal spray (0.48), hydrocode- done/APAP 10/650 mg (0.43), tramadol HCl/APAP 75/650 mg (0.35), and tramadol HCl/APAP 37.5/325 mg (0.17).

Conclusions

The treatment effect sizes of ketorolac nasal spray were similar to or higher than each of the opioid comparators in the setting of postoperative pain after third molar surgery, a well-accepted pain model. These results support that ketorolac nasal spray is an effective treatment for moderate to moderately severe short-term pain.

Nonmedical prescription pain reliever and alcohol consumption among cannabis users: Changes between 2003 and 2013 in the United States

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Purpose

This study examined whether more frequent use of cannabis was associated with a compensatory decline in the misuse of prescription pain relievers and alcohol. A secondary question addressed how changes in consumption of these substances were linked to expanded access to legalized medical cannabis and regulations targeting the availability of prescription pain relievers from 2003-2013. The current study used data from the 2003 to 2013 National Survey on Drug Use and Health, prior to the first statewide retail legalization of cannabis in 2014. Before 2003, three states legalized cannabis for medical purposes only. Between 2003 and 2013, seventeen additional states legalized medical cannabis. In 2014, cannabis was legalized for retail purposes in Colorado and Washington, and later in the District of Colombia, Oregon and Alaska. Under the substitution hypothesis, it should be expected that over the 10-year period from 2003 to 2013, alcohol and nonmedical prescription pain reliever users would shift toward using greater amounts of cannabis over time. There would also be compensatory decreases in the frequency of prescription pain relievers and alcohol use. Moreover, the relationship would be stronger in 2013, as more states had enacted medical cannabis while there were multiple policy policies implemented to restrict access to prescription pain relievers.
Method
The National Survey on Drug Use and Health (NSDUH) is an annual computer-aided, interviewer-assisted survey of non-institutionalized U. S. civilians aged 12 years or older. Additional sample details are available elsewhere. (SAMHSA, 2013) The yearly data from 2003 to 2013 were used to test for trends in substance use over time. Among dual users, the frequency of past-year cannabis use was categorized into separate quartiles for each year (i.e., 2003 and 2013) based on the number of days used. Separate cut-points were used for 2003 and 2013 rather than using the same cut-points across years. A Generalized Estimating Equation (GEE) modeling approach was first used to test for a linear statistical trend between 2003 and 2013 using a single continuously distributed variable representing survey year. Separate models were estimated for cannabis, NMPR, and alcohol. The next set of analyses examined the relationship between cannabis and the use of either NMPR or alcohol. A set of analyses were estimated for 2013, the most recent year of NSDUH data and also the year prior to the legalization of marijuana for retail sales. The comparison year of 2003 was chosen because it captured a window of ten years prior to 2013. Also, there was a NSDUH redesign such that the data from 2002 or prior cannot be directly compared to 2003 or later. Therefore, there was a natural break in the ability to compare years.

Results
Past-year cannabis use increased 16% (10.8% to 12.6%) from 2003 to 2013, whereas nonmedical prescription pain reliever use declined by 14% (4.9% to 2.2%). Alcohol use remained stable at about 65.5%. Persons engaging in both prescription pain reliever misuse and cannabis use declined from 2003-2013 (2.5% to 2.2%), but increased for dual users of cannabis and alcohol (10.2% to 11.6%). Higher levels of cannabis use were consistently associated with more frequent consumption of prescription pain relievers and alcohol, with findings replicating in both 2003 and 2013. The average frequency of nonmedical prescription pain reliever use (NMPR) for those who also used cannabis increased from 2003 to 2013, an average of 20 days. There were only modest changes in alcohol use among cannabis users over time.

Conclusions
Consistent with the changes in the larger policy-wide climate, the prevalence of past-year cannabis use over the 10-year period increased while the prevalence of prescription pain reliever misuse decreased. There were no changes in the prevalence of alcohol use. Overall, the findings presented here suggest a synergistic relationship, where NMPR and alcohol were observed to be positively associated with cannabis in terms of the frequency of use. Interestingly, the mean number of days of dual use actually increased over a 10-year period, suggesting greater opportunities for harmful side-effect interactions.
a function of nerve growth (figure 4) vs. no nerve growth (figure 5). Average pain and numbness scores and percent improvement were lower in the nerve growth group.

Data presented in this study document convincing anatomic evidence that CET regenerates nerves, and thus supports its clinical utility in improving the symptoms of neuropathy. Functional improvement has been presented elsewhere (4): a strong correlation in nerve conduction sensory testing (NCS) with A-Delta NCS has been shown between symptom improvement and improving A-Delta NCS score.

Conclusions

Previous studies confirm that CET is safe and effective in the treatment of peripheral neuropathy. Symptom improvement is noted in 70-80% of cases. In contrast, RCTs show 39% of patients receiving maximum doses of pregabalin have a 50% reduction in pain and at least 38% have complications.

Results with CET are in sharp contrast to inferior symptom improvement and undesired side effects of treating neuropathy with pregabalin. Potential cost savings with CET, based on annual pregabalin medication costs, absence of side effects with CET, prevention of chronic wound infections and amputations in diabetic patients with physiological healing of nerves will be substantial.

Pain and genetics: Study of different genes that are prevalent in different pain patients

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Purpose

The objective of study is to determine prevalent genes in patients diagnosed with lumbago (low back pain) versus patients diagnosed with pain in limb

Method

197 pain subjects diagnosed with low back pain (ICD9 code 724.2) or pain in limb (ICD9 code 729.5) were selected from fifteen clinical sites in the United States. 101 patients were diagnosed with low back pain (mean age 60, 68 females, 33 males). 96 patients were diagnosed with pain in limb (mean age 60, 65 females, 31 males). Subjects were genotyped for a panel of 12 SNP’s using TaqMan SNP genotyping assays (Life Technologies, Carlsbad, CA).

Results

A cross tab analysis using IBM SPSS found a significant association between low back pain and pain in limb with MTHFR C677T (p= 0.023, Two sided Fisher’s Exact 0.029) and 5-HTTLPR (p=.020; Two sided Fisher's Exact 0.026). A logistic regression found that MTHFR C677T homozygous (T/T) and heterozygous (C/T) variations are more prevalent amongst subjects with low back pain compared to those with pain in limb (p=0.023, OR: 1.952). The logistic regression also found that 5-HTTLPR homozygous (A/A) and heterozygous (G/A) variations are more prevalent amongst subjects with pain in limb compared to those with low back pain (p= 0.023, OR: 2.012).

Conclusions

This study suggests that certain genes may be prevalent amongst pain patients diagnosed with low back pain compared to those diagnosed with pain in limb. These findings suggest that different genes may be prevalent in different pain patients. Knowledge of these genetic differences can hopefully help guide clinicians in future genetic therapeutic approaches.

Genetics and drug response: study on the influence of genetics in individual variations in response to hydrocodone use

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Purpose

Opioids are one of the most prescribed classes of medications in the United States. In particular, hydrocodone and oxycodone account for more than half of all opioid prescriptions. Though it is known that drug response is subject to individual variation, little is known about the genes that may account for this variation. The objective of this study is to determine the role of genetics in individual analgesic response variations to hydrocodone use.

Method

This study included 637 pain subjects (292 males, 345 females) across 40 clinical research sites in the United States. The analgesic effect of hydrocodone was recorded using the Medication Efficacy Differentiation Scale (MEDScale), a scale of 0 to 5 used to rate efficacy of a drug. Subjects were first stratified into three groups by MEDScale score: subjects with a score of 0 to 2 were classified as poor responders, subjects with a score of 3 were classified as average responders, and subjects with a score of 4 to 5 were classified as good responders. Subjects were subsequently stratified into two groups by removing subjects classified as average responders (score of 3). Subjects using other opioid medication(s) in addition to hydrocodone were excluded from this study. Subjects were genotyped using TaqMan SNP genotyping assays (Life Technologies, Carlsbad, CA) for a panel of 12 single nucleotide polymorphisms involved in the mesolimbic reward pathway. These genes include: DRD1, DRD2, DRD4, DAT1, COMT, OPRK1, OPRM1, DBH, 5-HT2A, 5-HTTLPR, Gamma-Aminobutyric Acid (GABRA 6), and MTHFR.
Results

An ordinal regression performed using SPSS v21 with subjects stratified into three groups found a statistically significant relationship between hydrocodone response and DAT1 (p=0.044). In particular, the ordinal regression suggests using the recessive model of DAT1 (C/C-C/T vs T/T) found that a DAT1 genotype of C/C-C/T was more likely associated with good response to hydrocodone as compared to a DAT1 genotype of T/T (p=0.046). Additionally, the ordinal regressions of OPRM1(rs1799971) (p=0.052) and 5HTTL(rs140701) (p=0.057) were relatively close to significance. The ordinal regression using the recessive model of OPRM1 (A/A-A/G vs G/G) suggests that a OPRM1 genotype of A/A-A/G is more likely to be associated with good response to hydrocodone in comparison to an OPRM1 genotype of G/G (p=0.060). Similarly, the ordinal regression of the dominant model of 5HTTL (G/A-A/A vs G/G) suggests that a 5HTTL genotype of G/A-A/A is more likely associated with good response to hydrocodone in comparison to a 5HTTL genotype of G/G (p=0.058). In the second portion of the study, Chi Square tests performed using subjects stratified into two groups also found a statistically significant relationship only between hydrocodone response and DAT1 (DAT1: p=0.042, OR=2.761; OPRM1: p=0.072, OR=5.94, Fisher’s Exact=0.163; 5HTTL: p=0.083, OR=1.433).

Conclusions

This study suggests that genetic variations, in particular DAT1 (rs27072), may play a role in observed differences in response to hydrocodone usage. Findings in this study will hopefully help further illuminate the role of genetics in drug response as well as guide a more comprehensive pharmacological approach.

Genetics and drug response: Study on the influence of genetics in individual variations in response to oxycodone use

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Purpose

Oxycodone and hydrocodone account for 84.9% of opioid medication prescriptions. Given that opioid overdose is the second leading cause of accidental death in the United States, misuse and abuse of opioid medication is a major part of the Public Health Crisis of Prescription Drug Abuse. Genetic factors are believed to account for 20-95% of observed individual variation in drug response, however the role of unique genes is poorly understood. The objective of this study is to determine the role of genetic variations in individual response to oxycodone use.

Method

A population of 1518 subjects taking only oxycodone across 27 clinical research sites in the United States was obtained. The mean age of the population was 52 years, with 60% of subjects being female. The analgesic effect of oxycodone was recorded using the Medication Efficacy Differentiation Scale (MEDScale), a scale of 1 to 5 used to rate efficacy of a drug. Subjects were then stratified into three groups by MEDScale score: subjects with a score of 0 to 2 were classified as poor responders, subjects with a score of 3 were classified as average responders, and subjects with a score of 4 to 5 were classified as good responders. The mean MEDScale score was 3.75 (SD: 1.03). From this population, the average responders were excluded and a sample of 134 poor responders and 150 randomly sampled good responders of the 966 total good responders were obtained and matched for age, race, and gender to produce an overall sample of 284 subjects for analysis. Subjects were genotyped using TaqMan SNP genotyping assays (Life Technologies, Carlsbad, CA) for a panel of 12 single nucleotide polymorphisms involved in the mesolimbic reward pathway. These genes include: DRD1-48A>G, DRD2 A1 allele, DRD4-521C/T, DAT1, COMT Val58Met, OPRK1 36G>T, OPRM1 A118G, DBH-1021 C/T, 5-HT2A-1438G/A, 5-HTTLP, Gamma-Aminobutyric Acid (GABRA 6) (1519T>C GABA(A) alpha 6 gene), and MTHFR C677T.

Results

Analysis was performed using SNPStat® and JMP® Pro 10 Software. A Chi square test indicates a statistically significant association between oxycodone response and 5HT2a (rs7997012), COMT (rs4680) and GABA-A receptor gamma2 (rs1800497). Further analysis using logistic regression showed the following: 5HT2a: over-dominant model, G/G-A/A is more associated with good response to oxycodone use compared to G/A [p=0.0029, OR= 2.05 (95%CI: 1.27-3.29)], COMT: recessive model, A/A-G/A is more associated with good response to oxycodone use compared to G/G [p=0.0062, OR= 2.11 (95%CI: 1.23-3.62)], GABA: recessive model, C/C-A/A is more associated with good response to oxycodone use compared to C/A [p=0.024, OR= 1.80 (95%CI: 1.08-3.02)].

Conclusions

This study suggests that that 5HT2a, COMT and GABA-A receptor gamma2 may play a role in individual response variation to oxycodone response. Furthermore, it is suggested that that response to opioid medications may be more influenced by mesolimbic neural circuitry genes than previously known. Findings in this study will hopefully help identify genes that influence response to oxycodone, as well as other opioid medications, and the mechanism through which the differences are expressed. Such knowledge could help guide prescription decisions to avoid misuse and abuse.
Genetics and drug response: Study on the influence of genetics in individual variations in response to ibuprofen use

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Purpose

In 2013, ibuprofen sales in the United States totaled over 1.6 billion dollars, making it one of the highest selling drugs in the United States. Although deemed safe and effective in recommended doses, there appears to be variation in individual response to ibuprofen. The objective of this study is to determine if genetics influence individual response variations to ibuprofen.

Method

A sample of 90 subjects currently taking ibuprofen was obtained. The MEDScale (scale 0-5) was used to stratify patients into three groups: 25 poor responders (0-2), 30 average responders (3), and 35 good responders (4-5). Subjects were genotyped using TaqMAN SNP genotyping assays (Life Technologies, Carlsbad, CA) for a panel of 12 single nucleotide polymorphisms involved in the mesolimbic reward pathway. These genes include: DRD1, DRD2, DRD4, DAT1, COMT, OPRK1, OPRM1, DBH, 5-HT2A, 5-HTTLPR, Gamma-Aminobutyric Acid (GABRA 6), and MTHFR.

Results

Ordinal regressions using IBM SPSS v21 found significant associations between ibuprofen response and DBH (rs1611115) (p=0.003) and 5HT2A (rs7997012) (p=0.048). In particular, the ordinal regression of the overdominant model of DBH (C/C-T/T vs C/T) found that a DBH genotype of C/T is more likely to be associated with good response to ibuprofen as compared to a DBH genotype of C/C-T/T (p=0.004). Although not significant, an ordinal regression of the recessive model of 5HT2A (G/G-G/A vs A/A) found that a 5HT2A genotype of A/A is more likely to be associated with good response to ibuprofen as compared to a 5HT2A genotype of G/G-G/A (p=0.052).

Conclusions

This study suggests that DBH and 5HT2A may impact response to ibuprofen. In particular, it appears that the heterozygote genotype of DBH, C/T, may be more likely associated with good response to ibuprofen. Findings in this study will hopefully help further illuminate the role of genetics in drug response as well as guide a more comprehensive pharmacological approach.

Genetics and drug response: Study on the influences of genetics in variation to morphine response.

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Purpose

Morphine is an opioid analgesic drug and regarded as the gold standard, or benchmark, of analgesics used to relieve intense pain and suffering. However, the role of genetic in individual variations in response to morphine use clinically is not clearly understood. The objective of this study is to determine the role of genetics in individual variations in response to prescription morphine use.

Method

114 pain patients taking only morphine from five research sites in the US. Subjects taking other prescription opioids were excluded from the study. Subjects were divided into 2 groups on the MED Scale (a scale of 0-5 to determine medication efficacy): poor responders (n=52) had a score of 0 to 3 while good responders (n=62) had scores 4 or 5. Subjects were genotyped using Taqman® SNP Genotyping Assays (Life Technologies, Carlsbad, CA). It consists of a panel of 12 single nucleotide polymorphisms (SNPs) in genes encoding for proteins expressed in the mesolimbic reward pathway. These genes include: 5HT2a, 5-HTTL, COMT, ANKK1/DRD2, DRD1, DRD4, DAT, DBH, MTHFR, OPRK1, GABA-A receptor gamma2, and OPRM1.

Results

Chi2 test using IBM SPSS V21 found only OPRM1 (Rs1799971) to have significant association with response to prescription morphine use. OPRM1: Dominant Model (A/A vs. A/G-G/G) p=0.019, Two sided Fishers exact =0.030. Logistic regression found A/G-G/G variations to be more associated with good response to morphine while A/A genotype was found to be associated with poor response. p = 0.024. OR 3.47. 95% CI (1.18 -10.2).

Conclusions

This study showed that OPRM1 (Rs1799971) may play a role in the individual variations in response to prescription morphine. Findings in this study could help illuminate the role of genetics in varied individual therapeutic response to morphine use.
Study to comprehensively calculate risk of aberrant behavior to opioids by incorporating genetic and phenotypic risk factors in pain patients
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Purpose
According to the CDC, nearly three out of four prescription drug overdoses are caused by prescription opioid pain relievers. The misuse and abuse of prescription opioid pain relievers was responsible for more than 475,000 emergency department visits in 2009, a number that nearly doubled in just five years. A recent study estimated that in 2006 the total cost in the United States of nonmedical use of prescription opioids was $53.4 billion (Hansen et al. 2011). Thus, it has become extremely important to be able to effectively predict a patient’s risk of aberrant behavior if given opioid pain relievers. The objective of this study is to determine the predictability of aberrant behavior to opioids (misuse, abuse, dependence and addiction) by using a comprehensive scoring algorithm that incorporates single nucleotide polymorphisms affecting neurochemistry of the mesolimbic reward system and phenotypic risk factors.

Method
162 pain subjects randomly selected from five clinical sites in the US. 80 of these were diagnosed with Opioid drug dependence (ODD, ICD code 304.01) and 82 were not and served as controls. Subjects were genotyped using TaqMan SNP genotyping assays (Life Technologies, Carlsbad, CA). A scoring algorithm, the Opioid Risk Index (ORI) score was calculated to predict risk of aberrant behavior to opioid pain relievers. The ORI is a scale of 0-52 that predicts risk of aberrant behavior to opioid pain relievers by incorporating both genetics and phenotypic risk factors. <13 indicates low risk of aberrant behavior while 13 and greater indicates high risk of aberrant behavior.

Results
A cross tab analysis using IBM SPSS found a significant association between ODD and a NRI score of greater than or equal to 13. (Pearson Chi-Square = <0.05, Fishers Exact= <0.05, Sensitivity = 80.00% (95% CI: 69.56% to 88.11%), Specificity = 93.90% (95% CI: 86.33% to 97.97%), 92.75% (95% CI: 83.88% to 97.58%), 82.80% (95% CI: 73.57% to 89.83%), PLR = 13.12 (95% CI: 5.57 to 30.89) NLR = 0.21 (95% CI: 0.14 to 0.33). Low (0-11), Moderate (12-23) and High risk (24 and greater) groups were calculated for the ORI by comparing it to the ORT (Opioid risk tool). The results were much better for the low, moderate and high risk groups derived from the ORI compared to same groups in the ORT.

Conclusions
This study suggests that an ORI score of greater than or equal to 13 is a good cutoff to predict risk of aberrant behavior to opioid pain relievers. In addition, the study showed that the ORI test may be a more robust test to help clinicians predict a patient’s likelihood of aberrant behavior if given opioid pain relievers compared to the ORT test (current gold standard). It could therefore be employed before commencement or during therapy with opioid pain relievers to stem the tide of prescription opioid misuse/abuse.

Impact of adherence to treatment guidelines on healthcare resource use and cost in patients with chronic pain conditions
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Purpose
Chronic pain is a costly condition that impacts millions of patients in the United States and there is wide variation in the approaches to disease management. The objective of this analysis was to assess differences in healthcare resource use (HCRU) and costs comparing patients that were adherent versus non-adherent to pain management guidelines across five different chronic pain conditions that spanned three types of pain. The following conditions were selected: 1) for nociceptive pain, osteoarthritis (OA) and gout (GT); 2) for neuropathic pain, painful diabetic peripheral neuropathy (pDPN) and post-herpetic neuralgia (PHN); and 3) for sensory hypersensitivity pain, fibromyalgia (FM).

Method
This retrospective cohort study used administrative healthcare claims from MarketScan® Commercial and Medicare Supplemental Databases to identify patients age >18 and newly diagnosed with OA, GT, pDPN, PHN, or FM during 7/1/2010-6/30/2012. Patients had at least 12 months of continuous health plan enrollment with pharmacy benefits preceding and 12 months following the diagnosis (index date). Patients in the pDPN cohort were also required to have pharmacologic treatment with a pain medication on or within 90 days after the index date to confirm that the DPN was painful.

Patients were grouped by level of adherence (adherent, not adherent, unsure adherence) to publicized pharmacologic pain management guidelines through development of a claims-based algorithm analyzing treatment patterns of pain medications grouped as first-line, later-line, or not recommended.

HCRU and costs were identified and compared between the adherent and non-adherent populations using both descriptive analyses and generalized linear multivariate regression models to control for potential confounding bias due to differences in patient demographics, clinical
characteristics, and concomitant medications for each chronic pain condition. Comparisons of outcomes did not include the patients in the unsure adherence group. This group was created primarily for patients where adherence could not be adequately measured and kept separate to reduce misclassification error in the two primary groups (adherent and not adherent). Pain severity analysis was not feasible due to lack of score values in the medical records.

Results

The study sample of 441,465 OA, 76,361 GT, 10,645 pDPN, 4,010 PHN, and 150,321 FM patients were selected for analysis. Of these 25% of GT, 51.1% of OA, 59.5% of pDPN, 54.9% of PHN, and 33.5% of FM patients were adherent to the guidelines. The proportion of patients not adherent: 6.8% GT, 30.7% OA, 34.9% pDPN, 23.1% PHN, and 34.7% FM and with unsure adherence: 68.0% GT, 18.2% OA, 5.6% pDPN, 22.0% PHN, and 32.0% FM. Mean ages ranged from 48.6 for FM patients to 65.8 for PHN patients. At least 50% of all patients across all chronic pain conditions were commercially insured.

After adjustment for demographic and clinical covariates, adherent patients had significantly (all conditions p<0.05) fewer number of ER visits, compared with patients who were not adherent to the guidelines. Additionally, descriptive (unadjusted) results suggested that with the exception of FM, patients adherent to the guidelines (vs. not adherent) had a significantly lower proportion of patients with an inpatient admission (all p<0.001) or emergency room (ER) visit (all <0.05).

While mean healthcare costs increased following diagnosis across all 5 conditions, patients adherent to the guidelines had significantly lower increases in adjusted healthcare costs pre-index to post-index compared with patients who were not adherent to the guidelines (GT adherent $3,631 vs. not adherent $7,873, OA adherent $5,286 vs. not adherent $9,532, pDPN adherent $9,578 vs. not adherent $16,337, PHN adherent $2,975 vs. not adherent $5,146, and FM adherent $2,911 vs. not adherent $7,873; all conditions p<0.001 for adherent versus non-adherent comparisons).

Overall, the proportion of patients treated with opioids at any time during follow-up was significantly lower (<0.001) in patients' adherent vs. not adherent to pain management guidelines. Additionally, patients with chronic (>90 days of supply) opioid use had total healthcare costs double that of patients without any opioid treatment.

Conclusions

Adherence to the pain management guidelines is associated with lower increases in HCRU and costs among patients with five select chronic pain conditions that span three types of pain. These data suggest that improved adherence to pain management guidelines may potentially lead to reduced healthcare utilization and cost savings.

Development of a novel algorithm to determine adherence to treatment guidelines for chronic pain conditions

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Purpose

Chronic pain is a costly and prevalent condition in the US with wide variation in approach to disease management relative to guidelines for treatment. The objective of this analysis was to develop an algorithm that could identify patients that were adherent versus non-adherent to the pain management guidelines across five different conditions that spanned three types of chronic pain. The following conditions were selected: 1) for nociceptive pain, osteoarthritis (OA) and gout (GT); 2) for neuropathic pain, painful diabetic peripheral neuropathy (pDPN) and post-herpetic neuralgia (PHN); and 3) for sensory hypersensitivity pain, fibromyalgia (FM).

Method

Our algorithm, based on pain guidelines for each condition, was developed through analysis of treatment patterns (sequences and drug classes) identified in administrative claims, and used to group patients by category: adherent, not adherent, and unsure.

The MarketScan® Commercial Claims & Encounters Database and Medicare Supplemental & Coordination of Benefits Database were used to identify patients during 7/1/2010-6/30/2012. Patients were eligible if newly diagnosed with OA, GT, pDPN, PHN, or FM and 12 months of continuous enrollment with pharmacy benefits prior to and following diagnosis (index date). Patients in the pDPN cohort were required to have pharmacologic treatment on or within 90 days after index date.

Pain medication classes were grouped as first-line, later-line or not recommended according to pain guidelines for each condition. Patients were adherent to guidelines if they initiated treatment following diagnosis on a first-line drug class with ≥30 days of supply prior to any new (not present 90 days prior to index) drugs in the later-line or not recommended classes. Patients were not adherent if they initiated a new drug in the later-line or not recommended classes prior to utilizing a first-line drug. Patients had unsure adherence if they had no pain drugs (untreated), had no new treatments, or had <30 days of supply of first line drug.

Each of the five pain conditions was analyzed separately to evaluate the proportion of patient's adherence. Descriptive and multivariate analyses were conducted to examine demographic and clinical predictors of adherence and differences in healthcare costs.
Results

Study cohorts of 441,465 OA patients, 76,361 GT patients, 10,645 pDPN patients, and 150,321 FM patients were selected for analysis. The majority of patients in most cohorts were commercially insured and mean age ranged from 48.5 for FM patients to 65.8 for PHN patients. It was found that 25% of GT patients, 51.1% of OA patients, 59.5% of pDPN patients, 54.9% of PHN patients, and 33.5% of FM patients were adherent to the guidelines.

Overall, the majority (>50%) of patients that were not adherent to the pain management guidelines “failed” because they initiated therapy on a new later-line/not recommended drug class (e.g., opioids). Patients were most likely to be grouped into the unsure adherence category if they were untreated or had <30 days of supply of first-line therapy. GT and FM patients had a larger proportion of patients with no drug treatment (~25%) compared with patients with pDPN (0.0%), OA (11.0%), and PHN (9.9%).

Multivariate analysis suggested that in many of the pain conditions older age, poorer overall health status (higher Deyo Charlson Comorbidity index, higher number of unique conditions, the adjusted cost differences (pre-index to post-index), were significantly lower for patients adherent to the guidelines compared to patients that were not adherent (all p<0.001).

Conclusions

To our knowledge, this analysis is one of the first to develop a claims-based algorithm using treatment patterns in “real-world” data to evaluate adherence to pain management guidelines. Research findings suggest that adherence to guidelines is associated with lower healthcare costs across five different chronic pain conditions that span the three mechanistic areas of pain. This method for analyzing adherence to treatment guidelines may provide valuable insights that can help healthcare providers in managing the care provided in their patient populations.

Appropriate spinal vertebral level for lumbar sympathetic ganglion block

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Purpose

To assess the appropriate level of lumbar vertebra where the lumbar sympathetic ganglia principally aggregate

Method

60 consecutive patients, 30 female and 30 male, underwent lumbar sympathetic ganglion block (LSGB) either on the left (26 patients) or the right side (34). The primary site of needle entry was randomly selected between L3 (30 patients) and L4 (30) vertebrae. Less than 2 mL of radio opaque dye was injected with caution not to traverse one vertebral body level. The same volume of a mixture of 2% lidocaine and radio opaque dye was injected subsequently. The procedure was considered responsive when skin temperature of either the sole or dorsum of the foot increased more than 1°C within 5 minutes. When determined as unresponsive, the procedure was repeated in other vertebral levels sequentially. The space between the upper border of the sacrum (point 0) to the upper border of the L3 (point 12) was divided into 12 segments to allow numerical description of the spread of radio opaque dye.

Results

The median spread of radio opaque dye was 6.7 (middle 1/3 of L4 body level). The value was significantly different between female and male patients [7.5 (upper 1/3 of L4) and 5.9 (lower 1/3 of L4), respectively] (p=0.002). However, there was no significant difference between Lt.- and Rt.-sided LSGB patients [6.3 (middle 1/3 of L4) and 7.1 (upper 1/3 of L4), respectively] (p=0.203). The spread of radio opaque dye did not correlate with height or BMI. There were no serious complications on 3-month follow-up after neurolytic blocks.

Conclusions

The results demonstrate that presumably, the lumbar sympathetic ganglia aggregate at the L4 vertebral body level. In male patients, the lumbar sympathetic ganglion aggregated at a lower level (lower 1/3 of L4) compared to that in female patients (upper 1/3 of L4).

Neck tornado test as a physical examination for cervical radiculopathy

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Purpose

1. To introduce a new physical assessment tool regarding cervical radiculopathy
2. To verify sensitivity and specificity of neck tornado test compared with Spurling test

Method

Medical records of patients previously diagnosed of cervical radiculopathy on c-spine MRI and neurologic examination, referred to the Pain clinic of our center were reviewed. The sensitivity and specificity of Spurling test and Neck tornado test (NTT) was identified and compared.
[Neck tornado test application method]
- NTT is performed in the same position as Spurling test.
- Spurling test is performed in advance of NTT.
- Axial compression is applied with neck rotation in a tornado-like pattern.
- Soft, vertical pressure is applied on the patient's vertex while neck is relaxed.
- Rotation is initiated with the patient's neck flexed maximally from vertical axis.
- Full flexion → rotation in counterclockwise direction → left lateral bending → full extension → right lateral bending → full flexion (i.e. 360° rotation of neck achieved)
- Positive results: reproduction or provocation of pain in the neck, shoulder, or arm.

Results
Of 17 patients with cervical radiculopathy (CR), 7 demonstrated positive results in Spurling test and 12 in NTT. Within 4 patients without CR, while none were positive of Spurling test, 2 were positive for NTT. The sensitivity for Spurling test and NTT were 41.18% and 70.59%, respectively. The specificity for Spurling test and NTT were 100% and 50%, respectively. There was no statistical significance in the results.

Conclusions
Although Neck tornado test (NTT) did not have significant statistical difference from Spurling test in its sensitivity and specificity up to date, the higher sensitivity value of NTT suggests that appropriate sample size might reveal NTT as a useful diagnostic tool for cervical radiculopathy in the future.

Topical Analgesics: Knowledge, Attitudes, and Practices of Healthcare Providers
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Purpose
Oral analgesics are commonly prescribed for the treatment of acute and chronic pain, but these agents often increase pill burden and produce adverse systemic effects. Topical analgesics offer the potential to provide the same analgesic relief provided by oral analgesics, but with minimal adverse systemic effects. In addition, topicals can provide an option for those patients who cannot swallow pills or who may have issues with absorbing drugs through the gastrointestinal system. Evidence supporting topical analgesics is well documented for specific pain conditions such as soft tissue injuries or chronic joint-related conditions and for specific agents such as topical diclofenac, topical ibuprofen and topical lidocaine. However, use of topical analgesics are limited and therefore, the question of what healthcare providers think about topical analgesics as an efficacious and safe treatment alternative for pain management should be examined.

Method
Using a convenience sampling approach, healthcare providers from across the United States were invited to take part in a survey at the CME PAINWeek 2014 Conference in Las Vegas, Nevada. All practitioners, regardless of their pain management experience, were included in the survey. The survey consisted of 6 questions intended to gather information regarding healthcare provider knowledge, attitudes, and practices on topical analgesics. The survey was provided in paper form and healthcare providers were not compensated on completion of the survey.

Results
A total of 81 healthcare providers completed the 6 question survey. Diverse healthcare provider specialties included pain management physicians, physician's assistants, nurse practitioners, nurses, pharmacists, family medicine, physical therapist, acupuncturists, and oncologists.

Approximately 85% of the healthcare providers indicated that they currently recommend over-the-counter (OTC) topicals to their patients. Among the pain management physicians, all recommend OTC topicals. When asked about which products are recommended to patients, top responses included Biofreeze, Aspercreme, BenGay, Compound Cream, Icy Hot, Capsaicin, Salonpas, Voltaren gel, Arnica and Zostrix. Majority of healthcare providers are not concerned (e.g., safety and tolerability) about their patients using OTC pain creams and almost all healthcare providers (98.8%) think topical analgesics could be a good first step in relieving muscle and joint pain.

Conclusions
There are a variety of dosage formulations available for topical analgesics and many new and novel formulations are currently entering the market. Topical analgesics offer a number of advantages over oral and intravenous medications with minimal (does not eliminate) safety concerns. Healthcare providers are aware of the benefits of these products and the majority believe topical analgesics should be used as a first line agent for pain derived from muscle and joints. When outlining a pain management program, the inclusion of topical analgesics should be considered and discussed with patients.

Identification of Inappropriate Patient-Controlled Analgesia (PCA) Prescribing Patterns to Improve Patient Safety
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Purpose
Recent reports suggest the occurrence of PCA-related adverse events may be increasing, possibly due to inappropriately high bolus doses and use of basal rates in opioid-naive
patients. In 2011, the Food and Drug Administration (FDA) decreased the recommended initial intravenous hydromorphone dose from 1-2 mg to 0.2-1 mg, but prescribers may be unaware of this change. In 2013, opioid equianalgesic dosing information was added to the institution's PCA order form. This pilot study aimed to (1) determine if the frequency of potentially inappropriate morphine and hydromorphone PCA orders changed since 2012, and (2) identify factors associated with prescribing of potentially inappropriate PCA orders.

**Method**

An institutional review board-approved retrospective, single-center review of morphine and hydromorphone PCA orders in post-operative, opioid-naive adult inpatients from 1/2012-2/2012 and 7/2013-1/2014 was conducted. Patients who received morphine or hydromorphone PCA as inpatients were identified from the pharmacy order entry database. Patients were excluded if they were not opioid-naive adults receiving PCA for post-operative pain control. Patients were classified as opioid-naive if they did not meet the FDA's definition of opioid-tolerant. Patient demographics, surgery types, prescribers, and initial PCA order components were recorded. PCA orders were considered inappropriate if they were above the starting range recommended by the American Pain Society guidelines.

**Results**

332 PCA orders met the inclusion criteria, 111 (56 morphine, 55 hydromorphone) out of 381 screened in 2012 and 221 (64 morphine, 157 hydromorphone) out of 625 screened in 2013. There was no difference in the overall frequency of potentially inappropriate PCA orders (23.4% vs. 24.9%, p=0.90, Fisher's exact) between 2012 and 2013. However, prescribing of PCA basal rates increased from 14.4% to 24.4% (p=0.05, Fisher's exact), and potentially inappropriate PCA bolus doses decreased from 9% to 0.5% (p=0.0001, Fisher's exact), with the majority of potentially inappropriate PCA bolus doses in the hydromorphone group. There was also a statistically significant decrease in the mean dose bolus of hydromorphone PCA from 2012 to 2013 (mean difference=0.13mg, p=0.0002, t-test). Logistic regression did not identify factors associated with an increased likelihood of PCA basal rate prescribing.

**Conclusions**

Although prescribing of potentially inappropriately high hydromorphone PCA bolus doses decreased from 2012 to 2013 after addition of opioid equianalgesic dosing information to the PCA order form, the prescribing of PCA basal rates increased. Prescriber education and further modification of the PCA order form may help reduce the frequency of potentially inappropriate PCA starting orders in the future. Additional research will be required to determine if a reduction in inappropriate PCA starting orders will result in a reduction in PCA-related adverse events.

**Effects of Methadone versus Morphine Sulfate Extended-Release (MSER) on Electrocardiographic Corrected-QT Interval (QTc-I)**

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**Purpose**

Methadone has been associated with electrocardiographic corrected QT interval (QTc-I) prolongation. Most cases of QTc-I prolongation have been reported during high-dose (~80-120 mg per day) therapy in methadone maintenance patients. The association between methadone use and QTc-I prolongation in chronic pain management is unclear. The American Pain Society recommends obtaining a baseline electrocardiogram (ECG) in all patients newly initiated on methadone and a follow-up ECG in high-risk patients, however, data to support this approach are lacking. We aimed to (1) characterize current methadone monitoring practices in our institution, a comprehensive cancer center, and (2) determine the effects of methadone compared to morphine sulfate extended-release (MSER) on QTc-I in chronic pain patients.

**Method**

This was an institutional review board-approved, single-center, retrospective review of patients newly initiated on methadone or MSER (control group) for chronic pain between January 1, 2012 and June 30, 2013. Adult or pediatric inpatients with orders for methadone or MSER were identified from the pharmacy order entry database. Patient demographics, risk factors for QTc-I prolongation, opioid dose, managing physician service, baseline QTc-I within 90 days prior to first dose, and follow-up QTc-I within 30 days after first dose were recorded from the medical record. The primary endpoint was incidence of QTc-I greater than the upper limit of normal (ULN), defined as 460 or 450 milliseconds for females or males, respectively.

**Results**

118 patients newly initiated on methadone while hospitalized were included in the analysis of methadone monitoring practices. 83% of these patients were managed by Supportive Care Service physicians (SCC) and were more likely to receive a baseline ECG compared to those managed by Non-Supportive Care Service physicians (NSCC) [95% versus 55%; p=0.0001; Fisher's exact]. No difference was observed in the likelihood of receiving follow-up ECG between patients followed by SCC compared to NSCC [41% versus 25%; p=0.22; Fisher's exact]. To evaluate the effect of methadone on QTc-I, 48 patients (11 MSER patients, 37 Methadone patients) were found to have both normal QTc-I on their baseline ECG and at least one follow-up ECG and were included in the analysis. More MSER than Methadone patients developed an increase in QTc-I (82% versus 43%; p=0.04; Fisher's exact), however, there was no difference observed between groups in incidence of QTc-I > ULN (18% versus 8%; p=0.32; Fisher's exact).
Conclusions

The rate of follow-up ECGs within 30 days of methadone initiation was <50%, however, in chronic pain patients, no association between methadone and incidence of QTc-I > ULN was observed compared to MSER.

Effect of co-prescribing of prophylactic laxatives on the incidence of opioid-induced constipation in patients newly initiated on long-acting opioids

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Purpose

Opioid-induced constipation (OIC) presents a major challenge in the management of cancer pain. The National Comprehensive Cancer Network recommends prophylactic laxative use for the prevention of OIC. However, evidence for a lower incidence of OIC in patients on prophylactic laxatives compared to those not on prophylactic laxatives is conflicting. This study compares the incidence of development of any OIC between cancer patients who were and were not co-prescribed prophylactic laxatives upon initiation of long-acting opioids.

Method

An institutional review board-approved single center retrospective medical records review of adult inpatients and outpatients newly initiated on long-acting morphine or oxycodone between January 1, 2012 and January 1, 2015 was conducted. Patient demographics, prescribers, and opioids and laxatives prescribed were recorded. Patients were classified as having OIC if the presence of constipation was documented in the physicians’ progress notes within 2 months after initiation of long-acting opioid. Problematic opioid-induced constipation was defined as any OIC that required additional healthcare resource utilization for evaluation or treatment within 2 months after initiation of long-acting opioid.

Results

121 patients met the inclusion criteria. 49 patients (40.5%, mean age 54.9 years, mean daily oral morphine equivalent dose 61.4 mg) received prophylactic laxatives and 72 patients (59.5%, mean age 56.4 years, mean daily oral morphine equivalent dose 67.2 mg) received no prophylactic laxatives. OIC was noted in 44 (36.4%) of patients overall. However, there was no difference in the incidence of any OIC between the prophylactic laxative and no prophylactic laxative groups (28.6% vs. 41.7%, p=0.19, Fisher’s exact test). There was also no difference in the incidence of problematic OIC between the prophylactic laxative and no prophylactic laxative groups (2.0% vs. 2.7%, p=1, Fisher’s exact test). The frequency of co-prescribing of prophylactic laxatives was not different between supportive care physicians and other physicians (48.3% vs. 38.0%, p=0.39, Fisher’s exact test).

Conclusions

Within the first 2 months after initiation of long-acting opioids, there were no significant differences in the incidences of problematic and any OIC in cancer patients who were co-prescribed prophylactic laxatives compared to those who were not.

Population pharmacokinetic analysis for buprenorphine following the buccal administration of buprenorphine HCl

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Purpose

The objectives of this analysis were 1) to develop a pharmacokinetic model that characterizes the population pharmacokinetics of buprenorphine following single and multiple oral doses of a buccal soluble film formulation (utilizing a Bioerodible MucoAdhesive [BEMA®] drug delivery system) in healthy subjects and patients, and 2) to examine the impact of patient descriptors on pharmacokinetic parameters.

Method

A total of 12,012 plasma buprenorphine concentrations from 509 subjects were available for this analysis. The data were extracted from three studies (one phase 1 and two phase 3 studies). A two-compartment open mamillary model with linear elimination and a first order absorption with lag were used to describe the data, using NONMEM® (version 7.2). Covariate analysis was performed using standard forward selection followed by backward elimination processes. Model evaluation was performed using standard goodness of fit evaluations and a visual predictive check (VPC).

Results

The population estimates of apparent oral central volume of distribution and apparent oral clearance were 347 L and 68.4 L/h, respectively. The first absorption process was rapid. Though dose was found to be a statistically significant predictor of the apparent oral clearance and apparent oral volume of distribution, the effect was not considered clinically relevant. No other patient factors were identified as being influential. The VPC indicated that the model provided a robust and unbiased fit to the data.

Conclusions

A linear model for buprenorphine elimination provided an adequate fit to the observed data over the entire dose range, supporting the assumption that buprenorphine buccal films exhibit dose-proportional pharmacokinetics. The buprenorphine buccal film formulation results in absorption profiles that are variable across and within subjects. However, despite the variability in absorption profiles, a relatively simple
Time to first postdose laxation with naloxegol in patients with chronic noncancer pain and opioid-induced constipation

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Purpose

Opioids are prescribed to approximately 36% to 90% of patients with chronic pain. Although opioids provide highly effective pain management, 40% to 90% of patients taking these medications report bothersome symptoms that include opioid-induced constipation (OIC) and other gastrointestinal symptoms. Despite the use of available laxative options and diet and lifestyle modifications, many patients with OIC continue to experience deleterious symptoms and often reduce or stop their use of opioids to obtain relief from their constipation. It is important that once the condition is diagnosed, healthcare providers should initiate effective treatment for OIC. Treatments are available that target the underlying mechanism of OIC and increase the frequency of spontaneous bowel movements (SBMs) without compromising the analgesic effects of opioids. Naloxegol is a peripherally acting mu-opioid receptor antagonist approved for treatment of OIC in patients with chronic noncancer pain. Naloxegol binds to opioid receptors in the gastrointestinal tract and blocks pathophysiologic mechanisms that underlie constipating effects of opioid medications. Patient demographics, safety, and efficacy results over 12 weeks of treatment from 2 phase 3 studies were previously presented (Chey et al., N Engl J Med. 2014;370:2387); mean age was approximately 52 years and OIC symptoms for ≥2 years. We now present additional data on time to first postdose SBM with naloxegol versus placebo. Time to first SBM is important because it reflects onset of pharmacodynamic activity and is an early indicator of clinical efficacy for patients.

Method

Outpatients aged 18 to <85 years with OIC and taking 30–1000 morphine equivalents for chronic noncancer pain were randomized to receive naloxegol 12.5 mg, naloxegol 25 mg, or placebo once daily. Symptoms of OIC at screening (ie, ≥3 SBMs/week with ≥1 of the following symptoms: hard or lumpy stools, straining, or sensation of incomplete evacuation or anorectal obstruction in at least 25% of bowel movements during the 4 weeks before screening) were confirmed during the 2 weeks before randomization. Exclusion criteria included uncontrolled pain despite the use of opioid pain medications and evidence of conditions that conferred an increased risk of bowel perforation. The prespecified secondary endpoint of time to first postdose SBM from the 2 phase 3 studies (KODIAC-04 [NCT01309841] and KODIAC-05 [NCT01323790]) was analyzed for the intent-to-treat (ITT; multiplicity protected) and laxative-inadequate response (LIR) populations. LIR was defined as use of medication from ≥1 class of laxatives for ≥24 days 2 weeks before first study visit, and at least moderate symptoms in ≥1 of 4 stool symptom domains on a baseline laxative response questionnaire. Treatment comparisons (naloxegol vs placebo) were conducted using the log-rank test and median times estimated using the Kaplan-Meier approach. Proportions of patients achieving an SBM within 6, 12, and 24 h of initial dose are also presented.

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. ITT and LIR treatment groups were of similar size in KODIAC-04 (naloxegol 25 mg: n=214, n=117; 12.5 mg: n=213, n=115; placebo, n=214, n=118) and KODIAC-05 (naloxegol 25 mg, n=232, n=124; 12.5 mg, n=232, n=125; placebo, n=232, n=121). In KODIAC-04, median time to first postdose SBM was 5.9, 20.4, and 35.8 h with naloxegol 25 mg, 12.5 mg, and placebo, and in KODIAC-05, these values were 12.0, 19.3, and 37.2 h (Chey et al., N Engl J Med. 2014;370:2387). In the LIR population, median time to first postdose SBM was 5.4, 20.6, and 43.4 h with naloxegol 25 mg, 12.5 mg, and placebo in KODIAC-04, and 18.1, 12.8, and 38.2 h in KODIAC-05. Proportions of patients in the ITT population achieving their first postdose SBM in ≤6 h from the initial dose was 50.9%, 33.8%, and 15.4% with naloxegol 25 mg, 12.5 mg, and placebo in KODIAC-04 and 39.2%, 34.5% and 17.2% in KODIAC-05. Similarly, in KODIAC-04 and KODIAC-05 the proportions of ITT patients with first postdose SBM at ≤12 and ≤24 h were greater for naloxegol 25 mg (≤12 h: 57.0%, 49.6%; ≤24 h: 70.1%, 61.2%) and 12.5 mg (≤12 h: 43.7%, 44.0%; ≤24 h: 58.7%, 58.6%) versus placebo (≤12 h: 22.9%, 24.6%; ≤24 h: 36.9%, 36.6%). In the LIR population, the respective proportions of patients with first postdose SBM were greater for naloxegol 25 mg (≤6 h: 53.8%, 39.5%; ≤12 h: 60.7%, 47.6%; ≤24 h: 75.2%, 59.7%) and 12.5 mg (≤6 h: 33.0%, 36.8%; ≤12 h: 42.6%, 48.0%; ≤24 h: 59.1%, 63.2%) versus placebo (≤6 h: 16.1%, 16.5%; ≤12 h: 23.7%, 20.7%; ≤24 h: 36.4%, 36.4%).

Conclusions

Time to first postdose SBM was shorter with both doses of naloxegol compared with placebo in patients with chronic noncancer pain and OIC. Moreover, treatment responses were similar in the ITT population and the subpopulation of patients with LIR. These results, in addition to the primary responder analysis published previously, provide further evidence of clinical efficacy of naloxegol in patients with OIC, including patients with LIR.
The effect of H-wave therapy on a patient post total knee replacement with refractory severe neuropathic knee pain over 16 years: A case report
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Purpose

H Wave therapy has been used in medical field over 30 years. Recently we used it very successfully to treat a patient with refractory knee pain which is failed to a variety of interventions.

The patient is a 68 years old white male veteran who presented to VA physical medicine and rehab clinic with his chronic refractory severe knee pain after total knee replacement, which he attributes to jumping out of airplanes during his military service. He has been suffering with extreme knee pain for the last 16 years, after both knee replacement (left knee 1998, right knee 2011) with ongoing neuropathic pain. Was previously treated by orthopedic surgeon and pain specialist. Has failed a variety of interventions including IA hyaluronic acid, IA steroid injection, pulsed RF of femoral nerve, acupuncture and TENS. He has been on fairly high doses of morphine at one point 300mg/day with Fentanyl patch but still with poor pain control. He complaints of burning & stabbing pain in his knees, hardly to bend knee and hardly to wear socks or wash his feet and pain awaken at night. He is hardly walking. He has suffered this pain for at least 16 years.

Method

H Wave Therapy Device: Electronic Wave Lab, Inc., Huntington Beach, CA. Set up for H Wave therapy: for each session, high frequency (9/9), high Intensity (9/9) for 30 min, then switch to low frequency (1/9) and high intensity (9/9) for 30 min each day.

Results

Following the H Wave therapy, his severe knee pain was significantly reduced from 7/10 to 0/10 and last for 13 hours. So far he uses H-Wave home unit over 4 months and is still very helpful. He is able to use it every other day at one hour sessions for both knees with pain free and also has been able to reduce morphine from 300/day to 60 mg/day. He stated that “This is a miracle. I can't remember when I didn't have pain until now. I am forever grateful”. “I have my life again”.

Conclusions

H-wave device is a small-diameter fiber stimulator for treatment of pain associated with human neuropathies or soft tissue injuries. It promotes lymphatic fluid shifts and reduces the edema and chronic inflammatory conditions associated with chronic pain. H wave therapy is very effect treatment for refractory and severe neuropathic knee pain post total knee replacement. Further research needs to be conducted using H-wave device for pain control post total knee replacement patients with chronic severe neuropathic knee pain.

Long Term Effect of Botox Type A injection on a patient with refractory stump pain: A Case Report
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Northern California VA system, Martinez, USA

Purpose

Botox injection has been used to treat the spasticity and other hypertonic muscular disease for years and recently Botox has been explored as a potential tool to alleviate the phantom pain and residual stump pain. However, there is little data to report long term effect of Botox injection on refractory stump pain.

Method

100 units Botulinum-Toxin A diluted with 1ml preservative-free saline 0.9% injected into 10 sites of distal end of stump and followed up the patient 3, 6, 9 and 12 months.

The patient is a 68 y/o White male veteran with H/O HTN, PVD, Depression, s/p above knee amputation in 03/14 due to critical limb ischemia and necrosis admitted in VA subacute rehab unit. After physical therapy with gait training and exercise, he got preparatory AKA prosthesis 3 months from the surgery and was discharged to home. Patient was then followed by PT and Prosthetist as an outpatient with continuous gait and endurance training. Patient then developed phantom pain and stump pain and worsening even with prosthetic modification and pain medication management with Norco and gabapentin 600mg tid. Patient presented in VA amputee clinic one month after discharging. On physical exam, His AKA stump residual showed mild swelling, small sore on anterior stump, distal tenderness at least 3 spots, seems neuroma. Pain VAS was 7/10. AK Prosthesis: modified silicone pads in base of the socket. Patient was then received Deep Tissue Laser (MLS laser) treatment with pain relief after 1st treatment but no benefit after 2nd treatment. He then tried H wave therapy. S/P H Wave therapy with 5 days pain relief and did not take any pain meds > 4 days. After 2nd H wave treatment with pain relief for 8 hours he could “move a lot”. While he wears prosthesis for 3-4 hours then started stump pain again, then he tried of Botox injection.

Results

S/P Botox type A Toxin injection, his stump pain was significantly reduced at least 30% for 3 months and able to walk with prosthesis every day. He was followed at 3, 6, 9 and 12 months. With Botox injection every 3 months he could maintain his function as normal.

Conclusions

This case report demonstrates that long-term treatment for the refractory stump pain is effect and can also improve the tolerance of prosthesis limb in cases of severe stump pain.
Patient characteristics and health resource utilization of a chronic pain population within an integrated healthcare system

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Purpose

The purpose of this study was to characterize the non-malignant chronic pain (CP) population, including prevalence, comorbidity burden and resource utilization by pain condition. On the basis of these factors, we identified the most impactful conditions within an integrated healthcare system.

Method

This study was a cross-sectional analysis of electronic health records (EHR) data in 2012. Data were from Sutter Health, a community-based mixed-payer, integrated healthcare system, which provides ambulatory-care and inpatient services throughout Northern California. We included patients who were ≥18 years of age, had ≥2 ICD-9 encounter diagnoses for a CP condition in 2012 ≥30 days apart, and had ≥1 encounter of any type prior to 2010 to confirm prior health system contact. We excluded patients with diagnosis for cancer in the 2 years prior to 2012 or had surgery in the 3 months prior to the first CP encounter in 2012. Patients were categorized into 20 non-mutually exclusive CP conditions based on ICD-9 diagnoses that were then grouped into 5 categories: (1) Arthropathies/Arthritis/Joint Pain (Arthropathy, Osteoarthritis, Rheumatoid Arthritis, Joint Pain); (2) Back/Cervical Pain (Back Pain, Cervical Radiculopathy, Lumbar Radiculopathy, Spinal Cord Injury); (3) Neuropathies/Neuralgias (Postherpetic Neuropathy, Diabetic Neuropathy, Neuropathy, Neuralgia, Surgically-induced pain, Limb Pain); (4) Headaches and Migraines; and (5) Unclassified Pain (Pelvic Pain, Abdominal Pain, General Pain, Fibromyalgia). Patient demographics, comorbidities, and healthcare encounters for office visits, emergency department (ED) visits, hospitalizations, and 30-day hospital readmissions were extracted from the EHR. Disease burden was measured by the Charlson Comorbidity Index (CCI) score. Data were summarized by CP category. We used multivariable negative binomial regression models to assess predictors of healthcare resource utilization. Incident rate ratios (IRR) and 95% confidence intervals (CI) were generated. For all tests of hypotheses, a P-value <0.05 was considered statistically significant.

Results

Among 1,784,114 patients with any healthcare encounter in 2012, 120,481 (7%) met inclusion criteria. CP patients had a mean age of 56 years, 66% were female, and 63% were non-Hispanic white. Burden of disease was high (CCI score >3) in 21% of patients. Fifty-seven percent of patients were classified as having arthritis/joint pain, 49% had back/cervical pain, 40% had neuropathies/neuralgias, 23% had headaches/migraines, and 20% had unclassified pain. Patients with headaches/migraines and unclassified pain were, on average, younger than those in other CP categories (49 and 54 years, respectively) and were more likely female (81% and 82%). Patients with arthritis/joint pain and neuropathies/neuralgias tended to have the highest disease burden (CCI >3 in 25% and 28%, respectively).

Patients with unclassified pain had the highest rates of crude office visits per 1,000 patients (5,137), followed by patients with neuropathies/neuralgias (4,866). Crude ED visit per 1,000 patients were highest among patients with unclassified pain (209), followed by patients with headaches/migraines (180). Crude hospitalizations and 30-day readmission per 1,000 patients were highest among patients with neuropathies/neuralgias (70 and 14, respectively), followed by patients with unclassified pain (67 and 12, respectively).

After controlling for important demographic and clinical characteristics, patients with neuropathies/neuralgias compared with those in other CP categories combined had the highest rates of office visits (9% higher adjusted incidence rate); patients with unclassified pain had the highest rates of ED visits (9% higher adjusted incidence rate). Positive predictors of healthcare utilization included number of CP diagnoses, higher disease burden, African American race, multiple insurance payers, and number of concurrent prescriptions for any medications.

Conclusions

The management of chronic pain is a growing interest to health care organizations due to its prevalence and economic impact. Based on high disease prevalence, comorbidity burden, and resource utilization, several CP conditions including neuropathies/neuralgias (diabetic neuropathy, neuralgia, and post herpetic pain) and arthritis/joint pain (osteoarthritis and rheumatoid arthritis) are potentially most impactful to the healthcare system. The results of this study will help inform the management of CP patients within this integrated healthcare delivery system. Health systems can learn from these findings in order to focus on specific CP conditions with the greatest impact.

Characterizing neuropathic pain profiles: Enriching interpretation of painDETECT

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Purpose

Neuropathic pain (NeP) is heterogeneous with regard to presentation of sensory symptoms such that patients may be characterized by different symptomatic pain profiles that may differentially respond to treatment (Freeman et al. Pain.
The 9-item painDETECT (seven pain sensory symptom items, one pain course pattern item, and one pain irradiation item) is a validated patient-reported questionnaire (score range 1 to 38) for classifying pain as NeP (score ≥19), Nociceptive (score ≤12), or Unclear (score 13-18). A 7-item version consists only of the sensory symptoms (score range 0 to 35). Psychometric evaluation has shown that painDETECT can identify NeP across a range of conditions (Cappelleri et al, J Pain Res. 2015;8:159-67) and can distinguish levels of average NeP pain severity (Cappelleri et al. Clinicoecon Outcomes Res. 2014;6:497-504). To further expand on the measurement properties of painDETECT, the current analysis psychometrically evaluated its ability to characterize pain profiles by discriminating among the seven sensory pain symptoms (burning; tingling/prickling; light touching; sudden pain attacks/electric shock-type pain; cold/heat; numbness; pressure) across the range of scores.

Method

Subjects (n=614, 55.4% male, 71.8% white, mean age 55.5 years) with confirmed NeP across 6 conditions were identified during office visits to US community-based physicians as part of a study on the patient-reported burden of NeP. painDETECT was included in the battery of questionnaires administered during this cross-sectional study. For the current analysis, responses on the seven sensory symptom items, which rate the presence of the symptoms on a Likert-type scale from “never” to “very strongly,” were dichotomized into at “least moderate” (i.e., moderate, strongly, and very strongly) relative to the combined other responses (never, hardly noticed, slightly). The dichotomized variables were regressed on the total painDETECT score using logistic regression to provide probabilities of tangibly experiencing each symptom (i.e., with at least a moderate sensation) across the range of painDETECT scores. This regression both enables characterization of the symptom profiles that can be expected at different painDETECT scores and provides a narrative understanding of how painDETECT scores relate to their constituent symptoms, and, in doing so, enhances interpretation of painDETECT scores in a meaningful way.

Results

The probability (likelihood) of having experienced at least a moderate sensation for each of the seven sensory (symptom) items across total painDETECT scores were generally consistent on the 9-item and 7-item versions. While there was adequate discrimination among the symptoms, probability clusters of having experienced at least moderate sensation were observed: light touching and cold/heat appeared to jointly have a lower probability across the scores than did the other symptoms; there was distinct separation of pressure and pain attacks from each other and from other symptoms; and a cluster of burning, numbness, and tingling/prickling that generally had the highest probabilities of tangible sensation. These patterns were observed on both the 9-item and 7-item versions. Using these data, the probability of tangible sensation for each pain sensory item can be estimated for a particular score or score range, providing a pain profile. For example, for a score between 15 and 20 on the 9-item version, the probabilities of having experienced at least a moderate sensation were 80% for tingling, 78% burning, 73% numbness, 65% pain attacks, 46% pressure, 21% light touching, and 18% cold/heat. Additionally, the likelihood of tangibly experiencing each sensation can be determined for a discrete increase in score - for example, the odds of at least a moderate sensation of burning (versus less than a moderate sensation) was 1.29 for a 1-point increase in painDETECT score, 3.52 for a 5-point increase, and 12.42 for a 10-point increase.

Conclusions

This analysis enriches interpretation of painDETECT scores by differentiating among the symptom profiles that can be expected across the range of scores such that, for a particular score, the probability of experiencing at least a moderate sensation of each symptom can be determined and compared. These results can be used not only to characterize the NeP symptomatology of patients based on painDETECT scores, but also to provide a basis for individualizing NeP management.

What is the incidence of opioid-induced nausea and vomiting (OINV) in patients who do not have immediate post-operative nausea/vomiting?

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Purpose

Most post-operative patients are discharged “clean” from surgical facilities, without experiencing nausea or vomiting. How many of these patients develop nausea or vomiting after discharge, i.e., without contributing peri-operative factors? In a double-blind, randomized, placebo-controlled trial we conducted on patients with moderate to severe post-operative pain comparing treatment with CL-108 (hydrocodone 7.5 mg/acetaminophen 325 mg/promethazine 12.5 mg) to hydrocodone 7.5 mg/acetaminophen 325 mg (HC/APAP), we had the opportunity to document the frequency of opioid-induced nausea and vomiting (OINV) only after exposure to an opioid analgesic.

Method

Approximately 3 hours after surgical removal of third molar teeth, adult patients who had moderate or severe pain (on a categorical pain intensity scale, PI-CAT) were queried about the presence and severity of nausea (on a 0-10 Nausea Intensity Scale, NIS) and about the presence and frequency of vomiting (on an ordinal Vomiting Frequency Scale, VFS). Of 466 patients evaluated, 187 (40%) reported nausea or...
vomiting after surgery (i.e., before treatment). Of the remaining 279 patients without post-operative nausea or vomiting at baseline, 126 patients were randomized under double-blind conditions to HC/APAP, 128 patients to CL-108, and 25 patients to placebo. Patients used the PI-CAT, NIS and VFS at regular intervals following initial treatment and self-dosed as needed for pain every 4-6 hours.

Results

CL-108 and HC/APAP were demonstrated to be effective analgesics compared to placebo (both p<0.001). Moderate or severe nausea was experienced by 49% of patients treated with HC/APAP over the initial 48 post-operative hours (when most patients experienced and treated pain). Single-episode or repeat vomiting occurred in 36% of patients treated with HC/APAP over 48 hours. These nausea and vomiting outcomes were significantly reduced for patients who used CL-108 (29% and 18%, respectively, both p = 0.001), representing 41% relative reduction in the risk of developing nausea and 50% relative reduction in the risk of vomiting. There was also a significant reduction in the use of anti-emetics by patients who used CL-108 compared to HC/APAP (p<0.001), representing 21.7% relative reduction in the use of anti-emetics.

Conclusions

These findings indicate that 36-49% of patients without immediate post-operative nausea or vomiting proceed to develop OINV after discharge from the surgical facility following the intake of HC/APAP. For these otherwise “clean” post-operative patients, CL-108 is an effective analgesic that also reduces OINV.

Comparison of in-vitro test characterization of immediate and extended release products with abuse deterrent features

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Purpose

Abuse deterrent formulations offer significant improvements for the safety of drug products containing active pharmaceutical ingredients (API) susceptible to abuse and misuse. The clinical relevance of abuse deterrent features has to be demonstrated eg in pharmacokinetic (PK) and human abuse liability (HAL) studies. However, in-vitro characterization tests are required for the design of these clinical studies and the sample preparation of the clinical trial material.

Currently there are mainly long acting opioid drug products in the market exhibiting abuse deterrent features. However, in addition to the already existing abuse and misuse of immediate release formulations, it is also expected that there will be a shift in the abuse patterns and more un-protected formulations will be abused independently of their intended release profiles.

The purpose of this paper is to give an overview about in-vitro test methods and their applicability to immediate release (IR) and extended release (ER) abuse deterrent formulations which exhibit similar PK profiles to marketed non-abuse deterrent formulations. Grünenthal developed different in-vitro characterization tests according to the FDA guideline in order to assess the abuse deterrent features depending on the stage of development, general formulation characteristics, and the route of abuse. For IR and ER formulations, the assessment of the mechanical resistance, e.g. in terms of particle size reduction, is mandatory. These tests can be used for the assessment of intranasal and intravenous abuse. For ER formulations, extractions studies are required in order to assess the ease of defeating extended release properties when formulations are dissolved and swallowed.

Method

For manufacturing of IR pellets and ER matrices a hot-melt extrusion process was used, which embeds the active opioid into a homogenous matrix formulation based on polyethylene-oxide (PEO) of high molecular weight. A Leistritz twin-screw extruder together with a pelletizer for IR pellets and a cutting device for ER matrices were used.

For IR formulations the focus of the in-vitro characterization is on the preparation for intranasal and intravenous abuse. Samples were milled for two minutes in a coffee grinder (Bosch MKM 6000). Afterwards particle size distribution (PSD) was determined by sieve analysis. To simulate I. V. preparation samples were placed into 5ml water, heated until boiling and kept boiling for 5 min. The resulting supernatant was attempted to be drawn into a syringe (21G needle, with cigarette filter). The amount of liquid in the syringe was determined and tested for assay of API by HPLC measurements. The pure mechanical resistance against hammering was assessed with a standardized hammer apparatus (developed and constructed for Grünenthal) and breaking force tester.

For ER formulations, additional tests were conducted. In addition to grinding and sieve analysis and preparation for intravenous abuse, dissolution studies at different pH values (pH 1, 4.5 and 6.8) and with and without alcohol were performed. Dissolution was performed using Dissolution apparatus II (Sotax, paddle) with various parameters (50-75 rpm, 0.1N HCl or pH 6.8, 600 to 900ml). Furthermore, extraction studies in different media (water, ethanol 40%) in 30mL over 30min and 60min were performed.

Results

PK data from extended release and immediate release INTAC® formulations (abuse deterrent formulation technology developed by Grünenthal) demonstrated that the relative bioavailabilities of the developed abuse deterrent formulations are similar to the marketed non-abuse deterrent formulations2, 3, 4, i.e. 90% CIs calculated for the ratios of mean AUC and Cmax were within the range commonly accepted for demonstrating bioequivalence.

For ER INTAC® formulations it could be demonstrated that several media such as corn oil, acidic or basic aqueous
or organic solvents are not suitable for extraction of the API in a short period of time (less than 20% extracted after 60 minutes). In contrast to that, the use of other media that are also used for analytical purposes (e.g. methanol) led to the extraction of significant API amounts (>20% within 60 minutes). However, the extraction rates did not exceed the amounts of API released during regular dissolution tests. Moreover, it could be demonstrated that the release rate in alcoholic dissolution media is reduced when compared to ethanol-free media. Extraction studies in 4 different media with IR INTAC® formulations revealed that in-depth extractions studies are not reasonable. The API was released completely (>80%) within a short period of time (max 30 minutes).

For IR and ER products, the assessment of particle size distribution after manipulation was shown to be relevant for intravenous and intranasal abuse. To make intranasal abuse less attractive and unpleasant particles should exceed a limit of 500μm based on literature data. INTAC® IR and ER products exhibit a particle size distribution after grinding where the majority of the particles are larger than 500μm.

With regard to intravenous abuse, it was found that the extraction rates depend not only on the formulation but also on the API used. (i.e., four opioids in identical formulation: <10-50% extraction rate).

Conclusions
Methods for in-vitro characterization tests have to be selected based on the intended routes of abuse to be addressed. The properties of the formulation addressing non-oral routes of abuse can be assessed by investigating mechanical properties and the properties after dissolving the drug product in small amounts of water. For ER formulations the resistance to extraction and the potential effect of alcohol on the release profile (alcohol induced dose dumping) is more important than for immediate release formulations. During later phases of the development a full test battery with additional tests and more conditions (time, temperature, and agitation) are required.

Effect of tramadol/acetaminophen combination tablets for patients with postherpetic itch
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Purpose
Pruritus originating after herpes zoster is called postherpetic itch (PHI), which is found in 20-30 percent of all herpes zoster patients and intractable. However, there is little data available on the effect of tramadol/acetaminophen combination tablet for PHI. This study aimed to determine the safety and efficacy of tramadol 37.5 mg/acetaminophen 325 mg combination tablets (TAC) in patients with PHI.

Method
We retrospectively performed a chart review of 25 outpatients (mean age, 61.3 years; range, 28 to 84 years) with postherpetic itch. They were treated by different 3 physicians, who regulated TAC dosage at every visit for better anti-pruritic effects (less than a visual analog scale 30mm) and relief of adverse effects by TAC. A visual analog scale (VAS) from 0 to 100mm was utilized to subjectively measure the severity of itch at the time of visit. Recently a new method for quantitative measurement of pain intensity using a painless electrical stimulation, PainVision® (PV; Nipro Co., Osaka, Japan) has been developed. Furthermore, we demonstrated PV was helpful for the quantitative measurement of itch sensation. Two different types of current perception threshold (CPT) were measured by PV at every visit. One CPT was the minimum perception threshold (MPT) defined by the lowest electrical current detected; the other CPT was itch equivalent threshold (IET) at which the subject starts to perceive the equivalent strength as ongoing itch. ID is calculated from two parameters as follows. ID was calculated as (IET-MPT)/MPT. Statistical analysis was carried out by paired t-test and p values less than 0.05 were considered as statistically significant.

Results
TAC therapy decreased the average VAS scores from 47.6 ±15.8 mm to 18.9±15.3 mm (p< 0.0001) and the average ID from 129.4±78.1 to 39.8± 25.7 (p= 0.0011). No patients experienced a serious adverse event. The antipruritic effects of TAC may occur by inhibition of the pre-synaptic uptake of the neurotransmitters norepinephrine and serotonin.

Conclusions
Our data demonstrated that TAC therapy has antipruritic activity in patients with PHI. PV may be useful for quantitative assessment of therapeutic efficacy of antipruritic agents.

Safety and effectiveness of minimally invasive sacroiliac joint fusion in women with persistent post-partum posterior pelvic girdle pain: 12-month outcomes from a prospective, multi-center trial
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Purpose
Postpartum posterior pelvic girdle pain (PPGP) affects nearly 20% of women who experience back pain in the peripartum period. The sacroiliac joint is a source of this pain in 75% of women with persistent PPGP. A subset of women will fail to obtain acceptable pain relief from the current array of non-surgical treatment options. The purpose of this study is to assess the safety and effectiveness of minimally invasive sacroiliac (SI) joint fusion in women with chronic SI joint dysfunction whose pain began in the peri-partum period whose symptoms were recalcitrant to non-surgical management.
Method
A sub-group analysis of subjects with sacroiliac joint disruption and/or degenerative sacroiliitis enrolled in a prospective, multi-center trial of SI joint fusion (SIFI) was performed. Subjects with PPGP were identified and compared with women without PPGP and with men.

Results
Of 172 enrolled subjects, 52 were male, 100 were females without PPGP and 20 females had PPGP. PPGP subjects were significantly younger (43.3 years, vs. 52.8 for females without PPGP and 50.5 for men, p=0.002). There were no differences in any other demographic or baseline clinical measure. Women with PPGP experienced a significant improvement in pain (-51mm on VAS), function (-20.6pts on ODI) and quality of life (SF-36 PCS +10.4, MCS +7.2, EQ-5D +0.31) at 12 months after surgery. These improvements were characteristic of the overall study results; no difference was detected between sub-groups.

Conclusions
The sacroiliac joint can be a source of pain in women with persistent PPGP and should be investigated as a pain generator. In this study, women with carefully diagnosed chronic SI joint pain from PPGP recalcitrant to conservative therapies experienced clinically beneficial improvements in pain, disability and quality of life after minimally invasive SI joint fusion using a series of triangular porous plasma spray coated implants.

Sub-anesthetic ketamine for the treatment of adolescents with chronic pain: A single outpatient center experience
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Purpose
Chronic pain is common in adolescents and can be associated with severe functional disability and mood disorders. The pharmacological treatment of chronic pain in adolescents can be challenging, suboptimal, and is often based on expert opinions and consensus. Ketamine, an N-Methyl-D-aspartate receptor antagonist, has been successfully used as an adjuvant for treatment of adult chronic pain. Here we examined the feasibility of administering subanesthetic ketamine in an outpatient setting and the effects of ketamine on pain intensity and opioid use in adolescents with complex regional pain syndrome (CRPS) and other chronic pain syndromes.

Method
The study protocol and waiver of informed consent was approved by the Children’s National Health System Institutional Review Board. We performed a longitudinal case-series of sixty-three children and adolescents with chronic pain syndromes treated with sub-anesthetic doses of ketamine in a tertiary outpatient interdisciplinary Pain Medicine center from January 2013 to April 2014. Outcome measurements included self-reported pain scores (numeric rating scale) and morphine-equivalent intake. At the outpatient tertiary pain center, diagnoses of chronic pain syndromes are made following criteria from the International Association for the Study of Pain. For the purpose of this investigation, patients with CRPS types 1 and 2 were included jointly in the CRPS group. Patients with chronic pain syndromes other than CRPS are referred to as having other chronic pain syndromes.

Results
Sixty-three adolescents with chronic pain received a total of 111 treatments delivered over 277 ketamine infusions. The majority treated were female Caucasian. Thirty-seven percent (23/63) of patients had CRPS (Type 1, N=21 and Type 2, N=2), and 63% (40/63) had other chronic pain syndromes including headache (13%) and fibromyalgia (5%). Indications for ketamine administration included requirement of escalating doses of opioid associated with non-tolerated side effects or lack of improvement in pain intensity, failure of standard treatment modalities (anticonvulsants and/or antidepressants) to yield improvement in pain intensity and/or disabilities. Associated clinical diagnosis included psychiatric/psychological disorders in 23% (anxiety, depression, bipolar disorder, and autism spectrum disorder), history of trauma in 10%, postural orthostatic tachycardia syndrome (POTS) in 10%, diabetes mellitus in 7%, malignancy in 7%, and sickle cell disease in 5% of the patients. Ketamine significantly reduced pain (p<0.001) and yielded greater pain score reductions in patients with CRPS than in patients with other chronic pain syndromes (p=0.029). Ketamine-associated reductions in pain scores were the largest in postural orthostatic tachycardia syndrome (POTS) and trauma patients and the smallest in patients with chronic headache (p=0.007). In 37% of infusions, patients had a greater than 20% reduction in pain score. However, ketamine infusions did not change overall morphine-equivalent intake (p=0.3). In this longitudinal study, administration of subanesthetic ketamine infusions to adolescents with chronic pain in an outpatient setting was safe, well tolerated, and not associated with undesirable psychotrophic effects or hemodynamic changes.

Conclusions
Ketamine yielded significant decreases in pain intensity overall but the greater reductions in pain were observed in adolescents with CRPS. Interestingly, when looking at associated clinical diagnosis, we showed that ketamine-associated pain intensity reductions were highest in adolescents with history of trauma and POTS and lowest in adolescents with chronic headache. These data suggest that administration of
subanesthetic ketamine infusions is feasible and may have a role in the treatment of adolescents with chronic pain and patients with CRPS, POTS, and history of trauma-related chronic pain are more likely to benefit from this therapeutic modality. Future investigations should test these hypotheses.

Acute pain management due to sprains, strains and contusions in the medicare population
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Purpose
Research to date on sprains, strains, and contusions (SSCs) has focused mostly on the analysis of sports-related injuries, occupational injuries, injuries resulting from automobile accidents, and severe injuries that result in inpatient hospital stays. Little is known about real-world acute SSCs in an aging population. It was presumed that patients are often treated with over-the-counter (OTC) oral non-steroidal anti-inflammatory drugs (NSAIDs) for acute SSCs, but some patients may prefer or require use of prescription NSAIDs due to the specific SSC, a comorbid condition, the patient's prior experiences with available OTCs, out-of-pocket cost, or concerns about safety due to the patient's current treatment mix. Based on a specific patient's condition and medical history, a non-NSAID or NSAID medication may be selected, and in cases where a NSAID is prescribed, a topical may be preferred over an oral route of administration. For Medicare patients 65 years or older, we sought to identify; a) the most prevalent comorbid conditions for patients with evidence of a SSC and identify the medications used to treat SSCs by drug class and b) determinants of treatment with topical versus oral prescription NSAID medications among patients treated with a prescription pain medication for an acute SSC.

Method
A retrospective cohort of patients with a SSC was selected using Humana's Research Database (Louisville, KY) based on administrative claims data. Patients had to be aged 65-89 years and continuously enrolled for 12 months prior to and 3 months after the first identified SSC diagnosis (index date) between 1/1/2010 and 3/31/2014. Patients were required to have a pharmacy claim for a newly-initiated topical or oral pain medication within 3 months after the index date to be included in the analytical model. Over-the-counter NSAIDs were not identified because data were unavailable. Logistic regression, adjusted for demographic and clinical factors, was used to identify factors associated with the use of topical vs. oral pain medications and, more specifically, NSAIDs.

Results
Of 3.1M Humana MAPD members aged 65-89, 630,013 (20%) were diagnosed with a SSC. After applying enrollment criteria for the sample, 423,017 patients were available for analysis. The mean age was 74, 61% were female, and 85% were white. 64% of patients were diagnosed in a physician’s office and 23% were diagnosed in an emergency room. The most common comorbidities were hypertension (77%), dyslipidemia (73%), myofascial pain (45%), back pain (36%), and arthritis (36%). Patients were prescribed an average of 5.6 concomitant medications, with the most common being antihyperlipidemics (53%) and antihypertensives (52%). 63% of patients were prescribed at least one pain medication in the 12 months prior to the index SSC diagnosis. Opioids (37%) were most common, followed by NSAIDs (22%) and steroids (15%).

Of the 252,363 patients treated with pain medication post-SSC diagnosis, 53,178 (21%) were prescribed an NSAID; 1,730 or 3% of NSAIDs were topical. While overall pain medication use and NSAID use decreased with age, topical NSAID use increased slightly with each year of age (odds ratio (OR)=1.04, p<0.01 in an adjusted logistic regression model). Additional factors associated with topical NSAID use were hypertension (OR=1.18, p=0.01), myofascial pain (OR=1.46, p<0.01), site-specific osteoarthritis (OR=2.36, p=0.02 for upper arm; OR=1.34, p<0.01 for lower leg), gastro-intestinal (GI)/hepatic disorders (OR=1.17, p<0.01), and number of medications per month (OR=1.28, p<0.01). Conversely, prior use of prescription pain medications (OR=0.29 and 0.46 for NSAIDs and other pain medications, respectively; p<0.01 for both) and diagnosis of SSC in an emergency room (OR=0.26, p<0.01) were less associated with topical NSAID use and favored oral NSAID use instead. While history of GI disorders was associated with the use of topical NSAIDs, oral NSAID use was still evident among those with GI bleeding (27% of patients), as well as with diabetes (34%) and cardiac disease (23%).

Conclusions
Following the SSC, opioids were the most frequently prescribed pain medications, followed by NSAIDs. Considering oral versus topical prescription NSAIDs, topicals were more likely to be prescribed in a physician's office than an emergency room or inpatient setting. Primary care doctors may be more familiar with patients' medical histories and comorbidities. Patients with GI disorders, hypertension, and myofascial pain were more likely to be prescribed a topical NSAID; however, the use of oral NSAIDs among patients with GI bleeding, cardiac disease and diabetes was substantial, given that oral NSAIDs are contraindicated. Topical NSAIDs may be a more appropriate choice.

Reduction in parasympathetic autonomic nervous system function in fibromyalgia patients
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Fibromyalgia syndrome (FMS) is characterized by chronic, widespread pain, fatigue and difficulty with sleep. Fibromyalgia patients often experience cognitive impairment, irritable bowel symptoms and posturally-mediated hypotension. The lack of restorative sleep in fibromyalgia patients is a particularly troubling symptom and may help to explain the daytime fatigue and many of the other symptoms described. Studies have indicated that autonomic nervous system (ANS) function is altered in fibromyalgia patients as revealed by objective ANS testing. The ANS is intimately involved in maintenance of blood pressure, heart rate, bowel function, pain perception as well as initiation and maintenance of sleep. These abnormalities may help to explain the symptoms patients have with fibromyalgia. Heart rate variability (HRV) measures temporal differences between consecutive heart beats. One can determine the relative function of the ANS using Holter monitor to look at patterns of ANS function, particularly circadian rhythms.

In the frequency domain, High Frequency (HF) activity is known to be associated with parasympathetic nervous system activity, which is significantly active in normal subjects from midnight to 5am and slows down the body's system functions for restoration during sleep. Low Frequency (LF) is associated with sympathetic nervous system activity. We employed this methodology in order to understand parasympathetic and sympathetic ANS in this population while looking for a consistent pattern that might objectively separate FMS patients from patients with similar complaints who do not have FMS.

Method

58 control patients and 329 FMS patients from a single medical practice (DS) were tested using a Holter Monitor (ECG). FMS patients were defined as meeting the 1990 American College of Rheumatology criteria, were diagnosed as mild to severe and were consecutive patients presented at the medical practice.

Control patients were randomly selected from a cohort of patients in a larger database and were characterized as having the majority of their circadian index above the normal range and having an increase over 1500% during the hours of midnight to 5:00 am, which represents the 5th percentile.

Subjects wore Holter monitors for a period of 24 hours and went about their daily routines. HRV data was performed by Laboratory Services Industry. HRV, sympathetic (LF) and parasympathetic (HF) data points analyzed were: SDNN, LF (0.04 to <0.15 Hz), HF (0.15 to <0.40 Hz), Total Power, Normal LF, Normal HF, LF/HF ratio and Circadian increase between the hours of 0:00 (midnight) to 5:00am. The means of these points were compared between the control and active groups using a Two-Sample t-Test, Assuming Equal Variances. Hypothesized Mean Difference was 0. QRS complexes were reviewed on a Pathfinder 710 (Reynolds Medical) by a specialized technician who censored aberrant complexes and artifacts using an algorithm based on the Lomb-Scargle method of spectral analysis (23) to produce the standard measures of high frequency, low frequency and very low frequency (VLF, 0.003 to <0.04 Hz) spectral power, expressed in msec2.

Results

The FMS patients demonstrated decreased total power and parasympathetic ANS function, specifically reduction in parasympathetic nervous system function at night. The mean LF, corresponding to sympathetic function, of the 329 fibromyalgia patients was 388.99 Hz and the mean of the 58 normal patients was 470.0 Hz. (p < 0.03) The mean HF, corresponding to parasympathetic function, of the 329 fibromyalgia patients was 246.95 Hz and the mean of the 58 normal patients was 262.25 Hz (p > 0.3) The mean Total Power of ANS function for fibromyalgia patients was 1347.53 Hz and the mean of the 58 normal patients was 1625.13 Hz. (p < 0.02) The mean LF to HF ratio of the FMS patients of 1.718 was significantly higher (p < 0.001), demonstrating lack of parasympathetic activation at night in the fibromyalgia patients.

Conclusions

Patients with fibromyalgia have persistently reduced parasympathetic ANS activity, specifically at night. The role of parasympathetic ANS function in initiation and maintenance of sleep may help to explain the sleep disturbance and daytime somnolence patients report. The ANS is closely tied to many physiologic functions that are involved in symptoms FMS patients including irritable bowel syndrome, posturally-mediated hypotension, sleep disturbance, widespread pain and anxiety, which can be explained by the relative sympathetic hyperreactivity. Holter monitor may represent an objective diagnostic tool for FMS and therapies that target abnormalities in ANS function may represent a new therapeutic option for FMS patients.

TRV130, a G protein-biased ligand of the µ-opioid receptor, demonstrates analgesic efficacy following bunionectomy in an adaptive phase 2 study

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Purpose

Efficacy truncated by adverse events (AEs) and the multifactorial nature of pain may result in inadequate analgesia following treatment with conventional opioids. Preclinical
and healthy volunteer studies suggest that biased activation of μ-opioid receptor G protein signaling without β-arrestin recruitment may have the potential to increase analgesia with fewer AEs compared with conventional opioids. TRV130 is an investigational biased ligand of the μ-opioid receptor that activates G protein signaling with little β-arrestin recruitment. Here, we present the results of the second stage of an adaptive phase 2 study investigating the efficacy and tolerability of TRV130 in patients with acute pain following bunionectomy.

Method

This was a 2-phase, randomized, placebo- and active-controlled study. In the pilot phase, 144 patients aged 18 to 66 years with moderate-to-severe acute pain (pain intensity of ≥4 on a numeric rating scale [NRS]) following bunionectomy surgery were randomized to intravenous TRV130 1, 2, 3 or 4 mg; placebo; or morphine 4 mg, administered every 4 hours (q4h) in a double-blind fashion to initially test estimated dose regimens and efficacy measurement time points. First-line acetaminophen 650 mg q4h as needed (pm), then second-line intramuscular ketorolac 30 mg (or 15 mg) q6h pm were permitted for rescue. Pilot phase TRV130 dose regimens were analyzed for clinical utility, defined as efficacy (time-weighted average change in NRS pain intensity over 48 hours [NRS TWA 0-48]) and tolerability (prevalence of vomiting) compared with morphine to determine dose regimens for the second phase. The magnitude of TRV130 efficacy was demonstrated but q4h dosing was suboptimal; dosing shifted to q3h for the second phase and these data are reported hereafter. In the second phase, 195 patients aged 18 to 67 were adaptively randomized to double-dummy TRV130 0.5, 1, 2 or 3 mg every 3 hours (q3h); placebo; or morphine 4 mg q4h. The primary endpoint was the time-weighted average NRS change with TRV130 vs placebo over 48 hours. Secondary endpoints included categorical and stopwatch assessments of pain relief and rescue medication use. Safety and tolerability were measured by AE reporting and assessments of vital signs, physical examinations, clinical laboratory testing, electrocardiography and oxygen saturation.

Results

Most patients enrolled in the second phase were female (169/192, 88.0%) and white (141/192, 73.4%); mean age (standard deviation [SD]) was 40.0 (11.81) years. TRV130 2 mg and 3 mg q3h, and morphine 4 mg q4h, achieved the primary endpoint of the study by producing statistically greater least-squares mean (95% confidence interval [CI]) reductions in point mean (SD) decrease in NRS pain intensity (–6.0 [1.91]), and TRV130 2 mg and 3 mg produced significantly greater categorical pain relief vs placebo (P<0.0001) and morphine (P=0.0005 and P<0.0001, for TRV130 2 and 3 mg, respectively). TRV130 1, 2 and 3 mg produced more rapid median (95% CI) stopwatch time to onset of analgesia in the first 30 minutes placebo (placebo: >30 [52.0, nonestimable] minutes; TRV130 0.5 mg: >30 [2.0, nonestimable] minutes; TRV130 1 mg: 3.5 [2.0, 5.0] minutes, P=0.0063; TRV130 2 mg: 2 [1.0, 3.0] minutes, P = 0.0014; TRV130 3 mg: 1 [1.0, 2.0] minutes, P<0.0001; morphine 4 mg: 6 [3.0, nonestimable] minutes). As is typical in bunionectomy studies, most patients required rescue medication. Mean (SD) area under the curve for oxygen saturation change from baseline over 0- to 24.5 hours was numerically smaller for TRV130 vs morphine, (placebo: –2.1 [29.66]%*hour; TRV130 0.5, 1, 2 and 3 mg: –1.5 [33.53]%*hour, 0.5 [28.70]%*hour, 2.3 [24.66]%*hour and –5.1 [32.37]%*hour; morphine, –14.5 [28.77]%*hour). The most frequent AEs reported in patients receiving active treatment were nausea (85/164, 51.8%), dizziness (78/164, 47.6%), vomiting (43/164, 26.2%) and headache (38/164, 23.2%). No serious AEs (SAEs) were reported.

Conclusions

TRV130 2 mg and 3 mg rapidly produced profound analgesia in patients experiencing moderate-to-severe acute pain following bunionectomy, with up to a 6-point mean decrease in NRS pain intensity and meaningful pain relief in less than 5 minutes. These doses also produced significantly greater categorical pain relief compared with placebo and morphine. TRV130 produced no serious AEs, with tolerability similar to morphine. Small changes in oxygen saturation with TRV130 suggest that this level of efficacy can be achieved safely. These results suggest that G protein-biased μ-opioid receptor activation may provide increased efficacy with acceptable tolerability versus conventional unbiased opioids.

TRV734, a G Protein-biased Ligand of the μ-opioid Receptor, Demonstrates Oral Bioavailability, Displays Predictable Pharmacokinetics and Pharmacodynamics, and Provides Analgesia in Healthy Adults

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Purpose

Conventional opioids (μ-opioid receptor agonists, such as oxycodone and morphine) are among the mainstays of therapy for moderate-to-severe acute pain. However, their use is limited by adverse effects such as constipation, nausea and vomiting, sedation and respiratory depression. The analgesic and adverse effects of opioids are mediated by the μ-opioid receptor with high affinity and stimulates G protein signaling with little β-arrestin recruitment. In preclinical studies, TRV734 has demonstrated potent analgesia with an improved side effect profile compared with morphine. Here, we present the first clinical data from two phase 1 studies (single ascending dose [SAD]) and
multiple ascending dose (MAD) conducted to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), safety and tolerability of TRV734 in healthy adult subjects.

Method

The SAD was a single-blind, placebo-controlled, parallel-group study that randomized cohorts of healthy adult males to a single oral dose of TRV734 or placebo (3:1 ratio); 64 subjects were studied. The TRV734 doses studied here covered a wide range: the starting dose was 2 mg (administered as a solution) and subsequent doses (10, 20, 40, 80, 150, 200 and 250 mg capsules) were chosen based on safety and tolerability after each cohort. PK parameters included maximum plasma concentrations (Cmax, ng/ml), time to maximum (tmax, h), areas under the time-concentration curve (AUCs, ng h/ml) and apparent elimination half-life (t1/2, h). Pupilometry was performed to assess PD. The MAD was a double-blind, double-dummy, active- and placebo-controlled study that randomized cohorts of healthy adult males and females to multiple doses of TRV734, oxycodone immediate-release (IR) 10 mg, or placebo (3:1:1 ratio) every 6 h for 5 doses; 62 subjects were studied. The starting dose was 60 mg, and subsequent doses (80, 125 and 175 mg) were based on safety and tolerability after each cohort. PK assessments included Cmax, tmax, AUCs, t1/2, apparent total clearance (CL/F) and apparent steady-state distribution volume (Vz/F) of TRV734 and oxycodone; PD assessments included pupillometry and analgesia (latency of hand withdrawal from 2°C water in the cold pain test [CPT]). The Bowel Function Index (BFI) was used to measure subjects’ perceptions of constipation. Safety and tolerability were assessed in both studies using adverse event (AE) reporting, electrocardiography, cardiac telemetry monitoring, vital signs, oxygen saturation and laboratory tests.

Results

In the SAD, plasma TRV734 Cmax and AUC generally increased with dose, while tmax was similar across doses (0.5–1.3 h). The t1/2 was indeterminable at 2 mg, increased with dose from 10 mg through 150 mg (0.75–2.28 h) and was similar from 150 mg through 250 mg, likely an artifact of assay sensitivity at latter sampling times. Pupil diameter correlated with higher plasma TRV734 concentrations; the greatest reductions occurred between 0 and 4 h postdose (~2.9 mm; reduction peaked at 1 h), returning to baseline by 8 h. In the MAD, Cmax and AUC for TRV734 125/175 mg were higher than for 60/80 mg after the first and last doses. The CL/F and Vz/F appeared to increase with dose. The tmax (1–2 h) and t1/2 (1.2–2.5 h) were similar across doses. Accumulation of exposure (ratio) ranged from 1.28 to 1.46 and was slightly greater than expected, based on the t1/2. The CPT latency-to-hand-removal with all dose strengths of TRV734 was greater than with placebo, both after the first and last doses, and similar to oxycodone (except after the first dose of TRV734 175 mg, which produced greater latency). Mean overall BFI scores were generally proportional to TRV734 dose strength (0.1, 7.4, 8.5 and 9.5 for TRV734 60, 80, 125 and 175 mg, respectively; for oxycodone, 17.5; for placebo, 2.2), with score changes of >12 representing a clinically meaningful change in constipation. In both studies, there were no serious AEs; the most frequent AEs were somnolence, dizziness and nausea. The frequency of AEs in the MAD was similar between TRV734- and oxycodone-treated subjects. The SAD had no early study discontinuations from AEs; the MAD early discontinuations paralleled allocation: 3, 1 and 1 with TRV734, oxycodone and placebo, respectively.

Conclusions

In these studies, TRV734 was orally bioavailable and pharmacologically active. Administered as a single dose (2–250 mg) or as multiple doses (60–175 mg every 6 h), TRV734 was generally safe and well tolerated. Following a single dose, TRV734 Cmax and AUCs increased in an approximately dose-proportional manner and pupil diameter decreased in a dose-proportional manner, reflecting TRV734 exposure. Following multiple doses, TRV734 exposure parameters increased in a dose-proportional manner; the analgesic effect of TRV734 was generally dose-proportional and similar to that of oxycodone 10 mg IR. There was a favorable trend in BFI scores, warranting continued study.

Formulation and food effect studies of TRV734, an oral, G protein-biased ligand of the µ-opioid receptor

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Purpose

Conventional opioids such as morphine are effective and potent analgesics to treat moderate-to-severe acute pain. However, typical adverse effects (AEs) such as constipation, nausea, vomiting, sedation and respiratory depression can be intolerable and possibly life-threatening. The pharmacological actions of conventional opioids are mediated primarily through the µ-opioid receptor, a G protein-coupled receptor. Prior research has shown that biased ligands that selectively activate G protein coupling of the µ-opioid receptor without significantly stimulating β-arrestin signaling potentiate analgesic activity with reduced AEs of constipation and respiratory depression. We present here the results from 3 open-label crossover studies of TRV734, an investigational oral, G protein-biased ligand of the µ-opioid receptor, examining the pharmacokinetics (PK) of various formulations and food effect on bioavailability in healthy adult male subjects.

Method

The 2 studies investigating food effect on TRV734 randomized 12 and 13 subjects, respectively, into 3 sequential treatment periods separated by single-day washout periods. TRV734 125 mg was used. For the first study, subjects...
received TRV734 as 1) a capsule in fasted state; 2) an oral solution in fasted state; and 3) a capsule following a standard-fat meal. For the second study, subjects received TRV734 1) after a high-fat meal; 2) after a standard-fat meal; and 3) split in 3 portions over 120 minutes in a fasted state.

The third study was a 4-period, incomplete block design investigating the bioavailability of various TRV734 formulations. Eighteen subjects were randomized into 1 of 6 sequences (treatments A–F) of TRV734 on Days 1, 3, 5 and 7: A) fast-dissolution-rate drug in capsule (DIC) 150 mg; B) medium-dissolution-rate tablet (Q80/6h) 50 mg; C) medium-dissolution-rate tablet (Q80/6h) 150 mg; D) slow-dissolution-rate tablet (Q80/10h) 150 mg; E) medium-dissolution-rate tablet (Q80/6h) 150 mg coadministered with fast-dissolution-rate DIC 50 mg; and F) slow-dissolution-rate tablet (Q80/10h) 150 mg coadministered with fast-dissolution-rate DIC 50 mg. Pharmacokinetic parameters included areas under the concentration-time curve (AUCs, ng·h/ml), maximum concentration (Cmax, ng/ml) and time to maximum concentration (tmax, h). Treatments were compared using the ratio of geometric least squares (LS) means and 90% confidence intervals (CI).

Results
In the first study, the Cmax, AUC0–4 and AUC0–∞ for the fasted state were generally similar for capsule vs solution (geometric LS means ratios [90% CI]; Cmax: 0.90 [0.78, 1.05], AUC0–4: 0.95 [0.90, 1.02] and AUC0–∞: 0.96 [0.90, 1.02]), indicating similar pharmacokinetics for these formulations. The Cmax was 47% lower for the fed than for the fasted state (geometric LS means ratio [90% CI]: 0.53 [0.46, 0.61]); however, the geometric LS means ratios for AUCs were close to 1 for the fed vs fasted states (AUC0–4: 1.07 [0.95, 1.20]; AUC0–∞: 1.08 [0.96, 1.21], with 90% CIs within the range of 0.8 to 1.25. In the second study, the geometric LS means ratios of high-fat/standard-fat, standard-fat/split-portion fasted state, and high-fat/split-portion fasted state for Cmax, AUC0–4 and AUC0–∞ were close to 1 (Cmax: 0.90, 1.08 and 0.97; AUC0–4: 1.02, 1.02, 1.04; AUC0–∞: 1.02, 1.02 and 1.05, respectively) with most 90% CI values within 0.8 to 1.25. In the third study, the geometric mean AUC0–∞ (90% CI) values (ng·h/ml) were: 150.7 (124.7, 191.9), 43.6 (34.7, 56.2), 160.0 (135.2, 194.7), 137.7 (116.8, 173.8), 193.2 (165.6, 231.1), 202.0 (159.6, 266.0) for treatments A through F, respectively. The median (min, max) tmax values (h) were: 1.0 (0.5, 1.5), 2 (0.25, 9.0), 3 (0.5, 7.0), 1.5 (1, 10.0), 1.0 (1.0, 4.97) and 1.5 (0.5, 3.0) for treatments A through F, respectively.

Conclusions
Various drug in capsule (DIC) and modified-release (MR) formulations of TRV734 have similar bioavailability, suggesting that TRV734 is absorbed throughout the gastrointestinal tract. Food did not significantly alter TRV734 exposure. Treatments C, D, E and F (medium- and slow-dissolution-rate tablets 150 mg in the absence [C, D] or presence [E, F] of fast-dissolution-rate DIC 50 mg) show potential as MR formulations; with prolonged exposure relative to DIC, dosing every 6 to 8 hours may be feasible.

Efficacy, safety, and tolerability of fulranumab as adjunctive therapy for cancer-related pain: A randomized, double-blind, placebo-controlled, multicenter study
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Purpose
To evaluate the efficacy, safety and tolerability of fulranumab as an adjunct to standard pain therapy in inadequately controlled, moderate to severe, chronic cancer pain patients.

Method
Study consists of a 4-week double-blind (DB) phase and a 48-week open-label extension (OLE) phase. Cancer patients (83% terminally ill) were randomized to the 9 mg/0.9 mL Q4week fulranumab subcutaneous injection or placebo in 2:1 ratio.

Results
In total 98 patients received study drug (placebo: 31, fulranumab: 67); men (56%); mean age 58.3 years; 69 patients entered OLE. Primary endpoint: Change in average cancer pain intensity score from baseline (average of last 3 days prior to randomization) to end of DB (average of last 7 days), mean [SD] was: -0.8 [1.3] for fulranumab group and -0.7 [1.6] for placebo. Secondary endpoints: a responder rate based on 30% average cancer pain adjusted improvement (p=0.020) and change in BPI-SF Pain Intensity Subscale (p=0.003) and Pain Interference Subscale (p=0.006) from baseline to DB endpoint were significant in fulranumab-treated group vs. placebo. The most common adverse events for fulranumab vs. placebo were asthenia (16% vs. 10%), fatigue (10% vs. 0%), decreased appetite (12% vs. 6%), and malignant neoplasm progression (10% vs. 0%).

Conclusions
Adjunctive fulranumab therapy did not show significant improvement in average cancer pain intensity in terminally ill cancer patients. However, greater responder rate and improvement in BPI-SF scale in fulranumab-treated group vs. placebo support further research of anti-NGF therapy in cancer pain.

Insights from pain management specialists on the dual challenge of chronic pain treatment
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Purpose
Chronic pain affects approximately 100 million adults in the US and is among the most common complaints that bring a
patient to a clinician's office. The associated cost of health care and lost productivity is upwards of $635 billion per year. Despite the high prevalence and enormous health and economic burdens of pain, US medical schools provide limited training in pain management, and especially training in the safe and appropriate use of opioid therapy. It therefore is not surprising that clinicians may have a poor understanding of best practices for using opioids in the treatment of patients with chronic pain. Furthermore, concerns related to misuse, abuse, and diversion (MAD) may hinder the care of patients with chronic pain. Lack of knowledge/training among clinicians and concerns related to MAD must be addressed in parallel to ensure that clinically appropriate opioid therapy is considered for patients who would benefit from it. A survey of pain management specialists was conducted with the goal of understanding their perceptions about educational needs and practice gaps related to opioid therapy in primary care and the broader medical community.


Method

During 2 educational meetings on the use of extended-release opioid therapy, 85 clinicians involved in pain management were surveyed via electronic surveys and interactive automated response system questions embedded in educational presentations. The number of respondents varied per question. All data are reported. Related to PCPs, survey participants were asked about the perceived understanding of the distinctions between acute and chronic pain and pain therapy in the primary care setting; the perceived appreciation for the magnitude of opioid abuse; and the need for resources to identify appropriate patients for long-term opioid treatment. Related to the broader medical community, survey participants were asked about pain classification as a consideration when selecting treatment; the perceived understanding of MAD; the role of abuse-deterrent formulations in a universal precautions approach to opioid prescribing; and the need for a framework and clearer guidelines for long-term opioid therapy. Lastly, participants were asked about the importance of conducting urine screenings when planning opioid therapy for pain patients. The survey and meetings were sponsored by Pfizer Inc.

Results

Respondents (n=85) were pain management specialists involved with the treatment of patients receiving long-term opioid therapy.

Respondents were asked to indicate their level of agreement with several statements related to perceptions about PCPs and their practice settings. Sixty-two percent (n=85) agreed (rating of 5, 6, or 7 on a 7-point scale, “Strongly disagree” to “Strongly agree”) that PCPs lack an understanding of the definition of acute pain; 86% (n=85) agreed that distinctions in treatment planning are poorly understood; and 86% (n=85) agreed that resources to identify patients who could benefit from long-term opioid treatment are lacking. Fifty-six percent (n=79) disagreed (rating of 1, 2, or 3 on a 7-point scale, “Strongly disagree” to “Strongly agree”) that PCPs appreciate the magnitude of opioid abuse in the community.

Respondents also were asked to indicate their level of agreement with several statements about unmet needs and practice gaps with regard to long-term opioid therapy: 87% (n=84) agreed that classifying a patient's pain according to pathophysiology can help in the selection of appropriate therapy; 84% (n=83) agreed that definitions for misuse, abuse, and diversion are poorly understood by the broader medical community; 71% (n=80) disagreed that clinicians are easily able to assess a patient's risk of prescription opioid abuse; 84% (n=80) agreed that abuse-deterrent opioids are an important component of a universal precautions strategy; 87% (n=83) agreed that a framework for appropriate long-term opioid treatment, including how and when to use opioids, should be incorporated into clinical practice; and 86% (n=84) agreed that there is a need for clear guidelines on appropriate long-term treatment of pain with opioids. Finally, 86% (n=84) agreed that opioid treatment planning for different types of pain, and the perceived appreciation for the magnitude of opioid abuse is a major public health problem. Prescription opioid abuse is a major public health problem. Abusers of extended-release (ER) opioids may heighten positive subjective pharmacodynamic (PD) effects by
manipulating tablets to facilitate rapid routes of administration (eg, intranasal, intravenous), but ER morphine is also frequently abused by oral ingestion of intact, chewed, or crushed tablets. Abuse-deterrent (AD) technology aims to prevent tablet manipulation and/or maintain ER release characteristics despite manipulation without impeding the desired PD effect of analgesia. A novel AD, ER morphine product candidate (EG-001, Egalet Corporation, Wayne, PA) incorporates a proprietary plastic injection molding technology (Guardian™, Egalet Corporation, Wayne, PA) to resist physical manipulation and chemical extraction. This study compared the human abuse potential (HAP) of orally administered intact and manipulated EG-001 with a marketed formulation of ER morphine (MS Contin®, Purdue Pharma LP, Stamford, CT) and placebo. Secondary objectives included assessment of pupillary miosis (an objective PD measurement that may serve as a surrogate of analgesia or positive subjective effects of morphine), pharmacokinetic (PK) characteristics, and PK/PD relationships. Dose-dependent PD effects are proportional to peak plasma concentration (Cmax), but positive subjective effects are also inversely proportional to time to Cmax (tmax); hence, the abuse quotient (AQ=Cmax/tmax) is useful to compare PK and PD outcomes in HAP studies. This study was conducted in accordance with the US Food and Drug Administration April 2015 Guidance for Industry, Abuse-Deterrent Opioids - Evaluation and Labeling. However, because EG-001 is extremely hard and difficult to chew, more aggressive measures to manipulate the product were necessary.

Method

Adult (18-55 years of age) male or female volunteers, who were nondependent, experienced, recreational users of prescription opioids (≥10 occasions in the past year; ≥1 in the 12 weeks before the screening visit), were enrolled in a single-center, double-blind, triple-dummy, 4-way crossover study. A naloxone challenge test was used to exclude opioid-dependent enrollees, and a 2-day drug discrimination test (placebo vs immediate-release morphine; 30 mg) was used to exclude enrollees who could not distinguish or tolerate the subjective effects of morphine vs placebo. Participants were randomized in a 1:1:1:1 ratio to the following treatment groups with a ≥5-day washout period in between: EG-001 (60 mg, intact), EG-001 (60 mg, manipulated), ER morphine (60 mg, manipulated), and placebo. Manipulation of ER morphine was accomplished with mortar and pestle to achieve a fine powder, but EG-001 was resistant to this technique and required another method of manipulation that resulted in greater effort but larger particle sizes. The primary endpoint was the score on the Drug Liking Visual Analog Scale (VAS), a 0-100 bipolar VAS (0=strong disliking; 100=strong liking), and was analyzed for participants who completed all 4 treatment periods. Secondary PD measurements included pupillometry, the Drug Effects Questionnaire, the Take Drug Again VAS, and the Overall Drug Liking VAS. Blood samples were collected for PK analyses including Cmax, tmax, and AQ. Adverse events (AEs) were assessed.

Results

A total of 78 participants entered the qualification phase; 38 completed all 4 treatment periods. The majority of participants were men (92.1%) with a mean (SD) age of 24.3 (4.2) years. Peak Drug Liking (Emax, median VAS) of participants after treatment with manipulated ER morphine was significantly higher (74.0) compared with Drug Liking Emax after treatment with intact EG-001 (62.0; P<0.0001) and manipulated EG-001 (67.0; P<0.01); however, there was no significant difference in Drug Liking Emax between manipulated and intact EG-001 (P>0.05). Time to Drug Liking Emax (TEmax, median h) after treatment with manipulated ER morphine (1.02) was significantly shorter compared with Drug Liking TEmax after treatment with intact EG-001 (3.0; P<0.0001) and manipulated EG-001 (1.99; P<0.005). Manipulation did not significantly shorten the Drug Liking TEmax of manipulated EG-001 compared with intact EG-001 (P>0.05). Although pupillary miosis Tmax (median h) after treatment with manipulated ER morphine (3.09) was significantly shorter compared with Tmax after treatment with manipulated EG-001 (4.11; P<0.0001), miosis Emax (change from baseline, median mm) for these comparators was equal (2.80 for each; P>0.05). For the PK results, tmax values (median h; range) of morphine were shortest following treatment with manipulated ER morphine (0.88; 0.63-4.13) and longer following treatment with manipulated EG-001 (2.12; 0.88-4.15) and intact EG-001 (4.12; 1.63-6.13). The mean (± SD) AQ was lower in participants treated with intact EG-001 (5.73±3.51) or manipulated EG-001 (16.36±9.40) compared with participants treated with manipulated ER morphine (45.88±20.31). AEs with EG-001 and ER morphine were similar and typical of morphine analogs; there were no serious AEs in this study.

Conclusions

Intact and manipulated EG-001 demonstrated lower abuse potential compared with manipulated ER morphine when administered orally. Manipulation of EG-001 did not significantly increase Drug Liking Emax compared with the intact product. A positive PK/PD correlation was demonstrated as the AQ for manipulated ER morphine was much higher than the AQ for both manipulated and intact EG-001. These results, along with the hardness of the tablet and difficulty chewing it, suggest that EG-001 would be an important new treatment option for patients with chronic pain that would also help reduce misuse and abuse of this ER morphine product.

Effect of pulsed electromagnetic field (PEMF) treatment on programmed resolution of inflammation pathway markers in human neuronal cells in culture

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Purpose

Inflammation is a complex process involving distinct but overlapping biochemical and molecular events that are highly
regulated. Unresolved inflammation especially in nerve tissue can lead to chronic debilitating conditions causing to quality of life issues. Many current therapies for inflamed neuronal tissue treat the symptoms (pain and edema) but do not resolve the underlying condition. Pulsed electromagnetic field (PEMF) therapy is increasingly used to treat persistent and chronic pain associated with inflammation following surgery. However, understanding the molecular and cellular effects of PEMF therapy on pathways involved in the resolution of inflammation are poorly understood. We describe here recent in vitro experiments using neuronal derived human cells in culture to determine the molecular and cellular mechanism of action on metabolic pathways involved in the resolution of inflammation.

Method

Using neuronal derived cell culture lines, we investigated the effect of PEMF on the expression of genes that are involved in the acute and resolution phases of the inflammatory response. PEMF therapy was delivered at settings of 591 V/M, 6.8 A/M, in packages of 42 usec using a frequency of 1 kHz. We used whole genome microarrays and qRT-PCR of selected gene panels which contained genes involved in acute and resolution phases of inflammation to analyze treated cells. Also we studied the effects of PEMF on neurite in human neuron cultures.

Results

We found that PEMF treatment of human neuronal cells and astrocytes followed by changes in mRNA levels of key enzymes involved in heme catabolism, antioxidation of reactive oxygen species (ROS), and lipid mediator biosynthesis, which differed for each cell type. PEMF treatment was also followed by changes in mRNA levels of important cytokines involved in inflammation. Additionally, key genes, cytokines and growth factors associated with dendritic neuronal sprouting, networking and repair enhanced in vitro neuronal morphological response.

Conclusions

Based on our results, we propose a model in which one mechanism of PEMF therapy may be to promote chronic inflammation resolution via changes in expression of genes important for mediating anti-inflammatory effects and inflammation resolution, leading to morphological and phenotypical response.

Pain relief and its impact on sleep in treatment of neuropathic pain associated with postherpetic neuralgia

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Purpose

Postherpetic neuralgia (PHN) interferes with many aspects of patients' physical function. Because neuropathic pain tends to be worse during the night, its interference with sleep is one of the most common complaints among patients with PHN. Disturbed sleep may in turn enhance pain intensity and/or lead to reduction in pain tolerance. Consistent with these observations, there is evidence supporting a reciprocal relationship between pain and sleep in which pain disturbs sleep, and poor sleep enhances pain. Thus, in addition to pain relief, improvement in sleep quality may contribute to improvement in patients' overall quality of life.

Previous comprehensive analyses of patients with PHN who received gastroretentive gabapentin (G-GR; Gralise®) showed that reduction in pain intensity and in interference of pain with sleep were among key predictors of overall improvements in patients' functioning. Therefore, we further analyzed the complex relationship between pain and sleep and characterized factors important for clinically significant reductions in pain intensity and sleep interference, and how these reductions impacted other treatment outcomes.

Method

Data from two Phase 3 and one Phase 4 studies of patients with PHN who received G-GR 1800-mg once-daily (n=556) were integrated. Visual Analog Scale (VAS) for pain intensity, Brief Pain Inventory (BPI) for pain quality (worst, least, average, current pain) and pain interference with sleep (BPI Sleep) and with other measures of patients' functioning (general activity, mood, walking ability, normal work, relationships, enjoyment of life, and the average score) were completed at baseline, Week 2 of treatment, and end of study. Patients' Global Impression of Change (PGIC) for overall improvement (very much, much, and minimally improved; no change; minimally, much, or very much worse) was completed at end of study. Responders were patients with ≥30% reduction in VAS pain or BPI sleep; Non-Responders were patients with <30% reduction. Population and regression analyses were performed to characterize treatment outcomes for Responders vs. Non-Responders, and to describe relationships between these two patient populations. Statistical significance was set at p≤0.05.

Results

Responders in VAS or BPI Sleep were mostly females (65.6% and 64.3%, respectively), but there were no other significant differences in patient demographics and baseline disease characteristics between Responders and Non-Responders.

There were significant differences (all p<0.001) between Responders and Non-Responders in VAS or BPI Sleep in reductions in all treatment outcomes assessed on the VAS or BPI at Week 2 and at the end of study. Significantly more (all p<0.001) Responders vs. Non-Responders in VAS reported feeling very much (29.5% vs. 4.0%) or much (37.2% vs. 10.7%) improved on the PGIC. In contrast, more
Non-Responders in VAS reported no change on the PGIC compared with Responders (45.1% vs. 9.7%; p<0.001). For BPI Sleep, more Responders vs. Non- Responders reported feeling very much improved (23.9% vs. 8.0%; p<0.001), and numerically more Responders reported feeling much improved (33.3% vs. 24.4%; p=0.1902). As for VAS, more BPI Sleep Non-Responders vs. Responders reported no change on the PGIC (34.7% vs. 15.7%; p<0.001).

For both Responder groups, there was a linear correlation between percent reductions in VAS and BPI sleep interference (all p<0.001). However, being a Responder in VAS was not predictive of reporting significant changes in BPI sleep interference and vice versa.

There were no significant differences between Responders and Non-Responders in VAS or BPI Sleep in frequency or severity of adverse events (AEs). More Non-Responders discontinued early due to AEs (17.9-18.4% vs. 9.0-9.3%, p<0.01), mostly due to mild or moderate AEs.

Conclusions

The results of this analysis showed that clinically significant improvements in pain intensity or sleep interference were accompanied by parallel improvements in other outcomes. Importantly, although correlated, improvements in pain and sleep were independent of each other, i.e., experiencing a reduction in pain intensity had no effect on whether a patient also experienced a reduction in sleep interference and vice versa. The important factor for improvements in pain or sleep was early discontinuation due to AEs, but not AE severity, which suggests that focusing on patient's individual ability to tolerate AEs may facilitate more successful treatment of PHN.

Mitigating phantom-limb pain with electric cell signaling

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Purpose

The purpose of this report is to describe electric cell signal treatment (EST) for the therapeutic mitigation of phantom-limb pain. This is a case report of a successful application of this technology to a double amputee.

The incidence of this type of chronic pain of central origin has been climbing due to an overall increased prevalence of metabolic disease conditions, especially with an aging population, such as diabetes, osteomyelitis, etc. Additionally, there have been numerous injuries and amputations incurred by military personnel involved in the ongoing military conflicts.

When a limb is amputated, many severed nerve endings are terminated at the remaining stump and can become inflamed. Melzak (1999) proposed that a pain neuromatrix is activated in specific brain regions, ultimately resulting in painful sensations independent of the sensory source of the pain.

It is now widely accepted that phantom-limb pain is a central pain phenomenon caused by remodeling of the central nervous system, starting at the affected limb and moving throughout the entire sensory pathway all the way up to the cortex. In other words, phantom pain may be a maladaptive of the neuromatrix to maintain global bodily constructs. Research now indicates that the pathophysiology comes from changes at the dorsal horn and higher levels in the central nervous system (CNS).

Method

A promising and relatively new technology uses digitally produced, non-invasive electric wave signal energy, administered by an ultra-high digital frequency generating system (UHdfig). The complex, signal energy waveforms are first formed as electrically balanced, biphasic symmetrical primary energy waves, and then modulated by superimposed therapeutic frequencies with associated harmonic resonance. The dosage to the patient is continually varied to create rapidly changing energy signals that can easily pass through dermal tissue and avoid repetitive nerve accommodation.

These time-varying pulsed electric energy signals, associated harmonics, and resonance frequencies are typically introduced through the skin of injured or diseased tissue by special vasopneumatic electrodes and produce numerous physiologic advantages over other electromedicine devices. The advantages have been shown to enhance circulation and local blood flow, provide potent anti-inflammatory effects and increase cyclic adenosine monophosphate (cAMP), necessary for cell healing.

Our treatment protocols for central pain conditions, such as phantom-limb pain have shown unparalleled treatment success due to the use of a unique multiplexed signal configuration of digitally formatted amplitude-modulated energy signals (AM) and true frequency-modulated signals (FM), which are not available on other electromedicine devices. These FM signals allow for much greater depth of penetration of the varying therapeutic and healing signal energy through the dermal layers and into deeper tissues by using sequentially-generated, albeit randomly-changing, higher-frequency signals known to produce lowered skin and tissue impedance. FM signal energy also allows for optimum voltage application, which affects and manipulates voltage-gated channels and receptors within targeted tissue.

Results

The following case report details and outcomes are indicative of the phantom-limb pain patients treated at our medical facility in Las Vegas, Nevada.

Male patient (PC) is a 73-year old Hispanic man who is a bilateral amputee secondary to advanced peripheral vascular disease and a 30-year history of diabetes. He underwent a right above-knee amputation in 2006 and a left below-knee amputation in 2008. He has had phantom-limb pain for a number of years, partially controlled with hydrocodone/acetaminophen 10/500 mg qid and tramadol 50 mg tid. There were no aggravating factors for the episodes of his phantom-limb pain and the pain was equal on both sides, with the toes and heels being the primary site of the perceived severe pain.
PC described his pain as pins and needles, constant, and grades the severity as a 9 to 10 out of 10 on the NRS.

Treatment with the specific and varied parameter EST was initiated daily for the first week and then every other day for 20-30 minute sessions. On the first day alone, the patient reported that his NRS dropped to 5/10. Subsequent UHdflg EST programs were administered to include signal energy that addressed and treated varying stages of inflammation, pain, edema, circulation, and neural deficits. PC underwent an EST treatment regimen lasting approximately 6-weeks and was completely satisfied in the overall progress and results with his substantially diminished pain. He was recommended to continue treatment only on an "as-needed" basis. His last visit to the clinic was more than 12-months ago and routine telephone follow-up has indicated that the phantom-limb painful sensations in his lower leg, toes and heels are still absent. PC also states that if and when he has an episode of increased pain, it is now anatomically located only in the distal area of his stumps.

Conclusions

The advantages of electric cell signaling (EST) over centrally acting drugs are clear: reduced costs and reduced side effects. EST shows promise for not only the treatment of diabetic and other peripheral vascular disease-induced limb amputations, but also for efficacious treatment of our returning soldiers as well.

We envision future directions of research and clinical use to include the synergistic and cost saving incorporation of electric cell signaling technology with recent developments in quantum physics as they pertain to biologic oscillations, neural networks and cellular microtubule function in energy transfer, proton motive force, and cellular capacity.

PainNET: Impact of developing a chronic pain management online community of practice in the primary care setting

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Purpose

There are over 100 million people in the United States with chronic pain, and the majority will seek care from a primary care provider (PCP). Most primary care providers have little expertise in managing complex pain cases, or do not have access to a pain specialist, particularly in federally qualified health centers or safety-net primary care practices. PainNET is a comprehensive practice solution for primary care providers interested in improving the management of pain. The PainNET web-based platform provides a scalable, system-level intervention guided by the needs of PCPs, to improve the quality and safety of chronic pain, and to promote multidisciplinary and interprofessional learning and education specific to chronic pain. PainNET will create a learning community that will enable PCPs to develop expertise to treat patients with complex chronic pain through a combination of archived pain case presentations, resource libraries, community forums, and expert consultations. The goal will be to increase providers' knowledge, help primary care practices to manage chronic pain more systematically, and to ultimately serve patients more effectively with quality pain management expertise.

Method

The Weitzman Institute at the Community Health Center, Inc. is leading the development and evaluation of PainNET, a web-based platform which will be launched in Summer 2015 to provide practice-level access to indexed recordings of didactics and case discussions from Project ECHO Pain Management sessions; a resource library of best practices for pain management; tools and structured modules to support practice redesign and quality improvement initiatives; and bulletin-board forums for community discussion. PainNET is a scalable, system-level intervention guided by the needs of PCPs, to improve the quality and safety of chronic pain management and opioid prescribing. Thirty-five sites from five states will have full access to PainNET and will be invited to participate in testing and further development of this platform. It is anticipated that PainNET will foster and facilitate shared multidisciplinary and interprofessional learning and education specific to chronic pain through discussion boards, chat rooms, and direct messaging between providers and specialists. The project will employ a cluster randomized design to evaluate the impact of PainNET at the knowledge level, practice level, and patient level. A control group consisting of primary care practices that are not using PainNET will be utilized to compare changes in knowledge, self-efficacy and interprofessional collaboration pre-study and post-study. Project assessment will include an evaluation of the impact of PainNET on multidisciplinary chronic pain management strategies and best practices utilization. Project evaluation will specifically measure provider attitudes about interprofessional collaboration and adherence to evidence-based guidelines for management of chronic pain.

Results

Quantitative and qualitative methods will be used in combination to provide greater validity and enhanced understanding of the results of the intervention. Specific PainNET outcome measures include practice-level outcomes (adherence to selected pain management guidelines, adoption of best practices for pain management) and provider-level outcomes (knowledge and competency scores, acceptance and understanding of the need for collaborative, interdisciplinary care for chronic pain). Participation in PainNET is anticipated to increase overall knowledge and competency scores as demonstrated by values and changes on the Know-Pain 50 survey, Pain Care Beliefs survey and PainNET monthly survey and reports. In addition, the research team will assess the adoption of and adherence to best practices and guidelines at
participating sites using pre- and post-intervention practice assessment surveys, chart review, and PainNET monthly reporting by participating practice teams.

Conclusions
The potential impact of PainNET will be to create new tools to promote interdisciplinary communication and adoption of pain management best practices and to expand access to expert clinical advice to a wider range of providers. Opportunities for interactions between providers from different disciplines and professions are increasingly limited in today's primary care practice environment. Few PCPs still round in hospitals and increased pressure for productivity limits opportunities for telephone consultation and case discussions. PainNET will capitalize on well-established online tools to support such communication in an asynchronous, highly efficient manner.

Assessment of the low abuse potential of CR845, a kappa-opioid agonist
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Purpose
CR845, a potent, peripherally-acting, selective kappa opioid receptor agonist, is being developed for the treatment of acute and chronic pain. In receptor-binding experiments, CR845 demonstrated 30,000-fold selectivity to kappa receptors compared with mu- or delta-opioid receptors. CR845 is a hydrophilic tetrapeptide with limited membrane permeability. In two Phase 2 clinical trials, CR845 was significantly better at controlling post-operative pain than placebo following elective hysterectomy or bunionectomy. In the present clinical study, assessment of pupil diameter was performed to confirm the lack of mu-opioid receptor activity in humans, and to compare the abuse potential of CR845 to pentazocine, a centrally-active mixed kappa- and mu-opioid agonist.

Method
Recreational polydrug users experienced with, but not dependent on, opioids and hallucinogenic drugs were enrolled in this single-center, randomized, double-blind, active- and placebo-controlled study. Eligible subjects had to be able to discriminate between intravenous (IV) doses of pentazocine (0.5 mg/kg) and placebo administered on 2 consecutive days to qualify for the study. Qualified subjects received a single bolus IV dose of the following 4 treatments in a balanced Williams crossover design, with a 48-hour washout period between treatments: CR845 5 mcg/kg (therapeutic dose), CR845 15 mcg/kg (supra-therapeutic dose), placebo, and pentazocine 0.5 mg/kg. Pupillary diameter was measured with a NeurOptic® VIP-200 pupillometer under controlled lighting conditions after at least 1 minute adaptation to dim lighting. Pupillometry was performed at baseline, 0.5, 1, 1.5, 2, 3, 4, and 8 hours postdose. A Drug Liking visual analog scale (VAS) (0="strong disliking"; 100="strong liking") was administered on a similar schedule.

Results
A total of 44 subjects (age, 28.0±7.7 years [mean±SD]) enrolled in the study and 41 subjects provided pupillometry data. There was no statistically significant change from baseline in mean pupillary diameter observed at any time in subjects who received either dose of CR845 or placebo. By contrast, subjects who received pentazocine had a mean pupillary diameter decrease of -2.3±0.9 mm (mean±SD) 30 minutes after dosing that gradually returned toward baseline over the 8-hr observation period. For the Drug Liking VAS, subjects who received pentazocine reported the highest score 5 min after dosing (84±17), compared with scores of 59±17 in each of the CR845 groups and 51±5.5 in the placebo group.

Conclusions
The results of this study provide objective evidence that CR845 demonstrates little or no centrally-mediated mu-opioid activity compared with pentazocine as assessed by changes in pupillary diameter. This observation combined with the Drug Liking VAS results suggests that CR845 has a low abuse potential compared with mu-opioids.

CR845, a peripheral kappa opioid, provides better pain relief with less nausea and vomiting than placebo in patients after bunionectomy
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Purpose
CR845, a potent, peripherally-acting, selective kappa opioid receptor agonist, is being developed for the treatment of acute and chronic pain. In receptor-binding experiments, CR845 demonstrated 30,000-fold selectivity to kappa receptors compared with mu- or delta-opioid receptors. CR845 is a hydrophilic tetrapeptide with limited membrane permeability. The present clinical study was performed to assess the analgesic effectiveness for the treatment of post-surgical pain.

Method
This Phase 2, single-center, randomized, double-blind, placebo-controlled, parallel-group study enrolled patients undergoing elective unilateral first metatarsal bunionectomy surgery. One day after bunionectomy, patients were randomized 2:1 to CR845 (5 mcg/kg, IV) or placebo after reporting a visual analogue scale (VAS) pain score ≥40 (out of 100) at rest. Within 30-60 minutes after the initial dose of study drug, patients could receive an additional dose as needed and then every 8 hours as needed over the next 48 hours. Rescue
medication (fentanyl 50 mcg IV) was available as needed. Pain intensity (VAS) was assessed during the 48-hour study period. The mean summed pain intensity differences from baseline over 24 hours (SPID0-24) was the primary efficacy measurement.

**Results**
A total of 51 patients were randomized to either CR845 (n=34) or placebo (n=17). Most patients were female (88%), white (92%), and had an average age of about 42 years. Twenty-six CR845 patients and 15 placebo patients completed the study. In the prespecified analysis of the complete population, a statistically significant reduction in SPID0-24 with CR845 compared to placebo (P=0.033) was observed, with only CR845 having a 95% CI significantly less than 0 (P=0.0007). This observation was supported using the modified intent-to-treat population in which a greater decrease in SPID0-24 was observed with CR845 than placebo, although this difference was not significant (P=0.116). Again, only CR845 had a 95% CI significantly less than 0 (P=0.022). The mean summed pain intensity differences from baseline over 48 hours (SPID0-48) difference between treatment groups was statistically significant for the complete population (P=0.024). Compared to placebo, patients treated with CR845 experienced fewer treatment-emergent adverse events (AEs) of nausea (23.6% vs. 58.8% for placebo, P=0.028) and vomiting (5.9% vs. 23.9% for placebo, P=0.034). Mild transient facial tingling (paresthesia) and somnolence were observed with CR845 (11.8% for both), but there were no reports of psychiatric AEs characteristic of centrally-acting kappa opioids.

**Conclusions**
This study demonstrated that CR845 resulted in reduced pain intensity with lower incidence of nausea and vomiting versus placebo in patients after bunionectomy surgery.

**Method**
This Phase 2, multicenter, double-randomized, double-blind, placebo-controlled, parallel-group clinical trial was approved by institutional review boards. Patients undergoing elective laparoscopic hysterectomy received CR845 (IV infusion, 0.04 mg/kg) or placebo before surgery. Following surgery and upon reaching post-operative pain intensity ≥4 on a 10 cm visual analog scale (VAS), patients were randomized a second time to receive either an IV infusion of CR845 (0.04 mg/kg) or placebo. Rescue medication (IV morphine) was permitted following the second infusion. Efficacy measurements included VAS pain intensity scores and total use of rescue medication during the 24-hr post-operative period and patient global evaluation at discharge.

Two hundred-three patients were randomized for study entry. Patients receiving CR845 both pre- and post-operatively had an overall 2-fold decrease in pain intensity over 24 hours (SPID0-24, P<0.01) and used 36% less rescue medication (P=0.03) compared with patients receiving only placebo. Sixty-two percent of CR845-treated patients rated their treatment as “excellent” or “very good” compared with 36% of placebo-treated patients. Opioid-related adverse events of nausea and vomiting were significantly reduced in patients receiving CR845 by 51.2% (P<0.001) and 79.5% (P<0.05), respectively, compared with placebo-treated patients.

**Conclusions**
CR845 demonstrated significant analgesic activity for post-operative pain and was generally well-tolerated, thus establishing its potential for development for the treatment of acute pain.

**Improvements in knowledge, skills, and attitudes regarding medication management in patients with advanced illnesses: an educational needs assessment for surveyors in the state of Maryland**
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**Purpose**
Clinicians who provide care for patients with an advanced or life-limiting illness or are possibly hospice appropriate must balance appropriate medication management for pain and non-pain symptom control, while striving to adhere to state regulations. Evidence-based interventions that are appropriate for end-of-life care, such as off-label use of medications and medications known to increase the risk of adverse events in certain populations, may be viewed as partially or completely noncompliant with state regulations. The purpose of this educational program is to assess and improve the knowledge,
skills, and attitudes of State of Maryland surveyors for long-term care, assisted living, and hospice facilities.

**Method**

An online, voluntary educational program on appropriate medication management in advanced illness will be developed. Intended participants are State of Maryland surveyors and other potentially interested participants. The course is tentatively planned to be delivered as five modules, as follows: principles of palliative care, pain assessment and management, non-pain symptom assessment and management, de-prescribing in patients with advanced illness, and the medication use process with a focus on regulatory and safety implications. To best determine the educational needs of the intended audience, this project will detail the results of the educational needs assessment. This will include expert interviews, a focus group session, and an online educational needs assessment survey.

**Results**

Data collection is underway. Results are pending and will be presented at the PAINWeek 2015 national conference.

**Conclusions**

We believe State of Maryland surveyors of long-term care, assisted living, and hospice facilities would benefit from an educational course on medication management in patients with advanced illnesses, and would improve the provision of care to patients in these settings. Results of this educational needs assessment will allow the research team to tailor the educational intervention for maximal impact.

**Tapentadol: 14 characteristics inform use as first-line therapy**

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**Purpose**

Tapentadol is a novel-acting analgesic that combines both opioid (MOR) agonist activity and neuronal norepinephrine-reuptake inhibition (NRI). With such duality of action, it combines inhibition of ascending (afferent) pain-transmitting pathways plus the activation of descending adrenergic pain-modulatory systems (DNIC, diffuse noxious inhibitory controls). Tapentadol has been shown to be effective against a variety of nociceptive and neuropathic type pains in animal models and clinical practice. With the growing amount of evidence and experience regarding its clinical profile, we sought to identify characteristics of tapentadol that inform its use as possible first-line therapy for moderate to severe pain of multiple modalities.

**Method**

A search of MedLine, PubMed, and other sources was conducted in order to identify and evaluate current published information available on tapentadol regarding its safety, efficacy, and other features. Relevant search terms, used alone and in various combinations, included “tapentadol,” “mechanism of action,” “pain management,” etc. Initial “hits” were followed up using additional search strategies.

**Results**

We identified 14 characteristics of tapentadol that could help inform clinicians’ decision regarding its use as first-line therapy for moderate to severe pain of multiple modalities: (1) due to its engineered dual mechanism of action, it is the first new opioid in 25 years; (2) the dual (MOR-NRI) mechanisms interact synergistically; (3) it has a favorable metabolic profile (no significant active metabolites and little CYP450 interaction); (4) it has linear dose proportionality for easy titrating, tailoring and tapering (the 3 Ts); (5) it allows direct conversion between the IR and ER formulations; (6) it is effective in treating severe acute pain; (7) in treating chronic non-cancer pain; (8) in treating painful diabetic neuropathy; (9) and it is effective in cancer pain management; (10) it is possible to safely and effectively combine with adjuvants; (11) it has low tolerance that allows for stable dosing; (12) it has little known effect on the hypothalamic-pituitary-adrenal axis or cause hypogonadism; (13) it may have a lower abuse potential than other Schedule II opioid agents; and (14) it has extensive managed-care access.

**Conclusions**

In light of evidence for efficacy, safety, versatility, and other positive characteristics, tapentadol is a rational choice for consideration as first-line therapy for patients with moderate to severe pain of multiple modalities. As always, the ultimate decision regarding use and cautions must be based on good medical practice and tailored to the individual patient.

**Impact of a nurse-initiated, pharmacist-led acute pain management consultation service for medical inpatients: Results of a pilot study**

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**Purpose**

Nurses are well positioned to identify patients with poor pain control, and pharmacist involvement in drug therapy management has proven successful in the past. Despite this, there are no data detailing an inpatient nurse-initiated, pharmacist-led acute pain management service. The purpose of this pilot study was to evaluate the impact of a novel Acute Pain Service (APS), provide education regarding pain management, and assess the sustainability of such an APS. Previous to this
research, no APS was available at the institution where the study was conducted.

Method
This prospective, single-center, nonrandomized, interventional study included adult medical patients 18 years or older who had taken at least one analgesic since admission, had an anticipated length of stay of more than 24 hours, and had at least two consecutive pain scores greater than or equal to 5 (on a numeric rating scale from 0 to 10). Pregnant or lactating patients, those receiving neuraxial analgesia, and patients requiring more than a 120 mg morphine equivalent dose (MED) at baseline were excluded. The primary outcomes were the proportion of patients achieving pain control (defined as a mean pain score less than or equal to their goal pain score) at (1) 24 hours and (2) end of eligibility. Secondary outcomes were intervention acceptance rate, time to pain control, change in analgesics from baseline, and the number and type of missed consults. Nurses identified eligible patients on the medical floor and then initiated an electronic consult order. Within 24 hours, the pharmacist reviewed eligibility criteria and contacted the patient’s attending physician to gain approval to see the patient. If approved, then patients provided written informed consent, an initial intake and assessment was completed, and then a pharmaceutical care plan was developed and relayed to the physician. Patients were followed by the pharmacist at least daily thereafter until hospital discharge or end of eligibility. Data from the prospective treatment arm were compared to a retrospective control group using the same eligibility criteria. The study was approved by the Institutional Review Board of Billings.

Results
During the three-month study enrollment period, a total of 39 consults were initiated, including 27 missed consults which were most often due to an anticipated or actual length of stay of less than or equal to 24 hours. The remaining 12 patients included in the study were mostly male (58%), with an average age of 51 years (± standard deviation [SD] 18 years). The retrospective control (n=24) and prospective treatment groups (n=12) were well matched at baseline with respect to age, gender, weight, allergies to analgesics, opioid naivety, and chronic opioid status (p-values not significant [NS]). Additionally, mean baseline pain intensity (6.78 ± 0.93 vs. 6.88 ± 1.35), number of opioids prescribed (2.42 ± 2.11 vs. 1.83 ± 1.01), baseline MED (58.8 ± 43.3 mg vs. 42.1 ± 33.5 mg), and number and co-analgesics prescribed (1.17 ± 0.72 vs. 1.41 ± 1.06) were all matched at baseline between the treatment and control groups, respectively (p-values NS). At baseline, patients in the treatment group were significantly closer to their pain goal compared to the control (1.09 ± 0.93 vs. 2.00 ± 0.97 [p=0.01]). For the primary outcome at 24 hours, 66.7% of the patients in the treatment group met the criteria for pain control compared to 12.5% in the control group (p=0.001). At the end of eligibility, 83.3% and 45.8% of patients’ pain was controlled in the treatment and control groups, respectively (p=0.03). Significant secondary outcomes included time to pain control (15.4 ± 9.79 hours vs. 58.1 ± 41.6 hours [p=0.007]), mean pain intensity at 24 hours (5 ± 1.79 vs. 6.58 ± 1.05 [p=0.002]), and change in number of opioids ordered in the treatment group (-0.75 ± 1.82 vs. 0.63 ± 1.24 [p=0.003]). Ninety-eight percent the recommendations made by the pharmacist were accepted and implemented.

Conclusions
A nurse-initiated, pharmacist-led model is feasible and resulted in more rapid pain control using fewer opioids compared to the standard of care. This model deserves further investigation with a larger sample size and less stringent eligibility criteria.

Opioid monitoring clinic: A nurse practitioner managed clinic
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Purpose
A nurse practitioner managed Opioid Monitoring Clinic (OMC) was developed and established in Southern Nevada Healthcare System in February 2014 to assist primary care providers (PCPs) in monitoring patients at high risk for opioid abuse and misuse. Patients with past and family history of substance abuse as well as history of aberrant behaviors were the target patients for the OMC. Once high risk patients are referred to OMC, evidenced-based risk mitigation strategies are implemented to identify opioid abuse and misuse among patients who suffer from chronic non cancer pain and on chronic opioid therapy. These strategies include the use of urine drug screen (UDS), opioid confirmation testing, prescription drug monitoring database (PDMP) opioid utilization review, and frequent office visit. Additionally, patients at very high dose of opioids as well as patients on multiple dosing of short acting opioids per day (>4x per day dosing) are tried on long acting opioids for an opioid rotation and to also reduce their overall opioid dose per day. A chart review was done after a year of OMC operation to assess its effectiveness.

Method
All patients who were referred to the OMC by the PCPs from February 2014 through July 2015 were including in the chart review. An individual chart review of these patients were done to assess the effectiveness of the OMC in identifying abuse and misuse of opioids among high risk patients on chronic opioid therapy for non-cancer pain. Each patient chart was reviewed for baseline data including age, gender, major source of pain, morphine equivalent dose per day (MEDD) at referral, Brief Pain Inventory (BPI) scores at referral and at latest OMC visit, and current MEDD. Patients found to have abnormal UDS and PDMP report were also tallied.
Results
A total of five hundred thirty-two (N=532) patients were referred in the OMC from February 2014 through July 2015. The average age is 57 years old (range 23-82). The majority are men (522) with only 10 women. The average baseline MEDD at referral is 103mg. At the time of the chart review, the latest average MEDD dose of patients referred to the OMC went down to 34mg. The most common source of chronic pain is chronic low back pain (51%). Two hundred seventy-nine (279) patients were found to have an abnormal UDS with presence of cannabinoid (THC) as the most common abnormal UDS finding (#120) followed by negative confirmation of prescribed opioid (#75), cocaine (#21), meth/amphetamines (#15), and presence of other non-prescribed opioid (#12), respectively. A total of one hundred eighty-one (181) patients were eventually discontinued on opioid therapy due to consistent abnormal UDS and confirmation testing and/or positive PDMP report showing multiple filling of prescription opioid in the community while receiving opioid on a monthly basis from the VA. Among high risk patients found to be compliant with the recommendations in the OMC and found to have no abnormal UDS or abnormal PDMP report, the average pain intensity on BPI at admission was 6.18 versus 6.17 (lower score indicate lower pain intensity and better overall pain management) at latest OMC visit. The average functional intensity on BPI at admission was 9.79 versus 6.71 at latest OMC visit. However, among patients who were found to have consistent abnormal UDS and/or PDMP report, the average pain intensity on BPI at admission was 6.21 versus 7.56 (lower score indicate lower pain intensity and better overall pain management) at latest OMC visit. The average functional intensity on BPI at admission was 5.71 versus 8.09 at latest OMC visit.

Conclusions
The OMC has been very effective in identifying opioid abuse and misuse among high risk patients on chronic opioid therapy for non-cancer patient. Patients found to be misusing or abusing opioids were discontinued on chronic opioid therapy and referred for other non-opioid medical therapy for management of their chronic pain. Additionally, patients maintained in the OMC were found to have self-report of overall pain management through a combination of opioid rotation and opioid dose reduction. Interestingly, patient found to have an abnormal UDS and/or PDMP report, their overall scores (pain and functional intensity) increased.

How common is attention deficit disorder (ADD) in chronic pain patients?
Forest Tennant*
Veract Intractable Pain Clinic, West Covina, CA, USA

Purpose
To determine if ADD is a common comorbidity in chronic pain patients that may warrant treatment. Chronic pain patients frequently complain about poor concentration ability and memory loss. Some are notoriously non-compliant with therapeutic instructions and studies on centralized pain pathways, and catecholamine deficiencies. Given these physiologic disturbances, ADD should be a common comorbidity.

Method
A 16 item questionnaire was given to 45 consecutive chronic pain patients who routinely attended their treatment clinic in May, 2015. Questions were selected from symptoms reported in the adult ADD literature. 1,2 They were directed at whether the patient had deficiencies in: concentration, attention, distractibility, impulsivity, reading and retention, coordination, temper, and short-term memory. A positive answer to 5 or more questions was considered to indicate the presence of ADD.

Results
Seventeen (37.8%) of the 45 patients answered 5 or more questions in a positive manner indicating the presence of ADD.

Conclusions
In this pilot study a significant percentage of chronic pain patients reported classical symptoms of ADD. This finding may explain some of the poor functions in activities of daily living and non-compliance with therapeutic instructions frequently observed in chronic pain patients. Recognition of ADD in chronic pain patients and its treatment may enhance chronic pain management, and this issue needs to be a subject of future investigation.

Which chronic back pain patients have arachnoiditis?
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Purpose
To provide a short, simple, clinical interview that pain practitioners can use to identify the lower back pain patient who requires a diagnostic evaluation for the presence of arachnoiditis. Low back pain is the most common problem that brings a patient to pain treatment. While the cause of low back pain in the majority of cases is degenerative in nature, an unknown, but definite percentage, have arachnoiditis. This condition, which appears to be increasing in incidence, can be catastrophic in that it is an inflammatory, progressive process that may cause severe, disabling pain, lower extremity paralysis, bowel and bladder dysfunction, sexual inability, and a systemic autoimmune disorder.1 Although previously thought to be a hopeless disease, recent reports show significant improvement and recovery in patients who receive specialized pain and neurogenic management.
cogenetic testing, inflammatory markers, and family reports evaluated by history and physical, hormone profile, pharmacogenetic testing, and symptoms indicative of cerebrospinal fluid obstruction.

Results

Remarkably all 26 patients reported that their pain was constant and that: (1) severe pain occurred with standing too long which caused the patient to sit or lie down; and (2) jerking or tremors in their legs. At least 23 of 26 (88.5%) patients reported: (1) intense episodes of heat and sweating; (2) difficulty with initiation of urination and/or defecation, and; (3) episodes of blurred vision. All patients had undergone a wide variety of spinal surgeries and procedures.

Conclusions

Since arachnoiditis is increasing in incidence and perhaps the most catastrophic, disabling pain condition, it is essential that every back pain patient be quizzed for symptoms of arachnoiditis. A patient should be suspected to have arachnoiditis if they have a typical clinical profile which consists of inability to stand long without severe pain, tremors or jerking in the legs, intense episodes of heat and sweating, difficulty initiating urination or defecation, and episodic blurred vision.

High function and high serum levels in ultra-high dose oxycodone patients

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Purpose

Some severe, intractable pain patients appear to safely and effectively maintain with ultra-high dosages of oxycodone. They appear to mentally and physically function, have a good quality of life, and do not wish to change or reduce their daily oxycodone dosage. At this time we see no objective clinical reason to force a change and recommend that these patients be scientifically studied and treated in specialty settings.

Human abuse potential of an abuse-deterrent (AD) extended-release (ER) morphine product candidate (EG-001) versus a currently available non-AD ER morphine product administered intranasally in nondependent, recreational opioid users

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Purpose

Extended-release (ER) opioids have a significant risk of abuse and overdose because they are available in high-unit doses and have been vulnerable to manipulation and extraction. The defeat of these products can accelerate opioid release and/or facilitate alternate routes of administration, such as nasal insufflation. Recently, ER matrix technology designed to resist manipulation and extraction demonstrated...
effective abuse deterrence in epidemiologic studies, showing reduced abuse of controlled-release oxycodone following reformulation; however, these studies indicate that substance abusers migrated to other opioid formulations lacking abuse-deterrent (AD) technology, such as ER morphine. EG-001 (Egalet Corporation, Wayne, PA) is an AD ER morphine product candidate designed and manufactured utilizing Guardian™ Technology (Egalet Corporation, Wayne, PA), a proprietary technology combining formulation science and the process of plastic injection molding to create tablets that are extremely hard and resistant to both common and more rigorous methods of physical manipulation and chemical extraction. This study compared the human abuse potential of manipulated, intranasally administered EG-001 with a marketed non-AD formulation of ER morphine (MS Contin®, Purdue Pharma LP, Stamford, CT) and placebo on the basis of pharmacodynamic (PD) and pharmacokinetic (PK) measures. It was conducted in accordance with the April 2015 US Food and Drug Administration Final Guidance for Industry, Abuse-Deterrent Opioids-Evaluation and Labeling.

Method

A single-center, randomized, double-blind, double-dummy, active- and placebo-controlled, 5-period crossover study enrolled adult (aged 18-55 years) volunteers, nondependent but experienced in recreational use of prescription opioids, including nasal insufflation. Screening employed a naloxone challenge test to exclude opioid-dependent subjects and a 2-day, randomized, double-blind, opioid drug discrimination test. Manipulation of EG-001 involved a multi-step process using mechanical and electrical instruments, followed by sieving to yield particle sizes small enough to snort. Non-AD ER morphine was prepared via a single-step, mechanical manipulation process, without sieving, as it was reduced to a powder and all particle sizes were small enough to snort. All participants initiated with treatment A, a high-volume (HV) intranasal EG-001 60-mg dose that was not sieved, containing all particle sizes. Participants were then randomized to 1 of 4 sequences for the remaining treatments: B, a low-volume (LV) intranasal EG-001 60-mg dose that was manipulated/sieved; C, an LV intranasal non-AD ER morphine 60-mg dose that was manipulated (positive control); D, an oral, intact EG-001 60-mg tablet; and E, an LV intranasal placebo. The primary efficacy endpoint was the PD measure, Drug Liking, which was measured on a 0-100 bipolar Visual Analog Scale (VAS); secondary PD measures included Overall Drug Liking, Take Drug Again, Drug Effects Questionnaire, pupillometry, and bipolar VAS for the ease and pleasantness of snorting, among others. Blood samples were collected for PK measures, including peak plasma concentration (Cmax), time to Cmax (tmax), and abuse quotient (AQ; Cmax/tmax). Adverse events (AEs) were assessed throughout the study.

Results

Of 80 subjects enrolled, 46 passed screening and completed all 5 treatments. Completers were predominantly male (78.3%), with a mean (SD) age of 28.1 (8.1) years. Maximum

Drug Liking (E_{max}, median VAS) was significantly greater after insufflation of non-AD ER morphine (77.5) compared with LV IN EG-001 (52.5; P<0.0001), HV IN EG-001 (62.0; P<0.0001), and oral EG-001 intact tablets (68.0; P=0.0001). The secondary endpoints of Overall Drug Liking and Take Drug Again were both statistically significantly lower for both the HV and LV arms of EG-001 compared with non-AD ER morphine (P<0.0001 for all comparisons); the scores for HV and LV EG-001 were similar to placebo. Pupillary miosis E_{max} (change from baseline, median mm) was significantly greater after IN non-AD ER morphine (2.75) compared with LV IN EG-001 (0.85; P<0.0001), HV IN EG-001 (2.25; P<0.0001), and oral EG-001 intact tablets (2.20; P<0.0001). The mean (SD) AQ was much higher following IN non-AD ER morphine (37.2 [23.3]) compared with LV IN EG-001 (2.3 [2.4]), HV IN EG-001 (9.2 [6.1]), and oral EG-001 intact tablets (5.5 [2.6]).

Conclusions

After manipulation, IN administration of EG-001 (all particle sizes and sieved product yielding small particles amenable to snorting) has a significantly lower abuse potential compared with commercially available manipulated non-AD ER morphine, as measured by Drug Liking E_{max}. The Emax of the HV- and LV-manipulated IN arms were lower than that for intact oral EG-001 tablets. HV and LV IN arms of EG-001 had significantly lower AQ than IN non-AD ER morphine. These findings suggest that EG-001 could represent a new treatment option for patients with chronic pain that could help reduce the IN abuse potential of ER morphine products.

Analysis of opioid-mediated analgesia in studies with methylnaltrexone for opioid-induced constipation in patients with chronic noncancer pain

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Purpose

Subcutaneous methylnaltrexone is efficacious and well tolerated for opioid-induced constipation (OIC). Although methylnaltrexone is a peripherally acting mu-opioid receptor antagonist, the current analysis examined potential effects of methylnaltrexone on centrally mediated opioid analgesia.

Method

Changes in pain intensity scores and opioid use were evaluated in a phase 3, randomized, double-blind, placebo-controlled trial with an open-label extension (RCT) and an open-label safety trial in adults with chronic noncancer pain. In the RCT, patients taking ≥50 mg oral morphine equivalent dose (MED) daily with ≤3 rescue-free bowel movements weekly received methylnaltrexone 12 mg daily (QD), every
other day (QOD), or placebo for 4 weeks, followed by open-label methylnaltrexone 12 mg (as needed [prn]) for 8 weeks. In the open-label trial, patients on stable opioid doses with OIC during the month prior to screening received methylnaltrexone 12 mg prn for up to 48 weeks. Pain intensity scores were assessed during 24 hours using an 11-point pain intensity scale. Scores were calculated during RCT at baseline, Day 1, Weeks 2 and 4 (double-blind period), and Weeks 6, 8, and 12 (open-label period). Scores were calculated during the open-label trial at Weeks 4, 8, 12, 16, 24, 32, 40, 48, and early discontinuation/follow-up visit. For RCT double-blind phase comparisons versus placebo, an ANCOVA model with treatment as a factor and baseline as a covariate was used for pain intensity scores and MED calculations.

**Results**

In the RCT, individuals received methylnaltrexone 12 mg QD (n=150) or QOD (n=148) or placebo (n=162) for 4 weeks, followed by an 8-week open-label extension phase of methylnaltrexone 12 mg (prn; n=364) for 8 weeks. In the open-label safety study, 1034 individuals received methylnaltrexone 12 mg QD (prn) for up to 48 weeks. In the RCT, mean baseline pain scores, 6.2, 6.3, and 6.3, for methylnaltrexone QD, QOD, and placebo, respectively, exhibited no significant changes at Week 2 (0.0, -0.1, and -0.1; \(P \geq 0.7\) vs placebo) and Week 4 (-0.2, -0.3, and -0.1; \(P \geq 0.1\) vs placebo), and also remained stable during the open-label extension (range, 6.1-6.2). Similarly, mean pain scores remained unchanged from baseline (6.1) during the open-label safety study (range, 6.0-6.1). Median MED at baseline (161.0, 154.8, and 160.8 mg/day for methylnaltrexone QD, QOD, and placebo, respectively) had no significant changes at Week 4 of the RCT double-blind phase (168.0, 150.8, and 160.0 mg/day; \(P \geq 0.3\) vs placebo) and remained stable during the open-label phase (range, 150.0-171.4 mg/day). Median MED also remained unchanged from baseline (120.0 mg/day) at each time point in the open-label safety study (range, 117.3-121.1 mg/day).

**Conclusions**

Results show no demonstrable effects of methylnaltrexone on opioid-mediated analgesia in patients with chronic noncancer pain and OIC.

**Prescriber attitudes regarding treating patients with extended release/long acting opioids**

*Synne Wing*, Kevin Zacharoff & Cristina Los

**Inflexxion, Inc., Newton, MA, USA**

**Purpose**

Studies have shown that provider attitudes and beliefs may influence how they perceive and treat people with chronic pain, particularly with Extended-Release/Long-Acting (ER/LA) opioid analogics. The purpose of this study was to analyze such beliefs as indicated while healthcare providers completed the PainEDU REMS Education Program, an educational program developed as part of the FDA-mandated ER/LA opioid Risk Evaluation and Mitigation Strategy.

**Method**

An evaluation was conducted where healthcare providers (N=955 to date) were asked a series multiple choice questions incorporated into the educational program. Responders included Physicians (67%), Nurse Practitioners (26%), and Physician Assistants (5%). 39% were identified as pain specialists, and 28% were primary care clinicians. The healthcare providers (N=825 to date) were asked a series multiple choice questions while completing the course that evaluated: 1) common challenges associated with treating chronic pain patients, 2) challenges with treating patients with chronic opioids, 3) factors that influence the prescribing chronic opioid therapy, 4) view of family involvement when caring for patients with chronic pain, 5) concerns about patient non-adherence with opioid medications, 6) views of prescribing opioids for people who have a history of addiction or substance use disorder and 7) the most important information to review with a patient.

**Results**

The greatest concerns involving opioid prescribing identified were overdose and aberrant drug-related behavior. Respondents reported that many of the factors related to decisions about opioid prescribing are related to patient past and present medical history, and patients’ expectations for treatment. Only 30% of the respondents believed lack of education is a barrier to managing patients with chronic pain. A contributing factor to the difficulty managing patients is the lack of assessment for risk of Substance Use Disorder (SUD) and aberrant behaviors. Many participants also reported that they are influenced by best practices and regulations within their institutions. Providers agreed it is best practice to involve the family in chronic pain treatment regimens involving opioid therapy. Prescribers noted important conversations to have with patients included only taking the medications as prescribed, common adverse effects, and how to mitigate them. 85% of participants responded that they felt this activity provided them information that increased their competence in this area, showed them ways to modify their current practice, and improve patient outcomes. However, only 60% of participants agreed they would make actual changes to their current routines.

**Conclusions**

While concerns about educating healthcare providers on the subject of treating chronic pain patients continue to exist, challenges continue regarding the direct application of education into clinical practice as well. Our approach of incorporating queries directly into ER/LA REMS educational content was a novel approach to helping identify the intersection between education, perceptions, and clinical decision-making when ER/LA opioids are considered as a component of a chronic pain treatment plan.
Value of comprehensive urine drug monitoring in patients prescribed opioid medications
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Purpose
Oral opioid therapy is widely used in pain management. Medication monitoring is recommended for patients prescribed an opioid for an extended period, in order to optimize therapeutic benefits and mitigate risks associated with opioid use. In opioid-treated patients, urine drug monitoring may help identify potential nonadherence, as well as potential misuse of opioid medications and illicit drugs. However, use of urine drug monitoring for only a few selected items (eg, to assess adherence to a particular medication) may overlook other clinically relevant information. This analysis investigated the clinical utility of urine drug monitoring in patients who were prescribed opioid medications.

Method
Urine samples submitted to the laboratory were analyzed for the presence of prescription medications, alcohol, and illicit substances. Samples were tested for parent drugs and relevant metabolites using liquid chromatography-tandem mass spectrometry. Samples were categorized as positive for 1 parent drug(s) and/or relevant metabolite(s) were confirmed. Medications were classified as nonprescribed if they were unknown to the prescribing physician, based on the medication list submitted to the laboratory by the ordering clinician.

Results
A total of 971,395 samples were analyzed from patients with ≥1 prescription for an opioid medication. Nonprescribed medications detected in ≥1% of samples and tested in >1000 samples were nontricyclic antidepressants (16.5%; n=7295 samples tested), benzodiazepines (13.7%; n=964,368), nonprescribed opiates (11.5%; n=969,589), gabapentin (9.0%; n=313, 498), antipsychotics (8.2%; n=3224), tricyclic antidepressants (5.7%; n=64,332), tramadol (2.8%; n=448,003), nonprescribed oxycodone/oxymorphone (2.7%; n=969,587), amphetamines (2.2%; n=946,890), pregabalin (1.9%; n=298,576), barbiturates (1.6%; n=961,263), buprenorphine (1.4%; n=375,721), and methadone (1.2%; n=962,753). Illicit substances included marijuana (nonprescribed) in 10.7% (n=375,721), barbiturates (1.6%; n=961,263), buprenorphine (1.4%; n=375,721), and methadone (1.2%; n=962,753). Illicit substances included marijuana (nonprescribed) in 10.7% (n=666,222 samples), cocaine in 1.7% (n=946,032), and heroin in 1.2% (n=241,635). Ethanol was found in 3.1% of 119,753 samples.

Conclusions
Providers have options for customized test selection when utilizing urine drug monitoring, which offers flexibility based on medical necessity for each individual patient. Monitoring for nonprescribed medications and illicit substances, rather than testing only for presence of a prescribed medication, may identify signals of potential medication misuse or substance abuse, allowing for early clinical intervention to improve therapeutic outcomes in patients with chronic pain.

Total migraine freedom for a breath powered intranasal delivery system containing 22 mg sumatriptan powder (AVP-825) vs 100 mg oral sumatriptan from the COMPASS Study of Acute Treatment of Migraine
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Purpose
Migraine-associated symptoms—nausea, photophobia and/or phonophobia—can also contribute to disability and direct healthcare costs. The composite efficacy endpoint, total migraine freedom (TMF), which assesses rates of pain freedom and absence of migraine-associated symptoms, is more rigorous and comprehensive than the individual evaluation of items that is commonly used to assess treatment impact in migraine. TMF was assessed for AVP-825, an investigational Bi-Directional™ Breath Powered™ intranasal delivery system containing 22 mg sumatriptan powder (<15-16 mg delivered), vs 100 mg oral sumatriptan (oral-SUM) in the COMPASS study (NCT01667679).

Method
Randomized, multicenter, double-dummy, crossover, multiattack study with two 12-week double-blind periods. Patients (2-8 attacks/month) were randomized 1:1 to AVP-825 plus oral placebo or an identical placebo delivery system containing lactose powder plus 100 mg oral-SUM for the first period; treatment switched for the second period. Patients treated ≤5 qualifying migraines/period (<1 hour from onset, even if mild). Percentage of attacks with TMF (pain freedom and absence of migraine-associated symptoms, including vomiting) at time points from 10 minutes−2 hours post-dose was analyzed by chi-square test.

Results
185 patients treated migraines in both periods, yielding 1531 migraines assessed (765 AVP-825, 766 oral-SUM). The percentage of attacks with TMF was significantly greater with AVP-825 vs oral-SUM at all time points from 15-90 minutes: 15 minutes (7.2% vs 3.7%; P<.01), 30 minutes (18.0% vs 10.8%; P<.001), 45 minutes (30.7% vs 21.4%; P<.001), 60 minutes (40.9% vs 33.3%; P<.01), 90 minutes (52.7% vs 45.6%; P<.01). At 2 hours, TMF rates did not differ significantly between treatments (60.6% for AVP-825 vs 56.7% oral-SUM; P=.11).
Conclusions

Treatment of acute migraine with AVP-825 (intranasal delivery system containing 22 mg sumatriptan powder) resulted in higher rates of TMF at earlier time points than the most efficacious dose (100 mg) of oral-SUM, despite significantly less drug exposure. The results of this analysis demonstrate the superiority of AVP-825 using a more rigorous and comprehensive endpoint that addresses the patient’s desire for early and effective treatment of both their headache pain and migraine-associated symptoms. These findings are consistent with the other outcomes of COMPASS, indicating AVP-825 has superior early efficacy compared to oral-SUM.

Primary efficacy outcomes from compass: a controlled trial comparing an intranasal delivery system containing 22 mg sumatriptan powder (avp-825) vs 100 mg oral sumatriptan in acute treatment of migraine

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Purpose

AVP-825 is an investigational Breath Powered™ intranasal delivery system containing 22mg sumatriptan powder that delivers ~15-16mg of the drug into the nasal cavity. AVP-825 allows sumatriptan to reach the upper posterior segments of the nasal cavity where it can be rapidly and efficiently absorbed. The COMPASS trial (NCT01667679) evaluated comparative efficacy, safety and tolerability of AVP-825 (22mg sumatriptan powder) and 100mg oral sumatriptan (oral-SUM) in adults with migraine.

Method

Randomized, multicenter, double-dummy, crossover, multi-attack study with two 12-week double-blind periods. Migraineurs (2-8 attacks/month) were randomized 1:1 to AVP-825 plus oral placebo or an identical placebo delivery system containing lactose powder plus 100mg oral-SUM for the first period; treatment switched for the second period. Patients treated up to 5 qualifying migraines/period (<1 hour from onset, even if mild). The primary endpoint assessed summed pain intensity differences in headache severity scores through onset, even if mild. The primary endpoint assessed summed pain intensity differences in headache severity scores through 30 minutes post-dose (SPID-30). Key secondary endpoints included pain relief and pain freedom at each time point. Standard safety assessments were conducted.

Results

A total of 275 adults with migraine were randomized; 185 treated migraineurs in both periods (full analysis set; 1531 migraines assessed). Significantly greater reduction in migraine pain intensity over the first 30 minutes post-dose was observed with AVP-825 vs oral-SUM (SPID-30: 10.80 vs 7.41 P<0.001). At all time points from 15-90 minutes post-dose, significantly greater rates of pain relief and pain freedom were achieved with AVP-825 vs oral-SUM (e.g., at 30 minutes: 53.8% vs 38.7% P<0.001 and 18.2% vs 10.8% P=0.003, respectively). Pain relief/freedom were comparable at 120 minutes, 24 and 48 hours. At no time point and for no efficacy endpoint was the statistical comparison in favor of oral sumatriptan. No serious adverse events (AEs) occurred; ≤2% of patients discontinued due to AEs. Nasal discomfort and abnormal taste were more common with AVP-825 (16% vs 1%; 26% vs 4%) but ~90% were mild and led to only one discontinuation. Treatment was well tolerated, with a statistically significantly lower rate of atypical sensations with AVP-825 vs oral-SUM (2% vs 5% of attacks, P=0.02).

Conclusions

Despite significantly less drug exposure, AVP-825 provides earlier reduction of migraine pain intensity and confers faster pain relief/freedom vs 100mg oral-SUM, with no sacrifice in sustained efficacy through 48hr. The overall tolerability profile of AVP-825 was consistent with that observed in previous trials denoting mild administration site AEs. In addition, AVP-825 treatment had a significantly lower rate of atypical sensations than 100mg oral-SUM. As oral-SUM is the most commonly utilized triptan for the acute treatment of migraine, results of this trial may challenge the current migraine treatment paradigm. If approved, AVP-825 will constitute an important treatment option for migraine patients.

Safety of low-dose soluMatrix® meloxicam in adults with osteoarthritis: results of a 12-month, phase 3 safety study

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Purpose

Osteoarthritis (OA) is a frequent cause of disability in adults. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as meloxicam, are often prescribed to treat OA pain, but are associated with serious dose-related gastrointestinal (GI) and cardiovascular (CV) adverse effects, leading health authorities to recommend using the lowest effective NSAID dose for the shortest duration necessary. SoluMatrix® Meloxicam has been developed using SoluMatrix Fine Particle Technology™ to provide efficacy at low doses. In healthy volunteers, SoluMatrix Meloxicam capsules 10 mg, under fasted conditions, provided comparable peak plasma levels (C_max), but with an earlier time.
to peak plasma levels (2.0h vs 4.0h) and a 33% lower overall extent of exposure (AUC) compared with conventional meloxicam 15 mg tablets. In a 12-week, randomized, placebo-controlled study in patients with OA pain, SoluMatrix Meloxicam 5 and 10 mg once daily provided significantly greater relief from OA pain compared with placebo. We evaluated long term safety of low-dose SoluMatrix Meloxicam 10 mg in a 12-month, open-label phase 3 study in patients with OA.

Method

Six hundred (600) chronic NSAID/acetaminophen users, aged ≥40 years with knee and/or hip OA received SoluMatrix Meloxicam capsules 10 mg once daily. Patients were allowed acetaminophen (maximum of 3000 mg per day) as rescue medication. Safety assessments included adverse events (AEs) and clinical laboratory testing. Most patients were women (358/600; 59.7%) with a mean (range) age of 61.7 (40-86) years. Fifty-eight percent of patients were 60 years of age or older. The mean (± SD) BMI of patients was 30.65 (5.02) kg/m². Mean (± SD) study drug administration duration was 284.2 (123.6) days. Three hundred and ninety (390/600; 65%) patients completed the study. Few patients withdrew due to lack of efficacy (28/600; 4.7%).

Results

AEs were reported by 67.7% of patients (406/600) and most were generally mild (176/406; 43.3%) or moderate (207/406; 51.0%) in intensity. The most frequently reported events included: arthralgia (33/600; 5.5%), urinary tract infection (33/600; 5.5%), osteoarthritis (30/600; 5.0%), and hypertension (25/600; 4.2%). Approximately, one third (79/210; 37.6%) of the withdrawals were due to an adverse event. Serious adverse events (SAEs; resulting in death, hospitalization, significant disability, congenital anomaly, death, etc.) were reported in 5.8% (35/600) of patients. There were few serious CV or GI adverse events of the type associated with NSAID usage. No patients experienced myocardial infarction; one patient experienced hemorrhagic cerebral infarction. One patient experienced serious duodenal and gastric ulcer hemorrhage; an additional patient experienced diverticular intestinal hemorrhage. Two patients developed acute renal failure in the setting of staphylococcal sepsis and pneumonia with hypotension, respectively; both events were considered by the investigator to be unrelated to study drug. There were two deaths; one due to an aortic aneurysm and a second in a patient with metastatic adenocarcinoma. Both events were considered unrelated to study drug. Treatment-emergent hepatic transaminase elevations > 3x the upper limit of normal (ULN) were noted infrequently (2/505) in patients with normal hepatic transaminases at baseline. A treatment-emergent bilirubin elevation > 2x ULN was noted in a single patient with a normal baseline bilirubin; which resolved following study drug discontinuation.

Conclusions

SoluMatrix Meloxicam was generally well tolerated. Few serious CV and/or GI adverse events of the type associated with NSAID treatment were observed. This study extends the safety data for treatment with SoluMatrix Meloxicam up to 12 months.

The Integration of healthcare provider and patient education with a standardized chronic pain assessment

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Purpose

Pain is among the most common reasons that patients seek medical attention in the United States, and significant educational and procedural gaps continue to exist with respect to pain assessment, treatment planning, management, and follow-up. Healthcare provider education about chronic pain and its treatment is often lacking, with the burden of patient education being the responsibility of healthcare providers, and it can be difficult to have pertinent educational materials readily available for patient distribution that is valuable based on the specific medical circumstances. Additionally, there is often lack of standardization in the chronic pain assessment process, which can lead to inconsistent levels of care, poor patient-provider communication and transparency, and incongruent expectations of treatment. This presentation describes a unique system that encompasses a synergistic set of programs and tools designed to work as an integrated system directly linking both healthcare provider and patient education to the clinical setting utilizing a standardized, electronic pain assessment.

Method

Education about chronic pain and its treatment is often lacking for non-expert level healthcare providers. These educational deficits can sometimes have dramatic clinical impact. Examples include variability in assessment of patients with chronic pain, lack of utilization of potentially valuable tools in clinical practice, and negative impact on patient care resulting from a lack of standardized approaches, follow-up, and documentation. Additionally, the burden of chronic pain patient education is often the responsibility of healthcare providers, who may have difficulty finding pertinent educational materials that are tailored and specific to the patient's circumstances.

Results

The PainCAS Clinical Assessment System® was developed with research grants from the National Institutes of Health and is a comprehensive electronic pain and opioid risk assessment tool that takes an innovative approach to standardizing the pain assessment process, integrating validated opioid risk assessments into the process when appropriate, linking education to the patient's completed pain assessment (specifically offering clinically relevant clinician educational resources on
Pain patient outcomes.

Conclusions

This unique collection of programs has the potential to help provide clinically relevant healthcare provider and patient education, to standardize and guide pain treatment, and to reinforce treatment planning and ultimately improve chronic pain patient outcomes.

Secondary endpoints in the Phase III chronic low back pain trial of tapentadol ER

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Purpose

Chronic low back pain (CLBP) is a common debilitating condition that can lead to lost productivity and has the potential to greatly impact a patient’s life. CLBP is also a complex clinical entity, due in part to the number of anatomical structures involved and the varying quality and characteristics of the pain reported. CLBP has also become a model of chronic pain for new or reformulated analgesics. These trials typically use a numerical rating scale (NRS) to detect a decrease in pain as compared to placebo. While changes in patient-reported pain are certainly important to capture, they do not reflect the impact of back pain on the other domains of a patient’s life.

Tapentadol is the first new chemical entity to enter in the long-acting marketplace in over 20 years and is believed to have a dual mechanism of action – potentially acting as mu opioid receptor agonist and a norepinephrine-reuptake inhibitor - though the clinical relevance of this is unknown. Three pivotal trials were conducted leading to US approval: one in CLBP and two in the pain of diabetic peripheral neuropathy (DPN). Patients in these trials had pain severe enough to require daily, around-the-clock, long-term opioid treatment. As the molecule studied was an entirely new analgesic, it was necessary to include an active control (Oxycodone CR) to confirm the validity of the trial design and the measures used therein. Here we present the results of select secondary measures captured in the CLBP trial.

Method

All statistics were performed on the intention-to-treat population using the last observation carried forward (LOCF) method of imputation.

The Short Form 36 Health Survey is a research instrument used to capture a patient’s physical, social and mental well-being. This form was administered at five time points over the course of the 12-week trial. Data were analyzed using an ANCOVA model and presented as LS mean differences.

The Brief Pain Inventory is a questionnaire designed to assess both the intensity of pain and the degree of interference the pain has on function. This questionnaire was administered at four time points during the trial and each subscale analyzed using an ANCOVA model. Differences are presented as LS means.

Patient Global Impression of Change is a seven-point scale assessing status since initiating treatment at three different time points. The PGIC assessments were summarized with number and percentage of subjects by treatment group as per visit windows and analyzed at the end of the maintenance period using the CMH method.

The EuroQol-5 Dimension Questionnaire is a standardized instrument that measures health status in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 possible levels: no problems, some problems, and extreme problems. This was administered at five separate time points and analyzed using an ANCOVA model with differences presented as LS means.

Results

SF-36: For the SF-36 Health Survey, differences in the mean change from baseline favoring tapentadol ER compared with placebo were statistically significant for the “physical functioning”, “role-physical”, “bodily pain”, and “vitality” domains whereas oxycodone CR was significantly different from placebo in two of these domains (“role-physical” and “bodily pain”). Both tapentadol ER and oxycodone CR were significantly different from placebo on the physical component summary score, suggesting both treatments improved physical health status. No other statistically significant differences were observed between the tapentadol ER and placebo or between oxycodone CR and placebo.

BPI: At endpoint, both active-treatment groups showed statistically significant reductions from baseline (p-values ≤0.002 for all comparisons except pain interference score for oxycodone CR with p=0.023) in pain interference score, pain subscale scores, and the total score compared with placebo. Least square mean differences between tapentadol ER and placebo were -0.7, -0.8, and -0.7 on these 3 scores, respectively.

PGIC: The percentage of subjects with an improvement (“much improved” or “very much improved”) was higher in the tapentadol ER (55.5%) and oxycodone CR (60%) groups than in the placebo group (32.7%). The percentage of subjects with an improvement (“much improved” or “very much improved”) was higher in the tapentadol ER (55.5%) and oxycodone CR (60%) groups than in the placebo group (32.7%).
improved") increased over time (55.2%, 59.2%, and 63.3%, respectively) in the tapentadol ER group, but not in the placebo group (45.0%, 44.8%, and 47.5%, respectively) or the oxycodeone CR group (68.8%, 72.7%, and 68.8%, respectively).

EQ-5D: The EQ-5D health status index at endpoint was generally higher than at baseline for all 3 treatment groups. The mean change from baseline at endpoint in the EQ-5D health status index was significantly higher in the tapentadol ER group than in the placebo group (p=0.020) suggesting that tapentadol ER may have improved health status. Similar results were observed for the oxycodeone CR group compared with placebo group (p=0.019).

**Conclusions**

These secondary measures present a more qualitative picture of the relief that patients in this CLBP trial experienced as compared to placebo. The use of an active control confirmed the sensitivity of this pain model and these measures to detect relevant changes. Studies specifically designed and powered to detect changes in overall health and function would be a logical next step in the assessment of this molecule and validation of these results.

**A urinary test procedure for identification of cannabidiol (CBD) in patients undergoing medical therapy with marijuana**

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**Purpose**

It is in the interests of supporting physicians and their patients in the use of potentially medically effective forms of marijuana (6), as distinguished from recreational interests, that we have adapted a GC/MS procedure for detection of CBD in urine. The intended use is as a tool for physicians to determine the major components of marijuana being used by a patient and whether that composition is primarily THC, CBD or a combination of THC and CBD.

**Method**

The assay was reported by Bergamaschi, Queiroz and Huestis (7). The method employs hydrolsis by B-glucuronidase. This hydrolsis accounts for phase II metabolism of CBD to CBD-glucuronide or CBD sulfate.

SAMPLE: Voided urine without preservative. The volume for testing: 2 ml. Samples are tested undiluted and diluted 10X.

INSTRUMENTATION: The assay is a GC/MS procedure performed on an Agilent 6890 GC coupled with an Agilent 5973 Mass Selective Detector. The GC uses a Zebron ZB-5 capillary column, 15 meters, 0.25 mm ID, 0.25 um film. Results are normalized to urine creatinine.

The linearity of the assay is: 2 to 100 ng/mL The limit of detection of the assay is: 2 ng/mL

POPULATION STUDIED:

Arm One: Forty randomly selected specimens screened and confirmed positive for THC.

Arm Two: 15 volunteers that used CBD rich marijuana.

**Results**

Group One: All (40) urine samples tested negative for urine CBD. It is likely that this group represented individuals who had used marijuana for recreational purposes. All (40) tested positive for the THC metabolite, carboxy-THC.

Group Two: Fifteen (15) volunteers dosed with CBD. Urine samples were collected two hours post-dose except one collection at 6 hours post-dose. All (15) tested positive for CBD. Thirty five (35) urine samples were provided by these 15 volunteers: All urine samples (35) tested positive for CBD. 14 of the 15 volunteers tested positive for carboxy-THC as well as CBD. This is indicative that the CBD preparation used contained THC and CBD, or there is residual marijuana present from previous marijuana use by the participant. One (1) volunteer smoked a CBD rich, THC poor cigarette. A urine sample was collected 6 hours post-dose. This volunteer tested positive for CBD and negative for carboxy-THC, Indicative that the cigarette was CBD rich and low in THC. One volunteer dosed morning and night on consecutive days (6). Urine samples were collected 2 hours post-dose. All samples (12) tested positive for CBD and carboxy-THC, indicating that the herbal preparation contained CBD and THC.

These results indicate that the assay is reliable and useful for identifying the absence or the presence of CBD. In combination with an assay for carboxy-THC, the major cannabinoids present in marijuana used are disclosed.

**Conclusions**

This CBD assay is reliable, and is performed on standard laboratory equipment. The assay is suitable as a convenient test to provide an assessment of the marijuana being used.