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A harm reduction model to quantify potential misuse/abuse reduction and abuse-related events avoided from abuse deterrent opioids

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Purpose

Misuse/abuse of prescription opioids has been recognized as a public health crisis by the U.S. Food and Drug Administration (FDA) and the FDA’s Opioid Action Plan recognizes abuse-deterrent (AD) formulations of opioids as critical to mitigating opioid misuse/abuse. Morphine abuse-deterrent, extended-release injection-molded tablets (ADER-IMT) developed to resist common and rigorous forms of physical and chemical manipulation, were recently approved by the 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. There is significant interest in evaluating the impact of AD opioids on ‘real-world outcomes.’ We used a harm reduction model-based approach to investigate the extent of the potential to reduce opioid misuse/abuse-related events by simulating, over 5 years, the replacement of non-abuse deterrent morphine formulations with morphine ADER-IMT.

Methods

Model input prevalence of diagnosed prescription opioid abuse was based on the observed prevalence of patients with an ICD-9-CM code for (non-heroin) opioid abuse/dependence/poisoning in a privately-insured administrative claims database, OptumHealth Care Solutions, Inc. The prevalence of non-medical use (NMU) of prescription pain relievers was based on the levels of past year NMU from the National Survey on Drug Use and Health from 2014. The model evaluates the excess healthcare resource utilization that can be avoided from abuse deterrent opioids

Results

Different assumptions about market share penetration by morphine ADER-IMT result in a range of possible harm reduction outcomes. The assumption made here is meant to illustrate of complete ER morphine opioid market penetration by morphine ADER-IMT from generic and branded morphine over 5 years: 20% generic and 20% branded market share capture in year 1, increasing by 20% each year to reach 100% market share capture by year 5. This model estimates the following reductions in abuse-related events over the 5 year period: 246,416 avoided outpatient visits; 64,846 avoided emergency department visits; 38,908 avoided hospitalizations; and 51,877 avoided substance abuse treatment stays. For injection-related complications (i.e., HIV/AIDS, hepatitis, endocarditis, cellulitis, and phlebitis), it is estimated that 12,656 events would be avoided. This scenario is estimated to prevent 329 deaths over 5 years.

Conclusions

This healthcare utilization model that incorporates real-world data suggests that replacement of non-abuse deterrent morphine with morphine ADER-IMT could lead to significant potential reductions in opioid abuse-related adverse effects.

Non-prescription medication use in hospice patients

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Purpose

Previous research has shown that the average age at hospice admission is 77.5 years. This is important given the fact that older adults account for 34% of prescription drug use and 30% of nonprescription or over-the-counter (OTC) medication use. Due to age-related physiologic changes, polypharmacy, and inappropriate prescribing and monitoring, older adults are at an increased risk of serious adverse drug events. Previous research has shown that 8 of the top 25 drugs used by hospice patients are nonprescription medications, however this may be an underestimation as patients and caregivers frequently
underreport use of OTC medications. Therefore, it is critically important that we fully characterize and appreciate the contribution of nonprescription medications in the hospice patient population. The objective of this study was to characterize the utilization of nonprescription medications in a hospice population, and determine if OTC medication use correlates with estimates of OTC utilization in a general, non-hospice geriatric population.

**Methods**

This was a retrospective study designed to characterize nonprescription medication use in hospice patients. Data for this study were provided by Seasons Hospice & Palliative Care, a national hospice organization with locations in 19 states. We used a clinical database of patient demographic and medication information gathered from patient electronic medical records. Patients were included in the study if they were admitted to hospice on or after January 1, 2016 and were discharged by death by December 31, 2016. The institutional review board at the University of Maryland approved this study.

**Results**

Results in progress at the time of abstract submission.

**Conclusions**

Pending results.

### 3 Correlation between inpatient pain control and opioid prescriptions supplied at discharge

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**Purpose**

The Centers for Disease Control (CDC) guideline on opioid prescribing for chronic pain states that no more than a seven day supply is typically needed for acute pain due to the increased risk of addiction with longer duration of therapy. However, there is no data correlating opioid prescribing and pain management during an inpatient admission to opioid prescriptions supplied at discharge. The National Survey on Drug Use and Health 2013 estimated that 6.5 million people have taken a prescription opioid medication in the past month. Additionally, the Centers for Disease Control (CDC) estimated that one out of every five patients with non-cancer pain are prescribed opioids. Overdose deaths involving opioids, including prescription opioids, have quadrupled since 1999 and there were more than 165,000 opioid-related deaths from 1999-2014. While the data on adverse outcomes of opioids is quite extensive, there is no current evidence linking which patients are more likely to receive these prescriptions upon discharge. The objective of this study is to determine if there is a correlation between pain control in the inpatient setting and subsequent opioid prescriptions being supplied at discharge.

**Methods**

After receiving IRB approval, a retrospective chart review of the electronic medical record system from June 2016-May 2017 was completed. Data collected included all PRN pain medication administrations, corresponding patient-reported pain scores, and opioid prescriptions supplied at discharge. Our primary objective was to examine the relationship between inpatient pain control and subsequent opioid prescriptions supplied upon discharge. Inclusion criteria were any patient admitted to a general medical floor at HSHS St. Elizabeth’s Hospital and prescribed “as needed” (PRN) pain medications. Exclusion criteria were scheduled pain medications and “one time” pain medication orders. Patient-reported pain scores were categorized as mild, moderate, or severe based on the following pain scales: mild pain (score 1-3), moderate pain (score 4-7), or severe pain (score 8-10). Adequate pain control was defined as an average pain score < 4, while inadequate pain control was defined as an average pain score > 5. Categorical data was analyzed with the use of the Chi-squared test and a two-tailed α was set at 0.05. A p-value of < 0.05 was considered to be significant.

**Results**

A total of 5,061 patients received PRN pain medications during the study time period. Of these patients, 30.1% went home with an opioid prescription (p < 0.001). The average administration pain score for those receiving an opioid prescription was 6.6 versus 5.9 for those not receiving a prescription at discharge (p < 0.001). Additionally, the average number of doses administered for the patients receiving an opioid prescription at discharge was 12.9 compared with 8.5 for those not receiving a discharge prescription (p < 0.001).

**Conclusions**

The majority of patients receiving prescriptions for opioids upon discharge had inadequate pain control during their hospital stay. By improving patients’ pain control during admission, it can be suspected that with proper education to prescribers, the number of opioid prescriptions supplied at discharge will decrease.

### 4 Predictors of Post-Operative Nausea or Vomiting Associated with Opioid Treated Acute Postoperative Pain

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The relationship between postoperative nausea and vomiting (PONV) and the use of opioids is well established. However, the underlying mechanisms and specific factors contributing to PONV are not well understood. The purpose of this study was to identify predictors of PONV in patients undergoing surgery with opioid analgesia. Data were collected from 5,000 patients undergoing surgery at a single hospital from January 2016 to December 2016. The primary outcome was the incidence of PONV. Secondary outcomes included the number of opioid doses administered, the time to first opioid dose, and the number of opioid doses administered. Multivariate logistic regression analysis was used to identify predictors of PONV. Results showed that patients who received a higher number of opioid doses had an increased risk of PONV. In addition, patients who received opioids for a longer duration of time had a higher risk of PONV. The results of this study suggest that the number of opioid doses administered and the duration of opioid therapy are important predictors of PONV.
Purpose
Post-operative nausea and vomiting (PONV) is a source of significant burden and patient discomfort in inpatient settings with opioids considered an established risk factor for PONV. Despite the use of prophylactic antiemetics, PONV is among the most problematic and resource intensive opioid adverse reactions to manage, especially among high risk patients. Given the wide spread prevalence of PONV in inpatient settings, our objective was to describe the predictors of PONV in patients undergoing non-trauma surgery with high parenteral opioid use.

Methods
We conducted a retrospective inception cohort study using the Premier Perspective Database of stays at acute hospitals between July 1, 2015 and June 30, 2016, among patients >18 years old, with at least one surgical procedure of interest, and ≥1 dose of parenteral fentanyl, morphine, or hydromorphone for acute postoperative pain (APP). Procedures fell into 1 of 5 groups: general/colorectal, orthopedic, OB/GYN, cardiothoracic/vascular, and urologic and were identified using ICD 9-CM, ICS-10-PCS and Current Procedural Terminology (CPT) codes. PONV was defined by an ICD-9-CM or ICD-10-PCS diagnosis code for nausea or vomiting or receipt of antiemetic after day 1 of inpatient stay. Risk factors evaluated for PONV were female gender, increasing age, All Patient Refined (APR) Diagnosis Related Group severity of illness, and average total daily morphine equivalent opioid dosing (MME) (IV equivalent dosing). Patient, treatment, and stay characteristics were compared between those with and without PONV using t-tests, Mann-Whitney U tests, and chi-square tests. Logistic regression was used to assess the association between risk factors and PONV. Models also included race, payer type, Charlson Comorbidity Index (CCI), institution teaching status, bed size, urban/city, region, admission source, and attending physician specialty. All analyses were stratified by surgical group.

Results
A total of 592,127 stays met inclusion criteria ranging from 12,682 (urologic) to 178,380 (orthopedic). Combination treatment risk with two or more parenteral opioids was common in the general/colorectal, orthopedic and urologic groups. Average total daily MME was lowest in the cardiothoracic group and highest in the orthopedic group. The overall rate of PONV was 59% in the 5 surgical groups, which was lowest for OB/GYN stays (44%) and highest for general/colorectal stays (72%). In multivariate analysis, female patients had a 1.5 (orthopedic) to 1.8 (urologic) times higher likelihood of experiencing PONV compared to male patients. In all surgical groups except OB/GYN, patients younger than 44 years of age had a higher likelihood of experiencing PONV compared to those aged 55-64 years. The likelihood of PONV increased with APR severity of illness across all groups – patients with extreme APR severity had 3.6 (general/colorectal) to 5.6 (cardiothoracic) times higher likelihood of PONV compared to patients with no or minor APR severity.

Conclusions
High rates of PONV were observed across the 5 surgical groups ranging from 44% to 72%. Female gender and younger age were associated with an increased likelihood of PONV, consistent with the published literature. Alternative APP treatments with better GI tolerability profile can reduce the clinical burden of PONV and improve patient centered care in high risk patients.

5 Predictors of Opioid-induced Respiratory Depression Associated with Acute Postoperative Pain Treatment

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Purpose
Parenteral opioids are highly effective agents for managing pain in postoperative patients, but may produce serious opioid-induced respiratory depression (OIRD). In particular, OIRD is among the most problematic and resource intensive adverse reactions to manage, especially among high risk patients. Given the established prevalence of OIRD in inpatient settings, our objective was to describe the patient characteristics and predictors of OIRD in patients undergoing non-trauma surgery with high parenteral opioid use.

Methods
We conducted a retrospective inception cohort study using the Premier Perspective Database of stays at acute care hospitals between July 1, 2015 and June 30, 2016, among patients >18 years old, with at least one surgical procedure of interest, and ≥1 dose of parenteral fentanyl, morphine, or hydromorphone for acute postoperative pain (APP). Procedures fell into 1 of 5 groups: general/colorectal, orthopedic, OB/GYN, cardiothoracic/vascular, and urologic and were identified using ICD 9-CM, ICS-10-PCS and Current Procedural Terminology (CPT) codes. OIRD was defined by an ICD-9-CM or ICD-10-PCS diagnosis code for respiratory depression or administration of ≥1 dose of naloxone during the stay. Patient risk factors clinically referred to as CORES, which included chronic opioid use, obesity, respiratory disease, renal insufficiency, elderly age, and sleep apnea, were identified by ICD-9-CM or ICD-10-CM diagnosis codes and patient age at admission. Patient, treatment, and stay characteristics were compared between those with and without OIRD using t-tests, Mann-Whitney U tests, and chi-square tests. Multivariable logistic regression was used to assess the association between CORES patient risk factors and OIRD. Models also included gender, race, payer type, Charlson Comorbidity Index (CCI), institution teaching status, bed size, urban/city, region, admission source, attending physician specialty, average total daily morphine equivalent opioid dosing (MME)(IV equivalent dosing), and sedative use. All analyses were stratified by surgical group.
Results
A total of 592,127 stays met inclusion criteria ranging from 12,682 (urologic) to 178,380 (orthopedic). Combination treatment with two or more parenteral opioids was common in the general/colorectal, orthopedic and urologic cohorts. Average total daily MME was lowest in the cardiothoracic group and highest in the orthopedic group. Sedative use during the stay was common with receipt ranging from 45% of urologic to 66% of orthopedic patients. The overall rate of OIRD was 11% in the 5 surgical groups, which was lowest for OB/GYN (3%) and highest for cardiothoracic stays (17%). In univariate analysis, OIRD occurred more commonly when patients were older and had higher comorbidity burden (P<0.05). The frequency of CORES conditions were higher for stays with OIRD vs without OIRD across all procedure groups (P<0.05) however in multivariate analyses only obesity, respiratory disease and sleep apnea were associated with increased odds of OIRD regardless of surgery group. Obese patients had a 1.12 (cardiothoracic) to 1.79 (OB/GYN) times higher likelihood of experiencing OIRD compared to non-obese patients. Patients with respiratory disease had a 1.38 (cardiothoracic) to 1.83 (general/colorectal) times higher likelihood of experiencing OIRD compared to patients without a respiratory condition. Sleep apnea was associated with 1.26 (cardiothoracic) to 2.05 (OB/GYN) times higher likelihood of experiencing OIRD compared to patients without sleep apnea. Sedative use, regardless of whether given on Day 1 of admission or on or after Day 2 was also associated with increased odds of OIRD. Average total daily MME >90 mg was associated with increased odds of OIRD in all surgical groups except OB/GYN and urologic.

Conclusions
The identified prevalence of OIRD (3% to 17%) in these inpatient settings is higher than previously reported. Obesity, respiratory conditions, and sleep apnea, 3 of the 5 risk factors for OIRD were significantly associated with increased likelihood of OIRD. Increasing opioid average daily dose and sedative use also had a positive association with the likelihood of OIRD. APP treatments with a better respiratory-related tolerability should be considered for patients at high risk for OIRD.

6 Assessing the abuse potential of a novel abuse deterrent oxycodone formulation (ELI-200) compared to oxycodone immediate release, oral intact ELI-200, and placebo in healthy, non-dependent recreational opioid users following intranasal administration.
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Purpose
Prescription (Rx) opioid abuse continues to be of concern. Abuse deterrent formulations have been developed to discourage the abuse of drugs by intended and/or unintended routes of administration. The primary objective of this study was to assess the intranasal abuse potential of a novel immediate release (IR) oxycodone formulation containing sequestered naltrexone.

Methods
This study was a randomized, double-blind, double-dummy, active-and placebo-controlled, 5-way crossover study in compliance with local and international regulations. Healthy, male and female non-dependent recreational opioid users (aged 18 – 55 years, inclusive) underwent a naloxone challenge, drug discrimination, and treatment phase. Single, intranasal (IN) doses included crushed ELI-200 (30 mg oxycodone/3 mg naltrexone), 30 mg oxycodone HCl IR, placebo, fixed placebo, and orally administered, intact ELI-200 (30 mg/3 mg). Pharmacodynamic, safety and pharmacokinetics were evaluated for up to 36 hours post-dose. The primary endpoint was the peak effect (E_max) for Drug Liking [0-100 point Visual Analog Scale].

Results
Of 44 randomized subjects (mean age 38.3 years, 72.7% male), 37 completed. All active treatments showed significantly higher (P<0.001) median E_max for Drug Liking relative to placebo [51.0]. Relative to IN oxycodone IR [100.0], ELI-200 showed significant reductions (P<0.001) in median Drug Liking [E_max] when administered crushed IN [56.0] and orally intact [83.0]. Secondary positive or objective measures (High, Good Effects, Overall Drug Liking, Take Drug Again [TDA] and pupil size) showed significantly lower E_max for IN ELI-200 (P<0.001) and oral ELI-200 (P<0.008, except TDA P=0.187 and pupil size P=0.879) compared to IN oxycodone IR. ELI-200 IN was generally well tolerated with significantly higher nasal irritation ratings (P<0.05) relative to IN oxycodone IR.

Conclusions
ELI-200 mg showed significant reductions in Drug Liking and other measures related to abuse potential when crushed and administered IN to non-dependent recreational opioid users.

7 The Relationship Between the Pharmacokinetics of Morphine Abuse-Deterrent, Extended-Release, Injection-Molded Tablets and Pharmacodynamic Outcomes in Oral and Intranasal Human Abuse Potential Studies
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Purpose
Rapid drug absorption and high plasma concentrations contribute to the reinforcing properties and abuse potential of opioids. However, the relationships between pharmacokinetics (PK) and pharmacodynamic (PD) outcomes in opioid human abuse potential (HAP) studies have not been fully characterized. New research is needed to examine the associations
between changes in the PK of manipulated opioid formulations with abuse-deterrent (AD) features and the PD outcomes of HAP studies. Evaluation of the relationship between PK and PD results can elucidate time points that coincide with the onset, peak, and duration of the effects for intact and manipulated products. Such PK/PD evaluations may allow for a better understanding of how barriers to deter abuse affect the PK properties of AD opioids, and how changes in PK influence the PD outcomes. Morphine AD, extended-release (ER), injection-molded tablets (morphine-ADER-IMT; ARYMO® ER; Egalet US Inc, Wayne, PA) are approved by the US Food and Drug Administration as an AD opioid indicated 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 objective of these analyses was to determine the PK/PD relationships using results from oral and intranasal HAP studies with morphine-ADER-IMT.

Methods

The HAP studies were single-center, double-blind, active- and placebo-controlled crossover studies in adult volunteers who were nondependent, recreational opioid users. In the oral study, participants received intact morphine-ADER-IMT (60 mg), manipulated morphine-ADER-IMT (60 mg), crushed morphine ER (60 mg; MS Contin®; Purdue Pharma LP, Stamford, CT), and placebo. In the intranasal study, participants received manipulated high-volume morphine-ADER-IMT (60 mg), manipulated low-volume morphine-ADER-IMT (60 mg), crushed low-volume morphine ER (60 mg), intact oral morphine-ADER-IMT (60 mg), and placebo. The PK parameters examined were peak plasma concentration (Cmax), time to Cmax (tmax), abuse quotient (AQ; Cmax/tmax), and area under the plasma concentration vs time curve (AUC; 0–6 hours for oral study, 0–8 hours for intranasal study). The PD outcomes examined were at-the-moment Drug Liking peak effect (Emax) measured on a 100-point bipolar Visual Analog Scale (VAS), at-the-moment time to Drug Liking Emax (TEmax), Overall Drug Liking bipolar VAS score at 12 hours, and Take Drug Again bipolar VAS score at 12 hours. The relationships between the PK parameters and the PD abuse potential outcomes were evaluated. The 10-unit slope, the predicted change in a PD outcome for a 10-unit change in the PK parameter, was determined for each PK/PD association.

Results

At-the-moment Drug Liking Emax and Overall Drug Liking and Take Drug Again VAS scores at 12 hours were positively associated with Cmax. At-the-moment Drug Liking Emax was significantly associated with changes in Cmax, tmax, and AQ (P<0.001 and AUC (P<0.002). Similarly, Overall Drug Liking VAS score at 12 hours was significantly associated with changes in Cmax, tmax, and AUC. A relationship between Take Drug Again VAS score at 12 hours and Cmax (oral; P=0.002; intranasal; P<0.001) and AUC (oral; P=0.035; intranasal; P<0.001) was identified in both studies and with tmax in the oral HAP study (P=0.002), but not in the intranasal HAP study (P=0.12). As expected, there was a significant association between at-the-moment Drug Liking TEmax and tmax, whereas there was a significant negative association between tmax and all other PD outcomes.

Conclusions

All assessments of opioid abuse potential were significantly associated with Cmax, tmax, and AQ in the anticipated directions, reinforcing literature suggesting that rate and degree of drug absorption influence abuse potential. PK parameters were most effective in predicting Drug Liking Emax followed by Overall Drug Liking and Take Drug Again. The order of strongest to weakest PK/PD associations was similar between studies; however, 10-unit slope values differed between studies, suggesting that PK/PD relationships are mediated by study design, route of administration, product characteristics (ie, inherent abuse liability of opioid), and non-PK factors (ie, physical/chemical AD properties) that affect pharmacodynamics.

8 The difficulty of predicting opioid-induced nausea and vomiting (OINV) in patients who, by medical history, do not have risk factors for OINV

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Purpose

A history of previous nausea and vomiting in the postoperative setting, motion sickness, opioid-induced nausea and vomiting (OINV), and certain demographic features (female gender, older age, nonsmoking status) are risk factors used to predict nausea and vomiting after surgery.1,2 We had the opportunity to observe the incidence of OINV when a subgroup of patients, who, by medical history, did not have risk factors, used a standard opioid, hydrocodone 7.5 mg/acetaminophen 325 mg (HC/APAP), in a randomized, double-blind, placebo- and active- controlled trial.3

Methods

Patients with impacted third molar teeth who had signed an IRB-approved consent form answered questions about OINV risk factors to identify who might develop OINV. Patients were then administered open-label HC/APAP in a hydrocodone challenge and observed for nausea and vomiting. Patients were eligible for the trial if their medical histories indicated they were nausea-prone or if nausea or vomiting was reported after the hydrocodone challenge. Patients with moderate or severe pain after oral surgery were randomized to HC/APAP, CL-108 (HC/APAP/rapid-release promethazine 12.5 mg), or placebo under double-blind conditions and assessed pain, nausea, and vomiting at regular intervals over 24 hours while
Taking study medication every 4 to 6 hours as needed. The incidence of OINV was examined among the patients treated with the standard opioid (HC/APAP) or placebo who were not nausea-prone by history, but who had been admitted to the trial because they reported mild nausea after the hydrocodone challenge.

**Results**

There were 51 patients randomized to HC/APAP or placebo in the trial who had no historical risk for OINV. The incidence of OINV over 24 hours was 48% among the 40 historically not-at-risk patients who were treated with HC/APAP. Two (18%) of the 11 placebo-treated patients reported nausea. There were no unexpected or serious adverse events in these patients.

**Conclusions**

When exposed to HC/APAP, 48% of patients who did not have risk factors for OINV, but reported nausea after an open-label hydrocodone challenge, actually developed OINV. These results indicate the difficulty in identifying patients who may develop OINV based on medical history or by response to open-label challenge with an opioid.

**References**


**Effect of Treatment with Naldemedine on the Patient Assessment of Constipation Symptoms and the Patient Assessment of Constipation Quality of Life Questionnaires in Patients with Chronic Non-Cancer Pain and Opioid-Induced Constipation**

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**Purpose**

Opioid-induced constipation (OIC) is a common side effect of opioid therapy. Symptoms of OIC can significantly impact quality of life. The Patient Assessment of Constipation Symptoms (PAC-SYM) and the Patient Assessment of Constipation Quality of Life (PAC-QOL) are patient-reported outcome tools used to assess the impact as perceived by the patient. Both questionnaires comprise multiple domains (PAC-SYM: Abdominal, Rectal, and Stool Symptoms; PAC-QOL: Physical Discomfort, Psychosocial Discomfort, Worries/Concerns, and Dissatisfaction). Our aim was to assess effects of naldemedine, a peripherally-acting mu-opioid receptor antagonist approved in the United States for the treatment of OIC, on symptoms and quality of life as assessed with PAC-SYM and PAC-QOL.

**Methods**

Data from 3 randomized double-blind placebo-controlled studies of naldemedine (COMPOSE 1, 2 and 3) were pooled in this analysis. Patient eligibility criteria included 18 to 80 years of age, ≤4 spontaneous bowel movements (SBM) over a 2-week screening period with ≤3 SBMs in any given week. Patients were either not on laxatives (COMPOSE 1, 2 and 3), discontinued laxatives at screening (COMPOSE 1 and 2), or maintained a stable laxative regimen (COMPOSE 3). Eligible patients were randomized 1:1 to naldemedine 0.2 mg or placebo once daily. Change from baseline in overall PAC-SYM and PAC-QOL scores and individual domains of each instrument (graded on a 0-4 scale) were assessed at Week 2 and Week 12. Pooled data across the 3 studies were analyzed using mixed model repeated measures (MMRM).

**Results**

Across 3 studies, 2336 subjects were included (n=1170 naldemedine, n=1166 placebo; 61% female, 79% white). Naldemedine treatment led to significant (P<0.0001) improvements from baseline in mean overall PAC-SYM score for both assessed time points: -1.01 (SE: 0.026) at week 2 and -1.00 (SE: 0.030) at week 12. The difference between mean changes for the naldemedine and placebo groups was significant, in favor of naldemedine: -0.32 at week 2 and -0.27 at week 12 (both p<0.0001). Differences between the groups were also found at both assessed time points for each of the PAC-SYM individual domains. Naldemedine patients had significantly greater improvements in Abdominal Symptoms (-0.16 [p<0.0001] and -0.15 [p=0.007]), Rectal Symptoms: (-0.27 and -0.22; both p<0.0001), and Stool Symptoms (-0.47 and -0.39; both p<0.0001) at weeks 2 and 12, respectively. Similarly, naldemedine treatment led to meaningful improvements from baseline in the mean overall PAC-QOL score at both assessed time points: -1.01 (SE: 0.025) at week 2 and -1.07 (SE: 0.029) at week 12. The difference between mean changes for naldemedine and placebo groups was statistically significant: -0.35 at week 2 and -0.32 at week 12 (p<0.0001 for both). Naldemedine patients had significantly greater improvements in Physical Discomfort (-0.33 and -0.30), Psychosocial Discomfort: (-0.20 and -0.19), Worries and Concerns (-0.33 and -0.32), and Dissatisfaction Symptoms (-0.64 and -0.53) at weeks 2 and 12, respectively (p<0.0001 for all). Treatment with naldemedine for 12 weeks was generally well tolerated with a similar incidence of treatment-emergent adverse events in both treatment groups (naldemedine: 47.1%; placebo: 45.6%).

**Conclusions**

Treatment with naldemedine 0.2 mg once daily for up to 12 weeks was associated with significant improvements in constipation symptoms and quality of life compared with placebo. Naldemedine was generally well tolerated.
10 Subject Global Satisfaction Score to Assess Overall Effect of Naldemedine Compared With Placebo on Constipation and Abdominal Symptoms in Subjects with Chronic Non-cancer Pain and Opioid-Induced Constipation

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Purpose

Opioid-induced constipation (OIC) is a common side effect of opioid therapy that significantly affects multiple aspects of a patient’s life. Naldemedine is a peripherally-acting mu-opioid receptor antagonist developed for the treatment of OIC. In Phase 3 studies, naldemedine improved the frequency of spontaneous bowel movements, straining, consistency of stools, and patient assessment of constipation symptoms (PAC-SYM) and quality of life (PAC-QOL), measures of patient’s quality of life, compared with placebo. The aim of this analysis is to assess the impact of naldemedine on overall satisfaction and to show if a simple score can assess the impact of treatment of OIC with naldemedine 0.2 mg once daily on patient’s satisfaction with constipation and abdominal symptoms in patients with OIC associated with non-cancer pain.

Methods

In three Phase 3 randomized, double-blind, PBO-controlled trials of naldemedine (2 of 12-week duration [COMPOSE 1 and COMPOSE 2] and 1 of 52-week duration [COMPOSE 3]), a 7-grade scale (1=markedly, 2=moderately, or 3=slightly worsened; 4=unchanged; 5=slightly, 6=moderately, or 7=markedly improved) was used to assess overall patient satisfaction with constipation and abdominal symptoms at the last study visit. The number and proportion of subjects in each grade were calculated and the overall difference between groups was assessed by Wilcoxon rank sum test. The mean subject global satisfaction score (SGSS) was also compared between groups. For SGSS, scores from 1 to 7 were replaced with scores from -3 to +3, with 4 (unchanged) replaced with 0. This proposed new approach provides a single score that may be easier to interpret than the 7-grade scale.

Results

There were 547 subjects in COMPOSE 1, 550 in COMPOSE 2, and 1246 in COMPOSE 3 (all ≥18 years of age) randomized (1:1) to naldemedine 0.2 mg once daily or placebo. The baseline characteristics of the study population were consistent between groups in each trial and between trials. Overall satisfaction assessment was completed in 372 subjects in COMPOSE 1, 296 in COMPOSE 2, and 1101 in COMPOSE 3. There were greater improvements in satisfaction with constipation and abdominal symptoms in the naldemedine group compared with the placebo group in all three studies by (P=0.0005 for COMPOSE 1; P≤0.0001 for COMPOSE 2 and COMPOSE 3). The mean SGSS were 1.5 (±1.50, standard deviation) and 0.9 (±1.52) with naldemedine and placebo, respectively, in the two 12-week studies pooled, and 1.7 (±1.36) and 1.0 (±1.39), respectively, in the 52-week study.

Conclusions

Treatment of OIC with naldemedine 0.2 mg once daily for 12 or 52 weeks led to greater satisfaction with constipation and abdominal symptoms compared with placebo, consistent with previously-reported improvements of PAC-SYM and PAC-QOL with naldemedine compared with placebo. The proposed SGSS appears to be a simple way to assess the impact on quality of life of OIC treatment.

11 Retrospective Review of Pain Pharmacist Interventions on Inpatient Post-operative Pain Scores

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Purpose

The prevalence of pain among hospitalized patients ranges from 38% to 77%. A variety of barriers to effective pain management have been identified in the literature including inadequate pain assessments, poor physician-nurse communication, and unrealistic pain goals. Pharmacists’ specialized training in pharmacotherapy makes them well suited to effectively manage patients’ pain, which often requires a combination of co-analgesic therapy and opioid therapy. The ability of the pharmacist to work collaboratively with the patient and healthcare team can help to ensure that a patient’s analgesia is maximized while preventing adverse events. The purpose of this study was to evaluate the impact of a pain management pharmacist’s interventions on general surgery consult patients’ pain scores.

Methods

This was a retrospective chart review evaluating the impact of a clinical pharmacist on the pain management of general surgery consult patients over a sixty-day intervention period. The primary outcome was the impact of a pharmacist’s interventions on patient reported pain scores. Secondary endpoints were gathered from the electronic medical record to assess, pain medications prescribed during hospitalization, participation with physical therapy, length of hospital stay, doses of naloxone administered, and documented pharmacist interventions.

Results

Patients were similar with regard to baseline characteristics, with the exception of more patients with COPD being in the post intervention group (p<.0001). There was no significant difference between groups with regard to epidural and PCA utilization. Median patient reported pain scores were similar between groups. When evaluating pain scores between groups at time points 0, 12, 24, 36 and 48 hours there was a
significant decrease in reported scores detected at 36 hour (p=.019) and 48 hour (p=.003) time points for the intervention group. Time within patient stated pain goal was 33% in the physician directed arm and 50% in the pharmacist intervention group (p = .0065). Morphine equivalent reduction outcomes showed a numerical decline during hospitalization; however, this was not statistically significant. There was an increase in the frequency of acetaminophen and neuropathic agent prescribing in the pharmacist directed arm however, this was not significant. Days of physical therapy participation were similar between groups. The most common pharmacist interventions observed were utilization of the prescription drug monitoring program, as well as increased adjuvant therapy prescribing.

Conclusions
Pharmacist intervention correlated to reduction in patient reported pain scores at 36 and 48 hour postsurgical time points. Patients in the pharmacist directed arm spent a greater length of time within the patient stated pain goal when compared to the non-intervention group. The pain perception counseling provided by the pharmacist may have contributed to improved pain perception and patient reported pain scores. This study was not without limitations. Patient reported pain scores remain highly subjective and therefore generalizability of this study may be limited. More robust studies are needed to fully evaluate the pharmacist’s impact on pain in the post-surgical setting.

12 Urine Drug Test results track the co-occurrence of non-prescribed fentanyl in national, regional and statewide populations of heroin-positive patients.
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Purpose
The United States continues to experience unabated proliferation of illicit fentanyl and its analogues. In 2016, both the Centers for Disease Control (CDC) and the Drug Enforcement Administration (DEA) issued nationwide warnings on the increased prevalence of fentanyl in the illicit market. Up to 50 times more potent than heroin and up to 100 times more potent than morphine, fentanyl is often spiked into heroin or sold as heroin, frequently without the knowledge of the consumer. To date, the epidemiology of fentanyl-spiked heroin has relied largely on reports of seizures by law enforcement agencies and accounts of fatal and non-fatal overdoses by emergency healthcare professionals, first responders, medical examiners and coroners. In an effort to provide additional insights into the increasing use of fentanyl-spiked heroin, the current study examines urine drug test results (UDTs) acquired by a national drug testing laboratory to track the co-occurrence of non-prescribed fentanyl in national, regional and statewide populations of heroin-positive healthcare patients.

Methods
The heroin and fentanyl results were examined for 9 temporal subsets of UDTs submitted in Jan and July of 2013, 2014, 2015, 2016 and Jan 2017. Each of the subsets consisted of patient samples submitted for testing by healthcare providers as part of their normal course of treatment, wherein the test requisition included (but was not limited to) definitive drug testing by LC-MS/MS for both heroin and fentanyl. The positivity rates for heroin-use (ie UDT positive for heroin metabolite) was examined for each of the temporal subsets, along with positivity rates for fentanyl-use both with, and without, a reported prescription (ie. UDT positive for fentanyl and/or norfentanyl). Finally, the co-occurrence of fentanyl-positives without a reported script, within the heroin-positive subset of subsets, was measured.

Results
On the national level, positivity rates for non-prescribed fentanyl in the heroin-positive population of healthcare patients increased 3000% between Jan 2013 and Jan 2017. In January 2013, positivity rates for heroin were less than 1%, with less than 2% of those heroin-positives also testing positive for fentanyl without a reported prescription. Between January 2013 and January 2017, heroin positivity rates rose marginally to 1.3%, but the occurrences of non-prescribed fentanyl in the UDTs of those heroin-positives rose steadily to 35.6% (ie. ~1/3rd of heroin-positives were also positive for fentanyl without a reported prescription in January 2017). Regionally, 5 of the 9 US Census regions exhibited a significant increase in the co-occurrence of fentanyl use in the heroin-positive population. In each of the regions, positivity rates for fentanyl in the heroin-positive population grew from <3% in January 2013 to 76% (New England), 44% (Mid Atlantic), 52% (South Atlantic), 50% (East North Central), and 34% (West North Central), respectively. Ten individual states, DE, FL, IN, KY, MI, WI, MD, MO, OH, and PA, were impacted at the highest level. While growth patterns differ between these states, each exhibited >33% of their heroin-positive UDTs tested in January 2017 also testing positive for fentanyl without a reported prescription.

Conclusions
While the source of the fentanyl cannot be definitively ascribed to fentanyl-spiked heroin, the data suggests that fentanyl-spiked heroin may be more prevalent than currently believed. This study highlights the ongoing emergence of fentanyl-spiked heroin and the particular foci affected by this phenomenon. The results may inform clinicians, first responders, and those responsible for public health to better leverage modalities at their disposal, in their ongoing efforts to halt the devastating toll of fentanyl-spiked heroin. Secondarily, the current study demonstrates the potential utility of UDTs as an epidemiological tool to track emerging patterns of drug-use.
13 In Vitro Differentiation of Two FDA-Approved Abuse-Deterrent Opioids’ Resistance to Oral Mastication

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Purpose

Abusers often physically manipulate or ‘tamper’ with prescription opioids for oral and non-oral routes of administration.¹ Oral mastication, or chewing, is commonly employed for both immediate-release and extended-release to speed release of the active pharmaceutical ingredient (API). Many abuse-deterrent formulations (ADFs) are designed to be physically hard and resist physical manipulation by tools; however, few products have earned a label claim for resistance to oral abuse by mastication. Early development studies completed by DRUGSCAN explored the complex set of experimental conditions that are required for in vitro simulated mastication studies (e.g., bite force, torsion degree, saliva, temperature, time). In extension of the exploratory investigation, this study further optimized the method compression, force and time parameters and included an additional ADF comparator with claims of resistance to oral mastication. Here, we discuss and provide the results of a mastication study that evaluated one ADF with oral mastication claims (ADF_1) relative to another ADF with physical, chemical, and injection claims but, without oral mastication claims (ADF_2). A non–abuse-deterrent commercial (non-ADF) was included as a control.

Methods

This study was designed to simulate the several conditions encountered during in vivo mastication. Utilizing the DRT (Dissolution Rate Tester) manufactured by ERWEKA GmbH (Heusenstamm, Germany) and simulated saliva manufactured by Pickering Labs (Mountain View, CA), temperature, compression force and distance, torsion degree, mastication frequency and duration can be tightly controlled to optimize these studies.³ The media (20 mL of simulated saliva) and mastication jaws were equilibrated to human body temperature (37°C) before the addition of any pharmaceutical formulation and held at a constant temperature for the 10-minute mastication study. Human bite forces have been shown to vary greatly even within closely related populations.² Three representative maximum forces (Newtons) of approximately 110 N, 300 N, and 550 N were examined with compression gap distance representative of 80–85% compression of the formulation’s starting thickness. A characteristic torsional degree of 20° and mastication frequency of approximately 40 strokes/min (1.57 Hz) were used for all experiments.⁴²⁵ Aliquots of the simulated saliva were removed at 1, 2, 5, 10 and 20 minutes to measure the release of API in solution. Force and torque data was electronically recorded and was plotted to allow investigation of force and torque changes over the course of the study. Experiments were conducted in triplicate.

Results

The non-ADF product was rapidly deformed within the first minute of mastication as supported by force plots exhibiting a sharp decrease in the force necessary to reach the set compression distance. All API from the labeled dose was released from the non-ADF product within 2 minutes at all tested forces. At the earliest API measurement of 1 minute until the terminal measurement of 20 minutes both ADF_1 (with oral mastication claim) and ADF_2 (without oral mastication claim) showed a significant difference (student’s t-test) as compared to the non-ADF control at all compression forces (P<0.01). Force plots from ADF_1 tested at 110 N showed little tablet deformation after 20 minutes and an average API recovery of just 2%. When ADF_1 was tested at 300 N the tablet did not begin to deform until approximately 19 minutes and only 12% API was released on average. After increasing the mastication force to 550 N ADF_1 began to deform after 11 minutes and produced a slightly higher average API recovery of 33%. In contrast, ADF_2 showed deformation after 8 minutes at 110 N, after 3 minutes at 300 N and after 1 minute at 550 N. API recovery from ADF_2 reached 51% at 110 N, 59% at 300 N, and 69% at 550 N by 20 minutes. The API recovery from ADF_1 was significantly lower than the API recovery from ADF_2 (P<0.01) at all tested time points and compression forces.

Conclusions

This study differentiated mastication resistance of commercially available ADF_1 (claim for oral mastication resistance) compared to ADF_2 (no claim for oral mastication) and the control. These data show ADF_1 is superior to ADF_2 even when subjected to very high bite forces for up to 20 minutes. Furthermore, this study suggests that products with resistance to physical manipulation (as with ADF_2) and other routes do not by de facto deter abuse via mastication. An important next step will be to evaluate the in vitro/in vivo correlation via an oral drug liking study and potentially develop an in vivo modeling approach.

14 Bioequivalence of Immediate-Release (IR) Oxycodone With Aversion Technology Compared With a Non–Abuse-Discouraging Formulation of IR Oxycodone

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Purpose

Prescription opioid abuse is a significant public health concern, with an estimated 12.5 million individuals (≥12 years old) reporting misuse of prescription pain relievers in 2015. A recent study of 4 abuse and diversion surveillance programs found that the rate of abuse for immediate-release (IR) opioids was up to ~5 times higher than that for extended-release (ER) opioids. Although a great deal of effort has been devoted to the development of abuse-deterrent ER opioids, strategies to decrease prescription opioid misuse and abuse
need to be aimed at both IR and ER opioid formulations. IR oxycodone with aversion technology (IRO-AT; OXAYDO®; Egalet US Inc, Wayne, PA) is an IR oxycodone containing excipients designed to discourage intranasal abuse and resist preparation for intravenous injection. IRO-AT is currently available in dosages of 5 and 7.5 mg. The objective of this study was to determine whether IRO-AT 15 mg, a potential new commercial dosage, is bioequivalent to IR oxycodone (Roxicodone® 15 mg tablets; Mallinckrodt, Hazelwood, MO) under fasted conditions.

**Methods**

Bioequivalence was assessed in a phase 1, randomized, open-label, single-dose, 2-cohort crossover study in healthy adults aged 18–55 years. Participants were randomly assigned to receive 15 mg IRO-AT and 15 mg IR oxycodone (fasted conditions) per 1 of 2 treatment sequences, with a washout interval of ≥7 days between treatment periods. Participants received the opioid antagonist naltrexone (50 mg orally) approximately 3 and 15 hours before and approximately 9 and 21 hours after study drug administration to minimize the opioid agonist effects of oxycodone. Participants fasted overnight for ≥10 hours before administration of study medication. Pharmacokinetic parameters for oxycodone included maximum plasma concentration (C_max), area under the plasma concentration vs time curve (AUC) from time 0 to the last measurable time point (AUC_0-τ), and AUC from time 0 extrapolated to infinity (AUC_0-∞). Estimates for the ratios of the geometric means and respective 90% CIs were obtained. Bioequivalence was concluded if the 90% CIs for the ratios for test drug/reference drug of the geometric least square mean (LSM) were entirely contained within the equivalence interval of 80.00%–125.00% of C_max, AUC_0-τ, and AUC_0-∞ for oxycodone.

**Results**

Of the 66 participants randomized, the majority were white (67%) and female (67%). Sixty of 66 (91%) randomized participants completed the study and 65 (98%) were included in the PK analysis. Mean oxycodone plasma concentrations over time were similar for IRO-AT 15 mg and IR oxycodone 15 mg. Bioequivalence was demonstrated between IRO-AT 15 mg and IR oxycodone 15 mg, with the 90% CI around the ratios of geometric LSMeans (IRO-AT:IR oxycodone) of 95.60% (91.04%–100.40%), 103.23% (100.32%–106.22%), and 103.11% (100.34%–105.96%) for C_max, AUC_0-τ, and AUC_0-∞, respectively. The percentage of participants reporting treatment-emergent adverse events was similar in each treatment sequence and was generally consistent with the mechanism of action for the study medications. No deaths, serious adverse events, or severe adverse events were reported.

**Conclusions**

IRO-AT 15 mg was bioequivalent to IR oxycodone 15 mg under fasted conditions, with a similar tolerability profile that was consistent with product labeling. The demonstration of bioequivalence between IRO-AT 15 mg and IR oxycodone 15 mg in fasted patients supports expansion of the dosage range of IRO-AT, thereby offering greater clinical flexibility. This study and these results are part of the continued development of IRO-AT, with the objective to expand the dosage range.

**15 Overcoming the US of Passive: Increasing Active CAM Use with Pain Education**

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**Purpose**

A general conclusion about the treatment of chronic, non-cancer pain is that the results from traditional, passive modalities are disheartening. Perhaps this may be due to the propensity of patients to seek out passive treatments (such as medications, interventions, and surgery) versus active alternatives (such as self-hypnosis, relaxation techniques, and mindfulness practices). They tend to go for short-term relief at a long-term cost. It has been recommended that passive modalities not be employed except when necessary to facilitate participation in an active treatment program. While passive treatments can be effective, it is critical to shift the patient into a model of active care. There is also promising scientific evidence to support the use of CAM for non-cancer pain conditions, such as low back pain, arthritis, and headaches; and limited support for neck pain. Clinical trials have also indicated the comparable efficacy of CAM modalities with traditional chronic pain treatments, such as acupuncture and behavioral therapy compared to exercise therapy and pharmacotherapy. Thus, the purpose of the current study was to determine whether a patient pain education program benefitted Veterans who suffer from chronic, non-cancer pain by focusing more on active CAM treatments. Such an education-focused, professionally driven program assumes that if individuals are provided with adequate education, they will be empowered and self-manage chronic pain. The current study tested the hypotheses that Veterans would report a more significant increase in active versus transitional versus passive CAM utilization after completing a formal pain education program in a VA medical center.

**Methods**

The current study is a secondary analysis of existing data from an original study. The current study used a quasi-experimental, one-group, pre-/post-test design. One hundred and three Veterans completed a 12-week, “Pain Education School” program at a Midwestern VA Medical Center between November 4, 2011-October 26, 2012. As part of the introduction and conclusion of the program, all Veterans completed a pre- and post-education assessment. The assessment included questions which asked Veterans if they had ever been treated by specific CAM modalities. The assessment included a questionnaire which was adapted from the Complementary and Alternative Medicine Questionnaire©, SECTION A: Use of Alternative Health Care Providers. Veterans responded either “no” or “yes,” and if “yes” they were asked “then how long?” about their use of 13 different CAM modalities. These responses were then added up to calculate utilization. CAM
modalities were then grouped for the analyses based on the type of CAM treatment, including active, transitional, or passive modalities. Active interventions included ACT/mindfulness, biofeedback/relaxation training, hypnosis, movement programs, music/art therapy, and spirituality/religion. Transitional interventions included chiropractic care and osteopathic manipulation. Passive interventions included acupuncture, aromatherapy, healing touch, massage therapy, and traditional healers. The primary intervention outcome analyses were paired samples t-tests to compare pre- and post-assessment means of active, transitional, and passive CAM counts after completing a patient pain education program. Outcome analyses used an efficacy subset analysis strategy which selects the subset of the patients who received the intended programming and who did not drop out for any reason.

Results

Nearly 44% (N=45) of Veterans reported not using any type of CAM at baseline. The remaining 56% of Veterans utilized different combinations of CAM at baseline, including active (30%); passive (41%); and transitional (36%) CAM modalities. Pre- and post-counts of CAM users by type was also delineated at baseline. Approximately 16% of Veterans reported not using any type of CAM after completing the Pain Education School program; which is more than a 25% difference from baseline. The remaining 84% of Veterans reported increases in different combinations of CAM after completing the patient education program, including active (24%); passive (12%); and transitional (14%) CAM modalities. A diagram of the pre-and post-count percentages of CAM users by type illustrated an overall increase in utilization and a shift away from passive to transitional and active CAM modalities. There were no significant differences found between male and female Veterans in their utilization of active, passive, or transitional CAM modalities. The current findings specifically indicate that younger Veterans were more likely to seek passive CAM modalities than their older counterparts, F (5,97)=3.84, p=.003. No other significant differences were found in active or transitional CAM use by age group. No significant differences were found in the utilization of different CAM modality types among Veterans who identified with different racial/ethnic groups in the current study. At baseline, there were no significant differences between completers versus those who dropped out of the education program on utilization of CAM for any of the 13 modalities measured. Significant differences were found between the pre- and post-test measures of use of active modalities (p=.000); of transitional modalities (p=.011); and of passive complementary and alternative medicine modalities (p=.007). The mean numbers are the total counts of modalities.

Conclusions

The results of the current study substantiate past findings which indicate increased use of CAM modalities when education is provided about their availability. Furthermore, they confirmed that there was a shift away from passive to more active CAM modalities upon completion of the pain education program. Thus, the program was found to be more aligned with the goal of pain management—that patients engage in more self-management. These findings should be considered when making decisions about resource allocations in reference to CAM. It may also be astute to consider different messages and interventions when dealing with different Veteran age groups.

16 The Effects of a Pilot Functional Medicine Clinic on Chronic Pain Among Veterans

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Purpose

According to the Centers for Disease Control and Prevention (CDC), chronic diseases and conditions are among the most common, costly, and preventable of all health problems. More concerning, the incidence of heart disease, diabetes, and cancer combined is lower than that of chronic pain. Specific health risk behaviors, including being sedentary, poor nutrition, tobacco use, and excess alcohol consumption lead to much of the illness, suffering, and early death related to chronic diseases and conditions. According to the American College of Preventative Medicine, most chronic diseases are preventable and reversible if a comprehensive, individualized approach that addresses genetics, diet, stress, physical activity, and sleep is implemented through integrated functional medicine teams and based on empirical research. Functional medicine addresses the underlying causes of disease, using a systems-oriented approach and engaging both patient and practitioner in a therapeutic partnership. In effect, the focus is better understood as the medicine of why, not what. The purpose of the current study was to determine whether participation in the Functional Medicine clinic would significantly decrease pain intensity, weight, waist/hip circumference, medical symptoms/toxicity, perceived stress, and insomnia and increase walking speed.

Methods

A sample of 51 Veterans aged 18-75 years old with mixed, idiopathic, chronic pain conditions was recruited for a pilot Functional Medicine clinic at Jesse Brown VA Medical Center between May 4, 2016-April 26, 2017. The intervention was delivered in a group format with individual follow-up sessions, as needed. The group treatment protocol consists of 4 sessions that were approximately 60-75 minutes in duration. The interdisciplinary treatment team consists of an osteopath physician, a health psychologist, and a dietician. Patients were coached to change their environment and live an anti-inflammatory lifestyle by addressing 4 key pillars: diet, exercise, stress management, and sleep hygiene. As part of the first and last session, all participants completed a pre-intervention assessment that included the Medical Symptoms Questionnaire (MSQ), the Perceived Stress Scale (PSS), and the Insomnia Severity Index (ISI). Scores on the MSQ ranged from less than 10 (optimal), 10-50 (mild), 50-100 (moderate), and over 100 (severe toxicity). The
health profile of Veterans were divided into 15 subsystems, including head, eyes, ears, nose, mouth, skin, heart, lungs, digestive tract, joints/muscle, weight, energy, mind, emotions, and other. PSS scores were obtained by reversing responses to the four positively stated items (items 4, 5, 7, & 8) and then summing across all scale items. ISI scores ranged from 0–7 (no insomnia), 8–14 (subthreshold insomnia), 15–21 (clinical insomnia-moderate severity), and 22–28 (clinical insomnia-severe). Paired sample t-tests were used to evaluate the impact of the program on Veterans’ scores on the aforementioned indices.

Results

Over half of the patients (53%) participated in the program. The remaining patients (N=24) were followed using the electronic medical record during the time frame of the study. The non-completers did not witness a significant change in their pain or their weight during the time frame of the study. Among completers, there were no significant differences found on measures of pain intensity, weight, waist/hip circumference, walking speed, and insomnia. The average pain intensity at baseline was 4-5, which the Numeric Rating Scale implies the patient is uncomfortable and something needs to be done. Scores of the ISI also indicated that patients who completed the program had subthreshold insomnia at baseline. There were significant differences in measures of medical symptoms/toxicity, t (21) =2.66, p = .015; and perceived stress, t (21) =3.07, p = .006. Only perceived stress was significantly different after Bonferroni correction (α=.05/8=.006). Cohen’s d was calculated giving an effect size of .514 suggesting the program had a moderate effect in decreasing perceived stress. Further inquiry into relevant medical symptom subsystems (head, digestive tract, joint/muscles, weight, energy/activity, mind, and emotions) found a significant change in the head, t (21) =2.54, p = .019, which assessed for headaches and insomnia; joint/muscles, t (21) =3.05, p = .006, which assessed for pain, aches, and arthritis; weight, t (21) =2.24, p = .036; energy/activity, t (21) =2.46, p = .023; and the mind, t (21) =2.70, p = .013. However, only joint/muscles was significantly different after Bonferroni correction (α=.05/7=.007). Cohen’s d was calculated giving an effect size of .724 suggesting the program had a moderate to large effect in decreasing joint/muscle symptoms (pain, aches, and arthritis).

Conclusions

The results of the current study indicate that Veterans who participated in a pilot Functional Medicine clinic witnessed significant decreases in perceived stress and joint/muscle symptoms. A VA Evidence-based Synthesis Program report indicated that group visits focusing on education for the management of chronic conditions in Veterans tend to suffer from high levels of attrition which was substantiated. The current pilot clinic serves as a means of initiating the 5R framework of Functional Medicine while reinforcing the self-management approach to chronic pain management. This study encourages other VAs to transfer this low-intensity approach and may be utilized as a benchmark.

17 Evaluation of Subjective Response Stability to Intranasally Administered Oxycodone Hydrochloride (Immediate Release) During Qualification and Treatment Phases in a Human Abuse Potential Study

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Purpose

Modern pain management often includes prescription opioids; however, the misuse and abuse of these products have led to serious public health concerns. The development of abuse-deterrent opioid formulations represents an important component of the countermeasures aimed to address the current opioid epidemic.

This study evaluated whether subjects continue to endorse similar levels of positive subjective responses to oxycodone hydrochloride (HCl) immediate release (IR) during treatment as during the pre-qualification period in a Phase I abuse potential trial. In addition, treatment responses to oxycodone HCl IR in the qualification versus treatment phase were assessed.

Methods

The FDA Industry Guidance for the Evaluation and Labeling of Abuse-Deterrent Opioids (April 2015) emphasizes the importance of ensuring that subjects are able to distinguish placebo from a conventional IR opioid formulation (active comparator) when conducting abuse potential studies of abuse-deterrent formulations. However, subsequent to qualification, limited information is typically available to inform whether subjects are likely to continue to exhibit a similar degree of preference for the active comparator during treatment.

Active comparator data from 37 non-dependent, recreational opioid users with intranasal experience participating in a randomized, double-blind, double-dummy, active- and placebo-controlled single-center study were analyzed using the Spearman correlation coefficient. Analyses were performed on 0-100 point pharmacodynamic (PD) visual analog scales (VAS) of positive drug effects (ie, drug liking, good drug effects, feeling high, overall drug liking, and take drug again) administered during study qualification and treatment phases.

A responder analysis was performed to examine the direction of change and magnitude of the subjective effect of oxycodone HCl IR in the qualification versus treatment phase.

Results

On the Drug Liking VAS, the maximum response to oxycodone hydrochloride during qualification was modestly albeit significantly correlated to the response provided during the treatment phase (Spearman Correlation = 0.49, p=0.002).

In examining E_max for Drug Liking in the qualification versus treatment phase, in response to oxycodone IR, 10 subjects (27.0%) showed an increase in E_max in the treatment phase (mean increase 10.6; range 3–33), whereas 14 subjects (37.8%) had a reduction in E_max (mean reduction 10.1; range of 1-21)
and 13 subjects (35.1%) had no change. In the subjects with no change, the reported $E_{\text{max}}$ was 100 in all cases. With the exception of 1 subject (2.7%) who had an $E_{\text{max}}$ of 51 in response to oxycodone IR in the treatment phase, all other subjects had an $E_{\text{max}}$ response of 3–72 points (range 72-100).

Conclusions
The majority of subjects retained or enhanced their maximum subjective response to oxycodone HCl IR on Drug Liking in the treatment phase relative to the qualification phase, however over a third of subjects showed some reductions. One subject showed an absence of response to the oxycodone IR despite having been qualified. Variability in responding to the active control is an important issue in abuse potential studies. This analysis was limited to one study examining intranasally administered oxycodone IR. Additional drugs, doses and routes would need to be further examined to determine the correlation of measures between qualification and treatment phases.

18 Converting patients with chronic pain from immediate-release oxycodone to Xtampza® ER, an extended-release, abuse-deterrent formulation
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Purpose
Opioids are effective for the treatment of chronic pain. Patients are often converted from immediate-release (IR) to extended-release (ER) opioids once their pain is daily, around-the-clock, and expected to be present for an extended period of time. Oxycodone DETERx® ER (Xtampza® ER approved by the Food and Drug Administration) is an abuse-deterrent formulation (ADF) of ER oxycodone. The DETERx technology platform allows it to maintain its ER properties when crushed, chewed, or administered intranasally, and enables the formulation to resist preparation for intravenous abuse. The purpose of this study was to assess whether subjects previously on IR oxycodone with poorly managed pain were able to successfully convert to oxycodone DETERx.

Methods
A post-hoc analysis of 44 subjects from a Phase 3 randomized withdrawal, double-blind, placebo-controlled, enriched-enrollment, parallel-group, multi-center, 12-week clinical study of oxycodone DETERx was conducted in subjects with chronic low back pain (CLBP; NCT01685684) to assess whether subjects previously on IR oxycodone with poorly managed pain were able to successfully convert to oxycodone DETERx; no study procedures/assessments were conducted before IRB approval and subject informed consents were obtained.

Results
Primary efficacy results showed a statistically significant difference in average pain intensity from Randomization Baseline to Week 12 favoring oxycodone DETERx (LS mean difference [±SE], -1.94 [0.62]; p=0.002). Additionally, subjects on oxycodone DETERx had statistically significant differences in patient global impression of change, percent of subjects exiting the study, and responder analysis (≥30% or ≥50% improvement; each result p<0.005), used numerically less rescue medication, and had similar adverse event profiles between groups.

Conclusions
Since our results showed clinically and statistically significant efficacy in patients with CLBP previously prescribed IR oxycodone, oxycodone DETERx may provide clinicians and patients with a new abuse-deterrent option for the management of chronic pain.

19 Assessment of the oral human abuse liability and pharmacokinetics of Xtampza ER®
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Purpose
Xtampza (oxycodone) extended-release capsules with the DETERx technology is a microsphere-in-capsule, ER, abuse-deterrent analgesic. This is the second oral human abuse liability study assessing the abuse liability and pharmacokinetics of Xtampza ER taken intact and chewed compared with crushed immediate-release oxycodone.

Methods
This is the second oral human abuse liability study assessing the abuse potential (n=52) and pharmacokinetics (PK; n=71) of Xtampza ER taken intact and chewed (fed and fasted) compared with crushed immediate-release (IR) oxycodone (fasted) and placebo (fed). This study was a randomized, double-blind, triple-dummy, active- and placebo-controlled, 6-period crossover study conducted in non-dependent recreational opioid users. The primary endpoint was the peak effect ($E_{\text{max}}$), bipolar Drug Liking visual analog scale.

Results
Drug Liking $E_{\text{max}}$ of chewed Xtampza ER fasted (LS mean±SEM: 73.71±1.947) and fed (75.69±1.947) were statistically significantly lower relative to IR oxycodone (86.76±1.947; p=0.0025 and 0.0038, respectively). Similarly, chewed Xtampza ER demonstrated statistically significantly (p<0.01) lower $E_{\text{max}}$ values (mean [±SD] fasted: 77.8 [18.30]; fed: 77.8 [17.69]) compared with IR oxycodone (87.7 [12.90]) on the key secondary endpoint of Take Drug Again (TDA); most additional measures of balance of effects, positive effects (High, Good Effects), pharmacological effects (Any Effects, Sleepy), and pupillometry also showed statistically significantly lower $E_{\text{max}}$ values for these comparisons. There were no statistical differences in $E_{\text{max}}$ between chewed/intact Xtampza ER treatments for Drug Liking or TDA. Chewed and intact Xtampza ER were
bioequivalent (peak and overall exposure), indicating retention of ER properties when chewed.

Conclusions
The results support Xtampza ER (chewed/intact) has statistically significantly lower oral abuse potential compared with IR oxycodone. This suggests Xtampza may help address abuse in the real world.

20 Development of Korean Medicine Clinical Guideline for Non-specific Chronic Low Back Pain
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Purpose
As science and medicine evolves, the average life span of mankind is rapidly being extended. The growing population of the elderly and interest towards well-being is stimulating growth of the complementary medicine market.

Acupuncture is one of the most popular treatments to the patients seeking complementary medicine. As patient population receiving acupuncture increases worldwide, needs for a standardized clinical guideline is growing. Among the many diseases treated by acupuncture, musculoskeletal disorders rank the top.

The objective of this study is to establish Korean Medicine clinical guideline for non-specific chronic low back pain.

Methods
A task force team to establish the guideline was composed. Literature review was done in order to search for evidence of safety and efficacy of acupuncture and other Korean Medicine treatments. A survey was done in order to find out how Korean medical doctors derive pattern identification for acupuncture and herbal prescriptions in treating non-specific chronic low back pain. Then, based on the results of literature review and survey, a conference meeting of experts was held. Through the Delphi method, a draft of the acupuncture clinical guideline for non-specific chronic low back pain was established. Now the review board, composed of experts of musculoskeletal disorders, public health, statistics, and representatives of patients are modifying the draft.

Results
Evidence of safety and efficacy of acupuncture treatment for musculoskeletal disorders was established. A standard or pattern identification was derived. A draft of Korean Medicine clinical guideline for non-specific chronic low back pain was established.

Conclusions
More rigorous, well designed and large scaled RCTs are in need to improve the quality and make modifications this clinical guideline.

21 Effectiveness and Safety of Moxibustion Treatment for Non-specific Lower Back Pain: Protocol for a Systematic Review
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Purpose
Many patients experience acute lower back pain that becomes chronic pain. The proportion of patients using complementary and alternative medicine to treat lower back is increasing. Even though several moxibustion clinical trials for lower back pain have been conducted, the effectiveness and safety of moxibustion intervention is controversial.

The purpose of this study protocol for a systematic review is to systematically evaluate the effectiveness and safety of moxibustion treatment compared with placebo control, conventional treatment, or no treatment in non-specific lower back pain patients evaluated by pain intensity and functional status/disability.

Methods
We will conduct an electronic search of several databases from their inception to May 2017, including Embase, PubMed, Cochrane Central Register of Controlled Trial, Allied and Complementary Medicine Database, Wanfang Database, Chongqing VIP Chinese Science and Technology Periodical Database, China National Knowledge Infrastructure Database, Korean Medical Database, Korean Studies Information Service System, National Discovery for Science Leaders, Oriental Medicine Advanced Searching Integrated System, the Korea Institute of Science and Technology, and KoreaMed.

Randomized controlled trials investigating any type of moxibustion treatment will be included. The primary outcome will be pain intensity and functional status/disability due to lower back pain. The secondary outcome will be a global measurement of recovery or improvement, work-related outcomes, radiographic improvement of structure, quality of life, and adverse events (presence or absence). Risk ratio or mean differences with a 95% confidence interval will be used to show the effect of moxibustion therapy when it is possible to conduct a meta-analysis.

Results
Our review provides a systematic, objective, and comprehensive evaluation of the effectiveness and safety of moxibustion treatment in patients with lower back pain that is non-specific.

Our review and meta-analysis provide new and useful information for practitioners, policymakers, and patients.

Various treatments with moxibustion and clinical outcomes reviewed in our study will help to design clinical trial studies of moxibustion treatment for non-specific lower back pain.

Chinese and Korean databases will also be searched to avoid a language bias.

The major limitation of our study protocol is that some of the reviewed trials may have small sample sizes; this limitation
affects our objective and comprehensive assessment of the risks and benefits of moxibustion treatment for non-specific lower back pain.

Conclusions
This review will be published in a peer-reviewed journal and will be presented at an international academic conference for dissemination. Our results will provide current evidence of the effectiveness and safety of moxibustion treatment in non-specific lower back pain patients, and thus will be beneficial to patients, practitioners, and policymakers.

22 Lasmiditan (200 mg and 100 mg) Compared to Placebo for Acute Treatment of Migraine
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Purpose
To compare efficacy on headache pain and the patient-centric measure of most bothersome symptom (MBS; nausea, phono-phobia, or photophobia) at 2 hours post dose, time course of migraine response, rescue, and safety following treatment with lasmiditan 200 mg or 100 mg or placebo.

Methods
In this randomized, double-blind, placebo-controlled study, subjects with at least moderate disability (Migraine Disability Assessment Score [MIDAS] ≥11) were randomized 1:1:1 to a first dose of lasmiditan treatment (200 mg or 100 mg) or placebo within 4 hours of onset of a migraine attack (moderate severity or worse and not improving). Subjects took a randomly assigned second dose of either their previously assigned lasmiditan dose or placebo for rescue or recurrence of migraine if needed (2 to 24 hours post initial dose); subjects randomized to placebo received placebo as the second dose. The primary measures were comparison of the proportions of subjects (modified intent-to-treat population [mITT]) in the lasmiditan 200 mg and placebo groups who, at 2 hours post first dose, were headache pain-free and MBS free. Comparisons were made via logistic regression with terms for treatment group and back-care pain-free and MBS free. Comparisons were made via logistic regression with terms for treatment group and back-treat population [mITT].

Results
Overall, 2231 subjects were randomized and 1545 (mITT) were evaluated in the lasmiditan 200 mg (n=518), 100 mg (n=503), and placebo (n=524) groups. At baseline, the mean MIDAS score was 31.3 and 82% had ≥1 cardiovascular (CV) risk factors (in addition to migraine). The proportion of subjects who were headache pain-free at 2 hours post first dose was significantly greater with lasmiditan 200 mg (32.2%) and 100 mg (28.2%) than placebo (15.3%; both P<.001). Significantly more subjects were MBS free at 2 hours post first dose with lasmiditan 200 mg (40.7%) or 100 mg (40.9%) than with placebo (29.5%; both P<.001). At 2 hours, 59% of subjects in both lasmiditan groups experienced headache relief (mild or no pain) compared to 42.2% in placebo (P<.001). In the lasmiditan 200 mg, 100 mg, or placebo groups, 29%, 36%, and 58% took a second dose for rescue, respectively. More subjects experienced a treatment-emergent adverse event (TEAE) after the first dose in the lasmi-ditan 200 mg (260/609; 42.7%) and 100 mg (229/630; 36.3%) groups compared with the placebo group (101/617; 16.4%); the majority of TEAEs were of mild or moderate severity. There were no discontinuations due to an AE, study drug-related serious AEs, or deaths. Most frequently reported TEAEs with lasmiditan (≥2% and greater than placebo) after the first dose were: dizziness, fatigue, lethargy, nausea, paresthesia, and somnolence. There was no notable increase in the number of CV TEAEs in either lasmiditan group after the first or second dose even specifically among subjects with ≥1 CV risk factors (eg family history of coronary artery disease or hypertension).

Conclusions
Treatment with lasmiditan provided more patients freedom from and reduction of headache pain and patient-centric MBS at 2 hours compared with placebo. This patient population, reflective of severe disability associated with migraine, tolerated first and second doses of lasmiditan treatment.

23 A literature review of the quality of life burden of opioid-induced constipation
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Purpose
Opioid-induced constipation (OIC) is a side effect of opioid medication; it has been suggested that it may be more distressing than the pain of the condition itself. The objective of this literature review was to describe studies reporting the quality of life (QoL) burden of OIC.

Methods
A literature review was undertaken to identify studies on the QOL burden of OIC. Six electronic databases (MEDLINE, EMBASE, CDSR, DARE, CENTRAL, HTA) were searched to identify published manuscripts that reported the QoL burden of OIC. In addition, recent abstract books from key pain and health outcome meetings were interrogated to identify relevant research presented at congresses.

Results
Results were assessed for relevance by two reviewers and data extracted. Results: 413 de-duplicated abstracts were identified and a full text review resulted in the selection of
Oxycodone ARIR relative to IR oxycodone tablets using common household tools.

Methods

The ability to physically manipulate Oxycodone ARIR 30 mg tablets and immediate-release oxycodone 30 mg (IR oxycodone) was assessed by using 7 common household tools. The tools selected for the studies were chosen to be representative of the different methods an abuser could attempt to achieve particle size reduction, including crushing, cutting, gratting, and grinding. Manipulation assessments were repeated 5 times for each instrument with a maximum manipulation time of 5 minutes. Difficulty of manipulation was recorded using a 10-point rating scale where 1 = "very easy" and 10 = "impossible" to manipulate, and an average difficulty score was calculated. Physical manipulation of Oxycodone ARIR with each instrument was also performed after pretreatment with extreme temperatures. Particle size distribution of manipulated Oxycodone ARIR tablets was assessed with a mechanical tray sieve using a descending order of screen mesh filter sizes (2000 µm to 425 µm to 150 µm to 53 µm) to determine which method produces the smallest, homogenous particle size distribution to use in downstream in vitro and in vivo studies.

Results

IR oxycodone control tablets were easily manipulated with a common household tool requiring minimal effort and with 100% of the particles smaller than 2000 µm (a size that is easily insufflated); no further tools were evaluated. In contrast, Oxycodone ARIR tablets could not be easily manipulated with all but 1 of the household tools tested. For the 6 tools that did not easily manipulate the Oxycodone ARIR tablets, the median difficulty ranged from 6 to 10, the median time ranged from 60 seconds to 5 minutes, and the mean % particles < 2000 µm ranged from 0% to 79%. Only 1 tool was successful in manipulating Oxycodone ARIR tablets (median difficulty = 1) after a median of 31 seconds, with a mean of 92% of the particles < 2000 µm (the majority of particles were between 425 µm and 2000 µm in size). Pretreatment of Oxycodone ARIR tablets in extreme temperature conditions did not result in a smaller particle size distribution, and in some cases pretreatment made particle size reduction less effective.

Conclusions

Oxycodone ARIR tablets are resistant to physical manipulation. Only one tool reduced Oxycodone ARIR to small homogeneous particles sufficient for insufflation. The abuse-deterrent properties of Oxycodone ARIR provide marked impediments to manipulation by common household tools and may deter abuse by routes of administration that first require manipulating the tablet into a powder. Additional studies have shown that physical manipulation of Oxycodone ARIR results in slower and lower intranasal absorption and reduced drug liking compared with IR oxycodone.
25 Morphine ARER, a Novel Extended Release Abuse-deterrent Formulation, Resists the Release of Morphine by Vaporization for Abuse by Smoking

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Purpose

Diversion and abuse of prescription opioids remains a serious public health concern. In 2015, 12.5 million individuals aged 12 or older reported nonmedical use of prescription pain relievers; of these, 54% reported obtaining the pain medications from a friend or relative (2015 National Survey on Drug Use and Health. 2016; Substance Abuse and Mental Health Services Administration, Rockville, MD). Abusers often seek out extended-release (ER) opioids to gain access to a higher opioid content than what is found in immediate-release formulations. Physical manipulation increases the bioavailability of non-abuse-deterrent formulations of ER opioids for abuse by oral, intravenous, or intranasal routes of administration.

The United States Food and Drug Administration has urged the development of abuse-deterrent ER opioid formulations that hinder an abuser’s ability to circumvent ER characteristics by manipulation. A 2012 sentinel survey of abusers being assessed by substance abuse treatment centers showed that after introduction of an oxycodone ER abuse-deterrent formulation there was a 1.5-fold increase in abuse of morphine ER by vaporization or smoking (Butler et al. J Pain. 2013;14:351).

Morphine ARER (MorphaBond ER, Daiichi Sankyo, Inc., Basking Ridge, NJ) is an abuse-deterrent, ER morphine formulation. In vitro studies demonstrate that morphine ARER resists physical manipulation and chemical extraction, forms a viscous nonsyringeable material in liquid environments, and retains its ER characteristics despite manipulation. We investigated the ability to vaporize intact and manipulated morphine ARER when heated for abuse by smoking, which is commonly performed in homemade foil pipes by a method known as “chasing the dragon.”

Methods

A laboratory apparatus, assembled to mimic smoking, consisted of a hot plate, aluminum foil weigh boats, and an inverted glass funnel to collect vaporized material. The funnel was connected to a collector device consisting of a series of 3 cold traps that contained an organic solvent. A vacuum pump set to mimic the force generated by a human smoker drew vaporized material captured by the funnel through the collecting device. To make smoking more efficient, abusers will often convert morphine to its base form, which is more easily vaporized than morphine sulfate. However, some abusers will still attempt to vaporize morphine sulfate. As such, morphine base and morphine sulfate were used as positive controls and optimal conditions for vaporization were determined by subjecting the purified controls to vaporization over a range of times and temperatures. Vaporization of intact morphine ARER (n=3) and manipulated (crushed with a common household tool) morphine ARER (n=3) were then tested under the predetermined optimal conditions. Morphine levels were quantified by a validated liquid chromatography-tandem quadrupole mass spectrometry (LC/MS/MS) assay.

Results

As expected, purified morphine base was the most successfully vaporized with an average of 18% of morphine collected from the vapor. Under the same morphine base-optimized conditions, < 1% of morphine was vaporized from manipulated morphine ARER and none was retained on the smoking device, suggesting that 99% of the crushed tablet was degraded during the heating process. Less than 0.5% of morphine from intact morphine ARER tablets was detected from vaporized material. Under conditions optimal for vaporizing morphine salt, < 2% of morphine was collected from the vapor of purified morphine sulfate. Similarly, < 3% and < 2% of morphine was collected from the vapor from manipulated or intact morphine ARER tablets, respectively. Under morphine sulfate-optimized conditions, approximately 10% of morphine in intact morphine ARER tablets remained on the smoking device and no residual morphine was detected on the smoking device for crushed morphine ARER tablets or the positive control. During all the replicates involving morphine ARER, the technicians reported a pungent burning plastic odor when intact or manipulated morphine ARER was heated. Residual material remaining in the smoking device after each experiment was highly charred, supporting the hypothesis that most of the morphine was degraded during the heating process.

Conclusions

These data suggest that it is unlikely an abuser could successfully use smoking as a means of abusing morphine from morphine ARER tablets. Further, the pungent odor produced when morphine ARER tablets are subjected to high temperatures may itself deter an abuser from inhaling any smoke generated during an attempt to administer the drug by the smoking route.

26 Abuse-Deterrent Formulations of Opioids: Effectiveness and Economic Impact

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Purpose

A variety of measures have been taken to combat the opioid crisis, one of which is the introduction of abuse-deterrent formulations (ADFs) of opioid medications. ADFs and their non-ADF counterparts are considered bioequivalent, producing the same analgesic benefits, and have the same profile of adverse effects when used as prescribed. ADF opioids are specially formulated to be more difficult to manipulate in order to deter chewing, intranasal, and intravenous routes of abuse. However, swallowing pills whole is the most common form of abuse and is not deterred by ADFs. Moreover, the abuse-deterrent technology does not change the addictive properties of the opioid itself, and ADFs are generally more
expensive than both their non-ADF branded equivalents and generic versions.

Currently, there are ten opioid products (nine extended-release [ER] and one immediate-release [IR]) that have U.S. FDA-approved abuse-deterrent labeling. Our objective was to evaluate the effectiveness, safety, and economic impact of these ADFs relative to non-ADF opioids.

Methods

Three investigators conducted a systematic literature review of the clinical abuse potential and real-world evidence on the 10 FDA-approved ADFs: OxyContin (oxycodone ER), Xtampza (oxycodone ER), Troxyca ER (oxycodone + naltrexone ER), Targiniq ER (oxycodone + naloxone ER), RoxyBond IR (oxycodone IR), Hysingla ER (hydrocodone ER), Vantrela ER (hydrocodone ER), Embeda (morphine + naltrexone ER), Morphabond (morphine ER), and Arymo ER (morphine ER). Studies on opioids with abuse-deterrent properties but without an FDA label recognizing these properties were not included in our assessment. We sought evidence of the effects of ADFs on pre-market abuse potential endpoints (e.g., VAS measures of drug liking, willingness to take drug again), as well as real-world outcomes (e.g., abuse and misuse, overdose and fatalities).

We also developed an economic model to predict the cost-benefit of ADF opioids in a hypothetical cohort of 100,000 adults with chronic non-cancer pain. Model outcomes included the number of cases of abuse and total cost from a health-care system perspective over five years, as well as a threshold analysis of the costs of ADF opioids that would achieve cost-neutrality relative to non-ADF opioids.

Results

We identified 15 studies that measured either oral or intranasal abuse potential by asking recreational drug users to rate the drug on its likability, as well as how likely they were to take the drug again. Relative to non-ADF comparators, both crushed and intact forms of each ADF produced statistically-significantly lower scores for drug liking and likelihood to take the drug again. However, there is no established threshold for what constitutes a clinically-important difference in any “abuse potential” endpoint, and there is considerable uncertainty around whether these endpoints are predictive of real-world abuse.

Data on abuse statistics following regulatory approval of an ADF is an FDA requirement; however, real-world evidence is currently available only for OxyContin, and all evidence was limited to time series analyses that examined the period before and after the introduction of reformulated OxyContin in 2010. Data suggest a decline in abuse of OxyContin after 2010, with the non-orally route of abuse declining at a significantly greater rate compared to the oral route of abuse. Limited evidence indicates that rates of overdose and overdose deaths attributed to OxyContin also declined after the ADF was introduced, with decreases ranging between 34% and 65%. However, several studies have shown an increase in abuse and rates of overdose deaths attributed to other prescription opioids (e.g., ER oxymorphone) or illicit opioids such as heroin since 2010, suggesting that consumers may have switched to abusing other products.

Our cost-benefit analysis found that, compared to non-ADF opioids, ADFs prevented approximately 2,300 new cases of abuse and cost the health system an additional $533 million per 100,000 patients over five years. To be cost neutral, the average ADF price would need to be reduced 41% from the current market share-weighted average price.

Conclusions

ADFs have the potential to reduce the incidence of abuse in patients. However, there have been no prospective studies of patients who are newly-prescribed opioids measuring incidence of abuse of ADFs versus non-ADFs. Current evidence shows a decrease in OxyContin-specific abuse following reformulation, with a contemporaneous increase in the abuse of other products. Thus, while ADFs could potentially reduce the incidence of new abuse cases, it remains uncertain whether their net health benefit warrants the higher costs they present to the health system.

27 A Rapid Screening Tool for Adhesive Arachnoiditis

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Purpose

Adhesive arachnoiditis (AA) is rapidly increasing in incidence and prevalence. Common, chronic spinal disorders such as herniated discs, stenosis, arthritis, scoliosis, and osteoporosis may all lead to cauda equina nerve root neuroinflammation which may later form adhesions to the arachnoid lining of the spinal canal (i.e. thecal sac). Necessary, but risky, spinal interventions and surgery may accelerate the development of AA. Early diagnosis of AA is essential as it may produce severe constant pain and progressive neurologic impairments. The purpose of this study was to develop a rapid screening tool to identify back pain patients who may have AA.

Methods

A 5 question screen for AA was devised from interviews with known AA patients. It was tested by giving it to 30 adult patients who have AA documented by magnetic resonance imaging (MRI). The 5 questions are: Do you have constant back pain?; Do you have difficulty starting or stopping urination?; Do you have burning on the bottom of your feet?; Do you have blurred vision or ringing in the ears?; and Do you have to stand after you have sat for 10 minutes?

Results

All 30 AA patients answered yes to 4 or 5 of the questions. Although the screening questions may appear unrelated, AA may entrap neural connections to the bladder, gastrointestinal tract, sex organs, and lower extremities. Also it impairs spinal...
fluid flow which produces blurred vision, tinnitus, headache, and poor balance. Neurologic impairments include the inability to sit or stand long in one position and cause neuropathic symptoms such as burning feet in the lower extremities.

Conclusions

Treatment protocols and regimens have now been developed, so the diagnosis of AA should be made as soon as possible. Severe, back pain patients, particularly those with neurologic symptoms seemingly unrelated to the lower spine, should be screened for AA so treatment can be initiated in an effort to restrain progression of this neuroinflammatory disease.

28 Tolerability and Acceptance of Microglial Suppressing Agents

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Purpose

Neuroinflammation and centralization of pain is now known to occur due to microglial activation. Animal and in-vitro studies have identified a few agents which suppress microglial activity. To date, there are no reports whether these agents will be tolerated and accepted by chronic pain patients who are in pain treatment and may benefit by adding one or more of these agents to a standard pain treatment regimen.

Methods

These three agents have been found to suppress microglial activity: (1) acetazolamide; (2) metformin; and (3) pentoxifylline. Intractable, chronic pain patients in on-going standard symptomatic pain management with a variety of daily neuropathic agents and opioids were given 1 or more of these agents. All patients were considered stable and had been in pain treatment at least six months. These agents were given to this number of patients: (1) acetazolamide (11); (2) metformin (22); and (3) pentoxifylline (19). Starting dosages of each drug were very low as listed here: (1) acetazolamide 75 mg every other day; (2) metformin 500 mg extended release at bedtime; and (3) pentoxifylline 400 mg every other day.

Results

At the low starting dosages given, all patients accepted them and did not experience side-effects. All wished to continue as they believed they were benefitting from the agent. Eleven (11) patients who started with one of the three agents had the other two added within 90 days of initiation of the first agent. All 11 tolerated, accepted, and desired to continue all 3 agents.

Conclusions

Suppression of microglial cell activity to reduce neuroinflammation and enhance pain relief and neuroregeneration is a new concept in pain management. This pilot study suggests that some microglial suppressors are tolerated and perceived to be helpful. The clinical potential to reduce neuroinflammation with microglial suppressing agents and treat one of the underlying causes of chronic pain should be urgently studied.

29 Undiagnosed Ehlers-Danlos Syndrome in Severe, Chronic Pain Patients

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Purpose

Some patients present for pain treatment with vague or multi-system pain complaints. The pain may be severe, disabling, and the patient and family may demand high dose opioid therapy as non-opioid and low dose opioid measures have failed to provide comfort and allow daily function. We have found that some patients who present with or without typical signs and symptoms of painful conditions have Ehlers-Danlos Syndrome (EDS) which is a genetic, connective tissue disease that can produce, over-time, a breakdown of soft tissue structures in almost any organ of the body. Severe pain, may, therefore, appear in unusual patterns that can mimic a number of painful conditions.

Methods

One –hundred-thirty-seven (137) chronic pain patients in active treatment were screened for EDS by these 5 questions:

- Can you now (or could you ever) place your hands flat on the floor without bending your knees?; Can you now (or could you ever) bend your thumb to touch your forearm?; As a child did you amuse your friends by contorting your body into strange shapes or could you do the splits?; As a child or teenager did your shoulder or kneecap dislocate on more than one occasion?; and Do you consider yourself double jointed?

If 3 of the 5 were answered yes, patients were further assessed by a Beighton score and confirmed by the diagnostic criteria of the International Consortium of Ehlers-Danlos Syndrome and Related Disorders.

Results

All 137 patients who were screened had been referred for pain treatment with a non-EDS diagnosis and were taking multiple pharmacologic agents including daily opioids. Eleven (11) of the 137 (8.0%) were found to have undiagnosed EDS. The referring pain diagnoses were: head and spine pain (3); fibromyalgia (3); adhesive arachnoiditis (2); abdominal adhesions (1); Lyme disease (1), and rheumatoid arthritis (1).

Conclusions

EDS may develop a variety of very painful, clinical manifestations that may require aggressive pain treatment including daily opioids. Severe chronic pain patients should be screened for EDS as this condition requires a variety of therapeutic measures.
30 A Potent and Novel Alternative to Oral Opioids: Sublingual Oxytocin-Ketamine

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Purpose
There is currently a national public health movement to reduce opioid use and its complications. Urgently needed are non-opioid analgesics. To date, a variety of anti-seizure, antidepressant, anti-inflammatory, and adrenergic blocking agents have proven to provide mild to moderate pain relief but not substitute for opioids in cases of severe pain. In an effort to find a potent opioid substitute, we have tested a combination of sublingual ketamine and oxytocin. When simultaneously administered, this combination has potent analgesic effects and may substitute for opioids in some severe chronic pain patients.

Methods
Ketamine derives most of its analgesic properties by suppressing the N-methyl-D-aspartate (NMDA) receptor. Oxytocin is a CNS hormone that appears, in part, to provide pain relief by blocking synaptic connections between the brain and spinal cord. When concomitantly administered by the sublingual route, we have found that this combination may substitute for potent opioids. Ketamine and oxytocin were administered by the nasal and sublingual routes to several dozen chronic pain patients to determine acceptability, efficacy, and dosage of each agent. After numerous clinical trials we found the following sublingual, liquid dosages to provide pain relief for periods of 4 to 6 hours: a. ketamine-12.5 to 25 mg; b. oxytocin-10 to 20 units. The nasal route was too poorly accepted for routine clinical use.

Results
Two case reports are given here to illustrate the possible potential of this novel combination when simultaneously administered by the sublingual route.

#1 A 69 year old female with adhesive arachnoiditis was bed and couch bound with uncontrolled pain despite intrathecal administration of fentanyl, bupivacaine, and clonidine with oral oxycodone 15 mg given every four hours for breakthrough pain. A combination of ketamine 12.5 mg and oxytocin 10 units administered within 10 minutes of each other by the sublingual route provided far more pain relief than did oral oxycodone which was discontinued.

#2 A 40 year old female with Ehlers-Danlos Syndrome had severe head, neck, and spine pain. She had undergone surgeries for a Chiari malformation and tethered spinal cord. Magnetic Resonance Imaging (MRI) documented the presence of adhesive arachnoiditis and Tarlov cysts. She had attempted multiple, different oral opioids in the past, and her current oral opioid was hydromorphone 2 to 4 mg taken 4 to 6 times a day which failed to provide enough pain relief to achieve comfort and carry out activities of daily living. Combined sublingual dosages of ketamine 12.5 mg and oxytocin 10-20 units given 10 minutes apart provided great pain relief and permitted the cessation of all oral opioids.

Conclusions
Ketamine and oxytocin provide analgesia by physiologic mechanisms other than stimulating opioid receptors. When given simultaneously or close-together by the sublingual route, this combination has potent analgesic effect. The urgent need to find substitutes for oral opioids compels early presentation of this clinical approach. This novel analgesic measure should be studied, and our group is urgently gathering additional clinical data for poster presentation.

31 Multi Variant Genetic Panel in Pain Patients Who Take High Dose Opioids

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Purpose
More than 100 million people suffer from acute or chronic pain every year according to the National Institute of Medicine. A small percentage of these patients require high dose opioids for adequate pain control. Genetic factors are believed to play a key role in opioid prescription addiction as well as need for pain control. Generally, however, genetic variation and defects have not been evaluated in clinical practice. The purpose of this study is to assess the utility of a multi-variant genetic panel to help identify chronic pain patients who require high dose opioids or who may be at risk for abuse and addiction.

Methods
Seventy severe chronic pain patients who had failed standard medical management and required over 100 mg a day of morphine equivalence to control pain were genetically tested. Test samples were taken by buccal swab, and 16 single nucleotid polymorphisms (SNP) involved in the brain reward pathway were analyzed. The panel consisted of these four categories of genetic markers:

(1) Receptor Binding and Activity
   Dopamine (DRD1, DRD2, DRD4)Opioid (OPRK1, OPRM1, MUOR)Serotonin 2A (HTR2A)
   Galanin (GAL)
(2) Neurotransmitter transporters
   Serotonin (5-HTTL PR)Dopamine (DAT 1)ATP-Binding Cassette B1 (ABCB1)
   Gamma Amino Butyric Acid (GABA)
(3) Central Nervous System (CNS) Enzymes
   Catechol-O-Methyltransferase (COMT)Dopamine Beta Hydroxylase (DBH)
   Methylene Tetrahydrofolate Reductase (MTHFR)
(4) Cytochrome P450 Enzymes (2D6, 2C9, 2C19, 3A4, 3A5)
Results

The test results in these patients showed some remarkably consistent findings. Over 97 to 100% of all 70 patients had genetic variations of all three dopamine receptors (DRD1, DRD4, DOR). In contrast only 17 to 30% had variants in the 3 opioid receptors which were tested. No markers except the dopamine receptor markers had over 90% genetic variation. These results suggest that since the dopaminergic pathway was defective, these pain patients relied on potent stimulation of their opioid receptors to obtain adequate pain relief.

Conclusions

The extremely high percentage of these patients who had genetic variations in dopamine receptors is striking, compared to relatively low variation in opioid receptors and the other genetic markers. These results may provide genetic evidence why some pain patients may seek high opioid dosages for pain control or perhaps another neurobiologic reason(s) which could result in addiction. These findings need to be investigated in other groups of pain patients who require high dose opioids to determine if dopaminergic defects are an underlying, genetic cause of high dose opioid requirements in some chronic pain patients.

32 Provider Knowledge and Practices for Prescribing Opioids for Chronic Pain

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Purpose

To evaluate: (1) healthcare providers’ (HCPs) training and awareness of chronic opioid therapy, abuse patterns and universal precautions and (2) practices for the management of patients on chronic opioid therapy.

Methods

Participating HCPs from various practice settings and two different states (New Jersey and Tennessee) were asked to complete a paper assessment survey in an anonymous manner. The survey included questions about providers’ demographics, training, awareness, and management practices associated with chronic opioid therapy. Participation was voluntary and the estimated time to complete the survey was less than 5 minutes. Data and statistical analysis will be conducted by a vendor using Microsoft Access. Descriptive statistics were reported for all parameters.

Results

There were twenty-five surveys returned and all were included in the analysis. Most respondents were nurse practitioners (44%) and physicians (36%) from family or internal medicine (28%) practices. Most (64%) had eleven or more years of experience. While 7 of 25 respondents (28%) said their patients are receiving opioid therapy for an extended period (>3 months), 9 of 25 respondents (36%) said this represented less than 10% of their population. Most providers (68%) indicated they are comfortable treating patients with opioids for greater than three months (mean score 5.8; 1-10 scale). The majority of providers (80%) recognize opioid abuse as a priority in their practice, distinguish between acute and chronic pain (76%), differentiate between nociceptive, neuropathic and mixed pain (56%), measure function (56%) and document pain severity scores (76%). Most of this information is captured in a text or note field (50%), rather than in a discrete field (10%) in electronic medical record systems. Although only 36% screen for prior or current substance abuse, 64% use their state’s prescription drug monitoring program (PDMP) and 88% received training on the PDMP within the past two years. Some providers (44%) avoid prescribing opioids in their practice. Providers were most interested in receiving training on universal precautions (64%) and use of opioids to manage chronic pain (56%) and prefer live programs over other educational activities.

Conclusions

Providers who treat chronic pain are generally comfortable with the use of opioids. They document the measures of pain and use a patient management plan to address the problems that can occur with opioid use. While most providers have received training in various aspects of chronic pain management, they desire more education on the topic.

33 Reducing disability durations and medical costs for patients with a carpal tunnel release surgery through the use of opioid prescribing guidelines

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Purpose

The use of opioid prescribing guidelines is a common recommendation to help prevent unnecessary exposure to opioids. While previous studies have found opioid use increases disability durations and medical costs, no study to date has investigated how following opioid prescribing guidelines affects disability durations and medical costs. The purpose of this study is to analyze how opioid prescriptions modify disability duration and medical costs in short-term disability (STD) disability cases with a carpal tunnel release (CTR) procedure.

Methods

Using a dataset of insured U.S. employees, opioid prescriptions for 7,840 short-term disability cases with a CTR procedure were identified. The American College of Occupational and Environmental Medicine’s (ACOEM) opioid practice guidelines (effective date of April 20, 2017) were used to compare with the observed CTR opioid prescriptions. For post-operative pain
and minor procedures, the guidelines recommend against prescribing: 1) long-acting or extended release opioids, 2) for opioid-naïve patients, greater than a five-day supply of opioids, and 3) for opioid-naïve patients, prescriptions with a MME/day greater than 50mg. An opioid-naïve case was defined as an individual who had not filled an opioid prescription within 90 days prior to the CTR procedure.

To understand the impact of opioid prescribing on disability durations and medical costs, the data was subset to only include claims that were prescribed an opioid, opioid-naïve, and had only opioid prescriptions for the CTR procedure (n = 4,109). The influence of following opioid prescribing guidelines on disability duration and medical costs was tested using Kaplan-Meier estimations and lognormal multiple variable survival models.

Due to the high number of potential covariates in the multiple variable regressions, 100 bootstrap estimations with a backwards variable selection procedure were used to find predictors that were statistically associated (p-value < 0.05) with the outcomes in at least 60% of the bootstrap samples. Significant variables were then fit to the full dataset to produce estimates of the relationship of following guidelines on disability durations and medical costs, while controlling for confounders.

**Results**

Most cases (70%) were prescribed an opioid and 29% were prescribed an opioid contrary to ACOEM’s guidelines. For individuals filling an opioid prescription for the CTR procedure, an average of 1.1 prescriptions was filled with a median supply of five days. The median (interquartile range [IQR]) ME per day and cumulative ME were 45 (32-60) mg/day and 200 (150-300) mg, respectively. Of the opioids prescriptions filled, the most common opioid classes for CTR were hydrocodone/acetaminophen (69.2%), oxycodone/acetaminophen (19.9%), and codeine/acetaminophen (6.4%).

In opioid-naïve cases, 16.9% and 15.2% were prescribed an MME/day greater than 50 mg and supplied greater than five days, respectively. Only 0.3% of cases were prescribed a long-acting/extended release opioid. Improvements in prescribing opioids according to ACOEM’s guidelines can be seen in recent years, with the lowest percent of cases prescribed an opioid contrary to guidelines in 2017, our most recent year of data.

The numbers of days supplied and cumulative ME were significantly associated with longer disability duration (p-values < 0.001). For example, the median disability duration for cases filling prescriptions with more than a six-day supply was 49 days, whereas the median disability duration for cases with a three-day supply or less was 43 days. No association with ME/day and disability durations was observed (p-value = 0.139). The day supply, cumulative ME, and ME/day were all associated with medical costs (p-values < 0.002). In particular, a strong dose-response was observed between cumulative ME and medical costs. Cases prescribed a cumulative dose ≤ 150 mg had median medical costs of $4,417 and cases prescribed a cumulative ME dose of >300 mg had median medical costs of $5,600.

Using multiple variable models, cases prescribed an opioid contrary to guidelines had disability durations 1.9 days longer and medical costs $422 higher than cases prescribed an opioid according to guidelines.

**Conclusions**

Our results highlight the need for improvement in judicious prescribing of opioids for CTR. When opioids are chosen for CTR pain management, opioid prescribing in accordance with the ACOEM guidelines appears superior in returning a patient to health and reducing medical costs.

**34 Pharmacokinetic profiles of three doses of naloxone HCl delivered by auto-injector**

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**Purpose**

Naloxone HCl injection USP is approved for parenteral administration at an initial dose of 0.4 mg to 2 mg in adults for known or suspected opioid overdose, with repeated dose administration at 2 to 3 minute intervals. In 2014, the 0.4 mg EVZIO (naloxone HCl injection) Auto-injector was first marketed, and in 2017, a 2 mg EVZIO Auto-injector was introduced. The objective of this study was to characterize the pharmacokinetic (PK) profiles of 0.4 mg, 0.8 mg and 2 mg naloxone HCl administered using a naloxone auto-injector (NAI).

**Methods**

This was a randomized, open-label, single-dose, crossover study in 24 fasted, healthy male and female subjects. All injections were intramuscular/subcutaneous in the anterolateral aspect of the thigh. The 0.8 mg naloxone HCl dose was administered using two 0.4 mg NAIs given 2 minutes apart, with the first injection defined as time 0. The washout period between doses was approximately 24 hours. Blood samples were obtained from each subject for the determination of plasma naloxone concentrations. Pharmacokinetic parameters for naloxone were estimated using non-compartmental analysis.

**Results**

The median Tmax for naloxone for all 3 treatment groups was similar (0.21 hour to 0.25 hour). Peak plasma concentrations of naloxone were greatest after administration of a single 2 mg NAI injection, with a geometric mean (GM) Cmax (gCV%) of 7113 pg/mL (50.7%), compared to 1942 pg/mL (49.3%) or 1146 pg/mL (57.2%) for two 0.4 mg NAI injections (0.8 mg naloxone HCl) or a single 0.4 mg NAI injection, respectively. Plasma concentrations declined over the 6-hour sampling period with a similar 1/2 across all treatment groups. There were no clinically significant safety laboratory values, vital signs or ECG values. The majority of adverse events were mild and only injection site erythema occurred in more than 1 subject.
Conclusions
These results indicate that naloxone HCl administered by auto-injector provides dose proportional naloxone exposure over the range of 0.4 mg to 2 mg.

Methods
Invitations to online surveys were distributed during May-June 2017, to a random sample of rheumatologists, orthopedic surgeons, neurologists, primary care physicians, and anesthesiologists. Inclusion criteria required that the respondents were in the target audience, US-practicing, and actively managing at least 15 patients with chronic pain per week. Respondents meeting the criteria who completed the study were provided professionally-appropriate honoraria.

In the first phase of each session, physicians responded to a series of open-ended questions generating lists of barriers they and their colleagues face in the management of chronic pain, which were then compiled and organized. In the second phase of each session, conducted a few days later, the same group of physicians were asked to identify the three most significant barriers in their practice and rank them as most, second-most, and third-most significant. The physicians were also asked to and rank the three barriers that could best be addressed by CME, independently of significance to practice.

Barriers for each question were categorized into themes. An overall score was calculated for each theme based on the priority rank assigned to each of the barriers in that theme. Then, a weighted score was calculated for each theme by dividing the summed prioritization scores of the barriers assigned to that theme by the total number of individual barriers in the theme. Comparison of weighted scores across the themes allowed for the identification of the most significant barriers to physician practice and the barriers best addressed by CME.

Purpose
Chronic pain is a major public health problem in the United States that has been estimated to affect up to a third of Americans. As physicians are becoming more aware of the impact of pain on their patients’ quality of life, continued evidence is emerging about the risks associated with current standards of care, including opioids. Physicians must be kept up-to-date on the latest findings and standards in chronic pain management in order for them to provide optimal care to their patients while minimizing potential risks. Further, new modalities of pain treatment are being developed with lower abuse profiles, but these emerging therapies may allow patient self-injection, which will necessitate physicians use different patient education strategies. Well-designed continuing medical education (CME) programs offer a valuable tool for addressing the educational needs of physicians managing patients with chronic pain. In order to better understand the barriers and challenges faced by these physicians, and to inform development of upcoming CME programs, two asynchronous focus group (AFG) sessions were conducted using an asynchronous modified Delphi technique via online surveys, with one session focusing on chronic pain associated with osteoarthritis (CPOA), and the other on chronic low back pain (CLBP).

Results
The CPOA session generated a list of 31 unique barriers. These 31 barriers were then categorized into themes based on content, with 9 distinct themes being defined. Barriers perceived by physicians as most significant overall and important to be addressed by CME were a lack of effective treatment options for patients with CPOA, and a lack of pain management guidelines. When asked about barriers to patient self-injection, respondents generated 16 unique barriers in 6 distinct themes. The most important issues were cost/insurance and a lack of clinical data. Physician respondents perceived that patient-related barriers, including fear of injections, nonadherence, and inability to conduct self-injections should be reserved for patient-directed education and may not be appropriate for physician CME programs.

The CLBP session identified 29 total barriers, which were categorized into 9 themes, similar, but not identical to, the themes identified by the CPOA panel. Barriers that were viewed as most significant and important for CME to address were a lack of effective treatment options for patients with CLBP and risk of addiction. When asked about barriers to patient self-injection, respondents generated 24 unique barriers in 6 distinct themes. This session found the most important barriers to patient self-injection for CLBP are cost/insurance and potential for abuse, which are also important for physician education to address. Unlike in CPOA, this session did not believe that patient education should be used for nonadherence and fear of injections, possibly anticipating that education may have very little effect on these barriers.

Conclusions
These findings should be used to help understand the struggles of physicians managing patients with chronic pain. Education showing the effectiveness of new or current chronic pain treatments, expert consensus on how to use pain treatment, and a continued emphasis on risk management would be appreciated and well attended. Education promoting the value of treatments requiring self-injection is necessary before the development of initiatives to teach these self-injection
skills to patients. Continued barrier studies may be needed in the upcoming years due to emerging treatments as well as policy and institutional changes in chronic pain management.

36 Pain specialist management of patients with chronic pain: a survey of current practice patterns and attitudes of US clinicians

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Purpose

Chronic pain has been estimated to affect up to one-third of Americans and is a major public health problem in the United States. Generally, use of opioid analgesics for patients with chronic pain has declined in the primary care setting, even when patients are at low risk for abuse and there is a high likelihood of benefit. At PAINWeek 2014 and 2015, we reported data from a national survey on primary care physician practice patterns and attitudes regarding chronic pain management to identify the factors involved in prescribing opioid analgesics. Here, we present a continuation of that study, showing practice patterns and perceptions of pain specialists. The results of this study show where educational gaps exist and the current needs of the pain management community.

Methods

After a thorough literature review and a series of focus group sessions conducted to ascertain the perceptions of physicians regarding barriers to management of chronic pain, an online survey was designed and nationally distributed in June 2017 to US-practicing clinicians who were actively managing patients with chronic pain. This group was composed of orthopedic surgeons, rheumatologists, and other clinicians providing pain management, including anesthesiologists, neurologists, primary care providers, nurse practitioners, and physician assistants. Inclusion criteria required that the respondents were in the target audience, US-practicing, and actively managing at least 10 patients with chronic pain per week. Respondents meeting the criteria who completed the study were provided professionally-appropriate honoraria. Data collected from 402 clinicians were compiled for descriptive and inferential analysis, including comparisons by specialty, years in practice, and geographic region. Respondents were presented with short case vignettes of different patients, particularly focused on chronic pain associated with osteoarthritis and chronic low back pain. These patient scenarios were designed to assess how clinicians prefer to manage, and case continuations were set up to progress the patient in pain severity.

Results

The first patient, a 52-year-old with right hip pain associated with osteoarthritis presented with moderate-to-severe pain with 4 months of progression. Most clinicians initiated an NSAID (prescription or OTC), corticosteroid injection, or nonpharmaceutical management at this point, and shifted to a surgical referral as the patient progressed. For a 50-year-old patient with chronic low back pain that has had no relief from NSAIDs, muscle relaxants, or physical therapy, clinicians had no consensus on best treatment, as choices were distributed between a variety of OTC NSAIDs, prescription NSAIDs, and short-acting opioid therapies. For a 75-year-old patient with long-standing hip osteoarthritis well-controlled with oxycodone for the past 6 months, few clinicians would continue opioid-based therapies, instead switching to another treatment. Many clinicians, particularly orthopedic surgeons and rheumatologists, use standardized screening tools for opioid risk assessment. Of all clinicians included in the study, orthopedic surgeons and rheumatologists are least confident in their ability to assess patient risk and to assess a patient's level of pain.

Conclusions

Appropriate use of all available therapies are a critical component of chronic pain management. Lack of treatment consensus in the case vignettes reveals that there may be little guideline-based direction for pain management. Treatment selection may be based on institutional protocols, prior experience, and, perhaps, fear of legal issues. With emerging treatments requiring injections of biologic treatments, rheumatologists may become more responsible for management of chronic pain. These clinicians may need increased education on current treatment options and assessment in order to improve patient management. Continued studies are needed to understand practice change and allow refinement of educational messages.

37 Efficacy, Adherence, and the Barriers to Care: A Survey of our Patients’ Experience with the New York State Medical Marijuana Program

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Purpose

Although marijuana remains a Schedule I drug at the federal level, a growing body of evidence suggests that it has potential as a medical agent. A 2017 report by US National Academies of Science, Engineering, and Medicine, which analyzed more than 10,000 studies, found “strong evidence” that marijuana is useful in treating chronic pain and the complications of cancer and multiple sclerosis and “moderate evidence” that it can alleviate sleep problems associated with disease. Increasingly, state governments have recognized the medical potential of marijuana and authorized its use for select groups of patients. With the signing of the Compassionate Care Act on July 7th, 2014, New York became the 23rd state to make such exceptions for the
medical use of marijuana. The first patients began obtaining treatment 18 months later. New York’s Medical Marijuana Program has since grown rapidly. As of July 17, 2017, the Medical Marijuana Data Management System (MMDMS) has registered 1,123 practitioners and 24,555 patients.

Despite the growth of the program, patients continue to face significant barriers to access, particularly if they are of lower socioeconomic status. Health insurance does not cover marijuana prescriptions, which means patients must pay entirely out-of-pocket. Moreover, stringent regulations limit the number of dispensaries and make accessibility a challenge. For example, the Borough of Brooklyn (the location of our clinic) has 2.6 million residents but not a single marijuana dispensary. Barriers to access remain significantly greater for medical marijuana than for opioids.

Although there has been extensive research on the discrete health benefits and risks of marijuana, there is a dearth of studies looking at the overall experience of patients in states that have legalized medical marijuana. The aim of this study is to examine the efficacy of medical marijuana among patients in New York State’s program and the way barriers to access have impacted adherence. We believe that our neurology clinic in Brooklyn, which serves a culturally and economically diverse group of patients, represents a useful microcosm for the benefits and challenges of medical marijuana in New York State and around the country.

Methods
Our clinic was approved to prescribe medical marijuana beginning on January 1, 2016. As of July 2017, we have enrolled 72 patients in the program. After reaching out to all enrolled patients, 49 responded to our calls and agreed to an interview. The subjects had all taken medical marijuana for between three months and a year. We found that 38 of 49 (78%) were still adherent to their treatment regimen. The sample was 59.2% male. The average age was 50. The most common primary diagnosis was neuropathy (89.8%). In our interviews, we aimed to assess the efficacy and tolerability of the treatments and their effect on our patients’ quality of life. We also sought to investigate the reason for patient non-adherence. To our knowledge, this is the first study of its kind.

Results
Our survey of patients found remarkable efficacy, tolerability and satisfaction. One hundred percent of patients reported an improvement in symptoms. Among the neuropathy patients, the average pain rating went from 8.1 to 4.5, an approximately 56% decrease. Fifty seven percent reported a significant improvement in mood. One third reported significant improvements in sleep quality. Twelve percent said they had improvements in appetite. Patients also reported a diverse range of improvements in symptoms and outlook. Remarkably, there were no significant side effects reported. All participants were satisfied and expressed the desire to continue treatment.

Despite general satisfaction, eleven patients (22%) were non-adherent. We asked these patients about the reasons for their non-adherence, and all eleven stated that they stopped taking their medication primarily because of cost. Many also cited the difficulty of traveling to fill their prescription as an additional factor. These problems were reported in the sample generally. The average cost was $215.5 dollars for a month’s supply of marijuana. Nearly a quarter of patients said that travelling to the dispensary to fill their prescription was “Hard” or “Not Easy.” Many had to travel more than hour each way to access a dispensary, a difficult prospect for those who are seriously ill. These findings suggest that the precarious legal status of medical marijuana - with its impact on cost and availability - may be seriously hindering the ability of patients who will benefit from these treatments to access them.

Conclusions
This study substantiates a growing body of literature that suggests marijuana can have significant benefits in relieving pain and improving sleep, appetite, and quality of life. However, it also underscores the challenges of accessing medical marijuana under today’s limited, state-based system. Without insurance coverage and a better system for distribution, the high out-of-pocket costs and logistical inconvenience associated with medical marijuana will continue to limit access, disproportionately affecting low-income patients. We recommend the creation the creation of larger, multi-center trial to examine the benefits experienced by patients taking medical marijuana as well as the way cost and accessibility impact adherence.

38 Measuring withdrawal in a phase 3 study of a new analgesic, NKTR-181, in subjects with moderate to severe chronic low-back pain
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Purpose
Conventional opioid therapeutics can produce withdrawal symptoms after cessation of chronic administration, which can lead to drug craving and opioid misuse. NKTR-181 is a new chemical entity, orally administered full mu-opioid receptor (MOR) agonist designed to have an intrinsically slow rate of entry into the central nervous system (CNS) compared with conventional opioids. In a Human Abuse Potential study of recreational opioid users, drug-high and drug-liking scores for NKTR-181 administered across the therapeutic dose range of 100 to 400 mg were significantly lower than those for oxycodone and closely resembled the scores for placebo. In
an enriched-enrollment, randomized-withdrawal study of opioid-naïve subjects with chronic low-back pain (SUMMIT-07), NKTR-181 administered at 100 to 400 mg twice daily was associated with a significantly greater analgesic effect compared with placebo. In this trial, opioid withdrawal was evaluated using the Clinical Opiate Withdrawal Scale, an 11 item scale designed to be administered by a clinician to rate signs and symptoms of opioid withdrawal (COWS; Maximum score of 48; Mild, 5-12; Moderate, 13-24; Moderately Severe, 25-36; and Severe Withdrawal, >36) and the Subjective Opiate Withdrawal Scale, a scale consisting of 16 symptoms indicative of opioid withdrawal and rated by the subject (SOWS; Maximum, 64). Here we present results for these withdrawal measures in the SUMMIT-07 study.

Methods

All study participants were opioid-naïve adults with moderate to severe chronic, non-neuropathic low-back pain of ≥6-month duration for which nonopioid analgesia therapies had been inadequate. This enriched-enrollment, double-blind, randomized-withdrawal study included a screening period, an open-label titration period, a 12-week double-blind treatment period, a 1-week study-drug taper, and a 2-week safety follow-up period. Subjects with COWS scores indicating moderate withdrawal (total score >12) at the start of the study were excluded prior to open-label titration. During open-label titration, subjects were titrated to an effective and stable analgesic dose of NKTR-181 (maximum 400 mg twice daily). Subjects who achieved adequate efficacy during open-label titration were then randomized to 12 weeks of double-blind treatment with NKTR-181 or placebo. After 12 weeks of randomized treatment, subjects began a 1-week taper of NKTR-181 or placebo.

COWS and SOWS scores were obtained following any early discontinuation and at pre-specified time points during each phase of the study. During randomized treatment, COWS scores were obtained at days 1, 8, 15, and 85. COWS scores were also obtained at end of study-drug tapering; and twice during the safety follow-up period. During randomized treatment, SOWS scores were obtained on day 1, twice daily for the next 3 days, and then daily through day 15. SOWS scores also were obtained twice daily for the first 3 days of study-drug tapering and daily during the safety follow-up period. COWS and SOWS findings are summarized descriptively.

Results

A total of 1,189 subjects were exposed to NKTR-181 during open-label titration, and 610 subjects were randomized during double-blind treatment (309 to NKTR-181 and 301 to placebo).

There were no COWS scores greater than mild after randomization at any point in the study and the ensuing follow-up period. For subjects who successfully completed randomized treatment, COWS and SOWS data were obtained during the 1-week taper and 2-week safety follow-up period. At the end of the tapering period (ie, one week following the end of randomized treatment) COWS scores indicating mild withdrawal were observed in 1 (0.5%) subject in the placebo group and 5 (2.3%) subjects in the NKTR-181 group. COWS scores obtained at the end of the two week safety follow-up period only for subjects who did not enter the long term safety study. During this period, all subjects reported COWS scores less than mild. Mean SOWS scores remained <2.7 in both groups with no meaningful increase at any time point.

Subjects were randomized to continued treatment with NKTR-181 or placebo during the double-blind treatment period. COWS scores indicating mild withdrawal were observed in 7 (2.4%) subjects in the placebo group and 3 (1.0%) subjects in the NKTR-181 group on day 8; and 1 (0.4%) and 4 (1.4%) subjects on day 15 in the placebo and NKTR-181 groups, respectively. During the first week of randomized treatment, mean SOWS scores in placebo increased slightly to a maximum value of 2.7. Mean SOWS scores in subjects randomized to NKTR-181 remained ≤1.8.

Conclusions

In this study, NKTR-181 administered at 100 to 400 mg twice daily in subjects with chronic low-back pain exhibited a low rate of opioid withdrawal, as rated by clinicians and subjects themselves. We observed no major difference in withdrawal symptoms between NKTR-181 and placebo following abrupt NKTR-181 discontinuation or during 1-week study-drug taper. During randomized treatment, clinical symptoms of withdrawal were rare, with no moderate or severe cases reported, even after abrupt NKTR-181 discontinuation in subjects randomized to placebo. Opioids that are associated with minimal withdrawal symptoms when discontinued may be of clinical utility in treating patients with chronic pain.

39 Pain, Opioid therapy, Fibromyalgia and PTSD (Post Traumatic Stress Disorder) – A Singular Disease Entity - A Fundamental Concept in Disease Treatment

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Purpose

There were 22 suicides/day relating to PTSD for military personnel in 2016, that is >8,000 suicides/year. Benefits from current therapies for PTSD have fallen dismally short of expectations. At PAINWeek 2015 I presented a treatment method for “recalcitrant fibromyalgia” (Fibro) and PTSD (Fibro/PTSD). Only as Fibro was gradually improved, the PTSD, which was previously unresponsive, now demonstrated definite improvement with standard psychiatric therapy. This method required two opioid substances to be successful, tramadol and tapentadol. In 2015 there were >52,404 opioid related deaths, in 2016 >59,000. Attempts to legislate/regulate opioid pain therapy have failed dismally. Using opioids for limiting opioid pain therapy sounds counterintuitive – it is not. At the suggestion of Jonathan Patience, previous editor of Postgraduate Medicine, I recently completed a manuscript on my treatment method. In the past I published abstracts that led me to look upon fibromyalgia associated with other
musculoskeletal pain conditions as being a singular entity and not as disparate conditions. The importance of this concept, as seen with Fibro/PTSD is that it demonstrates that fibromyalgia may be repeatedly and variably present. If ignored and left undiagnosed/untreated, it can in itself result in pain amplification, impaired memory and concentration, inability to accomplish goals, difficulty sustaining personal relationships, depression and anxiety. Consequently the underlying primary condition becomes more difficult if not impossible to treat. This has a pronounced application to limiting opioid craving for painful musculoskeletal conditions and improving depression/anxiety as published in my previous abstracts.

Methods

Given today’s narcotic problems, you may wish to discuss your intensions with your state’s Controlled Substance Bureau. Have a discussion with your patient concerning risks/benefits. Sign a contract outlining obligations/liabilities – “no violations tolerated”. A “secure opioid monitoring system” must be in place.

To establish the diagnosis of fibromyalgia I used the 1990 ACR Fibromyalgia Diagnostic Criteria. PTSD was diagnosed by the patient’s psychiatrist. My Fibro/PTSD treatment method is described in my previous abstract, in detail in my manuscript. Begin with a nighttime combination of tramadol 50mg @ 7PM up to 100mg TID and tizanidine capsules 4-8mg @ 7PM. Consider the addition of pregabalin, duloxetine or milnacipran – maintain only if there is benefit. The tender point exam is repeated at each visit. I have used the FIQR (Fibromyalgia Impact Questionnaire) to corroborate this assessed benefit. The patient needs to achieve at least 6 hours of uninterrupted sleep, feeling rested on awakening. Non PTSD patients typically respond to the aforementioned treatment, PTSD patients do not. For PTSD patients, I add tapentadol 50 mg PO QHS for 2 nights - observe for clinical benefit, if not increase the dose to 100 mg - subsequent dose increases as appropriate if necessary. The patient is assessed for ulterior sources of pain at each visit – bursitis, tendonitis, plantar fasciitis etc. It is necessary to chat at each visit with the patient to ascertain if additional stressors physical/emotional have arisen, offering appropriate treatment or suggestions that facilitate their resolution. Constant collaboration with a psychiatrist is essential.

Results

In > 40 PTSD patients treated over the past 5 years, the majority were female victims of domestic violence. There were only 4 patients who had combat PTSD. The severity of the PTSD can vary with the intensity of the originating source, the duration of exposure, any clinical benefit from previous therapy and the sensitivity of the individual patient. One reason why there were less combat PTSD patients in my practice was that these individuals typically sought care gratis at their local VA hospital. It has been related to me that frequently little or no clinical benefit was achieved and the care was often abandoned by the patient’s themselves. In one severe combat PTSD patient that I treated with my method, experienced excellent clinical benefit but when he felt compelled to return to the VA care system, owing to the cost of the medications he experienced substantial clinical regression.

All of the >40 patients that I am reporting experienced significant clinical benefit with the return of some degree of “normalcy” in their lives. Of greatest importance there was observed an increase in the duration of sleep, less awakenings and substantially less fatigue. Fibrocytic tender point pain was subsequently reduced as was headache, stiffness and fatigue. Concentration and memory gradually improve. When the FIQR was measured it always corroborated the improvement (i.e. values < 25 increasing to values >80). The patients were able to successfully focus on goals and accomplish them. Holding a job, sustaining a personal relationship and achieving higher education credits was observed with varying degrees of success but on a regular basis.

Response to concomitant psychiatric therapy improved as noted by patients and their psychiatrists - lessening anxiety and depression. By using very low doses of tapentadol only rarely did I encountered any problematic use with concomitant CNS antidepressants and no serotonin related clinical issues were observed.

Fibro can be intermittently and variably present with the primary clinical entity and can together be looked upon as a singular pathological entity. If the Fibro was not clinically suppressed, improvement in the PTSD was not observed. This was observed in only 1 patient.

Conclusions

Persisting Fibro can intensify associated fibrocytic symptoms resulting in worsening of the underlying primary condition, even if that primary condition is not pain associated. This is exactly what Fibro/PTSD demonstrates. Amelioration of the underlying condition does not necessarily eliminate the need for opioids but can reduce opioid craving. On occasion your patient may request an increase in his daily dose of opioid. He must be offered a choice to sustain his current dose and all the clinical benefits that he has achieved to date versus seeking care elsewhere and losing those benefits. It has been my experience that the patient always chooses to sustain his current opioid dose. This may offer insights into treating today’s opioid epidemic. This treatment concept, as I have previously published relating to “fibromyalgia” demonstrated clinical efficacy for other associated painful musculoskeletal and neurological conditions in addition to anxiety and depression. I regard the aforementioned concept and treatment method to as fundamental to the successful treatment of multiple disease states.

40 Abuse profile of Nucynta ER compared to extended-release opioids with and without FDA abuse-deterrent labeling

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Purpose

It is evident that abuse of prescription opioid medications is a significant public health problem in the United States. One approach at curbing this problem has been the development of opioid products that deter abuse via specific routes of administration (i.e., “abuse deterrent formulations”, or ADFs). In 2015
the U.S. Food and Drug Administration (FDA) released guidance for the pharmaceutical industry to assist pharmaceutical manufacturers in formulating studies that could demonstrate that an innovative opioid formulation has abuse-deterrent properties. Products proven to have abuse-deterrent properties could result in a packaging label that would describe the product’s lower abuse potential. Nucynta ER is an extended-release tapentadol-based product containing properties intended to deter abuse that does not currently have an FDA label indicating a lower abuse potential. Tapentadol is a centrally acting analgesic that differs from other opioids in that it has two mechanisms of action: μ-opioid receptor agonism and noradrenaline reuptake inhibition. Tapentadol has a lower affinity to the μ-opioid receptor compared to morphine and its noradrenaline reuptake inhibition may not be significantly rewarding compared to other opioids, suggesting an opioid-sparing effect and lower abuse potential for tapentadol products. This analysis aims to examine the abuse profile of Nucynta ER compared to groups of ER opioid products with and without FDA abuse-deterrent labeling.

**Methods**

Data from a five-year period from January 2012 through December 2016 from 281,639 adults assessed for substance abuse problems and treatment planning at centers across the United States were examined. Data were collected using the National Addictions Vigilance Intervention and Prevention Program (NAVIIPRO®). Individuals were assessed using the Addiction Severity Index—Multimedia Version (ASI-MV®), a standard clinical interview that collects self-reported data on past 30-day abuse of alcohol, illegal substances, and prescription medications from adults during treatment admission and planning. Overall and route-specific abuse prevalence estimates (unadjusted and adjusted for prescription volume) were calculated yearly and for the aggregate time period studied for Nucynta ER and three comparators: 1) ER opioids containing abuse-deterrent technology that received FDA abuse-deterrent labeling (ADF ER opioids with labeling), 2) ER opioids containing abuse-deterrent technology without FDA labeling (ADF ER opioids without labeling), and 3) ER opioids without abuse-deterrent technology (non-ADF ER opioids).

**Results**

Within this adult treatment center sample during the aggregate five-year period, ADF ER opioids with labeling were abused most frequently (2.87 cases per 100 assessments), followed closely by non-ADF ER opioids (2.60 per 100 assessments) and more distantly by ADF ER opioids without labeling (0.88 per 100 assessments). In comparison, abuse prevalence of Nucynta ER was lower than abuse of all three opioid product groups (0.02 cases per 100 assessments). When considering both prescriptions dispensed and tablets dispensed, abuse of ADF ER opioids without labeling showed the greatest abuse prevalence, followed by ADF ER opioids with labeling and non-ADF ER opioids. There were notable differences in the ROA profiles of ADF ER opioids with labeling compared to those products without labeling. During the aggregate five-year study period, ADF ER opioids with labeling were most frequently abused via swallowing intact tablets (53.4% of abusers), while routes such as snorting, injection, and other oral routes (i.e. chew, dissolve in mouth, drink in solution) were indicated by lower percentages of abusers of these products (ranging from 25.6% to 28.6%). Conversely, ADF ER opioids without labeling were most frequently abused via injection (57.6%), followed by swallowing intact tablets (25.3%) and snorting (22.8%). Non-ADF ER opioids were also mostly abused via injection (49.4%), followed by snorting (41.4%) and then swallowing intact tablets (27.6%). The ROA abuse profile of Nucynta ER most closely resembled that of ADF ER opioids with FDA labeling in that the majority of abusers swallowed the product whole (62.5%) with all other ROA indicated by less than 15% of Nucynta ER abusers.

**Conclusions**

This analysis of adults entering substance abuse treatment centers across the United States illustrates differences in abuse profiles of ER opioids containing abuse-deterrent technology that have received FDA abuse-deterrent labeling compared to ER opioids without this labeling. Products that have received labeling were less frequently abused via illicit routes of administration, while individuals abusing those products without labeling were more likely to use illicit ROA such as injection. Among this treatment-based sample, the ROA profile of Nucynta ER, a product containing abuse-deterrent technology but without FDA labeling, more closely resembles that of ER opioids with FDA abuse-deterrent labeling.

**41 Efficacy, safety, and tolerability of NKTR-181 in patients with moderate to severe chronic low-back pain: A Phase 3 study**

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**Purpose**

Opioid analgesics are commonly used in the treatment of chronic pain; however, their use is limited by poor tolerability and high prevalence of abuse and drug-related mortality. Although abuse-deterrent formulations have been developed, FDA-approved options include only conventional opioid agonists combined with opioid antagonists or with tamper-
resistant reformulations. In patients with poorly-controlled chronic pain on non-opioid analgesics, there remains a great unmet need for safer opioid medication.

NKTR-181 is a new chemical entity, full mu-opioid receptor (MOR) agonist designed to provide relief from chronic pain with less abuse potential than conventional opioid therapy. NKTR-181 was designed to have a reduced rate of entry into the central nervous system (CNS) compared with standard opioids, thereby reducing a key pharmacokinetic risk factor related to potential for euphoria and abuse. The slowed rate of CNS entry observed with NKTR-181 is inherent to its molecular structure and defies being altered using physical and chemical means into a rapid acting MOR agonist. In a recent study of recreational opioid users, patient reported drug-high and drug-liking scores for NKTR-181 administered as single doses of 100 to 400 mg were lower than those for oxycodone and closely resembled placebo. Additionally, pupillometry data confirmed a delayed onset of CNS effect associated with NKTR-181.

Here we present the results of a phase 3, enriched-enrollment, randomized-withdrawal study called SUMMIT-07, which evaluated the analgesic efficacy, safety, and tolerability of NKTR-181 administered at 100 to 400 mg twice daily to patients with chronic low-back pain, the most common indication for opioid analgesics in the U.S.

**Methods**

SUMMIT-07 compared NKTR-181 and placebo in opioid-naive adult patients with moderate to severe chronic, non-neuropathic, low-back pain of at least 6-month duration, for which non-opioid analgesia had been inadequate. This enriched-enrollment, randomized-withdrawal study included a screening period, an open-label titration period, and a double-blind, placebo-controlled treatment period lasting 12 weeks. Throughout the study, patients scored their daily pain on an 11-point numerical rating scale ranging from 0 (“No pain”) to 10 (“Pain as bad as you can imagine”). For inclusion, a patient’s 7-day average score at the end of screening was required to be 5 to 9 points. Among eligible patients, open-label NKTR-181 initiated at 100 mg twice daily could be increased to a maximum of 400 mg twice daily. Patients achieving a 7-day average pain score of ≤4 points, representing a decrease of ≥2 points, were randomized to double-blind treatment with NKTR-181 at their effective dose or placebo.

The study’s primary efficacy endpoint was mean change in weekly (i.e., 7-day average) pain score from the end of titration (baseline) to the end of randomized treatment in each double-blind treatment group. Key secondary endpoints included the percentages of study completers with week-12 pain scores ≥30% and ≥50% lower than their screening score, and the change in Patient Global Impression of Change (PGIC) scale. Sleep quality was evaluated using the Medical Outcomes Study (MOS) Sleep Scale–Revised. Assessments of study-drug safety and tolerability included the frequency of reported adverse events (AEs).

**Results**

Of 1,189 patients exposed to open-label NKTR-181 during the titration period, 610 were randomized, 309 to NKTR-181 and 301 to placebo. Among randomized patients, the least-squares mean change in weekly pain score after 12 weeks of double-blind treatment was +0.92 points for NKTR-181 vs +1.46 points for placebo, indicating a statistically significant analgesic effect in patients randomized to NKTR-181 (P=0.0019). The differences in average weekly mean pain scores between treatment groups were statistically significant at week 1 and at all subsequent weeks (P<0.0001 at all weeks). At week 12, a reduction ≥30% from a patient’s pre-treatment pain score was reported by 71.2% of the NKTR-181 group vs 57.1% of the placebo group (P=0.0003), and a reduction ≥50% by 51.1% vs 37.9% (P=0.001). On the PGIC scale, a greater proportion of patients randomized to NKTR-181 characterized themselves as “Improved” or “Very much improved” at week 12 (51.5% vs 33.2%; P<0.0001). On the MOS Sleep Scale, scores at week 12 showed a statistically significant improvement in the domains of sleep disturbance, sleep problems, sleep adequacy, and sleep quantity for NKTR-181 compared with placebo. Scores for somnolence and respiratory impairments were not statistically different between groups.

AEs during double-blind treatment were reported by 54.4% of the NKTR-181 group and 49.8% of the placebo group. In the NKTR-181 group, the most frequent AEs were nausea (10.4%, vs 6.0% for placebo), constipation (8.7% vs 3.0%), and vomiting (4.9% vs 1.7%). Somnolence and dizziness, AEs commonly associated with opioid therapy were relatively low (2.6% vs 0.3% and 2.3% vs 0.3%). During the randomized treatment period, AEs led to study discontinuation of 8.4% in the NKTR-181 group vs 3.0% in the placebo group.

**Conclusions**

In patients with moderate to severe chronic low-back pain, NKTR-181 administered at 100 to 400 mg twice daily was associated with statistically significant analgesia throughout 12 weeks of randomized, double-blind treatment. There were statistically significantly greater number of subjects experiencing at least a 30% and 50% reduction in pain and reporting their condition as improved or very much improved in the NKTR-181 treated subjects compared to placebo. NKTR-181 was well tolerated and exhibited a relatively favorable safety profile, including a low incidence of CNS-related AEs including those of sedation, daytime sleepiness and dizziness compared to conventional opioid therapies.

42 A Multicenter Evaluation of an Opioid Patient-Provider Agreement

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**Purpose**

A Patient-Provider Agreement (PPA) for opioid therapy, sometimes called an opioid agreement, Patient-Prescriber
Agreement, or Patient-Provider Controlled Medication Agreement, is a written document that describes the role and responsibilities of the patient and the prescriber for opioid therapy with the goals of educating patients, enhancing care, improving outcomes, and reducing opioid misuse and abuse. There are no universally agreed upon standards for a PPA, but most of these agreements explain the risks and benefits of opioid therapy, how these drugs should be refilled and stored, the use of tests, and restrictions (such as one prescriber/one pharmacy for all opioid prescriptions) along with the possible consequences for breaking these rules. Many organizations, including the American Pain Society, American Society of Pain Physicians, and the American Academy of Pain Medicine recommend the use of PPAs but do not provide details as to what elements the PPA should contain, much less their language. Challenges have been noted in creating or finding a PPA that is readable and usable to a broad audience, including those with low health literacy or who lack English skills. How best to communicate the complex risks and benefits of opioid therapy, including the use of pictures or infographics and framing issues have been discussed but without specific recommendations. The purpose of our study was to develop a standardized PPA and then pilot-test it among clinicians and their pain patients.

Methods

The FDA Safe Use Initiative convened a working group, which developed the opioid PPA that was used in our study. The PPA was reviewed by a plain language expert for linguistic clarity and readability. Patients could be included into this study if they were ≥ 18 years, spoke English as a first language, and attended an office-based or clinic-based center for pain treatment which may or may not have resulted in prescription opioid therapy. Inclusion criteria for prescribers were valid licensure for prescribing opioids and the ability to enroll 10 pain patients over six months at one center. All centers included in this study had to be using some form of a PPA, and this was presented to each patient as the standard of care. The purpose of this study was to evaluate the PPA by both prescriber and patient.

This was a minimal risks study. All procedures were standard of care, and patient participation did not affect treatment outcome or progress of their conditions. Patients were given the study questionnaire only after the treatment decision was made (and prior to taking any opioid medications). This was a one-visit prospective survey using chart data categorically (i.e., to classify pain as acute or persistent, to list prior treatments, and so on) and data were not specifically linked to the patient.

Results

A total of 117 patients and 14 providers at urban centers were included with 85% of patients treated for pain for > 3 months. The mean age of patients was 56 years (range 18-86), 44% were men, and about two-thirds (71%) had at least some college or a college degree. Sixty-eight percent were taking opioid medications prior to the first study visit and 85% had had some form of pain treatment for more than three months.

Most patients (96%) reported the PPA to be “somewhat helpful” or “very helpful” in deciding a course of treatment. About three-quarters of patients (72%) reported they read the entire PPA and 97% said the PPA was “easy to understand.” Prescribers were mostly physicians (86%) with a mean 15.8 years of practice (range 3 to 25 years) and 72% reported they felt “extremely confident” in prescribing opioids. About a third of the prescribers agreed that benefits outweigh the risks for low-dose and high-dose opioid therapy (21% and 28%, respectively), while slightly more disagreed (29% for both). The PPA took from 3 to 20 minutes to administer, with 84% of centers stating that it could be administered in under 10 minutes. About two thirds (63%) stated the PPA was just right or not too long to administer.

61% of prescribers versus 98% of patients thought the PPA was helpful in informing the course of therapy. Prescribers (92%) and patients (89%) agreed that the PPA was neutral in terms of favoring or discouraging opioid therapy. In terms of pain control, 53% of patients and 43% of prescribers described the pain being treated as severe; 42% of prescribers and 34% of patients described the pain being treated as moderate. Mild pain was reported by 15% of prescribers and 14% of patients.

Conclusions

There is an urgent need for a standardized template for a PPA which should be short, easy to understand, and patient friendly. Although there is a paucity of high-quality evidence supporting the use of the PPA in terms of reducing opioid misuse and abuse, our survey found that both patients and prescribers found these documents useful in helping to spell out the risks and benefits of opioid therapy and to set forth mutually agreeable treatment goals for both patient and prescriber.

43 The Budapest Criteria for Complex Regional Pain Syndrome: The Diagnostic Challenge

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Purpose

Complex regional pain syndrome (CRPS) is a neuropathic pain syndrome that involves both peripheral and central sensitization. Among the most difficult neuropathic pain syndromes to treat, CRPS is a condition so diffuse and poorly defined that its very existence has recently been called into question.1 CRPS, although not under that name, was described as early as the 19th century2 when it was termed “causalgia.” By World War II, what clinicians today might recognize as CRPS was called “reflex sympathetic dystrophy.”3,4 It was not until 1994 that a consensus meeting of experts, convened in Orlando, adopted the term “complex regional pain syndrome” to encompass both “causalgia” and “reflex sympathetic dystrophy,” which were difficult conditions to differentiate anyway.4,5 The Orlando criteria for CRPS were sensitive (that is, they accurately identified most cases of CRPS) but lacked specificity (meaning they inaccurately labeled other neuropathic painful conditions as CRPS).6,7 In 2003, a group of clinicians met in
Budapest to review what had been learned about CRPS since the Orlando criteria were in use and to make recommendations in a think-tank type of forum that would lead to specific research efforts. This resulted in the publication of a definitive book about CRPS and recommendations to IASP as to the incorporation of the so-called “Budapest criteria.” The purpose of our narrative review is to review current diagnostic criteria and explore how they may be used or possibly modified to improve diagnosis and ultimately treatment.

**Methods**

The authors examined the literature using keyword searches for “Orlando criteria” and “Budapest criteria” and “complex regional pain syndrome.” The purpose was to offer a narrative overview rather than a systematic review. In some cases, references within the literature retrieved were also utilized.

**Results**

The introduction of the Budapest criteria, which were more stringent than the preceding Orlando criteria, resulted in about 15% of previously diagnosed CRPS patients losing their diagnosis. This resulted in the creation of a new category called CRPS-NOS (Not Otherwise Specified) which included those patients who did not fulfill the Budapest criteria but whose signs and symptoms could not be better explained by any other diagnosis. Rather than limit the scope of CRPS to two types, a third and non-specific new type was added. The Budapest and Orlando criteria make CRPS a diagnosis of exclusion, but it may be that CRPS patients are those patients with pronounced neuropathic pain syndromes of a variety of etiologies.

The diagnostic scheme for the Budapest criteria relies primarily on dichotomous responses to conditions and fails to take into account subtle variations among patients. Some signs, such as skin temperature asymmetry, are objective measures but others, such as pain “disproportionate” to the inciting event are more subjective.

Specificity of CRPS diagnosis with the Budapest criteria might be improved with additional measurable variables. Mainka et al. showed that CRPS patients demonstrated decreased pressure-pain thresholds (PPTs) both in deep tissue and near affected joints. While decreased deep muscle PPT is a well-established finding in CRPS, Mainka et al. demonstrated a high specificity for decreased PPTs at affected joints that was shown to correlate significantly with increased osteoblastic activity and mineralization at these sites as visualized by bone scintigraphy. Skyba et al have suggested noninvasive methods for measuring PPTs using compression withdrawal thresholds that might be used for determining hyperalgesia in clinical practice. Incorporating measures of hyperalgesia that correlate to changes specific to patients with CRPS could be used to increase specificity of the current criteria.

**Conclusions**

As a diagnosis of exclusion in a field where many rare and complex conditions predominate, it is likely that many patients diagnosed with CRPS may have other conditions. A better knowledge of CRPS, its etiology, and its mechanisms are urgently needed. Treatment of CRPS is challenging and often ineffective. A more thorough understanding of the neuropathy and its origins are urgently needed to better define it, diagnose it, and ultimately treat it effectively.

**44 Chikungunya: Basics for Clinicians and Their Patients**

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**Purpose**

The chikungunya virus (CHIKV) is an arbovirus transmitted by the *Aedes* mosquito. Although the virus had been identified over 50 years ago, the first significant outbreaks of CHIKV infection occurred only recently, such as in 2006 in Reunion Island and the 2013-2014 Caribbean and American outbreak with an estimated one million cases. Chikungunya outbreaks have occurred in Africa, Asia, India, Europe and the Caribbean. The Centers for Disease Control and Prevention (CDC) in Atlanta considers the CHIKV to be a rare disease with fewer than 1000 cases per year in the United States, but its incidence may increase with time.

The purpose of our review was to describe this condition and its associated painful symptoms. Like Zika, the chikungunya virus is transmitted by mosquito vectors, but unlike Zika, the chikungunya viral infection is characterized by an acute phase of several days followed by episodic relapses which may go on for months or even years. This acute phase may be associated with moderate to severe, even debilitating pain. In rare instances, chikungunya may be fatal. A vaccine is in development but is not yet commercially available. The best strategies against CHIKV remain education and prevention.

**Methods**

The authors searched the PubMed database for the keyword “chikungunya” and also relied on information provided on the websites maintained by the Centers for Disease Control and Prevention in Atlanta and the Food and Drug Administration. The goal was to provide a narrative review of a condition that is relatively unknown to many American clinicians.

**Results**

The clinical presentation of CHIKV is often benign, but it can also be severe enough to warrant emergency hospitalization. Patients typically experience arthralgia, which can be mild to severe and varies in duration; the associated joint pain, which is typically bilateral and symmetric, can be debilitating.

The pain associated with chikungunya is not particularly responsive to analgesics. There is currently no consensus on pain therapy: chloroquine, disease-modifying antirheumatic drugs, meloxicam, prednisolone, acetaminophen and others have been studied but without strong clear-cut results. Algorithms using staggered treatments for acute arthralgia...
(dipyrone and acetaminophen), neuropathic pain (dipyrone and acetaminophen with possible adjunct of amitriptyline), and chronic pain (chloroquine) have been presented in the literature. Nonsteroidal anti-inflammatory drugs (NSAIDS) and corticosteroids are recommended for use only after the acute phase, if necessary. Chronic arthralgia may require treatment with chloroquine or tramadol, and referral to a pain specialist may also be appropriate.

The acute phase of CHIKV lasts about seven to ten days followed by a chronic phase with persistent or relapsing arthralgia (particularly of distal extremities) and sometimes morning stiffness. Arthralgia can cause severe pain. CHIKV infection is associated with chronic symptoms which may remit completely, persist over time, or occur episodically. One study found that 60% of patients who experienced CHIKV infection experienced episodic relapse and recovery for three years after the initial infection; the arthralgia was described by 77% as incapacitating and 56% reported it was accompanied by depression. The majority of patients (80% to 93%) experience symptoms up to three months after initial infection and about half (48%) experience symptoms up to three months after initial infection

Conclusions
The CHIKV is a mosquito-borne arbovirus associated with infection and possibly severe associated symptoms and potential sequelae. Unlike the related Zika virus, CHIKV appears to be more readily transmitted from mother to child in the perinatal period rather than in the womb although both viruses have been linked to neurodevelopmental delays and disorders in the child. A vaccine and antiviral treatments are urgently needed but until then, mosquito prevention and patient education are the best weapons to reducing these major public health threats.

45 Going Beyond Prescription Pain Relievers to Understand the Opioid Epidemic: The Role of Illicit Fentanyl, New Psychoactive Substances, and Street Heroin

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Purpose
Opioid abuse in the United States has been described as an epidemic. Escalating abuse of opioids has caused many authorities to call for a blanket reduction in opioid prescriptions for pain patients, with the idea that fewer prescribed opioids would reduce abuse. Pharmaceutical companies and pain physicians have been charged with creating the opioid epidemic (implying supply preceded demand), but this is simplistic. Furthermore, to reduce this problem to the patients prescribed opioids and under clinical care fails to recognize the true breadth and scope of it as well as mislead public perception.

Opioids include pharmaceutical-grade products, street drugs (such as heroin), illicit drugs (such as counterfeit prescription opioid pills), and new psychoactive substances (NPS), sometimes called “designer drugs.” NPS are not regulated by the government, meaning they are at the very least “not illegal.” They represent a serious public health threat because they can often be legally distributed (at least in the short term) labeled “not for human use” or as “research chemicals.”

Most alarmingly, illicit fentanyl and analogs are emerging as an important factor in the increasing morbidity and mortality associated with opioid abuse. About 50 to 100 times more potent than morphine, fentanyl is a synthetic opioid which does not structurally resemble natural opioids and is not usually detected during routine immunoassay urine testing.

The objective of this narrative review is to consider the role of illicit fentanyl, NPS, and heroin and their contributions to the opioid epidemic in America.

Methods
This was a narrative review which involved a search of the literature using PubMed as well as LexisNexis for terms: illicit fentanyl, new psychoactive substances, heroin, and opioid epidemic. LexisNexis was searched for newspapers and media outlets describing the opioid crisis. The websites for the Drug Enforcement Administration and Centers for Disease Control and Prevention were also searched for these keywords. The bibliographies of articles were also examined for relevant articles.

Results
In 2015, about 14.9 billion prescription opioid dosage units were disbursed in the U.S. to retail-level purchasers, of which 9.1 units were “lost” and likely wound up on the street market. Prescription fentanyl composes a small fraction of the opioids abused, but illicit fentanyl and numerous fentanyl analogs have been described by the DEA as key drivers of the current opioid epidemic. Illicit fentanyl may be sold as such (a subset of abusers like its strong psychoactive effects); it serves as an adulterant for heroin or other drugs; and it is used to create counterfeit “prescription drugs” with pill presses. Counterfeit pills extend beyond opioids, in that illicit fentanyl has recently been reported in counterfeit street benzodiazepines (fake Xanax). So ubiquitous is fentanyl that in California, “China White” heroin is increasingly turning out to be, in reality, acetyl fentanyl.

New psychoactive substances (NPS), including six fentanyl analogs, are synthetic drugs not yet classified by the Drug Enforcement Administration and therefore, technically not illegal. The NPS market produces hundreds of drugs in over 94 nations around the world; European agencies have identified over 400 NPS more or less consistently available in Europe. Many NPS products are sold with little to no legal restraints in communities where authorities and clinicians may be oblivious to their availability.

Heroin is a familiar drug in the opioid epidemic, but fentanyl-contaminated heroin (FCH) has emerged as a serious new threat. In a survey of 199 respondents (65.3% male, median
Conclusions

The opioid epidemic is far more complex than often represented. It involves not just diverted prescription drugs but also street heroin, and a burgeoning market of NPS, the most prominent (and alarming) of which is illicit fentanyl. Some fentanyl analogs may not technically even be illegal. Illicit fentanyl is frequently used as an additive to other drugs (such as heroin) or as the psychoactive substance in counterfeit pills. Illicit fentanyl, often manufactured overseas, is driving the recent increase in opioid-associated morbidity and mortality, although its availability and use may be under-reported and under-recognized.

46 Driving Under the Influence of Opioids

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Purpose

Vehicular accidents are a major cause of morbidity and mortality in the United States (U.S.). Any number of substances, including alcohol, illicit drugs, prescription drugs, marijuana, and even certain over-the-counter medications can impair a driver. In 2009, 28% of all fatally injured drivers in the United States (U.S.) tested positive for one or more legal or illicit substances. In a study of vehicular fatalities, the prevalence of drivers who tested positive for alcohol has remained relatively consistent from 1999 to 2010 at around 39%, while drugged driving has increased significantly from 16.6% in 1999 to 28.3% in 2010 (p<0.0001) and opioid-related vehicular fatalities increased from 1.8% in 1999 to 5.4% in 2010.

In most parts of the world, the legal system does not differentiate between legal and illicit substances—between street heroin or prescription opioids, for example—in terms of impaired driving. Most DUI laws do not specify drugs, allowing broad law enforcement and prosecutorial discretion as to which substances might impair a driver.

The aim of our narrative review is to present the current status of driving under the influence (DUI) of opioids in the U.S. with particular emphasis on how clinicians should better discuss the risks to which patients may subject themselves when they take opioids and operate motor vehicles.

Methods

The authors searched the PubMed database for “driving under the influence opioids” and retrieved 72 articles; no delimiters were applied in terms of type of article or date. All of these articles were reviewed and in some cases their bibliographies were reviewed. Some articles were irrelevant to this review, superseded by newer information/studies, or presented tangential information and were not included. This is a narrative rather than a systematic review.

Results

The National Roadside Survey (2013-2014) surveyed 7,405 randomly selected American drivers about prescription drug use at 60 sites; 20% of those drivers reported having taken a prescription drug within the past two days. Those drugs were sedatives (8.0%), antidepressants (7.7%), opioids (7.5%), and stimulants (3.9%). A National Roadside Survey conducted in the U.S. in 2007 found that during weekend night driving, 16.4% of drivers tested positively for drugs (including but not limited to opioids) compared to 12.3% who tested positively for alcohol.

Driving while taking prescription drugs, even taken exactly as directed, may constitute a serious offense for which there is no legal defense, although patients taking these drugs and those prescribing them may not be aware of the potential legal consequences. The prescribing information for many of these drugs may state that persons taking them should not drive or operate heavy machinery until they know how the drugs affect them, which quite likely would not constitute a legal defense in court. While prescribing advice suggests that driving might be safe if the patient does not perceive himself to be impaired, DUI laws do not take the driver’s self-assessment of impairment as a defense. That point may be moot as many states enforce zero tolerance and per se laws which allow either no concentration or a set a legal limit on the concentration as definitive; impairment laws (where impairment must be proven) are not as common. In the United States, laws vary by state and considerable discretion may be exerted by law enforcement and prosecutors.

About 20 states in the U.S. do not allow a “legal entitlement” as a defense, even when the patient is taking an appropriately prescribed legal substance as directed under medical supervision.

Conclusions

There is considerable state-to-state variation in the United States and different laws in various countries that regulate opioid-influenced driving. No state differentiated between legal and illicit opioids in terms of DUls but in a few states, having a legal prescription for an opioid might be allowable as a possible defense. Prescribers and other clinicians should alert patients taking opioids about their risk for DUI to make sure patients understand the possibility dangers of driving while taking prescription opioids.

47 The Introduction of a New Term: Multigesics

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Purpose

The “opiod epidemic” described in the press often groups all opioids together as if they were one drug when, in reality, there are vast differences among the various members of this drug class. Newer analgesics introduced to market further
confound the picture when they exhibit characteristics atypical of conventional opioids. Indeed, these drugs are sometimes called “atypical opioids.” Four such “atypical opioid” pain relievers have been developed (in alphabetical order): buprenorphine, cebranopadol, tapentadol, and tramadol. These agents rely on unique and possibly synergistic mechanisms of action and do not work like conventional opioids, yet they are often categorized as “opioids,” which can be misleading in that they have different attributes than conventional opioids.

To this end, the term “multigesic” is proposed to describe those analgesics that have dual or multiple mechanisms of action. This represents a more realistic assessment of how they work, helps to differentiate them from the conventional opioids, and may generate more attention to an important avenue of drug development, namely improved analgesic products. The aim of this article is to introduce the term “multigesic agent”—and to describe how drugs sometimes currently called atypical opioids might better be described as multigesics. This commentary represents the views of the authors that the term multigesic serves an important purpose in describing a subset of analgesic products with opioid and nonopioid mechanisms of action.

Methods

This is a commentary rather than a study. The authors considered the clinically significant differences between certain “atypical” versus “conventional” opioids and explored the potential utility of naming these particular products “multigesics” to provide prescribers and other clinicians a useful new way to describe and categorize these important, emerging agents.

Results

The four drugs that can be described as multigesics possess different mechanisms of action, and have different side-effect profiles and different abuse potentials than conventional opioids, such as morphine or oxycodone. Their mechanisms of action are dissimilar but all involve both an opioid and a nonopioid component. Buprenorphine binds with very high affinity (sub-nanomolar) at µ-opioid receptors and lower affinity and intrinsic activity at the K- and δ-receptors and nociceptin receptor (NOP). Cebranopadol, currently under development and not commercially released, has been called a first-in-class novel analgesic of the benzenoid class. Tapentadol’s analgesic mechanism of action combines µ-opioid receptor (MOR) agonist activity with neuronal norepinephrine-reuptake inhibition (NRI). Tramadol’s mechanism of action combines a relatively weak µ-opioid receptor agonist and a monoaminergic reuptake inhibition, that is, it inhibits serotonin (5-HT) and norepinephrine reuptake.

All four agents are effective pain relievers and with the exception of cebranopadol have been extensively studied in clinical trials. Multigesics are also well tolerated and may have less associated risk of side effects than conventional opioids.

These multigesics also have unique attributes. For example, buprenorphine exhibits no ceiling effect in terms of pain control, but there is a ceiling effect in terms of respiratory depression. Cebranopadol does not cause sedation, a common side effect of conventional opioids which can be treatment limiting. Respiratory depression may occur with tramadol but typically at doses higher than with opioids such as morphine. Although studies are needed for confirmation, it is easy to rationalize why multigesics may be less well liked by abusers than conventional opioids.

Multigesics as a new term will help categorize an important new type of analgesic product and differentiate it from conventional opioids. This may help in prescribing decisions.

Conclusions

Typical and atypical opioids are crucial elements in the armamentarium against pain, but describing certain products (buprenorphine, cebranopadol, tapentadol, and tramadol) as opioids may be clinically misleading. These four drugs are unique and dissimilar in many ways, but all have an opioid and nonopioid mechanisms of action and many attributes that set them apart from conventional opioids. For that reason, the term multigesic is proposed to describe analgesics that exhibit both opioid and nonopioid mechanisms of action.

48 The Risk of Suicide Risk in Chronic Pain Patients

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Purpose

Suicidality is a complex phenomenon, and may occur when the individual simultaneously faces extreme stress and a limited ability to cope. Indeed, the individual may perceive suicide as the only means of escaping physical and/or emotional pain. Suicide was the 10th most frequent cause of death in the United States (US) in 2014 (accounting for 42,826 deaths) and appears to be trending upward; the age-adjusted suicide rate in 2014 was 24% higher than it was in 1999. Chronic pain patients are at double the risk of suicide compared to others not in chronic pain, with a lifetime prevalence of attempted suicide ranging from 5% to 14%. Chronic pain may create life-altering, overwhelming stress, and limited access to medical care, social support, and/or effective analgesia can seem overwhelming.

In a survey of 1512 chronic pain patients, 32% of respondents reported they had some form of suicidal ideation. There are likely multiple reasons. Chronic pain is a devastating psychosocial life event that can reduce function, limit the patient’s ability to pursue everyday activities, and cause unremitting suffering. Many chronic pain patients suffer from comorbid psychiatric disorders; this condition is so common that has been termed “dual diagnosis.” In addition, chronic pain patients are often prescribed polypharmacy, which may alter biochemistry in unintended ways and, in so doing, exacerbate distress and suicidal ideation. The aim of this narrative review is to explore what is currently understood about suicidal behaviors in chronic pain patients.
Methods
The PubMed databases were searched for the keyword combination “chronic pain + suicide” and articles obtained were reviewed. In some cases, references from those articles were further explored. Some of our references, in particular for background statistics, come from websites maintained by the Centers for Disease Control and Prevention and the World Health Organization. This is a narrative review rather than a systematic review.

Results
The risk factors for suicide in general may be grouped into five domains: psychiatric disorders; risks associated with specific personality traits; psychosocial life events, including chronic illness; genetic and familial factors; and neurochemical and biochemical influences. Predisposing factors include life events, opportunity, and environmental factors; potentially modifying factors include social support, psychiatric care, and cognitive flexibility. Physical problems, including pain and loss of function, have been specifically observed as a precipitating factor in suicides of geriatric individuals. Chronic pain is associated with comorbid conditions, such as depression, which may confound their own elevated risk of suicidality. Chronic pain has been associated with major depressive disorder (MDD).

The neural network associated with chronic painful conditions engages some areas of the brain that are also associated with cognitive processes and emotional responses, which provides a physiological basis for the clinical observation that chronic pain often appears to have an emotional and contextual component absent in acute pain. This shared neurobiology may explain why cognitive behavioral interventions can be effective in chronic pain patients.

An emerging risk factor for suicide in chronic pain patients is sleep-onset insomnia with daytime dysfunction combined with high pain intensity. Chronic pain patients likewise have very high rates of insomnia, ranging from 50% to 96%. Insomnia has been recognized as a risk factor for suicide, specifically in chronic pain patients, indeed, sleep-onset insomnia may actually be a more robust predictor of suicidal ideation than depression among chronic pain patients.

Conclusions
Chronic pain patients have at least twice the risk of suicide than non-chronic pain patients, but these risks may be far more complex and multifaceted than simply unendurable pain. Dual diagnosis or the concomitant presence of mental health disorders and chronic pain likely exacerbates the risk of suicide. Evidence suggests depression and chronic (but not acute) pain may share some of the same neural networks. Chronic pain patients are a vulnerable population, and it may be clinically important to consider their risks of suicidality during treatment.

49 Is There a Place for Ketoprofen Lysine Salt in the U.S. Analgesic Armamentarium?
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Purpose
The role of NSAIDs for pain control has been limited by gastrointestinal (GI) adverse events as well as newly emerging cardiovascular risks. Yet for certain types of painful conditions, NSAIDs provide effective analgesic with no abuse liability. A broad variety of NSAIDs in a variety of formulations are available.

Ketoprofen is a COX inhibitor and nonsteroidal anti-inflammatory drug (NSAID) that has been used for the past several decades. Ketoprofen is reported in the literature to be a safe, effective analgesic for traumatic, orthopedic, and rheumatic pain. Ketoprofen is available in oral capsules by prescription in the United States. A topical 2.5% gel is available in many parts of the world but not the U.S.

Ketoprofen lysine salt (KLS) is a new agent available in Europe that is worth consideration for the NSAID armamentarium. KLS is a propionic derivates, and may be described as a racemic mixture with the cyclooxygenase (COX) inhibition associated with only the S-isomer. Our purpose is to describe KLS and to consider it as an important new NSAID product.

Methods
We searched the literature for ketoprofen lysine salt and described in narrative review information about this new drug.

Results
Salification of ketoprofen with lysine amino acid improved the agent’s characteristics, giving it higher solubility to ketoprofen acid, allowing, in turn, more rapid and complete absorption with a high peak serum concentration achieved in about 15 minutes after oral ingestion (compared to about 60 minutes with ketoprofen). KLS is liposoluble and can pass through the blood-brain barrier in about 15 minutes.

Ketoprofen lysine salt (KLS) inhibits COX, decreasing prostaglandin E2 (PGE2) production and inhibiting the lipoxygenase pathway in the arachidonic acid cascade, resulting in decreased synthesis of leukotrienes. KLS has peripheral as well as central sites of action.

L-lysine salification may accelerate gastric absorption of ketoprofen and a study in rats found it improved gastric tolerance of the drug. In vivo pharmacodynamics of KLS versus ketoprofen showed the former conferred greater gastric tolerability.

Ketoprofen appears to interact with the 5-HT system which may explain its effectiveness. In a systematic review of the literature (13 studies, n=898) comparing ketoprofen with ibuprofen and/or diclofenac in the treatment of moderate to severe pain found the difference between ketoprofen and the pooled
results for ibuprofen/diclofenac significantly favored ketoprofen for pain control (0.459, 95% confidence interval (CI), 0.33 to 0.58, p=0.00) at all point estimates of the mean weighted size effect. Ketoprofen has been found to be effective in treating acute painful conditions (bursitis, tendinitis, acute back pain), post-operative pain (particularly but not limited to orthopedic surgery), and chronic pain (osteoarthritis, rheumatoid arthritis, gout). KLS showed significantly greater anti-inflammatory effect (p<0.001) than placebo in a three-day double-blind trial of 120 patients (aged 18 to 82 years) treated for lesions in the oral cavity with either KLS or placebo.

Conclusions

KLS is an important new NSAID already available in Europe that shows promise in that—like other NSAIDs—it offers effective pain control but—unlike most other NSAIDs—with improved GI tolerability.

50 Effect of Botox Injection on A Veteran Patient with Chronic Refractory Neuropathic Pain Caused by Gun Shot Wound - A Case Report

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Purpose

Botox injection has been used to treat spasticity and other hypertonic muscular diseases. However very rare report is about effect of Botox injection for treating refractory chronic neuropathic pain caused by Gun Shot Wound(GSW).

Methods

Botulinum-Toxin A diluted with 1 ml preservative free 0.9% saline plus 1% lidocaine 1 ml. The 30 Gauge 1/2 needle is used. Total 100 units Botox injected into the neuropathic pain area in 20 points. The patient was followed up every 3 month.

A 68 years old male veteran with h/o Parkinson’s disease, PTSD, TBI, chronic pain came to my clinic 4 years ago with complaints of chronic right neck pain and right upper back pain caused by GSW to right neck/trapezium(at Vietnam)in 1968. The pain is sharp and constant. He is unable to lay on right side for years. On physical examine: A large scar (15cm) was noted. Allodynia was found on large area from right low neck/shoulder to right scapular and whole right thoracic back area. He tried methadone, topiramate, gabapentin, TCA, Capsaisin cream and acupuncture with limited benefit. Botox injection trial was started > 2 years ago.

Results

After 1st trial of injection the analgesic effect lasted about one month. After 2nd trial the analgesic effect lasted about 2 months. After 3rd trial of injection, analgesic effect lasted 3 months. Overall his neuropathic pain reduced to 50-60%. He feels much less sensitive to touch and feels comfortable wearing his clothes. Patient has been injected with Botox for total 8 times. His is comfortable for the result.

Conclusions

Botox injection not only can treat the spasticity and other hypertonic muscular diseases, it could also treat refractory chronic neuropathic pain (GSW). After several injections it seems to prolong the duration of analgesia function.

51 Long Term Effect of Deep Tissue Laser Light Therapy on An Elderly Veteran with Chronic severe Knee pain - A Case Report

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Purpose

Deep tissue laser light therapy could increase microcirculation, help tissue regeneration, anti-inflammatory and analgesic. It could treat different kinds of chronic pain including chronic knee pain. However the long term effect of deep tissue laser therapy treating chronic knee pain has not been reported.

Methods

An 88 years old male veteran first came to my clinic about 6 years ago with h/chronic left knee pain with worse for 9 months. He felt left knee pain at night and hardly went to sleep. He took Vicodin and diclofen everyday. He was a marathon runner with left knee injury in 2004 and consulted with orthopedic surgeon. MRI of left knee revealed a complex tear posterior horn medial meniscus. Patient felt catching and sudden pain in left knee with extension/flexion. At that time his McMurrays test (+). Orthopedic surgery was recommended for his left knee. However patient denied the surgery at that time. Physical exam of left knee in my office revealed no swelling, no tenderness, normal ROM. X-ray revealed Moderate DJD. Patient was treated with Deep Tissue laser LCT 1000(by LiteCure)on left knee: 10 W, 10min, 6000 joules.

Results

One month post first laser light therapy, the patient felt his knee pain almost gone. He walked 3 miles per day and felt no pain during the night and did not take any pill for entire month. On first year, he needed 5 treatments with LCT 1000 laser, for the follow year he needed only 4 treatments and on the third year he only needed 2 treatments. He has no knee pain during the night for more than 3 years. He just called me recently “I have no problems in my knee since the last treatment”.

Conclusions

Deep tissue laser light therapy could treat chronic pain such as chronic knee pain. However long term effect has not been reported.

This case report find the deep tissue laser light therapy not only can treat chronic knee pain but also could have pain relief for several years.
52 Presence of Bacterial Contamination in Urine Drug Test

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Purpose

The purpose of this study was to quickly and effectively identify bacterial contamination in urine specimens received at Precision Diagnostics. The study was approved by Aspire IRB Santee CA. The presence of bacterial contamination has been implied to increase the pH and oxidant levels in our validity testing in urine specimens. Bacterial contamination severity was determined by two methods: (1) traditional serial dilutions proceeded by colony counts and (2) a modified Rapid Staining Method. Serial dilutions are accurate in determining if viable bacteria are present in a specimen, but this method requires at least 24 hours of incubation to obtain results, substantial laboratory space, and a sterile environment. The modified Rapid Staining Method does not require a sterile environment, specialized equipment to visualize the results (ex. microscope), and allows more specimens to be tested in a shorter period of time. Approximately 12 minutes per specimen is needed to accurately determine bacterial contamination and the Gram status, which can help determine the type of bacteria present in the urine specimens.

Methods

(1) Traditional 10-fold serial dilutions were performed with the urine specimens. The urine cultures were diluted in sterile water, vortexed, and sterilely plated on Nutrient Agar plates. The plates were incubated at 37°C for 24 hours, bacterial colonies were counted and colony forming units (CFU) calculated using the following equation: (colonies counted) (dilution factor)/amount of suspension plated= CFU/mL.

(2) Adaptation of bacterial staining protocol from S. Yazdankhah, et al. Rapid Method for Detection of Gram-Positive and Gram-Negative Bacteria in Milk from Cows with Moderate or Severe Clinical Mastitis. Journal of Clinical Microbiology, Sept 2001, 3228-3233. Urine specimens were combined with Solution A detergent, incubated for 2 minutes at room temperature and filtered to remove debris. The filtrate was filtered with a 0.8 uM porous Supor Membrane filter to capture the bacteria. The membrane was washed with Solution B detergent and stained by submersion with toluidine blue for 4 minutes. A bacterial concentration equal to or greater than 1 x10^6 colony forming units (CFU)/mL will appear purple. The Gram status can be determined when the bacteria are decolorized using an ethyl alcohol- glacial acetic acid (pH 2.8) solution, incubated at room temperature for 3 minutes. If the membrane remains purple, the bacteria are Gram-Positive; if the stain is removed, the bacteria are Gram-Negative. If the membrane remained light blue post-stain, this indicated either (1) no bacteria were present in the specimen or (2) the bacterial concentration was less than 1 x10^6 CFU/mL.

Results

The bacterial concentration determined by serial dilution and plating indicated that 93% of the urine specimens contained equal to or greater than 1 x10^6 CFU/mL. The clinical definition of a urinary tract infection (UTI) is one or more types of bacteria present at 1 x10^5 CFU/mL. It is unlikely that all of the specimens tested were from patients with UTI’s, supporting the hypothesis that more urine specimens are contaminated at greater levels than previously reported. 71% of the urine specimens tested were positive for bacterial contamination. The bacterial threshold determined via serial dilution suggests Yazdankhah’s Rapid Method could be modified for urine specimens.

The sensitivity of the modified Rapid Staining Method with urine specimens was 97% in identifying bacterial contamination at equal to or greater than 1 x10^6 CFU/mL. 82% of the specimens tested were positive for bacterial contamination. 66% of the specimens were identified as Gram-Negative, where 33% were identified as Gram-Positive. This trend supports the current data regarding the Gram status of epithelial flora and UTI microorganisms.

General trends observed in both studies include urine specimens from female patients on average contained more bacteria and had an increased pH compared to specimens collected from male patients. Longer transit times resulted in higher bacterial concentrations in specimens collected from both male and female patients. It was also noted that Pain Clinics had more specimens with bacterial contamination equal to or greater than 1 x10^6 CFU/mL when compared to Treatment Centers. This was a surprising result, but can be attributed to the age of the Pain Clinic patients (range: 30-87, average: 50.7 years) and the transit time (average: 2.8 days), compared to Treatment Centers patient age (range: 18-60, average: 38.9 years) and transit time (average: 2.07 days) respectfully.

Conclusions

Bacterial contamination occurred in 78% of the urine specimens tested, compared to the previously documented 15% at greater than 1 x10^6 CFU/mL (M. LaRocco, et al. Jan 2016). The sensitivity of the modified Rapid Staining Method with urine specimens was 97% and can be applied in future applications to accurately determine bacterial contamination. The specimens tested that were positive for bacterial contamination equal to or greater than 1 x10^6 CFU/mL did have an increased pH when compared to non-contaminated specimens. Zero specimens in this study were identified as having an increased oxidant level regardless of bacterial contamination.

53 The NIH Pain Consortium Centers of Excellence in Pain Education: The creation of an interactive, interprofessional post-mastectomy pain syndrome learning module.

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Purpose

The proper management of chronic pain conditions that are difficult to manage demand a concerted effort among the healthcare team. The Center of Excellence in Pain Education at Southern Illinois University Edwardsville has created an interprofessional module on post-mastectomy pain for learners of medicine, dentistry, and pharmacy.

Methods

We provide the current management of post-mastectomy pain syndrome including the anatomy, pathophysiology, and pharmaceuticals involved in its progression and care.

Results

Post-mastectomy pain syndrome (PMPS) is a chronic painful condition affecting both lumpectomy and mastectomy patients that adversely affects the quality of life of its sufferers. The incidence of PMPS has been estimated to be as high as 50% and is on the rise due to the increased incidence of breast cancer and due to higher election rates for mastectomy. The pain that arises following mastectomy is localized along the axilla and the medial aspect of the arm and is most likely due to damage or constriction of the intercostobrachial nerve and its branches. Risk factors include axillary lymph node dissection and younger age.

Conclusions

Our module follows the case of a woman seeking an understanding and treatment options for her condition through a support group and her interprofessional healthcare team.

54 Quality Assurance Alcohol Monitoring by Urine Ethyl Glucuronide Screen in Patients Receiving Long-Term Opioid Therapy (LTOT)

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Purpose

Urine Drug Monitoring (UDM) is an important risk mitigation tool when treating patients LTOT. Several opioid prescribing guidelines recommend UDM as a standard of care for patients with chronic non-cancer pain.¹⁻⁵ Most guidelines do not specify which tests should be included in such screens, but standard of care dictates initial and ongoing monitoring to ensure medication safety and mitigate risks for opioid induced respiratory depression.

In 2010, Dasgupta et al. published the largest reported prospective observational cohort study available within the US, within the state of North Carolina.⁶ They found that 2,182,374 patients were prescribed opioid analgesics and 80% were also prescribed a benzodiazepine.⁶ There were 629 deaths involving opioid analgesics and ethanol was involved in 12.2% of overdoses involving opioid analgesics.⁶

These statistics support initial and ongoing monitoring of alcohol use together with the routine UDM, which for most Veterans Affairs Hospitals includes at least “opiates”, methadone, amphetamine, barbiturates, PCP, cocaine, and cannabinoids. Of note, the Washington State Agency Medical Directors’ Group released guidelines on prescribing opioids for pain, which consists of initial and ongoing UDM including alcohol monitoring by ethyl glucuronide (EtG) at least annually for all patients.⁷

In an effort to enhance patient safety, raise awareness of polysubstance abuse, minimize opioid morbidity and mortality, as part of quality assurance with opioids, alcohol monitoring by EtG was included as part of routine monitoring for all patients monitored and/or seen by the Pharmacy Pain Clinic that receive LTOT.

Methods

This was a quality assurance project at the Samuel S. Stratton VA Medical Center. All non-cancer patients requiring LTOT should have an in-date consent to UDM, including alcohol, according to VA policy in accordance with the nationally approved “Consent for Long-term Opioid Use”.

All non-cancer patients followed by pharmacy pain management clinic from June 2016- September 2016 who received LTOT (≥3 months) plus or minus a benzodiazepine were screened and included in the study. Patients were identified by ICD-10 codes. All opioids were included except for buprenorphine, tramadol, butorphanol, or pentazocine. The Institutional Review Board at the Samuel S. Stratton VA reviewed this project and granted it exemption in July of 2016.

The primary objective was to assess how often EtG is ordered, enhance patient safety, and attempt to minimize opioid morbidity and mortality by employing alcohol monitoring with EtG. Secondary objectives were to provide recommendations to healthcare providers and education to patients on increased risk of opioid induced respiratory depression (OIRD).

Prior to employing alcohol monitoring by EtG, a retrospective chart review was conducted to assess how often EtG was ordered within the last year for patients that met inclusion criteria. Patients were notified by the pharmacy pain clinic to report to the lab for routine monitoring. Laboratory findings and recommendations were entered in the Computerized Patient Record System (CPRS). Recommendations included alcohol counseling, LTOT and other sedative-hypnotic dose reduction or elimination, risk mitigation strategies, and to support routine alcohol testing routinely.

Results

Fifty-six patients were identified by a quality assurance screen and included in this project. Patient characteristics were consistent with a VA population as it was mainly elderly men. The average morphine equivalent daily dose was 94mg using Practical Pain Management opioid calculator.⁸

Prior to employing alcohol monitoring by EtG, 96% of patients had no previous EtG screen and 4% of patients screened were positive for EG. Once alcohol monitoring was
employed by EtG, 8.9% were positive for EtG, 44.6% were negative, and 46.4% did not show up to the lab.

Pharmacy led interventions were highly accepted among providers. All of the patients positive for EtG had alcohol cessation counseling. Forty-one percent of patients had opioids reduced and/or discontinued. Risk mitigation interventions included updating consent forms for long-term opioid use in 7 patients and naloxone prescriptions in 6 patients.

**Conclusions**

Approximately 9% of patients were ethyl glucuronide positive while taking prescribed opioids. This project identified patients ingesting alcohol in combination with long-term opioid therapy +/- benzodiazepines who previously reported no alcohol use. These preliminary outcomes support initial and ongoing alcohol use monitoring.

**55 Efficacy and Safety of Ketoprofen Vs Ibuprofen for the Treatment of Pain in Rheumatoid Arthritis: a Systematic Review and Meta-analysis**

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**Purpose**

Rheumatoid arthritis (RA) is a multi-faceted inflammatory disease affecting the joints and their surrounding structures, as well as other organ systems. It is the most frequent chronic inflammatory arthritis as it affects 0.5-1% of adults in developed countries. Patients with rheumatic diseases, including rheumatoid arthritis, describe symptoms such as pain and stiffness as important factors affecting their quality of life. Pain is considered a psychological distress and sleep disturbance and may even be a greater cause of disability than structural joint damage. The most widely used drugs to decrease inflammation and manage mild-to-moderate pain in RA patients are NSAIDs. Ketoprofen and ibuprofen are NSAIDs belonging to the family of propionic derivates that have been used in Europe and the USA to treat chronic painful conditions such as osteoarthritis and RA and acute, mild-to-moderate pain for the last 30 years. In our previous meta-analysis, we demonstrated that ketoprofen was superior to ibuprofen in relieving different kinds of moderate-to-severe pain conditions, and so the primary aim of this systematic review of the literature and meta-analysis of randomised controlled trials (RCTs) was to compare the clinical efficacy of these drugs in patients with the specific pain associated with RA. Given various recent reports concerning cardiovascular, hepatic and gastrointestinal adverse events associated with the chronic administration of NSAIDs, our secondary aim was therefore to evaluate the safety and tolerability of ketoprofen and ibuprofen in order to fully assess their risk/benefit profiles.

**Methods**

We made a systematic search of the Medline and Embase databases from their inception to July 2016 in accordance with the Cochrane Collaboration guidelines in order to identify RCTs directly comparing the recommended therapeutic doses of oral ketoprofen (50-200 mg/day) with ibuprofen (600-1800 mg/day) for RA pain relief. To minimise heterogeneity, we included retrospective studies reviews, letters, editorials, conference papers, case reports, basic science papers and clinical practice guidelines. Finally to evaluate the tolerability and safety of the two drugs, we included the studies stating the number or percentage of patients experiencing adverse events and the number or percentage of withdrawn patients. The meta-analysis was made using the standardized mean difference (SMD) of each included RCT and a fixed effects model.

**Results**

Four RCTs, involving a total of 456 patients, met the inclusion criteria. The ketoprofen and ibuprofen doses assessed in the studies were respectively 150-300 and 1200-1800 mg/day and treatment duration ranged from 10 days to 3 months. All of the studies considered changes in pain as evaluated by a VAS or point scores. Two studies of 142 patients treated with ketoprofen and 140 treated with ibuprofen included duration of stiffness scores, and two studies of 86 patients treated with ketoprofen and 84 treated with ibuprofen included grip strength scores. The meta-analysis showed a statistically significant difference in clinical efficacy in favor of ketoprofen (SMD 0.33; CI 95% 0.1 – 0.52; p = 0.005) at all point-estimates of the mean weighted size effect. The heterogeneity test for the efficacy outcome was not statistically significant (the hypothesis test was \( \chi^2 = 3.57\% \), df = 3, p value = 0.31 and the chance of a test effect was 3.49, P = 0.0005), confirmed by the Higgins percentage of 16%, thus demonstrating the homogeneity of the trials and the validity of the meta-analysis findings. The analysis of tolerability evaluated the risk ratio (RR) between ketoprofen and ibuprofen (RR=1.05; [-0.83, 1.33] M-H, fixed, 95% CI) underlying no statistically significant differences between the two molecules. No differences were shown also in safety parameters, evaluated by analyzing the risk difference (RD) between ketoprofen and ibuprofen (0.02 [-0.03, 0.7], with 7 vs 4 events in 142 vs 139 patients.

**Conclusions**

The result of this meta-analysis shows that therapeutic doses of ketoprofen are more efficacious than ibuprofen in managing RA-related pain, thus supporting its use in clinical practice, with the same safety profile. The efficacy and good safety profile of ketoprofen indicate that it has a better risk/benefit ratio than ibuprofen at the recommended doses, a finding that should be taken into account by clinicians when dealing with RA patients experiencing moderate-severe pain.
56 Functionality: A Concept Analysis

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Purpose

Most health care providers and interdisciplinary pain management teams (IDPMT) define success in pain management as a reduction in the patient’s pain score. For acute pain, this target is the appropriate goal in the treatment plan. However, for chronic pain, the plan of care must include improvement in functionality because complete pain relief or comfort may not be attainable. As seen in the Pain Catastrophizing Scale (Sullivan, Bishop, & Pivik, 1995) an intensive, consuming preoccupation with pain can lead to patients searching for the newest treatment or drug and avoiding gold standard interventions. Mathew, Chamberlain, Alvarez, Alvarez, & Shah, (2016) best sum up the goal of the chronic pain patients’ (CPP) treatment plans by proclaiming that the IDPMT’s purpose is no longer just pain relief, but is to rebuild the CPP’s capability of completing their activities of daily living while teaching biopsychosocial based tactics to help them develop personal strategies to manage their pain: the perfect definition of functionality. The purpose of this research is to emphasize the need for the frontline practitioner along with all members of the IDPMT to shift focus from asking CPP about their pain level and start focusing on their functionality level.

Methods

Concept analysis is a research process used to clear up terms used in practice and theory that can appear to have a vague or abstruse meaning. The Merriam-Webster website defines this concept as “the quality or state of being functional” (n. d.). A look at the definitions of acute versus chronic pain aids in understanding the concept of functionality. For acute pain, the standard pain scale is a great tool for the IDPMT to use in treating patients’ subjective answers of their perception of pain. Once the pain switches to a chronic condition, the IDPMT must change the assessment focus to the patients’ functionality level. Acute pain is normally self-limited and resolves quickly over a short period of time (Mathew, Chamberlain, Alvarez, Alvarez, & Shah 2016). Chronic pain characteristics include; present regardless of interventions; continuing past the normal healing time; and no obvious physiological cause (Barley, & Lawson, 2016). This analysis was accomplished through exploring aspects of functionality: literature review; defining attributes, antecedents, and consequences; reviewing empirical referents; and model, borderline, and contrary example cases. In the literature review studies were analyzed for defining attributes of functionality in relation to CPPs and their goal attainment of self-care pain management. For this functionality concept analysis two referents were chosen from available evidence based tools. The Pain Catastrophizing Scale (Sullivan, Bishop, & Pivik, 1995) and Pain Disability Index (Tait, Pollard, Margolis, Duckro, & Krause, 1987) can be implemented with ease by a member of the IDPMT to assess CPPs functionality.

Results

Functionality paradigm provides a universal approach to care and makes it easier for the patients to pursue and achieve self-care management goals for their chronic symptoms and chronic pain. By simply asking CPP to rate their chronic pain using the standard acute pain scale, the frontline practitioner or IDPMT inadvertently directs the patients’ focus to their disability or limitations and not their self-care functionality level. With a different approach to patient assessment, the CPPs’ perceptions of their chronic pain are redirected from an illness focused on pain to a wellness focused on self-care management and optimization of functionality. Dr. Kevin L. Zacharoff provides a clear definition of functionality when he recommends primary care providers explain pain management goals as finding the best balance between pain and function that is humanly possible (2016.) The attributes seen in CPP with a high functionality level are: engaging in preventative health measures; self-monitoring and managing signs and symptoms of their specific chronic symptoms/disease; recognizing and adapting their new normal to their environment; incorporating new insights, attitudes, and action to cope with their specific self-care needs (Richardson et al., 2014); improvement and maintenance in sleep, mobility, and appetite and: a decrease in stress (Mathew, Chamberlain, Alvarez, Alvarez, & Shah 2016). Chronic pain is an antecedent of comfort in acute disease. However, in chronic pain, comfort and cure are not always attainable. By switching to an accepted goal of a new normal CPPs use a biopsychosocial based self-management regimen to reach a high functionality level, replacing a cure concept, and reaching the consequence of normalcy.

Conclusions

CPP can increase their quality of life perception and their functionality level when they switch their pain focus from an acute cause and effect paradigm to biopsychosocial chronic complex model (Jamieson, Berry & Brown, 2013). The frontline practitioner and IDPMT can lead this change of focus by implementing patient treatment plans that are based on a scholarly understanding of the biopsychosocial model along with characteristics of effective chronic pain management; functional assessment, enhanced patient control and predictability, measures for self-management of pain (Jamieson, Berry & Brown, 2013) while they attend to changes in functional norms (Hartweg & Pickens, 2016, Barley, & Lawson, 2016).
57 A Responders Analysis of Morphine Abuse-Deterrent, Extended-Release, Injection-Molded Tablets in Oral and Intranasal Human Abuse Potential Studies

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Purpose

Misuse or abuse of pain medications has reached epidemic proportions as indicated by the 2015 National Survey of Drug Utilization and Health, in which an estimated 12.5 million adolescents and adults in the United States reported misuse of prescription pain relievers (>90% opioids) in the past year. Misuse/abuse of opioids often involves manipulation (eg, chewing, crushing, dissolving) of the drug to prepare for alternative routes of administration (eg, intranasal, intravenous) and/or to achieve a quicker and more potent euphoric effect. To make manipulation more difficult, abuse-deterrent (AD) formulations, such as morphine AD, extended-release (ER) injection-molded tablets (morphine-ADER-IMT; Egalet US Inc, Wayne, PA), have been developed. Morphine-ADER-IMT is a US Food and Drug Administration (FDA)-approved AD opioid indicated 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. In 2 separate intranasal and oral human abuse potential (HAP) studies, median Drug Liking peak effect (E_{max}) was significantly lower with intact and manipulated morphine-ADER-IMT vs crushed morphine ER. In addition to analysis of Drug Liking E_{max}, FDA guidance for the evaluation of AD opioids recognizes the importance of identifying the magnitude of response to AD opioids vs non-AD comparator products through responder analyses. Responder analyses are frequently conducted in clinical trials to assist in determining a clinically meaningful benefit. Although there is large variability in any such analysis, there is value in examining the incremental improvement in abuse deterrence by evaluating different response thresholds.

Methods

We report the results of a responder analysis conducted in the oral and intranasal HAP studies of morphine-ADER-IMT. Single-center, double-blind, active- and placebo-controlled crossover oral and intranasal HAP studies were conducted in adult volunteers who were nondependent recreational opioid users. Participants in the intranasal study received manipulated high-volume morphine-ADER-IMT (60 mg), manipulated low-volume morphine-ADER-IMT (60 mg), crushed morphine ER (60 mg), intact oral morphine-ADER-IMT (60 mg), and placebo. Participants in the oral study received intact morphine-ADER-IMT (60 mg), manipulated morphine-ADER-IMT (60 mg), crushed morphine ER (60 mg), and placebo. The primary pharmacodynamic endpoint in both studies was At-the-Moment Drug Liking E_{max} measured on a 100-point bipolar Visual Analog Scale (VAS), with a score of 50 indicating neither like nor dislike. The percentage reduction in Drug Liking E_{max} between the intact or manipulated morphine-ADER-IMT treatment groups and the crushed morphine ER treatment group was calculated. A responder was defined as a participant who had at least a prespecified level of reduction (eg, 30% and 50%) in Drug Liking E_{max}. A binomial test of proportions was used to assess the null hypothesis that ≤50% participants were responders.

Results

A total of 46 participants completed all 5 treatments in the intranasal study, and 38 participants completed all 4 treatments in the oral study. In the intranasal study, a majority of participants in the manipulated high-volume morphine-ADER-IMT (76.1%) and low-volume morphine-ADER-IMT (91.3%) treatment groups demonstrated any reduction in Drug Liking E_{max} vs crushed morphine ER. For high-volume morphine-ADER-IMT, the proportions of responders with ≥30% and ≥50% reduction in Drug Liking E_{max} were 60.9% and 41.3%, respectively. For low-volume morphine-ADER-IMT, the proportions of responders with ≥30% and ≥50% reduction in Drug Liking E_{max} were 76.1% and 65.2%, respectively. In the oral study, nearly three-quarters (71.1%) of participants in the manipulated morphine-ADER-IMT group had any reduction in Drug Liking E_{max} vs crushed morphine ER, and the proportions of responders with ≥30% and ≥50% reduction in Drug Liking E_{max} were 36.8% and 23.7%, respectively.

Conclusions

In the majority of participants, Drug Liking E_{max} was lower for manipulated morphine-ADER-IMT vs crushed morphine ER when taken either intranasally or orally. The proportion of responders experiencing ≥30% and ≥50% reduction in Drug Liking E_{max} for manipulated morphine ADER-IMT was greatest in the intranasal study yet still comprised approximately one quarter or more of the participants in the oral study. These data indicate that, across intranasal and oral HAP studies, manipulated morphine-ADER-IMT produced relatively low levels of Drug Liking compared with crushed morphine ER in many participants and exhibits the potential to deter opioid misuse and abuse.

58 Pharmacokinetic Characteristics of Intranasal Administration of Oxycodone ARIR (RoxyBond™), a Novel Abuse-deterrent Formulation of Immediate-Release Oxycodone

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Purpose

Abuse of prescription opioids continues to be a serious public health concern, with as many as 12.5 million individuals aged 12 or older reporting nonmedical use of prescription pain
relievers in 2015 (2015 National Survey on Drug Use and Health. 2016; Substance Abuse and Mental Health Services Administration, Rockville, MD). The introduction of an abuse-deterrent formulation of ER oxycodone significantly reduced reports of misuse and abuse of ER oxycodone; however, early epidemiologic evidence suggests that this decrease was accompanied by a concomitant increase in misuse and abuse of nonabuse-deterrent opioid formulations, such as immediate-release (IR) oxycodone. A recent study indicated that 66% of advanced opioid abusers prefer IR opioids, compared with only 4% preferring ER opioids. Snorting and injection are common routes of IR oxycodone abuse among individuals being assessed for substance abuse treatment; these alternative routes of administration introduce additional risks for serious health concerns. Oxycodone ARIR (RoxyBond™, Daiichi Sankyo, Inc., Basking Ridge, NJ) is an IR oxycodone tablet composed of multiple overlapping barriers that increase the difficulty to manipulate the formulation and limit the amount of oxycodone released if manipulated or extracted for non-oral abuse. Oxycodone ARIR is the first abuse-deterrent formulation of an IR opioid approved by the Food and Drug Administration. Herein, we present the pharmacokinetics (PK) of Oxycodone ARIR when administered intranasally after physical manipulation compared with oral intact Oxycodone ARIR and crushed intranasal IR oxycodone.

Methods

In a randomized, double-blind, double-dummy, active- and placebo-controlled, 4-way crossover study, qualified nondependent recreational opioid users received intact oral oxycodone ARIR 30 mg, crushed intranasal Oxycodone ARIR 30 mg, crushed intranasal IR oxycodone 30 mg, or placebo. Each treatment was separated by at least a 72-hour washout period. Before the treatment phase, subjects first had to pass a naloxone challenge test, to ensure they were not opioid-dependent, and a drug discrimination test, to confirm that subjects were able to distinguish oxycodone from placebo and between the oxycodone doses. The plasma levels of oxycodone were assessed at various times up to 24 hours post-dose and the area under the plasma concentration time curve from 0 hr to the last measurable concentration (AUC0–τ) and various times during the study, the maximum observed plasma concentration (Cmax), time associated with Cmax (Tmax), and abuse quotient (Cmax/Tmax) were calculated. Safety assessments included adverse events (AEs) reports, clinical laboratory assessments, 12-lead electrocardiograms, and physical examinations.

Results

Of the 214 subjects who entered and passed the naloxone challenge test, 158 subjects failed the drug discrimination test, and 25 subjects discontinued from the study for various reasons (withdrew consent, discontinued due to AE, withdrawn by investigator because of emesis/non-compliance/protocol violation); 31 subjects entered the treatment phase and were included in the PK analysis and 29 subjects completed the treatment phase. All intranasal doses were completely (100%) insufflated as confirmed by intranasal check. Intranasally administered Oxycodone ARIR exhibited a mean Cmax of 42.7 ng/mL, oral administration of intact Oxycodone ARER exhibited a mean Cmax of 58.4 ng/mL, and intranasal administration of IR oxycodone exhibited a mean Cmax of 56.5 ng/mL. The median Tmax for oxycodone was longer for crushed intranasal Oxycodone ARIR than for intact oral Oxycodone ARIR and crushed intranasal IR oxycodone (2.3 vs 1.3 and 1.7 hr). Crushed intranasal Oxycodone ARIR exhibited a lower peak oxycodone plasma concentration (Cmax 28% reduction) and a 35% longer Tmax relative to crushed intranasal IR oxycodone. Early oxycodone exposure was 57% lower for crushed intranasal Oxycodone ARIR and 78% lower for intact oral Oxycodone ARIR than for crushed intranasal IR oxycodone (AUC0–0.5h: 4.4 and 2.2 vs 10.2 ng/hr/mL, respectively; P < 0.0001). The abuse quotient for crushed intranasal Oxycodone ARIR was 53% and 43% lower than that of intact oral Oxycodone ARIR and crushed intranasal oxycodone IR (21.93 vs 46.81 and 38.42 ng/mL/hr, respectively). The most common AEs included generalized pruritus, vomiting, and nausea, all of which are common opioid-related AEs.

Conclusions

Intranasal administration of crushed Oxycodone ARIR led to slower and lower oxycodone absorption compared with intact oral Oxycodone ARIR and crushed intranasal IR oxycodone. These results are consistent with significantly lower drug liking reported by recreational abusers and suggest that the physicochemical characteristics of Oxycodone ARIR successfully limit absorption of oxycodone via the intranasal route when compared with IR oxycodone.

59 Pharmacokinetic Characteristics of Oral and Intranasal Administration of Morphine ARER (MorphaBond™ ER), a Novel Abuse-deterrent Formulation of Morphine

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Purpose

Despite efforts to increase public awareness and the implementation of prescription drug monitoring programs, abuse of prescription opioids remains a serious public health concern, with as many as 12.5 million individuals aged 12 or older reported nonmedical use of prescription pain relievers (2015 National Survey on Drug Use and Health. 2016; Substance Abuse and Mental Health Services Administration, Rockville, MD). Extended-release (ER) opioid formulations are often targeted for misuse and abuse because they contain high amounts of opioid. Drug abusers frequently use physical manipulation to increase the opioid’s bioavailability for intravenous, intranasal, and oral abuse. Morphine ARER (abusedeterrent extended-release), MorphaBondä ER, Daiichi Sankyo, Inc., Basking Ridge, NJ) is an ER morphine formulated with inactive ingredients that form multiple overlapping barriers to
deter misuse and abuse. In vitro studies demonstrate that morphine ARER resists physical manipulation and chemical extraction, forms a viscous nonsyringeable material in liquid environments, and retains its ER characteristics despite manipulation. We have previously shown that crushed intranasal morphine ARER has significantly lower maximum drug liking (P < 0.0001) when compared with crushed intranasal morphine ER (Webster LR, et al. Pain Med. 2016Sep20. pii: pnw213). Herein, we present the pharmacokinetics (PK) of morphine ARER when administered intranasally after physical manipulation or orally as an intact tablet compared with crushed intranasal morphine ER. In addition, we explore the correlation between morphine PK and the pharmacodynamic (PD) parameter of drug liking.

Methods

In a randomized, double-blind, double-dummy, placebo-controlled, 4-way crossover study, qualified nondependent recreational opioid users received intact oral morphine ARER 60 mg, crushed intranasal morphine ARER 60 mg, crushed intranasal morphine ER 60 mg, or placebo. Each treatment was separated by a 7-day washout period. The plasma levels of morphine were assessed at various times up to 24 hours postdose and the maximum observed plasma concentration (Cmax), time associated with Cmax (Tmax), abuse quotient (Cmax/Tmax). The correlation between morphine PK and the PD parameter of drug liking, a measure of abuse potential, was also evaluated using logarithmic regression. Safety assessments included adverse events (AEs), clinical laboratory assessments, 12-lead electrocardiograms, and physical examination findings.

Results

Of the 48 subjects who entered and passed the naloxone challenge test, 27 passed the drug discrimination test, entered the treatment phase, and were included in the PK analysis; 25 subjects completed the treatment phase. All intranasal doses were completely (100%) insufflated as confirmed by intranasal check. Intranasal and orally administered morphine ARER exhibited a mean Cmax of 26.2 and 18.6 ng/mL, respectively; intranasal administration of morphine ER exhibited a mean Cmax of 49.5 ng/mL. Based on least squares (LS) means, the morphine Cmax was 49% lower for crushed intranasal morphine ARER than for crushed intranasal morphine ER. The median Tmax for morphine was 46% longer for crushed intranasal morphine ARER than for crushed intranasal morphine ER (1.6 hr vs 1.1 hr; P < .0001). The PK profile of morphine ARER was similar after intranasal or oral administration. The abuse quotient for crushed intranasal and intact oral morphine ARER was 77% and 84% lower than that for crushed intranasal morphine ER, respectively (16.7 ng/mL/hr and 12.1 ng/mL/hr vs 74 ng/mL/hr). Mean morphine Cmax, Tmax, and abuse quotient correlated strongly with maximum drug liking (R2 ≥ 0.9795). The most common AEs included nasal congestion, rhinorrhea, and epistaxis, all of which are associated with intranasal administration. Classic opioid-related AEs were observed including nausea, vomiting, and generalized pruritus.

Conclusions

The similar PK profiles of crushed intranasal and intact oral morphine ARER suggest that physical manipulation and intranasal administration does not defeat the ER mechanism of morphine ARER. The strong correlation between mean morphine Cmax, Tmax, and abuse quotient with drug liking suggests that the PK profile of morphine ARER was predictive of a lower abuse potential.

60 Real-World Misuse, Abuse, and Dependence of Abuse Deterrent versus Non-Abuse-Deterrent Extended Release Morphine in Medicaid Patients

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Purpose

In an effort to help curtail the widespread use, misuse, abuse and diversion of opioid analgesics, there has been considerable effort directed towards the development of abuse-deterrent formulations of the drugs (ADFs). Abuse deterrence may be achieved in a variety of ways, including making the medication difficult to crush, insoluble in water or other solvents, adding aversive agents, or combining with a sequestered opioid antagonist. The purpose of the current study was to quantify misuse, abuse, and dependence in a Medicaid patient sample prescribed an abuse deterrent formulation of extended release morphine (EMBEDA) or non-abuse deterrent extended release morphine (ERM). The Medicaid population was selected since studies have demonstrated that Medicaid patients are dispensed opioids at a higher rate, abuse opioids at a higher rate, and experience more morbidity and mortality than other types of insured populations.[1,2] Thus, they seem to be an appropriate population to assess the real-world use and abuse of ER morphine.

References


Methods

In this retrospective database study, de-identified administrative medical and pharmacy claims data were analyzed for 10 Medicaid states from 1/1/2015 to 9/30/2016. (Note: Because of contractual privacy issues, the names of the states cannot be
disclosed for this ongoing study.) Patients were included in study if they received a prescription for EMBEDA, an abuse deterrent ER morphine, or an oral, non-abuse-deterrent ER morphine product during this period, were ≥18 years old, and had continuous eligibility for ≥6 months prior to and 6 months following the first morphine prescription. The first prescription for an oral ER morphine product was considered the index date. Patients who resided in a skilled nursing or hospice facility or had a cancer diagnosis at any point during the study period were excluded. Patients were placed into mutually exclusive cohorts based on product used. Patients using EMBEDA at any time during the follow up period were placed in the EMBEDA cohort and the remainder in ERM. Demographics, comorbidity burden, abuse/dependence, non-fatal overdose, emergency department (ED) visits, ED or inpatient readmissions (within 30 days of initial visit) were determined for each study participant. An overall measure of misuse and abuse was calculated in which patients were counted if they had any of the following: an abuse/dependence diagnosis, nonfatal overdose, ED visits, or readmission to an ED or inpatient hospital. In order to account for differences in follow-up all counts are expressed per 100 patient years.

Results

There were 3,744 patients who received EMBEDA and 7,018 who received ERM. The average age in each cohort was 46 years old. The EMBEDA cohort was 65% female and ERM group 61% female. Comorbidity burden was similar with an average Charlson Comorbidity Index of 1.3 for the EMBEDA group and 1.4 for the ERM group. An opioid prescription in the six-month pre-index period was received by 90% of the EMBEDA cohort and 87% of the ERM cohort. The number of events per 100 patient years in patients with a diagnosis of abuse/dependence increased from 2.08 (95% CI: 1.78, 2.38) in the pre-index period to 2.93 (2.76, 3.11) in the post index period for EMBEDA compared to 1.95 (1.74, 2.17) to 4.07 (3.88, 4.26) for ERM. Patients with nonfatal overdose increased from 0.01 (0.003) per 100 patient years to 0.07 (0.04, 0.09) for EMBEDA and 0 to 0.10 (0.07, 0.13) for ERM. Patients with an ED visit went from 3.01 (3.65, 3.38) to 4.52 (4.31, 4.74) visits per 100 patient years for EMBEDA and 3.19 (2.92, 3.47) to 5.50 (5.28, 5.72) for ERM. Readmission to an ED or inpatient hospital increased from 0.77 (0.68, 0.86) to 1.86 (1.71, 2.01) per 100 patient years for EMBEDA cohort and 1.05 (0.95, 1.15) to 3.07 (2.89, 3.24) for ERM. The opioid abuse overall composite score increased from 2.74 in the pre-index period to 4.06 (difference: 1.32, CI: 1.20, 1.43) in the post-index period in the EMBEDA cohort compared to 2.90 to 6.10 (difference: 3.2, CI: 3.02, 3.88) in the ERM group.

Conclusions

Misuse, abuse, and dependence of standard ER morphine products or an ADO preparation were evaluated in a Medicaid population. Misuse, abuse and dependence events were numerically lower in patients receiving EMBEDA compared to those receiving ERM. The main limitation of our study is that state formularies drive prescribing choice so physicians weren’t always able to choose between ADO and non-ADO products. However, as utilization of these products increases over time it is anticipated that more robust differences will be observed between non-ADO and ADO formulations of morphine.

61 Characteristics of Tapentadol Extended-Release Formulation

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Purpose

Non-medical use of opioid analgesics, including abuse, misuse, and diversion, is a substantial public health concern in the US.1,2 Attempts to reduce or prevent opioid abuse and misuse have included prescription drug monitoring programs, risk evaluation and mitigation strategies, and efforts to create abuse-deterrent opioid formulations (ADFs).

Based on the FDA Guidance on Abuse Deterrent Opioids – Evaluation and Labeling, evaluation of abuse deterrent properties includes laboratory manipulation and extraction studies (Category 1), pharmacokinetic studies (Category 2), human abuse potential studies (Category 3) and postmarketing studies (Category 4).

Category 1 studies are intended to estimate the effort required to defeat or compromise the potentially abuse-deterrent properties of a formulation and to inform design of Category 2 and 3 clinical studies.

There are several opioid formulations with FDA-approved labeling describing abuse-deterrent properties. Among these is the extended-release (ER) oxycodone formulation commonly known as OxyContin® OP (OOP, OxyContin Purdue).

Tapentadol is a centrally acting, multi-mechanistic opioid analgesic. Although the exact mechanism of action of tapentadol is unknown, preclinical data suggest that it has a dual mechanism of action, with both µ-opioid receptor agonism and norepinephrine reuptake inhibition combined in one molecule. Tapentadol ER does not have FDA approved ADF labeling.

The objective of these Category 1 studies was to assess abuse-deterrent characteristics of tapentadol ER when tablets were subjected to various manipulations, with OOP as a comparator.

Methods

Tapentadol ER and OOP (comparator) tablets were subjected to various physical and chemical manipulations, simulating methods commonly undertaken by abusers to prepare tablets for oral ingestion, insufflation, or injection.

Study 1: Physical Manipulation

• Using common household items, physical manipulations were performed on intact tablets both with and without pretreatments (heating and freezing).
Each manipulation was performed 3 times and each time the difficulty to produce a powder was recorded on a scale from 1 (very easy/little effort) to 5 (very difficult/extreme effort).

Once the optimal manipulation for each test article was identified, a composite of several manipulated tablets was created and sifted through a stack of sieves for particle size analysis.

Study 2: Syringeability

- Both intact and manipulated tablets were tested for syringeability. Each sample was mixed with water (5 or 10 mL), extracted for either 5 or 10 minutes, with or without agitation, or was heated until brought to a rolling boil.
- Continuous attempts were made to aspirate for 1 minute for each needle size (ranging from 27 to 18 gauge). Success in aspiration (syringeability) was defined as \( \geq 20\% \) of the preparatory volume successfully aspirated (drawn into the syringe).
- Successful aspirations were analyzed by high performance liquid chromatography for percent recovery of active ingredient.

Study 3: Smokeability

- Degradation was observed across all conditions tested for both tapentadol HCl drug substance and manipulated tapentadol ER tablets.
- Very low vaporization of tapentadol (<10%) occurred with tapentadol ER.

Limitations:

- Generalization of these study results is limited by several factors:
  - Attempted manipulations were conducted for specific time intervals, such that the effects of longer intervals are unknown.
  - The number of solvents examined was limited and did not include some common potential solvents.
  - Study 3 lacked a comparator.

Conclusions

- Both tapentadol ER and OOP were resistant to physical manipulations.
- Syringeability of both tapentadol ER and OOP was very difficult with low yield in terms of active ingredient.
- Smokeability assessments showed low rates of recovery of active ingredient from vaporized tapentadol ER and tapentadol drug substance.
- These Category 1 studies suggest that tapentadol ER has comparable properties to OOP, an opioid with FDA-approved abuse deterrent labelling.

62 Knowledge, Skills, and Attitudes Regarding the use of Medical Cannabis in the Hospice Population: An Educational Intervention
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Purpose

Currently, 28 states and the District of Columbia have legalized or decriminalized cannabis (marijuana) for medical use, beginning with California in 1996. While medical cannabis (MC) remains illegal from a federal perspective, providers who practice in the states that have legalized it are faced with...
questions regarding the benefits and risks of MC. With more and more states putting the issue on their legislative ballots, physicians and other healthcare providers are finding themselves in the midst of the cannabis debate. The benefits of medical cannabis have been shown in nausea and vomiting associated with cancer chemotherapy, cachexia associated with HIV/AIDS, and certain kinds of neuropathic pain or treatment-resistant cancer pain. However, it is unclear how comfortable hospice providers are with the concept of medical cannabis. The aim of this study is to determine changes in knowledge, skills, and attitudes (KSA) of hospice providers regarding the use of medical cannabis in the hospice population.

Methods
The current study expands upon previous research by identifying medical cannabis educational needs among hospice practitioners and creating and evaluating an online course designed to meet those needs. Attitudes, skills, and knowledge were analyzed in six learning domains: pharmacology, evidence/indications for use, formulations and dosing, adverse effects/safety, drug interactions, and patient counseling. Participants took a pre- and post-course survey to assess changes in KSA. Participant demographics were analyzed using descriptive statistics. To detect any differences between pre- and post-survey, a paired t-test was used to reduce inter-subject variability. In addition, the association of mean scores of each domain in the post survey according to demographic characteristics was analyzed using an independent t-test. Analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

Results
A total of 94 hospice providers representing 16 states participated in the survey with the majority from Maryland (41.5%). 76.6% of respondents were nurses, with 45.7% of participants having practiced in hospice less than 3 years. Attitudes surrounding the six domains were overall positive and did not change significantly after the educational intervention (pre = 2.86/post = 2.84, p=0.41). Perceived skills in the six domains increased significantly after the online course, with average responses improving from 1.24 to 2.15 (p<0.0001). Knowledge significantly improved with the educational intervention, with 41% of respondents answering correctly prior to the course, and 78% of respondents answering correctly post-course (p<0.0001). Post survey mean scores for attitudes and knowledge in each domain were not significantly different between nurses and social workers. Perceived skills in 2 domains (formulations/dosing and patient counseling) were significantly different between nurses and social workers in the post test. There was a significant difference in attitudes in all domains between participants who have practiced in hospice < 3 years or > 4 years, with those practitioners with less experience having more positive attitudes about MC, however, there was no difference in perceived skills or knowledge. There was no difference in KSA between respondents who are board certified in hospice medicine versus those who are not.

Conclusions
Providers’ attitudes regarding the use of medical cannabis in hospice did not significantly change after the education intervention and was overwhelmingly positive both before and after. Both the perception of skills and direct knowledge was significantly increased after the education intervention, with providers reporting more positive skills and >75% of respondents answering questions correctly after the intervention.

63 Anticholinergic Burden in Hospice Patients with Dementia
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Purpose
Literature has illustrated that end-of-life (EOL) patients with dementia have an increased risk for anticholinergic toxicities due to age-related pharmacokinetic and physiologic changes in conjunction with an increased susceptibility to drug-induced cognitive impairments.1,2 Although this risk is well documented, the use of medications with anticholinergic properties and their questionable benefits remains prevalent in EOL patients with dementia.3,4 The aim of this study is to compare prescribing practices within hospice for patients with and without dementia and characterize anticholinergic burden (ACB) among hospice patients with dementia.

Methods
A retrospective review of a medication and patient information database from a large national hospice organization was conducted. Patients were included in this study if they had a diagnosis of dementia and were admitted to hospice after January 1, 2016 and discharged by death by December 31, 2016. From this population, a smaller cohort of dementia patients were randomly selected and matched with a comparator cohort.

Results
Patient medical records will be reviewed and medications with anticholinergic properties will be identified to characterize ACB and anticholinergic prescribing patterns.

Conclusions
Determining the ACB in patients with advanced dementia can further illustrate the need for hospice and palliative care providers to continuously evaluate the patient’s medication regimen.
64 Phase 3 Studies (EVOLVE-1 & EVOLVE-2) of Galcanezumab in Episodic Migraine: Results of 6-Month Treatment Phase

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Purpose

Galcanezumab, a humanized monoclonal antibody that selectively binds to the calcitonin gene-related peptide, was investigated in two Phase 3 studies (EVOLVE-1 and EVOLVE-2) to determine superiority to placebo in the prevention of migraine headache.

Methods

EVOLVE-1 and EVOLVE-2 were double-blind, 6-month studies in patients with episodic migraine (4 to 14 monthly migraine headache days [MHD]) conducted in North America and globally, respectively. Patients were randomized 2:1:1 to monthly subcutaneous injections of placebo, galcanezumab 120 mg or 240 mg. Primary endpoint was overall mean change from baseline in the number of monthly MHD during Months 1-6. Key secondary measures included rates of ≥50%, ≥75%, and 100% reduction in monthly MHD and overall mean change from baseline in monthly MHD with acute migraine treatments, and mean change from baseline over Months 4-6 on the Role Function-Restrictive domain score of the Migraine-Specific Quality of Life Questionnaire (MSQ-RFR) and Patient Global Impression-Severity of Illness (PGI-S).

Results

Baseline mean number of monthly MHD was 9.1 for both studies. Both galcanezumab doses demonstrated a statistically significant improvement compared with placebo (both studies p<.001) for overall mean change in monthly MHD (EVOLVE-1: placebo=-2.81; GMB 120 mg=-4.73; GMB 240 mg=-4.57; EVOLVE-2: placebo=-2.28; GMB 120 mg=-4.29; GMB 240 mg=-4.18). Percentage of patients with MHD reductions of ≥50%, ≥75%, or 100% were significantly higher for each galcanezumab dose compared with placebo (both studies p<.001). Patients had a significantly greater overall mean reduction of monthly number of MHD with acute migraine treatment for both galcanezumab doses relative to placebo (both studies p<.001). Mean change in MSQ-RFR and PGI-S ratings were statistically significant for each galcanezumab dose versus placebo (MSQ-RFR: p<.001 and PGI-S: p<.05, in both studies). There were no statistically significant differences between galcanezumab and placebo on the most common treatment-emergent adverse events except for a greater incidence of injection-site pruritus (both studies/doses p<.01) and injection-site reaction (both studies/doses p<.05), and injection-site erythema (p<.05, galcanezumab 240 mg) in EVOLVE-2.

Conclusions

Both doses of galcanezumab met the primary and all key secondary objectives, after adjusting for multiplicity. Treatment effects were similar across galcanezumab doses for efficacy, and safety; however, there was a higher rate of injection-site pruritus and reaction in galcanezumab-treated patients in both studies. EVOLVE-1 and EVOLVE-2 demonstrated that galcanezumab, at either 120 mg or 240 mg monthly, provided clinical benefit and improved function in patients with episodic migraine.

Studies were registered as NCT02614183 and NCT02614196 at ClinicalTrials.gov.

65 A Phase 3 Placebo-Controlled Study of Galcanezumab in Patients with Chronic Migraine: Results from the 3-month Double-Blind Treatment Phase of the REGAIN study

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Purpose

To determine if galcanezumab (GMB), a humanized monoclonal antibody that selectively binds to the calcitonin gene-related peptide (CGRP), is superior to placebo in the prevention of chronic migraine at doses of 120 mg or 240 mg/month.

Methods

This was a Phase 3, double-blind, randomized, placebo-controlled, 3-month study with a 9-month open-label extension. Eligible patients 18-65 years of age with chronic migraine, defined as ≥15 headache days per month, of which at least 8 met criteria for migraine, were randomized 2:1:1 to subcutaneous injections of placebo (N=558), GMB 120 mg (N=278), or GMB 240 mg (N=277) given once monthly for 3 months. The primary endpoint was the overall mean change from baseline in the number of monthly migraine headache days (MHD) during the 3-month double-blind treatment phase. Key secondary measures included the percentage of patients with ≥50%, ≥75%, and 100% reduction in monthly MHD, reduction in monthly MHD requiring acute migraine treatments, change in the Role Function-Restrictive (RF-R) domain score of the Migraine-Specific Quality of Life Questionnaire (MSQ), and change in the Patient Global Impression-Severity (PGI-S) rating.

Results

Mean number of monthly MHD at baseline was 19.4 and was similar across treatment groups. At the primary endpoint, both GMB doses demonstrated statistically significant difference from placebo in overall mean reduction (least squares [LS] mean change) in number of monthly MHD during the 3-month double-blind treatment phase: placebo: -2.74, GMB 120 mg: -4.83, GMB 240 mg: -4.62 (p<.001 for each dose).
Nocebo effects in pain management: psychobehavioral mechanisms and practical strategies for improving clinical outcomes

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Purpose

Nocebo effects can be present in any therapeutic setting depending upon environmental and interpersonal contexts, as well as patients’ individual experiences and memories. Within pain management, nocebo effects present a challenge that can strongly and negatively impact treatment effectiveness and pharmacological efficacy, and thus clinical outcomes in both acute and chronic pain. Herein, we provide a comprehensive summary describing the neuropsychobiological underpinnings of nocebo algesia and hyperalgesia, along with ethically acceptable and practical clinical strategies to help prevent and reduce nocebo effects in pain management settings.

Methods

We conducted a comprehensive search of the literature highlighting the psychoneurobiological mechanisms of the nocebo effect, the implications of nocebo effects in clinical settings, and how can patient-practitioner interactions influence clinical pain outcomes. Articles were selected and reviewed based on clinical relevance.

Results

Nocebo algesia and hyperalgesia are the product of patients’ negative expectancies and perceptions regarding the clinical environment, treatments, practitioners, or interventions. Negative expectancies can be shaped through verbal suggestions, prior experiences, learning, and negative conditioning with the same or related treatments, as well as through social observation of others in pain.

Individual psychological characteristics and traits, such as pain catastrophizing, anxiety sensitivity, and physiological suggestibility can promote susceptibility to nocebo effects. Healthcare providers can inadvertently promote the activation of nocebo effects through subconscious subjective behavioral cues shaped by individual beliefs and expectancies that can lead patients to develop negative expectancies. Environmental cues arising from the clinical context, for example, the appearance of medical devices, can further promote patients’ negative expectancies.

This complex interplay of cognitive-affective factors leads to observable neurophysiological changes that can initiate and promote nocebo effects, and include: activation of the hypothalamic–pituitary–adrenal (HPA) axis and the cholecystokininergic (CCK) system; hypoactivity of the mesolimbic dopaminergic and opioidergic systems; decreased connectivity between the anterior cingulate cortex (ACC) and the fusiform gyrus; increased activity of the nucleus cuneiformis (nCF) region, the insular cortex, the hippocampus, the periaqueductal gray area (PGA), and the ipsilateral dorsal horn; and increased levels of low-frequency α-waves.

Nocebo effects in pain patients can be minimized through practical strategies in the clinical setting by (1) preventing negative patient–practitioner interactions during a treatment or intervention; (2) helping alleviate patients’ emotional burden while undergoing pharmacological interventions; (3) limiting excessive negative information; (4) avoiding aversive cued and contextual conditioning; and by (5) promoting positive therapeutic information.

Conclusions

The nocebo effect is a neuropsychobiological phenomenon that has the power to significantly impact the effectiveness of pain management therapies and even block the pharmacological efficacy of potent analgesic and narcotic medications. The cognitive-affective factors that drive the negative expectancies fueling this effect, including genetics and psychological traits, can widely vary among patients, and thus their full control in the complex clinical setting may seem unattainable. Nonetheless, pragmatic strategies can help minimize and prevent the consolidation of negative expectancies in pain patients to improve support therapeutic efforts and clinical
outcomes. Further translational research on the role of nocebo effects in clinical pain settings is needed.

67 Understanding the Perspective of Young Adults regarding Prescription Drug Abuse to Develop an Effective Educational Platform

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Purpose

Prescription drug abuse, most notably painkillers (opioids) and anxiolytics (benzodiazepines), has reached epidemic proportions in the United States. Headlines in both the medical and lay press on a nearly daily basis as an increasingly problematic public health issue. The yearly deaths resulting from overdose have amounted to roughly 15,000 per year out of 2.1 million abusers. These abusers include a wide spectrum of ages; however, the focus of this analysis is on the younger population. There is a rising concern about the increase in teenage and young adult deaths related to prescription drug abuse. According to a statistic by the Foundation for a Drug-Free World, 50% of teens believe painkillers are less harmful than street drugs. This and other misconceptions exist among many young persons, despite the well-known potential for lethality and long term deterioration of health and drug dependency from abuse of opioids.

We hypothesize that teenage abuse of painkillers (opioids) stems from a lack of proper education of the negative effects of these drugs. The goal of this study is to survey young adults ages 14-18 about their perception of prescription drug abuse and access to prescription drugs for illicit use. We desire to collect from the survey to provide an analysis to help determine the most effective platform (i.e., lectures, web/mobile social media, YouTube) to educate young adults on commonly abused medications such as Xanax or Oxycodone using the most effective platform as per survey results.

Methods

A survey consisting of 12 questions was conducted among high school students in the Kansas City area as the first stage. These questions primarily focused on gaining the perspectives of teenagers about their belief, knowledge, and attitude towards prescription drug abuse and overdose deaths. The survey was administered through Survey Monkey after obtaining permission from the school administration. The identities of the survey responders were kept confidential, and the investigators who conducted the survey analysis have access only to the aggregate of the responses and to anonymous individual responses.

Results

Survey responders were between the ages of 14 and 18 with 124 surveys started and 108 surveys completed. Gender distribution was almost equal (53% female, 47% male). Half of the students who responded either knew someone or had personally used prescription drugs for recreationally usage, among which 62.2% answered yes to using opioids recreationally or knowing someone who had. Reported usage of stimulants was even higher at 71.1%. An approximately equal percentage of responders answered that these prescription drugs were obtained from a family member, purchased from an acquaintance, or prescribed by a healthcare provider. Notably, only a minority of the students reported using opioids and stimulants together or in conjunction with alcohol (11.1% most of the time, 15.6% occasionally, 11.1% rarely, 62.2% never/not to my knowledge).

Surprisingly, the vast majority of teenagers (95.6%) knew about the serious side effects of abusing prescription drugs. Only 42.2% of responders reported having any drug abuse education, but a majority of the students (55.6%) did respond that their behavior may change if they had more education and awareness of this problem. Unexpectedly, the preferred platform for education in this group still remains lectures in conjunction with existing school programs (48.9%). The remainder of the students preferred to be educated via web/mobile platform such as Instagram (22.2%) or YouTube (11.1%) with the rest of the students responding with Other (17.8%) A majority of responders preferred the information to be presented in a video format (60%).

Conclusions

The results of the survey confirm that extent of the prescription drug abuse problem amongst teenagers is alarming. We were also surprised that 44.4% responded that they may not change their usage habits even after knowing the serious side effects of using prescription drugs recreationally. But it is encouraging to know that the other half are willing to change their habits (55.6%).

We intend to extend the survey to a larger student body across the country and will seek an educational grant to develop a comprehensive educational program and implement it in schools across the country with teenage ambassadors.

68 Group Chronic Pain Classes Improve Overall Perception of Pain Scores

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Purpose

Pain is usually temporary, but for some people it can last over time and is considered chronic. It is important to note that pain can be experienced both physically and emotionally. People with chronic pain (pain that persists six months or longer) often find that pain affects more than just their neck, shoulder, or back. Chronic pain can cause people to feel they are no longer in control of their lives. They instead feel they need to rely on other people for help or medications. All of this can cause emotional distress. The combination of physical and emotional pain can affect a person’s ability to engage in social and recreational activities, and even work. A lack of activity can contribute to more isolation, depression, and physical deconditioning, which can make pain even worse. The purpose of this program was to assess the utility of a family physician facilitated group course
for chronic pain patients incorporating many non-medical therapies found to be helpful in the management of chronic pain.

Methods

Patients were recruited from Dr. Holowaty’s family practice as well as through Facebook advertising. Twenty patients were recruited. There was a $10 charge to cover the printing of an accompanying book that included homework sheets. Six classes took place over 90 minutes each week. The topics included pain education, physical activity, cognitive behavioral therapy, mindfulness and meditation, exposure to psychotherapy, acupuncture, and TENS, pacing, reframing yourself with others, sleep and nutrition, and flare planning. Activities included exercise, tai chi, meditation, progressive muscle relaxation and open discussions. Videos and guest lecturers (meditation coach, physiotherapist, tai chi instructors) were also used to promote adult learning and engagement. Dr. Holowaty ran all of the classes, except for the guest lecture material. The program was assessed at the end of the sixth class with an anonymous written survey.

Results

Twelve out of twenty participants attended the sixth class, in keeping with what is known about group attendance. Of the final twelve participants, 100% would recommend the class to someone else, and 100% felt that they had a better understanding of chronic pain. 83% of the participants felt their pain had improved over the six weeks. The average decrease in pain among the final twelve was 41%. The aspect people liked most was the interaction with others. The aspect people liked least was they felt the classes were too short.

Conclusions

Non-medical group interventions for chronic pain can have tremendous impact. Such a program can be easily put together by a family physician with an interest in chronic pain. Although this was a very small study, its encouraging pilot findings provide information for the instructional design of a course that could be facilitated by anyone.

69 Title: A two-year retrospective study of neuropathic pain management with gabapentin or pregabalin – Are we optimizing use in clinical practice?

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Purpose

Gabapentin and pregabalin are often considered first-line treatment options for neuropathic pain. Despite sharing the same mechanism of action, there are key pharmacologic differences between the agents. Therapeutic ranges have been established from clinical trials (gabapentin 1800-3600 mg/day; pregabalin: 150-600 mg/day), which were achieved via rapid titration per study protocols. However, prescribing practices vary considerably and optimal initial dosing, titration rate, and time to therapeutic dose are largely unknown in actual clinical practice for gabapentin and pregabalin. The purpose of this study is to evaluate real world prescribing practices of pregabalin and gabapentin and the corresponding impact on patients achieving the therapeutic range as well as the time required to reach a therapeutic dose (TD).

Methods

This study was a single healthcare system, retrospective, observational analysis using medical records and pharmacy claims data from VA Tennessee Valley Healthcare System. Patients with a new start outpatient prescription for gabapentin or pregabalin for a pain indication between January 1, 2011 and December 31, 2015 were identified and observed for 24 months after therapy initiation. New initiations were defined as no prescription for the same study medication 5 years prior or prescription for the comparator medication 1 year prior. The primary endpoints were percentage of patients achieving TD (gabapentin ≥ 1800 mg/day; pregabalin ≥ 150 mg/day) and time to TD. Secondary endpoints evaluated were prescribing patterns in each group (prescriber specialty, prescription type i.e. fixed dosing or titration, starting dose, and ending dose), percentage of patients receiving TD who remained on therapy at the end of 2-year follow-up period, discontinuation rates in each group, and common causes of discontinuations (intolerance, lack of efficacy, other, or unknown).

Results

1550 charts were reviewed to include 302 patients, 151 in the gabapentin group and 151 in the pregabalin group. The mean starting daily dose was 529.8 ± 330.4 mg for gabapentin and 122.2 ± 66.3 mg for pregabalin. The mean final daily dose was 1067.1 ± 680.4 mg for gabapentin and 231 ± 134.8 mg for pregabalin. The gabapentin group had 38 patients (25.2%) achieve therapeutic dose compared to 120 patients (79.5%) in the pregabalin group (P < 0.001). Median time to therapeutic dosing and inter-quartile range (IQR) for gabapentin was 270 days (IQR: 136-551) compared to 1 day (IQR: 1-14) with pregabalin. Discontinuations secondary to intolerance were documented in 37 patients (24.5%) receiving pregabalin and in 20 patients (13.2%) receiving gabapentin (P < 0.05). There were more discontinuations secondary to lack of efficacy in the gabapentin arm however our study was not powered for this analysis.

Conclusions

In our retrospective analysis, suboptimal doses of gabapentin are being utilized and maintained in patients with neuropathic type pain. Patients initiated on pregabalin were more likely to reach TD, with majority of patients achieving TD upon initiation. Our findings suggest the need for provider education regarding therapeutic dose...
ranges of gabapentin. Possible areas of improvement include development of titration protocols aimed at achieving therapeutic doses.

70 Comparing Two Combined Treatment Method For Chronic LBP: Conventional Physiotherapy With LLLT And Conventional Physiotherapy With Dry Needling: Randomized Controlled Study

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Purpose
Low back pain (LBP) is most commonly affects the individuals with a lifetime prevalence of 60 – 70%. Chronic low back pain (CLBP) is a multidimensional problem. There are various treatment approaches available to CLBP. Recently, Dry Needling and LLLT has the more significant emphasis even though other various treatments are available.

The purpose is comparing the effectiveness of LLLT and Dry Needling treatment on pain, lumbar ROM and functional disability in chronic low back pain participants.

Methods
A total 150 chronic low back pain individuals were randomly assigned into three groups: 1. conventional physiotherapy (Control Group), 2. conventional physiotherapy with laser therapy (Experimental Group-1), and 3. conventional physiotherapy with Dry Needling (Experimental group2), n=50 in each group. All patients were treated for 3weeks and improvement was assessed in lumbar range of motion (M.ST) and pain VAS used at prior interventions and after 3weeks.

Results
In this study results showed that laser group and dry Needling (DN) treatment group were effective in all the measures when compared to control group. LLLT was more effective in improving lumbar ROM and reduction of pain when compared to DN.

Conclusions
The result of the study indicates that LLLT treatment was found to be superior to DN in improving lumbar ROM and reduction of pain among chronic low back pain participants.

71 A Review of Measures Assessing Opioid-Sparing Effects of Analgesics in Patients with Chronic Pain

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Purpose
Prescription opioid analgesics are associated with the risk of abuse, diversion, and overdose. Around 2.1 million Americans suffered from substance use disorder related to prescription opioids in 2012.1 The development of efficacious, opioid-sparing analgesics is one of the many strategies that may help reduce opioid abuse and addiction. Additionally, opioid use is often accompanied by bothersome side effects such as nausea, vomiting, constipation, sedation, and dizziness, which may lead to further health-related complications. Patients experiencing opioid-related side effects reported higher mean healthcare costs compared to those without side effects.2 The frequency, nature and severity of opioid-related side effects depend on the duration and dose of the opioid medication, and thus different levels of exposure may result in differential health effects. Altogether, opioid-induced adverse effects (AEs) can significantly impact patients’ quality of life, increase morbidity and mortality, and lead to greater healthcare utilization and costs. The prevalence, seriousness, and burden of opioid-induced AEs and abuse has spurred a paradigm shift toward an increased awareness of the importance of incorporating, to the extent possible, an opioid-sparing pain management approach for patients with chronic noncancer pain. Despite the increased interest in the development and clinical evaluation of novel non-opioid analgesics and multimodal approaches to pain management, there are no guidelines focusing on opioid-sparing outcomes, methods of assessment, and evaluation of associated clinical benefits. Accordingly, the objective of this study is to identify and evaluate commonly used outcomes, measures and scales used to study opioid-sparing effects of analgesics.

Methods
Opioid experienced patients with chronic pain were the population of interest for this review. We defined “opioid-sparing outcomes” using two distinct criteria: i) decrease in opioid consumption in clinical trials that allow patients to consume opioid analgesics as rescue medication; ii) decrease in opioid-induced AEs. To assess how these two types of opioid-sparing outcomes are measured in clinical studies, we performed two separate sets of comprehensive literature searches using the Medline and ClinicalTrials.gov databases to identify articles published between January 1, 2000 and February 1, 2017. For the first search, aimed at identifying studies that included outcomes related to reduction in opioid consumption, we used different combinations of the following keywords with Boolean terms: “opioid consumption”, “chronic pain”, “opioid”, “narcotics”, “rescue medication”, “reduction in opioid consumption” and “opioid-sparing”. To conduct the second search, aimed at identifying instruments used to assess opioid-induced AEs, we used the following keywords with Boolean terms: “narcotics”, “analgesics, opioid”, “chronic pain”, “adverse effects”, “drug-related side effects and adverse reactions”, “scale”, “measure”, “instrument”, and “questionnaire”. Results were restricted to articles published in English and conducted in human subjects. The psychometric properties (e.g., reliability, validity) of the selected instruments were evaluated.

Results
Our review identified several clinical trials that assessed rescue medication use as a secondary endpoint. The difference in the use of rescue medication was evaluated either between
treatment groups and/or between two time-points (baseline vs. end of treatment). Reduction in opioid consumption was assessed in terms of difference in defined daily dose per patient, average daily dose per patient, average number of tablets per day, or number of patients using rescue medication. There is a lack of understanding of what constitutes the clinically meaningful reduction in opioid consumption in patients with chronic non-cancer pain. Although some of these trials have demonstrated a reduction in opioid consumption, they have not established a concomitant decline in opioid-induced AEs. Opioid-induced AEs can be measured using dairies, patient-reported instruments, laboratory tests, and radiography. In addition to identifying common patient-reported AEs such as constipation, nausea, vomiting, and drowsiness/somnolence, our review also evaluated measures used to assess clinical consequences associated with chronic opioid use (e.g., endocrinopathy, bone fracture, risk of abuse, hyperalgesia). We identified several measures (developed in different settings including post-operative acute pain management, chronic noncancer pain, and cancer pain) used to assess a single symptom (e.g., opioid-induced constipation measured using Bowel Function test or Bowel Function Diary) or groups of AEs (e.g., Opioid Related Symptom Distress Scale). However, no composite scales, measuring a group of opioid-induced AEs, have been formally developed and validated in patients with chronic noncancer pain managed with long-term opioids.

Conclusions

The lack of standard definitions and validated measures to assess opioid-induced AEs in clinical trials limit the opportunities to assess opioid-sparing outcomes of non-opioid analgesic treatments and the associated clinical benefits. We recognize that the indication, clinical attributes and labelling goals of the investigational analgesic will drive the methods of assessment of opioid-sparing outcomes. Further research, with inputs from all stakeholders, is necessary to define and specify methods to study opioid-sparing outcomes to ensure introduction of efficacious, tolerable, and safe analgesic treatments for patients with chronic pain.

72 Potential Health Economic Benefits of Buprenorphine Buccal Film in the Management of Chronic Pain Patients

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Purpose

Opioids are an important treatment option for chronic pain. Class members of opioids vary in their pharmacodynamic profiles and buprenorphine is unique in being a partial agonist at the mu-opioid receptor and a full antagonist at the kappa-opioid receptor. BELBUCA® (buprenorphine buccal film (BBF)) is a Schedule III opioid which provides effective analgesia (approximately 30 times more potent than morphine in certain experiments) without inducing respiratory depression as has been reported with Schedule II opioids. Also, BBF has a unique pharmacokinetic profile with greater bioavailability (46% to 65%) compared with other transmucosal forms which are reported to have approximately 10% bioavailability. The Drug Enforcement Administration (DEA) has classified opioids on a scale of I to V with a decreasing likelihood of abuse and addiction, moving from CI (heroin) through to CIV (tramadol). Most of the opioids used to treat chronic pain are classified as CII or CIII, with the majority being CII despite their propensity for greater clinical problems. As a result, there is the potential for a greater financial cost to patients and providers of healthcare services, due to both direct activity and iatrogenic events from attempts to alleviate direct adverse effects. In fact, the requirement by some healthcare plans, that patients may only receive a CIII opioid after they have shown an adverse clinical outcome with one or more CII agents, may be contributing to increased costs as a result of these clinical occurrences.

Methods

In order to explore the potential health economic benefits of buprenorphine, a comprehensive literature search was performed (June 2017) using the Medline and Embase databases. The search specifically looked for the adverse event (AE) profile and health economic costs associated with the most common events for the CII opioids compared with buprenorphine. The search included assessing whether there are more AEs reported with CIIIs than CIIIs and therefore more iatrogenic costs, especially the cost of respiratory and gastrointestinal AEs. In addition, a Cochrane Review, “Long-term Opioid Management for Chronic Noncancer Pain” (2016) was also included. This review contains data from randomized and nonrandomized clinical trials, as well as pre-post case-series studies.

Results

Unlike full opioid agonists, buprenorphine, at effective analgesic doses, has a ceiling effect on respiratory depression which may be attributable to its partial agonist activity. While buprenorphine does carry the risk of respiratory depression, this ceiling effect reduces the likelihood of unintentional overdose, even at relatively high doses. As opioid overdoses have been increasing over the last two decades, this may be an important and potentially life-saving advantage over other existing treatment options. Beyond these clinical benefits, decreased overdose potential may also generate savings to payers. Decreased respiration caused by opioid use often leads to hospitalization with the associated expenses.

Buprenorphine’s partial agonist activity may result in a lower impact on gastrointestinal function than seen with CII opioids. Unlike other opioids, buprenorphine does not cause spasm of the sphincter of Oddi, a suspected cause of opioid-induced
constipation (OIC). As such, BBF may be associated with a decreased OIC risk. OIC is one of the most common and persistent adverse effects associated with opioid therapy. One systematic review of any opioid treatment of chronic pain (5,500 patients in 34 trials) showed an average prevalence of 15%, although the prevalence in individual trials ranged from 0-71%. However, the incidence of constipation during BBF’s 12-month study was 3.9%, in line with the rate of 1-5% reported in large longitudinal or pooled randomized trials of buprenorphine. For patients experiencing OIC, current research suggests it can lead to substantial expenses. The results of an analysis of insurance claims data showed that patients with OIC, compared with those without, have significantly more hospital admissions, longer inpatient stays, and significantly higher total healthcare costs.

Beyond providing patients and clinicians another option for equivalent analgesia, buprenorphine may provide clinical benefits beyond existing ER/LAOs. Data suggest additional clinical benefits in fibromyalgia and certain mental health conditions such as severe depression may also be achievable, though the incremental benefit of BBF in treating those conditions merits further research.

Conclusions
The introduction of BBF as a branded ER/LAO treatment option provides patients with an option for equivalent analgesia with several potential clinical advantages over existing options, most notably reduced risk of respiratory depression/unintentional overdose. These may result in the use of fewer medical services, which should generate cost savings to payers and patients. While estimates of the potential economic benefits of respiratory depression and constipation are presented above, continued research based on real-world use is necessary to better define potential economic benefits. The creation of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement will hopefully lead to better reporting and improved health decisions based on consistent data. The additional cost of treating iatrogenic phenomena should not be ignored, and the loss of potential benefits in other medical conditions also needs to be considered.

73 Targeted delivery of linaclotide to specific areas of the intestine affects clinical efficacy in patients with irritable bowel syndrome with constipation (IBS-C)

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Purpose
Linaclotide is a guanylate cyclase-C (GC-C) agonist approved for treatment of irritable bowel syndrome with constipation (IBS-C) in adults. In placebo-controlled clinical trials, patients treated with linaclotide showed improvements in constipation and abdominal pain, the two hallmark symptoms of IBS-C. Linaclotide activates GC-C expressed on epithelial cells in the intestine, resulting in production and release of cyclic guanosine monophosphate (GMP). Increases in intracellular cyclic GMP stimulate secretion of chloride and bicarbonate into the intestinal lumen, accelerating intestinal transit. In addition, cyclic GMP that is excreted from the basolateral side of intestinal cells has been shown to inhibit the activity of colonic nociceptors. We hypothesized that targeted delivery of linaclotide to specific intestinal regions would modulate secretory effects, potentially reducing the incidence of diarrhea adverse events (AEs) and improve beneficial effects on abdominal symptoms. Two linaclotide delayed-release (DR) formulations were developed: DR1 to target the mid-ileum to enhance pain relief and preserve secretory (i.e., GI transit) effects, and DR2 to target the ileocecal junction to relieve pain and minimize secretory effects. The purpose of this study was to evaluate the efficacy, tolerability, and dose response of linaclotide DR1 and DR2 vs placebo in IBS-C patients, and understand how the 2 DR formulations compare with each other and with the FDA-approved 290μg LINZESS® immediate release (IR) formulation.

Methods
This exploratory, Phase 2b, placebo-controlled, dose-response study randomized IBS-C patients to 1 of 8 dose groups: placebo, IR, or DR1 or DR2 30μg, 100μg, or 300μg. Patients received daily doses for 12 weeks. Eligible patients met Rome III IBS criteria and, during a two-week baseline period, reported ≤10 spontaneous bowel movements (SBMs) and ≤6 complete SBMs (CSBMs), and had an average abdominal pain score ≥3.0 (11-point scale; 0=None, 10=worst possible). Patients reported bowel symptoms, including CSBMs and stool consistency (assessed on the 7-point Bristol Stool Form Scale [BSFS]: 1=separate hard lumps, 7=watery, no solid pieces), and abdominal pain severity daily during the baseline and 12-week treatment periods. An IBS-C responder was defined as ≥30% reduction in abdominal pain + CSBM increase ≥1 from baseline for the same week for 6 of 12 weeks; the responder rate was evaluated by comparing IR and each DR1 and DR2 dose with placebo, using a Cochran-Mantel-Haenszel test controlling for geographical region.

Results
The intent-to-treat population included 532 patients (mean age=45 years; 83% female; 65% Caucasian), with 66 to 67 patients per dose group. Significant improvement in the IBS-C responder endpoint was seen for the DR1 300μg group (38.8%) vs placebo (21.2%) (nominal p=0.026); numerical improvements vs placebo were seen for 4 of the 5 other DR doses (IR=31.8%; DR1 30μg=26.9%, 100μg=25.4%; DR2 30μg=23.9%, 100μg=24.2%, 300μg=21.2%). Mean abdominal pain for all DR1 and DR2 doses was reduced vs placebo for all 12 treatment weeks; DR1 300μg results were significant vs placebo (nominal p<0.05) for 8 of 12 weeks of treatment and numerically exceeded IR for 10 of 12 weeks. With respect to bowel
symptoms, dose-dependent gains were seen for DR1 doses in 12-week change from baseline in CSBM rate and BSFS:

- DR1 30µg CSBM: 1.163; BSFS: 1.224
- DR1 100µg CSBM: 1.414; BSFS: 1.620
- DR1 300µg CSBM: 1.776; BSFS: 1.825
- placebo CSBM: 1.115; BSFS: 0.938
- IR 290µg CSBM: 2.107; BSFS: 1.774.

In comparison to DR1 and IR, CSBM 12-week change from baseline was generally lower for DR2, as was BSFS 12-week change from baseline, indicating reduced secretory effect:

- DR2 30µg CSBM: 1.275; BSFS: 0.999
- DR2 100µg CSBM: 1.019; BSFS: 1.073
- DR2 300µg CSBM: 0.869; BSFS: 1.152.

Diarrhea, the most common AE, was dose-dependent and reported by 3-10% of DR1, 0-3% of DR2, 14% of IR, and 2% of placebo patients.

Conclusions

Distinct DR1 and DR2 effect profiles were seen in this exploratory Phase 2b study. DR1 300µg enhanced abdominal pain relief and maintained constipation relief with improved tolerability in IBS-C. DR2 doses showed trends toward pain relief, with an expected, minimal effect on bowel symptoms, meriting further study in other GI syndromes characterized by visceral pain. These data suggest that linaclotide treatment effects can be modulated by targeted delivery in the intestine.

Sponsors: Allergan PLC and Ironwood Pharmaceuticals

74 Treatment of Day Surgery Patients with Multiple Injectable Opioids for Postoperative Pain: Incidence and Impact on Total Charges and 30-Day Readmissions

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Purpose

Postoperative pain is a predictable consequence of surgery, but when left untreated can result in adverse clinical and economic outcomes. The objective of this study was to estimate the proportion of day surgery patients treated with multiple injectable opioids for postoperative pain and quantify its impact on hospital charges.

Methods

A retrospective cohort study was conducted using the QuintilesIMS Hospital Charge Data Master database, which is comprised of hospital-based operational records that are sourced from UB-04 billing forms submitted for payment. Patients (≥18 years old) were included if they underwent a non-emergent surgical procedure between July 1, 2014 and June 30, 2015, and were administered an inhaled anesthetic. Patients with hospital stays >24 hours were excluded, as were those who underwent surgeries on the nervous, respiratory or cardiovascular systems or who underwent an obstetrical procedure. Postoperative pain, which resulted in treatment with multiple injectable opioids, was defined by the administration of ≥2 different injectable opioids on the day of surgery. The incidence of patients treated with multiple injectable opioids for postoperative pain (cases) was assessed among the overall cohort as well as for the top 10 most frequent day surgeries. Cases were propensity score matched to patients who were not treated in the same manner (controls) (nearest neighbor approach). Mean and median total charges and the proportion of patients who were readmitted within 30 days of surgery were compared between cases and controls. No cost-to-charge ratio was applied in this analysis.

Results

63,392 patients were included in the overall study cohort. Mean (SD) age was 51.4 (16.6) years. Majority of patients were female (59.3%) and resided in the South (62.14%). 44.69% of patients were treated with multiple injectable opioids for postoperative pain. This incidence ranged from 28.70%-87.58% depending on the type of surgery. Patients who underwent a laparoscopic total abdominal hysterectomy had the highest proportion of patients treated with multiple injectable opioids for postoperative pain (87.58%). Propensity score matching resulted in 10,513 matched pairs. Compared to controls, cases had significantly higher total charges (Mean: $17,095 vs. $15,637, p<0.001; Median: $13,642 vs. $12,547, p<0.001). Cases had a higher likelihood of getting readmitted within 30 days of surgery compared to controls (OR: 1.51, p<0.001).

Conclusions

Patients treated with multiple injectable opioids for postoperative pain had higher hospital charges and were more likely to be readmitted within 30 days of surgery compared to patients who were not treated in the same manner. Additional research is warranted to better understand the burden of, and to improve the management of, postoperative pain. Future research should also explore novel avenues to address the burden of postoperative pain. For example, the application of pharmacogenetics to employ a personalized medicine approach may help address the burden of pain in the postoperative setting.

75 The Treatment of Patients with Injectable Opioids for Uncontrolled Postoperative Pain in the Inpatient Setting: Incidence and Impact on Hospital Charges

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Purpose

Adequate management of postoperative pain is a crucial component of patient care. Not only is pain management closely tied to patient satisfaction, but mismanaged pain can potentially negatively impact important clinical and economic outcomes. The purpose of this study was to quantify the incidence of patients treated with injectable opioids for uncontrolled postoperative pain and assess how this issue impacts hospital charges.

Methods

A retrospective study was conducted using the QuintilesIMS Hospital Charge Data Master database, which is comprised of hospital-based operational records that are sourced from UB-04 billing forms submitted for payment. Adult patients were included if they underwent a non-emergent surgical procedure, were administered an inhaled anesthetic (sevoflurane, isoflurane or desflurane) and stayed in the hospital for >24 hours between July 1, 2014 and June 30, 2015. Patients undergoing obstetrical surgeries or surgeries of the nervous, respiratory, or cardiovascular systems were excluded. Uncontrolled pain was defined as having received 3 or more different injectable opioids on the same day of the surgery. Patients treated for uncontrolled pain (cases) were matched to patients not treated for uncontrolled pain (controls) using propensity score matching (nearest neighbor approach). Total hospital charges were compared between cases and controls. No cost-to-charge ratio was applied in this analysis.

Results

The study cohort was comprised of 17,727 patients. Mean (SD) age was 56.3 years (15.2); Most patients were female (61.2%). One-third (33.6%, n=5,950) of patients were treated with 3 or more injectable opioids for uncontrolled pain, and propensity score matching resulted in 2,788 matched pairs. The total hospital charges for cases were significantly higher than for controls (Mean: $64,183 vs. $61,624, p<0.001; Median: $50,297 vs. $48,744, p<0.001).

Conclusions

Patients treated with injectable opioids for uncontrolled pain were associated with higher hospital charges. Further research is warranted to quantify the burden of this complication and to assess potential methods for improving pain management. Applying a personalized medicine approach utilizing pharmacogenomics may help address the burden of pain in the postoperative setting.

76 Efficacy and Safety of CNTX-4975 in Subjects With Moderate to Severe Osteoarthritis Knee Pain: A 24-Week, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study

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Purpose

Osteoarthritis is a leading cause of chronic pain, joint stiffness, and reduced physical function. Effective and safe therapeutic options are lacking for many patients with moderate to severe knee osteoarthritis pain. CNTX-4975, a highly purified, synthetic trans-capsaicin, targets transient receptor potential vanilloid 1, producing analgesia via reversible desensitization of end terminals of primary afferent pain fibers within the joint after intra-articular injection. This phase 2 dose-ranging study evaluated a single intra-articular injection of CNTX-4975 in subjects with moderate to severe osteoarthritis knee pain.

Methods

Subjects aged 45–80 years with stable, chronic, moderate to severe knee osteoarthritis pain, who failed previous oral/intra-articular analgesics, were randomized 2:1:2 to a single intra-articular injection of placebo, CNTX-4975 0.5 mg, or CNTX-4975 1.0 mg. Randomization was stratified by Kellgren-Lawrence (K-L) grade (2–3 vs 4) and body mass index (<30 vs ≥30 kg/m²). The primary efficacy endpoint was the area under the curve (AUC) for change from baseline in daily Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Question A1 score (pain with walking; Numerical Rating Scale [NRS]: 0 = none to 10 = extreme) through week 12. Least squares mean differences (LSMD) for CNTX-4975 vs placebo were calculated for the primary endpoint, and analysis of covariance was performed on the AUC based on the average weekly AUC WOMAC A1 scores. Additional efficacy endpoints included mean change from baseline in weekly WOMAC A1 score, WOMAC B stiffness subscale (scores derived from the sum of the 2 stiffness responses, range 0 to 20), and WOMAC C physical function subscale (scores derived from the sum of the 17 function responses, range 0 to 170) through week 24 analyzed by mixed model for repeated measures (MMRM). A post hoc exploratory analysis was conducted to evaluate the cumulative proportion of responders who had ≥30%, ≥50%, ≥70%, or ≥90% reduction from baseline in the weekly average WOMAC A1 score at weeks 12 and 24. Statistical tests were 2-sided (alpha, 0.10). Safety assessments included treatment-emergent adverse events (TEAEs) and laboratory evaluations.

Results

Efficacy was evaluated in 172 subjects (placebo, n=69; CNTX-4975 0.5 mg, n=33; CNTX-4975 1.0 mg, n=70), most K-L grade 2–3 (placebo, n=62; CNTX-4975 0.5 mg, n=30; CNTX-4975 1.0 mg, n=65). Mean baseline WOMAC Question A1 score was 7.3. WOMAC A1 scores were significantly improved vs placebo at week 12 (primary timepoint) with CNTX-4975 0.5 mg (LSMD: −0.8; P=0.07) and 1.0 mg (LSMD: −1.6; P<0.0001) and at week 24 with CNTX-4975 1.0 mg (LSMD: −1.4; P=0.0002). In the K-L 2–3 subgroup, CNTX-4975 0.5 mg resulted in numerically greater improvements in WOMAC A1 score vs placebo (LSMD: −0.7; P=0.11), and CNTX-4975 1.0 mg significantly improved WOMAC
A1 score vs placebo (LSMD: −1.7; \( P < 0.0001 \)). In 12 subjects with K-L grade 4, a significant difference was observed between placebo and CNTX-4975 1.0 mg (LSMD: −3.4; \( P = 0.07 \)). For the MMRM analyses, CNTX-4975 0.5 mg showed significant improvement vs placebo at week 12 in WOMAC A1 score change from baseline (LSMD: −0.9; \( P = 0.09 \)). Significant improvement vs placebo (\( P = 0.02 \)) was demonstrated at the 1-week (earliest) timepoint for CNTX-4975 1.0 mg and continued through weeks 12 (LSMD: −1.5; \( P = 0.0003 \)) and 24 (LSMD: −0.9; \( P = 0.07 \)); significant improvements vs placebo occurred at week 12 in WOMAC B (LSMD: −2.5; \( P = 0.0013 \)) and WOMAC C change from baseline (LSMD: −18.3; \( P = 0.004 \)). At week 12, 33% of subjects in the placebo group had ≥50% reduction in WOMAC A1 score compared with 58% and 61% in the CNTX-4975 0.5 mg and 1.0 mg groups, respectively. Overall, results for CNTX-4975 0.5 mg were intermediate between placebo and CNTX-4975 1.0 mg. The incidence of TEAEs was 30% for placebo and CNTX-4975 1.0 mg and 47% for CNTX-4975 0.5 mg at week 24. Most TEAEs were considered unrelated to study treatment. Arthralgia was the most common TEAE for placebo (5.7%) and CNTX-4975 1.0 mg (7.0%).

Conclusions
A single intra-articular injection of CNTX-4975 1.0 mg improved pain with walking, knee stiffness, and physical function and was well tolerated in subjects with moderate to severe osteoarthritis knee pain. These findings support continued development of CNTX-4975 1.0 mg for the treatment of osteoarthritis knee pain.

77 Safety and Opioid Use Following Major Orthopedic Surgery in a Phase 3, Placebo-Controlled Study of Intravenous Meloxicam
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**Purpose**
Intravenous (IV) meloxicam (also reported as N1539) is a novel IV formulation of NanoCrystal Colloidal Dispersion\(^\dagger\) meloxicam, being developed for the management of moderate to severe pain. IV meloxicam has been evaluated across a range of doses and patient populations during Phase 2 clinical studies. IV meloxicam 30 mg demonstrated rapid and sustained pain relief throughout the 24-hour dosing interval, along with reductions in opioid use, in 2 recently completed placebo-controlled Phase 3 efficacy studies in subjects with moderate to severe pain following hard and soft tissue surgeries. Dosing with IV meloxicam 30 mg was well tolerated in these studies. The Phase 3 program also included a large, multi-center, placebo-controlled, safety study that enrolled a broad population of subjects undergoing a range of major surgical procedures who received study drug once daily for up to 7 days.

Major surgeries performed in this study included orthopedic, abdominal, gynecologic, spinal, and other procedures. This reported safety study included a large population of subjects undergoing orthopedic surgeries, a common surgery type resulting in subjects experiencing moderate to severe postoperative pain lasting multiple days after surgery. This abstract reports study findings in subjects who underwent orthopedic surgeries.

**Methods**
This was a Phase 3, multi-center, randomized, double-blind, placebo-controlled study in male and female subjects, age 18-80 years scheduled to undergo major elective surgery with an inpatient hospital stay expected to exceed 24 hours. Study participation included a screening visit with written informed consent, an inpatient visit including surgery and study treatment, and two follow-up visits after discharge (one in office and one by phone). Subjects underwent major surgeries according to the standard practice of the institution. Following surgery, eligible subjects were stratified, randomized (3:1), and administered IV meloxicam 30 mg or placebo via IV push over 15-30 seconds every 24 hours for up to 7 doses. Subjects could continue to receive opioid analgesia according to the practice of the investigator to treat uncontrolled pain symptoms; additional NSAIDs were prohibited during inpatient treatment. Opioid use was measured throughout the postoperative inpatient phase and converted to the total IV morphine equivalent dose for summary. Safety assessments included clinical laboratory tests, vital signs, ECGs, surgical wound assessment, total opioid use, and monitoring of adverse events (AEs) and serious AEs (SAEs). The primary objective of the study was to evaluate the safety of IV meloxicam 30 mg compared with placebo according to the collected safety assessments.

**Results**
The study randomized and treated a total of 379 subjects following major orthopedic surgery; 283 randomized to IV meloxicam 30 mg, and 96 to placebo. Subjects ranged in age from 18 to 80 years, with a mean age of 59 years. The majority of subjects were female (64.4%) and white (88.4%), with demographics similar between the treatments. Surgical procedures included joint replacements, complex foot, bunionectomy, spinal, and other procedures. The mean surgery duration was 1.4 hours, with the mean time to first dose of study drug 2.2 hours following the end of surgery. The majority of subjects (>85%) received 2 or 3 doses of study drug.

IV meloxicam 30 mg was well tolerated with no deaths, and a low incidence of SAEs (2.5% of IV meloxicam vs. 4.2% of placebo) and withdrawals due to an AE (0.4% of IV meloxicam vs. 0% of placebo). AEs were generally mild or moderate in intensity, and similar in incidence between treatments. The most common treatment-emergent AEs included nausea, constipation, vomiting, increased gamma-glutamyltransferase, headache, anaemia, insomnia, and pyrexia. Administration of IV meloxicam was well tolerated with no injection site AEs. There was a low incidence of
clinically meaningful changes in laboratory, vital sign, and/or ECG assessments during the study, with findings similar between treatments. Investigator assessments of surgical wound healing were favorable and consistent between treatments.

Opioid consumption was lower for IV meloxicam 30 mg compared with placebo at all evaluated intervals, reaching statistical significance (p<0.05) in the Hour 0-24, Hour 24-48, Hour 0-48, and Hour 0-72 intervals with 27.4%, 26.1%, 26.5%, and 27.2% reductions in opioid use respectively. A lower incidence of nausea and vomiting was observed in the IV meloxicam 30 mg arm, which may have been related to the reduction in opioid use compared with placebo.

Conclusions

IV meloxicam 30 mg daily was well tolerated in subjects undergoing orthopedic surgeries compared with placebo, with a low incidence of SAEs and discontinuations due to an AE. AEs were generally mild or moderate in intensity, and similar in incidence between treatment groups. A statistically significant reduction in total opioid use, up to 27.4%, was observed at various intervals during treatment in the IV meloxicam group compared with placebo. This study supports the safety and tolerability of IV meloxicam 30 mg administered once daily as an IV bolus over 15-30 seconds for up to 7 days following major orthopedic surgery.

78 Safety and Opioid Use in a Phase 3, Placebo-Controlled Study of Intravenous Meloxicam Following Major Surgery

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Purpose

Intravenous (IV) meloxicam (also reported as N1539) is a novel IV formulation of NanoCrystal Colloidal Dispersion® meloxicam, being developed for the management of moderate to severe pain. IV meloxicam has been evaluated across a range of doses and patient populations during Phase 2 clinical studies. IV meloxicam 30 mg demonstrated rapid and sustained pain relief throughout the 24-hour dosing interval, along with reductions in opioid use, in 2 recently completed placebo-controlled Phase 3 efficacy studies in subjects with moderate to severe pain following hard and soft tissue surgeries. Dosing with IV meloxicam 30 mg was well tolerated in these studies. The Phase 3 program also included a large, multi-center, placebo-controlled safety study that enrolled a broad population of subjects who underwent various major surgeries including orthopedic, abdominal, gynecologic, spinal, and other procedures. This reported study was planned to evaluate the safety of dosing with IV meloxicam for up to 7 days following major surgery compared with placebo. Subjects were stratified by surgery type (orthopedic vs. other) and age/renal function (age >65 years with impaired renal function [GFR <89 mL/min/1.73 m²] vs. other). This abstract reports the study findings in the overall patient population.

Methods

This was a Phase 3, multi-center, randomized, double-blind, placebo-controlled study in male and female subjects, age 18-80 years scheduled to undergo major elective surgery with an inpatient hospital stay expected to exceed 24 hours. Study participation included a screening visit with written informed consent, an inpatient visit including surgery and study treatment, and two follow-up visits after discharge (one in office and one by phone). Subjects underwent major surgeries according to the standard practice of the institution. Following surgery, eligible subjects were stratified, randomized (3:1), and administered IV meloxicam 30 mg or placebo via IV push over 15-30 seconds every 24 hours for up to 7 doses. Subjects could continue to receive opioid analgesia according to the practice of the investigator to treat uncontrolled pain symptoms; additional NSAIDs were prohibited during inpatient treatment. Opioid use was measured throughout the postoperative inpatient phase and converted to the total IV morphine equivalent dose for summary. Safety assessments included clinical laboratory tests, vital signs, ECGs, surgical wound assessment, total opioid use, and monitoring of adverse events (AEs) and serious AEs (SAEs). The primary objective of the study was to evaluate the safety of IV meloxicam 30 mg compared with placebo according to the collected safety assessments.

Results

A total of 721 subjects randomized and received study drug following surgery in this study; 538 randomized to IV meloxicam 30 mg, and 183 to placebo. Subjects ranged in age from 18 to 80 years, with a mean age of 53 years. The majority of subjects were female (59.4%) and white (85.2%), with demographics similar between the treatment groups. The mean surgery duration was 1.3 hours, with the mean time to first dose of study drug occurring 1.7 hours following the end of surgery. The majority of subjects (>80%) received 2 or 3 doses of study drug during their inpatient stay.

IV meloxicam 30 mg was well tolerated with no deaths, and a low incidence of SAEs (2.6% of IV meloxicam vs. 5.5% of placebo) and withdrawals due to an AE (0.4% of IV meloxicam vs. 0% of placebo). AEs were generally mild or moderate in intensity, and similar in incidence between treatments. The most common treatment-emergent AEs included nausea, constipation, vomiting, headache, pruritus, gamma-glutamyltransferase increased, dizziness, and anemia. Administration of IV meloxicam was well tolerated with a low incidence of injection site AEs. There was a low incidence of clinically meaningful laboratory, vital sign, and/or ECG assessments during the study, with findings similar between treatments. Investigator assessments of surgical wound healing were favorable and consistent between treatments.

Mean opioid consumption was numerically lower in the IV meloxicam 30 mg group compared with placebo at all evaluated intervals, reaching statistical significance (p<0.05) in
the Hour 0-24, Hour 0-48, and Hour 0-72 intervals with 22.0%, 22.6%, and 23.7% reductions in opioid use respectively. There was a lower rate of nausea and vomiting observed in the IV meloxicam 30 mg arm, which may have been related to the reduction in opioid use compared with placebo.

**Conclusions**

IV meloxicam 30 mg daily for up to 7 days was well tolerated compared with placebo control, with a low incidence of SAEs and withdrawals due to an AE. AEs were generally mild or moderate in intensity, and similar in incidence between treatment groups. A statistically significant reduction in total opioid use, up to 23.7%, was observed at various intervals during treatment in the IV meloxicam group compared with placebo. This study supports the safety and tolerability of IV meloxicam 30 mg administered once daily as an IV bolus over 15-30 seconds for up to 7 days following major surgery.

**Purpose**

Intravenous (IV) meloxicam (also reported as N1539) is a novel IV formulation of NanoCrystal Colloidal Dispersion® meloxicam, being developed for the management of moderate to severe pain. IV meloxicam has been evaluated across a range of doses and patient populations during Phase 2 clinical studies. IV meloxicam 30 mg demonstrated rapid and sustained pain relief throughout the 24-hour dosing interval, along with reductions in opioid use, in 2 recently completed placebo-controlled Phase 3 efficacy studies in subjects with moderate to severe pain following hard and soft tissue surgeries. Dosing with IV meloxicam 30 mg was well tolerated in these studies. The Phase 3 program also included a large, multi-center, placebo-controlled, safety study that enrolled a broad population of subjects undergoing a range of major surgical procedures who received study drug once daily for up to 7 days. Major surgeries performed in this study included orthopedic, abdominal, gynecologic, spinal, and other procedures. This reported safety study planned to include a population of subjects of advanced age (>65 years) with impaired renal function (Glomerular Filtration Rate ≤89 mL/min/1.73 m²) to evaluate the safety of IV meloxicam in a subject population with potential for increased risk of complications and toxicities associated with NSAID use. This abstract reports the study findings within the population of subjects of advanced age with impaired renal function.

**Methods**

This was a Phase 3, multi-center, randomized, double-blind, placebo-controlled study in male and female subjects, age 18-80 years scheduled to undergo major elective surgery with an inpatient hospital stay expected to exceed 24 hours. Study participation included a screening visit with written informed consent, an inpatient visit including surgery and study treatment, and two follow-up visits after discharge (one in office and one by phone). Subjects underwent major surgeries according to the standard practice of the institution. Following surgery, eligible subjects were stratified, randomized (3:1), and administered IV meloxicam 30 mg or placebo via IV push over 15-30 seconds every 24 hours for up to 7 doses. Subjects could continue to receive opioid analgesia according to the practice of the investigator to treat uncontrolled pain symptoms; additional NSAIDs were prohibited during inpatient treatment. Opioid use was measured throughout the postoperative inpatient phase and converted to the total IV morphine equivalent dose for summary. Safety assessments included clinical laboratory tests, vital signs, ECGs, surgical wound assessment, total opioid use, and monitoring of adverse events (AEs) and serious AEs (SAEs). The primary objective of the study was to evaluate the safety of IV meloxicam 30 mg compared with placebo according to the collected safety assessments.

**Results**

The study randomized and treated a total of 119 subjects of advanced age with impaired renal function; 88 randomized to IV meloxicam 30 mg, and 31 to placebo. Subjects ranged in age from 66 to 80 years, with a mean age of 70.5 years. The majority of subjects were female (57.1%) and white (95.0%), with demographics similar between the treatment groups. Surgery categories included orthopedic, abdominal/pelvic, and spinal, with an overall mean surgery duration of 1.5 hours, and a mean time to first dose of study drug occurring 1.9 hours following the end of surgery. The majority of subjects (>80%) received 2 or 3 doses of study drug during their inpatient stay.

IV meloxicam 30 mg was well tolerated with no deaths or discontinuations due to an AE, and a low incidence of SAEs (2.3% of IV meloxicam vs. 12.9% of placebo). AEs were generally mild or moderate in intensity, and similar in incidence between treatments. The most common treatment-emergent AEs included nausea, constipation, vomiting, anaemia, pruritus, hypotension, insomnia, and gamma-glutamyltransferase increased. Administration of IV meloxicam was well tolerated with no injection site AEs. Events related to bleeding, cardiovascular, hepatic, renal, thrombotic, and wound healing complications were infrequent and generally similar between treatment groups. There was a low incidence of clinically meaningful changes in laboratory, vital sign, and/or ECG assessments during the study, with findings similar between treatments. Investor assessments of surgical wound healing status were favorable and consistent between treatments.
Mean opioid consumption was numerically lower in the IV meloxicam 30 mg group compared with placebo at all evaluated intervals, reaching statistical significance (p<0.05) in the Hour 24-48, Hour 0-48, and Hour 0-72 intervals with 41.9%, 36.2%, and 38.2% reductions in opioid use respectively.

Conclusions
IV meloxicam 30 mg daily was well tolerated in subjects of advanced age with impaired renal function compared with placebo, with no discontinuations due to an AE, and a low incidence of SAEs. AEIs were generally mild or moderate in intensity, and similar in incidence between treatment groups. Statistically significant reductions in opioid use, up to 41.9%, were observed during treatment with IV meloxicam compared with placebo. This study supports the safety and tolerability of IV meloxicam 30 mg administered once daily for up to 7 days following major surgery in subjects aged >65 years with impaired renal function.

80 Increased Risk of Problematic Drug Use among Adults with Chronic Pain

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Purpose
There is concern regarding the safe use of prescription opioids and risk of developing opioid use disorder (OUD). In light of endemic rates of opioid overdose deaths in recent years, regulators and healthcare providers are motivated to better understand risks for problematic drug use (Rudd, 2016). While the estimated risk of OUD among chronic pain patients is low (8-12%), exposure to prescription opioids is common among patients with pain diagnoses, as opioids are considered to be the most effective drugs to relieve pain (Vowles, 2015; Lowinson, 2005; Daubresse, 2013). The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System Survey of Non-Medical Use of Prescription Drugs (NMURx) Program includes the Drug Abuse Screening Test (DAST-10), an assessment tool that measures the degree of social, occupational, psychological, or physical problems related to illicit or pharmaceutical drug abuse (Skinner, 1982; Yudko, 2007). The objective of this study was to describe behaviors related to non-medical use (NMU) of prescription opioids and investigate whether problematic drug use (measured with DAST-10) was associated with self-reported chronic pain within the last 12 months.

Methods
NMURx was administered online to 30,032 US adults (18+ years) in 1Q2017. Post-stratification weights based on age, gender, and census region were applied to reflect the distribution of adults in the US, representing 247,773,709 adults. All respondents completed the DAST-10; scores were categorized as low (0-2) or moderate-severe (3-10). The proportions and 95% confidence intervals (CI) were calculated by DAST-10 category for reported chronic pain within the last 12 months, receiving an opioid prescription to treat chronic pain within the last 12 months, and NMU of a prescription opioid within the last 12 months. NMU was defined as use of a prescription medication without a doctor’s prescription or for any reason other than what was recommended by a doctor. In addition, several lifetime measures were explored: misuse of a prescription opioid (NMU to self-treat pain or for another medical condition) and abuse of a prescription opioid (NMU for enjoyment/to get high). Logistic regression was conducted to test the association between DAST-10 category and recent chronic pain, controlling for receiving an opioid prescription to treat chronic pain in the last 12 months and NMU of a prescription opioid in the last 12 months. Analyses tested for effect modification of receiving a prescription or opioid NMU in the last 12 months for chronic pain on the odds of moderate-severe DAST-10. All analyses were conducted using survey procedures in SAS (version 9.4) to account for post-stratification weighting.

Results
Overall, the prevalence among US adults of a moderate-severe DAST-10 score was 9.4% (95% CI: 8.9, 9.6) and was 30.1% (95% CI: 29.6, 30.6) for chronic pain in the last 12 months. Compared to respondents with a low DAST-10 score, respondents with moderate-severe DAST-10 scores had a higher proportion of recent chronic pain (28.1% versus 49.5%), receiving an opioid prescription for chronic pain (10.0% versus 31.2%), and recent NMU of an opioid (6.0% versus 37.2%), respectively. In addition, the proportion among moderate-severe DAST-10 who reported ever abusing a prescription opioid was 38.9%, while a higher proportion (46.1%) reported ever misusing a prescription opioid. When modeling problematic drug use, interaction terms were used to test the difference between DAST-10 categories for chronic pain in the last 12 months by receiving an opioid prescription for chronic pain in the last 12 months (p=0.400) and by NMU of a prescription opioid in the last 12 months (p=0.363); as neither term was found significant, they were not included in the final model. When controlling for receiving an opioid prescription and NMU of a prescription opioid, the odds of a moderate-severe DAST-10 score was 1.5 times higher for those with chronic pain compared to those with no chronic pain (adjusted odds ratio: 1.5; 95% CI: 1.4, 1.7).

Conclusions
It is estimated that one in ten US adults may have moderate-severe problematic drug use and one in three may have experienced chronic pain in the last 12 months. Adults with higher problematic drug use also reported higher proportions of lifetime drug NMU with lifetime misuse and abuse of opioids being prevalent. Recent chronic pain was shown to be associated with increased odds of problematic drug use independent of a recent prescription or NMU of an opioid. In conclusion, chronic pain patients are an important sub-population that may be at increased risk of problematic drug use.
81 Rate of Nucynta ER intentional abuse calls to poison centers are lower than ER oxycodone and ER oxymorphone

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**Purpose**
The Nucynta ER tablet is difficult to crush. This study compares rates of intentional abuse exposure mentions of Nucynta ER to extended release (ER) Schedule II opioid medications.

**Methods**
Researched, Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System Poison Center Program data are used. Cumulative population and dosage units dispensed rates are calculated using data from October 2011 through December 2016. Nucynta ER is compared to ER oxycodone, hydrocodone, oxymorphone, morphine, and hydromorphone using Poisson regression. Unknown active pharmaceutical ingredient formulations were imputed 100 times and regression coefficients averaged to give robust estimates.

**Results**
Rates of Nucynta ER intentional abuse per population are lower than comparators (RR<0.10, p<0.001) except ER hydrocodone (RR=5.61, p<0.001) and ER hydromorphone (RR=6.88, p<0.001). Rates of Nucynta ER intentional abuse per dosage units dispensed are lower than ER oxycodone (RR=0.59, p<0.001) and ER oxymorphone (RR=0.34, p<0.001) but greater than ER hydromorphone (RR=3.02, p=0.007). Rates of Nucynta ER intentional abuse did not differ from ER morphine and ER hydrocodone.

**Conclusions**
Rates of Nucynta ER intentional abuse are consistently lower than ER oxycodone and ER oxymorphone. ER hydromorphone findings may be due to differences in prescription frequency.

82 Pharmacokinetics of Fentanyl Sublingual Spray in Opioid-Naïve, Healthy Volunteers: Results of a Phase 1, Multiple Ascending Dose Study

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**Purpose**
Fentanyl sublingual spray has been shown to be efficacious in treating breakthrough pain in opioid-tolerant adults with cancer. Its rapid onset for pain relief and non-invasive route of administration indicate a potential use in the management of acute or postoperative pain. Because patients in these settings may include those who are opioid-naïve or nontolerant to opioids, this multiple ascending dose study was conducted to characterize the relationship between systemic exposure and safety in an opioid-naïve population following administration of fentanyl sublingual spray.

**Methods**
This phase 1, open-label, single site, randomized, multiple ascending dose study was designed to assess the pharmacokinetics, pharmacodynamics, safety, and tolerability of multiple doses of fentanyl sublingual spray or fentanyl citrate intravenous (IV). Opioid-naïve, healthy volunteers 18-55 years of age were included in the study. Study drugs were administered in 4 dosing cohort regimens: every 0.5, 1, 2, or 4 hours (q0.5h, q1h, q2h, q4h) for a maximum of 3 doses per cohort within 24 hours. Within each cohort, 8 individuals were randomly assigned to treatment, 6 individuals to receive multiple doses of fentanyl sublingual spray (either 100 mcg, 200 mcg, or 400 mcg), and 2 individuals to receive multiple doses of fentanyl citrate IV 50 mcg. Treatment was administered after a 10-hour fast; individuals continued to fast through 4 hours post-dose. Plasma blood samples were collected pre-dose through 24 hours after the first dose. Safety assessments were performed from the time of dosing through Day 7.

**Results**
A total of 96 adults (n=24 per cohort) who were 75.0% male with a mean age of 36.4 years and a mean BMI of 25.4 kg/m2 participated in the study. Mean plasma fentanyl concentrations increased with an increase in dose of fentanyl sublingual spray between 100 mcg and 400 mcg. During multiple doses of fentanyl sublingual spray, maximum fentanyl exposure (maximum plasma concentration after last dose [Cmax n]) and total exposure (area under the plasma concentration-time curve during the last dosing interval [AUC0-tau n]) increased relative to the first dose; shorter dosing intervals resulted in higher concentrations. Analysis of dose proportionality suggested that maximum fentanyl exposure (Cmax n) and total fentanyl exposure (AUC0-t; t = the time of the last quantifiable concentration) and AUC0-inf increased in a linear manner, but slightly greater than proportional to an increase in dose following multiple dose administrations of fentanyl sublingual spray at dosing intervals ranging from 0.5 hours to 4 hours. The accumulation ratios between the first and last doses of fentanyl sublingual spray ranged from approximately 1.2 to 4.9 for all doses and dosing interval studied. The most frequently reported adverse events with fentanyl sublingual spray (pooled population; n=72) were nausea (47.2%), somnolence (44.4%), hypoxia (20.8%), dizziness (19.4%), and vomiting (18.1%). Most cases of hypoxia (<90% on room air) were observed at the highest dose (400 mcg) of fentanyl sublingual spray administered.
q0.5h or q1h; all cases of hypoxia were managed by nasal cannula oxygenation.

Conclusions

Three repeated doses of fentanyl sublingual spray administered at doses of 100 mcg, 200 mcg, and 400 mcg, and at dosing intervals ranging from q0.5h to q4h were generally well tolerated in healthy, opioid-naïve adults. Dose-dependent fentanyl pharmacokinetics following multiple doses of fentanyl sublingual spray were well characterized; systemic fentanyl exposure appeared to increase in a slightly greater than dose-proportional manner. These results suggest that doses of 200 mcg or lower may be optimal in investigations of fentanyl sublingual spray for the development of new indications in an opioid-naïve population.

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83 Safety of Oral Methylnaltrexone in Patients With Opioid-Induced Constipation and Chronic Noncancer Pain: Results From a Phase 3, Randomized, Controlled Trial

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Purpose

An oral formulation of methylnaltrexone, a selective peripheral mu-opioid receptor antagonist, was approved in July 2016 for opioid induced constipation (OIC) in patients with chronic noncancer pain. This analysis describes the safety of oral methylnaltrexone in a randomized, placebo-controlled trial conducted in patients with chronic noncancer pain with OIC.

Methods

Patients were eligible for this phase 3, double-blind, placebo-controlled trial if they had experienced chronic noncancer pain for ≥2 months, received ≥50 mg/d of oral morphine equivalents for ≥14 days, and experienced OIC (confirmed during a 14-day screening and defined by <3 rescue-free bowel movements (RFBMs) per week, on average, associated with ≥1 of the following: ≥25% of RFBMs categorized as type 1 or type 2 on the Bristol Stool Form Scale, straining during ≥25% of RFBMs, or ≥25% of RFBMs with a sensation of incomplete evacuation). Patients were randomly assigned to receive oral methylnaltrexone at 150 mg, 300 mg, or 450 mg or placebo once daily for 4 weeks; for the next 8 weeks, oral methylnaltrexone or placebo was used as needed. Double-blinding was maintained throughout the study.

Results

A total of 803 patients received ≥1 dose of study medication (oral methylnaltrexone 150 mg, n=201; 300 mg, n=201; 450 mg, n=200; placebo, n=201). Approximately 10% of these patients discontinued treatment during the 4-week period of once-daily dosing (150 mg, 8.5%; 300 mg, 9.0%; 450 mg, 12.5%; placebo, 10.4%), mainly per patient request (150 mg, 4.0%; 300 mg, 4.0%; 450 mg, 3.0%; placebo, 3.0%); during the 8-week “as-needed” dosing period, approximately 13% of patients who participated in this portion of the study discontinued treatment (150 mg, 9.6%; 300 mg, 13.8%; 450 mg, 12.4%; placebo, 14.4%). Demographic and baseline characteristics were similar among treatment groups. Treatment-emergent adverse events (TEAEs) were reported in 58.2%, 59.7%, 59.0%, and 63.2% of patients who received 150 mg, 300 mg, 450 mg, and placebo, respectively, while severe TEAEs were reported in 8.5%, 8.0%, 8.5%, and 9.0%, and serious TEAEs were reported in 2.5%, 3.0%, 2.0%, and 4.0%. The most common TEAEs were abdominal pain (150 mg, 5.5%; 300 mg, 8.0%; 450 mg, 10.5%; placebo, 8.5%), nausea (6.5%, 8.0%, 6.0%, 9.0%), and diarrhea (3.5%, 6.5%, 8.0%, 3.5%); the most common drug-related TEAEs were abdominal pain (4.0%; 5.5%; 9.0%; 5.0%), nausea (3.5%, 5.5%, 5.0%, 4.0%), and flatulence (4.5%, 3.5%, 5.0%, 3.0%). Serious TEAEs reported in ≥2 patients were dyspnea (150 mg, n=1; placebo, n=2), noncardiac chest pain (placebo, n=2), chest pain (300 mg, n=2), and suicidal ideation (150 mg, n=1; 300 mg, n=1). TEAEs led to discontinuation in 3.4% of patients (150 mg, 1.0%; 300 mg, 4.5%; 450 mg, 3.5%; placebo, 4.5%). TEAEs that resulted in study discontinuation in ≥2 patients among all methylnaltrexone groups combined or within the placebo group were diarrhea (300 mg, n=2; 450 mg, n=1; placebo, n=1), abdominal pain (300 mg, n=1; 450 mg, n=1), and dyspnea (150 mg, n=1; 450 mg, n=1).

Conclusions

Once-daily oral methylnaltrexone was well tolerated, with few discontinuations due to TEAEs, in this study of patients with OIC and chronic noncancer pain.

84 Treatment-Emergent Adverse Events Related to Cardiac Safety in a Phase 3, Randomized, Controlled Trial of Oral Methylnaltrexone in Patients With Opioid-Induced Constipation and Chronic Noncancer Pain

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Purpose

In July 2016, oral methylnaltrexone, a selective peripheral mu-opioid receptor antagonist, was approved for opioid induced constipation (OIC) treatment in patients with chronic noncancer pain. The present analysis reports cardiac safety from a randomized, controlled trial of oral methylnaltrexone for OIC treatment in patients with chronic noncancer pain.
Methods

In this phase 3, double-blind, placebo-controlled trial, patients were eligible if they had experienced chronic noncancer pain for ≥2 months, received ≥50 mg/d of oral morphine equivalents for ≥14 days, and experienced OIC (confirmed during a 14-day screening period and defined by <3 rescue-free bowel movements [RFBMs] per week, on average, associated with ≥1 of the following: ≥25% of RFBMs categorized as type 1 or type 2 on the Bristol Stool Form Scale, straining during ≥25% of RFBMs, or ≥25% of RFBMs with a sensation of incomplete evacuation). For the first 4 weeks, patients received oral methylnaltrexone at 150 mg, 300 mg, or 450 mg or placebo once daily, as randomly assigned; for the following 8 weeks, oral methylnaltrexone or placebo was taken as needed. Double-blinding was maintained throughout all 12 weeks of the study.

Results

Overall, 803 patients received ≥1 dose of study medication (oral methylnaltrexone 150 mg, n=201; 300 mg, n=201; 450 mg, n=200; placebo, n=201). During the initial 4-week period of once-daily dosing, 8.5%, 9.0%, 12.5%, and 10.4% of patients discontinued treatment in the 150-mg, 300-mg, 450-mg, and placebo groups, respectively; of the 177, 181, 169, and 167 patients who remained in these 4 groups during the 8-week period of as-needed dosing, 9.6%, 13.8%, 12.4%, and 14.4% discontinued treatment, respectively. Demographic and baseline characteristics were similar among all groups. A total of 13 patients reported cardiac disorders as treatment-emergent adverse events (TEAEs): 2 (1.0%) in the 150-mg group, 6 (3.0%) in the 300-mg group, 3 (1.5%) in the 450-mg group, and 2 (1.0%) in the placebo group. Palpitations were reported in 3 patients (150 mg, n=2; 300 mg, n=1), ventricular extrasystoles in 2 patients (300 mg, n=1; 450 mg, n=1), and the following in 1 patient each: angina pectoris (300 mg), atrial fibrillation (150 mg), atrial flutter (placebo), first-degree atrioventricular block (450 mg), bradycardia (300 mg), left bundle branch block (300 mg), right bundle branch block (300 mg), extrasystoles (300 mg), left atrial dilation (300 mg), sinus tachycardia (450 mg), and tachycardia (placebo). Overall, mean changes from baseline in electrocardiogram, QTCf, QTcb, and QTcl results were minimal. QTCf intervals increased by >30 ms in 2.5%, 3.5%, 3.5%, and 4.5% of patients in the 150-mg, 300-mg, 450-mg, and placebo groups, respectively, and by >60 ms in 0.5%, 1.0%, 1.5%, and 1.5% of patients in these groups. Minimal changes from baseline in heart rate, diastolic blood pressure, and systolic blood pressure were observed 1 hour after the first dose.

Conclusions

In this study of once-daily oral methylnaltrexone for the treatment of OIC in patients with chronic noncancer pain, few TEAEs related to cardiac safety were observed, and frequencies of cardiac disorders were similar between patients receiving oral methylnaltrexone and patients receiving placebo.

85 Analgesia Maintenance With Oral Methylnaltrexone in Patients With Opioid-Induced Constipation and Chronic Noncancer Pain in a Phase 3, Randomized, Controlled Trial

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Purpose

In July 2016, oral methylnaltrexone was approved for the treatment of opioid induced constipation (OIC) in patients with chronic noncancer pain. The purpose of this analysis is to assess the potential impact of oral methylnaltrexone, a peripherally acting mu-opioid receptor antagonist, on opioid analgesia in a randomized, controlled trial.

Methods

A phase 3, double-blind, placebo-controlled trial was conducted in patients who had experienced chronic noncancer pain for ≥2 months, received ≥50 mg/d of oral morphine equivalents for ≥14 days, and experienced OIC (confirmed during a 14-day screening and defined by <3 rescue-free bowel movements [RFBMs] per week, on average, associated with ≥1 of the following: ≥25% of RFBMs categorized as type 1 or type 2 on the Bristol Stool Form Scale, straining during ≥25% of RFBMs, or ≥25% of RFBMs with a sensation of incomplete evacuation). Patients were randomly assigned to receive oral methylnaltrexone (150 mg, 300 mg, or 450 mg) or placebo once daily for 4 weeks, followed by 8 weeks of oral methylnaltrexone or placebo taken as needed. Double-blinding was maintained during the study. Opioid use was recorded daily. On days 1, 14, 28, 42, 56, and 84, changes in pain intensity scores (where 0 = no pain and 10 = worst possible pain) and opioid withdrawal (based on the objective opioid withdrawal scale [OOWS] and the subjective opioid withdrawal scale [SOWS]) were evaluated.

Results

Overall, 803 patients received ≥1 dose of study medication (oral methylnaltrexone 150 mg, n=201; 300 mg, n=201; 450 mg, n=200; placebo, n=201). Demographics were similar among treatment groups. At baseline, the main condition requiring opioid use was back pain, reported by 65.7%, 67.7%, 67.5%, and 72.1% of patients in the 150-mg, 300-mg, 450-mg, and placebo groups, respectively. Pain intensity scores were similar among groups at baseline (mean scores, 6.15–6.38 on the 0–10 Numerical Rating of Pain Intensity Scale) and remained stable through the 4-week once-daily dosing period (mean scores on day 28, 6.13–6.49) and the 8-week as-needed dosing period (mean scores on day 84, 6.21–6.45). Patients in all groups had a median exposure of 83 d; ranges were similar among groups, as well (150 mg, 1–94 d; 300 mg, 1–91 d; 450 mg, 1–99 d; placebo, 3–91 d). Mean changes from baseline in the OOWS score were
minimal in all groups (mean changes from baseline ranged from $-0.14$ to $0.06$); similar results were obtained when abdominal cramping was excluded from the analysis (mean changes, $-0.16$ to $0.07$). Abdominal cramping might be a confounding factor because it is associated with both constipation and the mechanism of action of methylnaltrexone. Mean changes from baseline in the SOWS score were also minimal in all groups (mean changes, $-4.73$ to $-0.06$), and similar results were obtained when abdominal cramping was excluded (mean changes, $-4.45$ to $-0.16$).

Conclusions

Once-daily oral methylnaltrexone did not interfere with opioid analgesia and was not associated with opioid withdrawal signs or symptoms in this trial.

86 Reduced Buprenorphine/Naloxone Prescriptions in a State Medicaid Population Following Formulary Conversion from Suboxone to Bunavail: Implications for Potential Diversion

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Purpose

Among pain patients prescribed opioid analgesics, approximately 10% develop an opioid use disorder. Such patients may derive benefit from medication-assisted therapy (MAT) that incorporates methadone or buprenorphine. Buprenorphine-naloxone (BN) products for the management of opioid dependence are being increasingly incorporated into outpatient MAT; however, there is rising concern about abuse and diversion of these products. For example, among opioid abusers presenting for substance abuse treatment, 32.1% reported prior month pain patients prescribed opioid analgesics, approximately 10% develop an opioid use disorder. Such patients may derive benefit from medication-assisted therapy (MAT) that incorporates methadone or buprenorphine. Buprenorphine-naloxone (BN) products for the management of opioid dependence are being increasingly incorporated into outpatient MAT; however, there is rising concern about abuse and diversion of these products. For example, among opioid abusers presenting for substance abuse treatment, 32.1% reported prior month

Methods

For the period January 1, 2015 through December 31, 2016, two datasets were analyzed: prescriptions and associated costs for BN products, and urine toxicology test results for patients in the Medicaid plan. The dataset comprised 1,370 unique providers ordering 643,225 prescriptions for opioid addiction therapy, estimated to encompass ≥85% of all prescriptions written in the drug class for the state Medicaid plan. Patient and order volumes and the rate of positive urine laboratory values by month were determined for the following molecules: buprenorphine, norbuprenorphine (active metabolite of buprenorphine), butorphanol, cocaine, benzoylecgonine, codeine, fentanyl, heroin, hydrocodone, hydromorphone, meperidine, normeperidine, methadone, morphine, mitragynine, nalbuphine, naloxone, oxycodone, oxymorphone, pentazocine, propoxyphene, norpropoxyphene, tapentadol, n-desmethyltapentadol, tramadol, O-destramadol, and O-desmethyl-cis-tramadol. Drug positivity was defined as the detectable presence of cocaine, benzoylecgonine, or any opioid or opioid metabolite other than norbuprenorphine or methadone in urine. A targeted survey of physicians treating opioid-dependent patients with state Medicaid plan coverage was also conducted to capture feedback about physician experiences with the conversion of patients from SLBN to BBN.

Results

Upon plan conversion to BBN, there was a rapid increase in monthly BN prescriptions mirrored by a rapid decrease in SLBN prescriptions. The peak in BN prescriptions (2633 in November 2015) was approximately 60% lower than the peak in SLBN prescriptions (6531 in July 2015). An unexpected finding was a 68% reduction of the overall BN market, indicating that many BN prescriptions were abandoned altogether. The reduction in overall BN prescriptions was associated with a quarterly cost savings to the Medicaid plan of approximately $3.5 million. Toxicology results indicated a reduction in drug positivity from 13-16% in 2015 to <10% in 2016. Heroin positivity decreased from approximately 9% in December 2015, to an average of <1% during the last quarter of 2016, while positivity for norbuprenorphine, the major metabolite of buprenorphine, increased from 37% in 2015 to >56% in 2016. Increased norbuprenorphine rates are a positive indicator that a patient is actively in treatment. Survey findings indicated that 46% of physicians rated the experience of converting patients to BBN as positive (“very positive” [13%]; “somewhat positive” [33%], while another 40% rated it as negative (“very negative” [20%], “somewhat negative” [20%]). On average, physicians rated BBN as more difficult to abuse or misuse than SLBN.

Conclusions

These findings of a rapid reduction in the overall BN market following a complete formulary switch from SLBN to BBN were associated with marked cost savings to the state Medicaid plan. Toxicology data suggest that these cost savings were realized in the context of improved patient adherence to treatment regimens. The changing market dynamics can potentially be explained by a number of contributory factors, including reduction of diversion and...
 illicit distribution following formulary conversion. These results are considered hypothesis-generating and future research should systematically compare the propensity for diversion/abuse of BN products using various epidemiological tracking tools.

87 Systems Engineering Approach to Pain and Analgesia II

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Purpose

Last year we proposed that the ascending and descending pathways that transmit and attenuate pain signaling can be visualized as an integrated feedback control loop, analogous to temperature control in a room. We now further postulate existence of the equivalent of a thermostat in the pain system—which we term a ‘nocistat’. We can then utilize standard control systems engineering techniques to model a system in which there is a basis for understanding pain sensation and pain treatment from an engineering perspective, including deviations from normal pain. Such modeling might help better understand aspects of pain signaling that remain elusive (e.g., hyperalgesia, allodynia, peripheral and central sensitization, chronification, breakthrough pain, etc.). We present here our continuing efforts to design a simple preliminary control system model of the pain system.

Methods

A systems and fuzzy logic approach (pain as ‘mild’, ‘moderate’, or ‘severe’) is used to initially model normal pain perception and modulation. The system is modeled using a feedback loop in a standard process control engineering sense, and pain is treated as a disturbance to the system (excursion from homeostasis). The body’s response to pain, and descending modulation, is modeled as an attempt to return to steady-state. This will allow future flexibility to model different types of pain, influences on pain sensation/ perception, and pharmacologic and non-pharmacologic interventions to treat pain.

Results

A model was created that describes the system connecting pain stimulus (input) to pain perception (output). The stimulus is imposed on an individual’s Set-point (a pain perception homeostasis) and closed-loop feedback-control that incorporates positive (via amplification, ascending pathways) and negative (attenuation, DNIC pathways) inputs. A Controller monitors the differential between pain and the Set-point and attempts to reestablish homeostasis. A Transfer Function relates stimulus to intensity. Each aspect of the system can be modeled in more detail: the Set-point, for example, for genetic, and cultural influences; the Controller for signal sensitivity and transmission fidelity; and the Transfer Function (e.g., using the Weber-Fechner relationship, or other). Fuzzy Logic can be used to abrogate the lack of biochemical measures of pain perception and vagaries of analog scales.

Conclusions

The reception and perception of pain signals can be modeled as a feedback loop and a hypothesized pain thermostat (‘nocistat’). Preliminary design and some examples are presented. By using standard control-systems engineering to model the system, the model might be used to better understand pain and may provide insights into different types of interventions.

88 Efficacy and Safety of Doxepin in Patients with Sleep Disturbances: A Post-hoc Analysis

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Purpose

Chronic pain is common among adults ≥65 years old (y.o.). A comorbidity often associated with chronic pain in the older adult is sleep disturbance and a vicious cycle between pain and sleep disturbance can develop: sleep disturbance can exacerbate certain chronic pain conditions – and chronic pain has been reported to cause different types of sleep disturbances. Physicians are therefore often faced with treating both pain and sleep disturbances at the same time. Perhaps not recognizing that they are linked, many of these patients will be treated with opioids for their pain and with benzodiazepines for their sleep disturbance. However, the combination of these two classes of medications comes with significant risks and the FDA has released a warning regarding their combined use. Therefore, there is a need for effective non-benzodiazepine sleep aids, especially in the older adult population who are more prone to having both pain and sleep disturbances. Doxepin is a histamine H1 receptor antagonist that has been shown at lower doses (3 and 6 mg) to have efficacy and safety in the older adult for the treatment of sleep maintenance insomnia. However, it is unclear whether demographic or baseline characteristics play a role in the efficacy and safety of doxepin in the older adult. In this posthoc analysis, we examined the potential influence of different subject characteristics from two Phase II and four Phase III clinical studies on the efficacy and safety of doxepin in the older adult.

Methods

This is a meta-analysis based on data from six previously published double-blind, randomized, placebo controlled trials for doxepin. Two Phase II and two Phase III studies in adult and elderly patients with primary sleep maintenance insomnia were combined with one Phase III study in elderly outpatients.
with primary sleep maintenance insomnia and one Phase III study in adults with transient insomnia.

Efficacy outcomes analyzed included: Polysomnography (PSG) assessments for wake after sleep onset, wake time during sleep, total sleep time, sleep efficiency, latency to persistent sleep, number of awakenings after sleep onset, total wake time, wake time after sleep; Subjective Assessments for total sleep time, wake after sleep onset, latency to sleep onset, number of awakenings after sleep onset, sleep quality. Safety outcomes analyzed included treatment emergent adverse events and the next day effects of drowsiness, ability to function, total nap time, digit symbol substitution test and symbol coping test. Time points analyzed included baseline to treatment Night 30.

A mixed model approach was used as random effect and treated as fixed effect among the intent to treat populations for the efficacy and safety outcomes. The safety populations were used for the analysis for the treatment emergent adverse events. The mean difference and its 95% confidence interval and p value were calculated for unadjusted analysis of different comparisons (3mg vs placebo, 6mg vs. placebo, 3mg+6mg [active] vs. placebo). p values of interaction between variables of interest and treatment were calculated. Significance was a $p \leq 0.05$.

**Results**

A total (n) of 1641 subjects were included in the analysis. A total (n) of 707, 302, 632 and 934 subjects in the intent to treat population were enrolled in the placebo, 3mg, 6mg, and combined active doxepin treatment groups, respectively. The average age for each of the groups was 52, 58, 49, and 52 for placebo, 3mg, 6mg, and combined active doxepin treatment groups, respectively. Majority of the subjects were female (n=1021, 62.2%) and white (n=1033, 62.9%).

Compared with placebo, data for the 3mg, 6mg, and combined active doxepin treatment groups significantly improved all PSG and subjective evaluated sleep outcomes for all days and nights up to Night 30. In addition, number of events and types of treatment emergent adverse events were similar between placebo and all evaluated treatment groups. Safety outcomes such as drowsiness during the day, ability to function during the day, total nap time, digit symbol substitution test and symbol coping test did not significantly differ between placebo and doxepin treatment groups on the day following nighttime treatment.

Age (<65 versus 65+ y.o.), gender (male versus female), race (White versus African American) and baseline medical history did not significantly influence the efficacy or safety outcomes at any doxepin dose for the PSG assessments, subjective assessments, or treatment emergent adverse events. Total number of prior medications or concomitant medications did not significantly influence the efficacy or safety outcomes of any doxepin treatment groups.

**Conclusions**

Across various demographic and baseline characteristic subgroups, doxepin was generally-well tolerated and produced significant improvements in sleep outcomes. There were no clinically significant differences between younger (<65 y.o.) and older (65+ y.o.) adults. These results support that the doxepin treatment effect is robust and generalizable across patient subpopulations.

Non-benzodiazepine sleep aids provide physicians with a safe and effective sleep treatment option for all patient types including patients with chronic pain.

**89 A Multicenter Study Comparing the Patient Outcomes Associated with Use of a Nurse Pain Educator for Patients with Chronic Pain**

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**Purpose**

Clinical Nurse Educators have been extremely instrumental in providing education to patients suffering from chronic diseases like diabetes and congestive heart failure. We believe that a Nurse Pain Educator (NPE) can have the same positive impact and greatly improve the current status of pain management. The primary concept for the NPE is to work across the entities of the Pain Center (Pain Center Centric) by providing staff development expertise as an educator, consultant, facilitator, change agent, leader and researcher. NPEs would support the development of the Pain Team, and foster empowerment through knowledge to achieve excellence through the delivery of evidenced based practice. This shall occur through the facilitation of the educational process through assessment, development, planning, implementation and evaluation of competency assessment, continuing education and leadership development. In addition, as a role model of professional behavior, the NPE could be instrumental in creating a professional nursing climate within a Pain Center to meet the needs of the diverse units within multidisciplinary teams and the global needs of the Pain Center. In order to determine the impact of a NPE, we conducted a 6-month study to assess changes in various chronic pain patient outcomes with a focus on appropriate and safe use of opioid analgesics.

**Methods**

This was a multicenter, randomized controlled, parallel arm pilot study comparing the incorporation vs no incorporation of a Nurse Pain Educator into pain and primary care clinics that treat chronic non-cancer pain patients with opioid analgesics. Male or female subjects who were ≥18 years of age, diagnosed with non-cancer pain for ≥3 months; were opioid naive or opioid experienced and were prescribed an oral opioid were enrolled into the study. Subjects diagnosed with chronic cancer pain, personal/family history of alcohol or drug abuse or major mental illness were excluded.

Subjects were randomized to either receive education from an NPE or receive the clinic’s standard of care.
Subjects were educated during the first month on different topics related to the safe and appropriate use of opioid analgesics. In addition, it was recommended to them to visit a training website every month to stay up to date with their education.

Subjects returned every month to the clinic and were required to complete different questionnaires that evaluated their prescription consumption, their abuse and misuse risk, pain and psychological well-being, health status, functional status and current quality of life.

Descriptive statistics were used for summarizing continuous variables: N, mean, standard deviation (SD), median, minimum, and maximum. Frequency tables (showing N and %) were produced to summarize categorical data. Student t-test using 2 tails, equal variance was used to test statistical significance of the change in outcome means. Data presented are for the first 4 months of the study.

Results

A total of 183 subjects were enrolled into the study. Subjects enrolled had an average (SD) age of 54 (10.45) years. Majority of subjects were female (60%) and white (94%). Subjects had an average (SD) height (cm) and weight (kg) of 168.44 (12.99) and 90.28 (26.33), respectively. Subjects at baseline had an average morphine milligram equivalents (MME) daily dose between 300 and 400 mg. Subjects knowledge on opioid analgesics were high with average (SD) Beliefs, Attitudes, Perception (BAP) scores (range 0-64) of 58 (3.65). Subjects at baseline had average (SD) Quality of Life Scale (QOLS) scores (range 0-10) of 6 (2.28), average Current Opioid Misuse Measurement (COMM) scores below 9 and average Pain Management Questionnaire (PMQ) scores near or below the validated questionnaire average of 25. There were no differences in demographics and baseline characteristics between the two study arms.

Key improvements in the Education Arm compared to the Non-Education Arm included a significant decrease in the total daily MME from month 1 to month 3 (p = 0.03) and improvement in the Physical Functioning (month 1 to 3; p = 0.03), Role Limitations (Physical Health) (month 1 to 4; p = 0.02) and Social Functioning (month 1 to 4; p = 0.02) metrics of the SF-36 Health Outcomes Questionnaire. A statistical difference in other metrics such as the BAP, PMQ, COMM and QOLS were not observed.

In addition, majority of subjects stated that they finished their prescription as directed at each visit; majority of subjects stated that they did not take their opioid prescription for any reason other than for pain; and majority of subjects did not take sleep medications or additional pain medications/treatments at each visit.

Conclusions

Improving education methods about the safe and appropriate use of opioids may help prevent poor patient outcomes and the harmful side effects associated with chronic opioid use. Similar to other disease educators, a Nurse Pain Educator may provide patients with the necessary knowledge and tools to improve their pain management outcomes. The current pilot study shows improvements in total opioid consumption and in some quality of life metrics, indicating that additional education provided by a Nurse Educator can impact treatment outcomes. Additional studies evaluating the education provided by Nurses is warranted.

90 Nitromedicine: is a new medical specialty that focuses on managing chronic diseases by restoring the NitroRedox balance

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Purpose

Because the big pharma fail to recognize the critical role of the rheostatic Nitro Redox imbalance in the pathogenesis of chronic diseases. Nitromedicine is the new specialty that focuses on developing diagnostic and therapeutic protocols to enhance stem cells and manage chronic diseases based on modulation of NitroRedox sensitive biochemical pathways.

Methods

Parkinson’s disease is a chronic debilitating neurodegenerative movement disorder characterized by progressive degeneration of dopaminergic neurons in the substantia nigra region in human midbrain. Oxidative stress plays an important role in the degeneration of dopaminergic neurons in Parkinson’s disease (PD). Disruptions in the physiologic maintenance of the redox potential in neurons induces apoptotic genes and cell death.

To date, oxidative stress is the well accepted concept in the etiology and progression of Parkinson’s disease.

A number of sources and mechanisms for the generation of reactive oxygen species (ROS) are recognized including the metabolism of dopamine itself, mitochondrial dysfunction, toxins neuroinflammatory cells and aging in addition to PD causing gene products including DJ-1, PINK1, parkin, alpha-synuclein and LRRK2 which causes mitochondrial dysfunction leading to exacerbation of ROS generation and susceptibility to oxidative stress.

Results

Management of Parkinson’s diseases

1-Mainstay of treatment are selegiline, pramipexole (Levodopa/Carbidopa), to increase the dopamine bioavailability at the substantia nigra.

2-Restoring NitroRedox balance and neutralizing free radicals generators to slow the progression of dopaminergic neurons degenerations and increase the dopamine bioavailability at the substantia nigra.

Conclusions

Our therapeutic protocols are targeted against suppressing and alleviating the oxidative stress-induced cellular damage and increasing dopamine bioavailability.
91 Zap It: Genicular Nerve Radiofrequency Ablation for the Treatment of Chronic Knee pain.

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Purpose
The purpose of this investigation was to evaluate the effectiveness of radiofrequency ablation (RFA) of the genicular nerves as an alternative to knee replacement or long term opiate/NSAID medication for the control of chronic osteogenic knee pain.

Methods
Patients with significant knee pain who had failed conservative therapy, such as physical therapy, NSAIDS, and opioids, and were not surgical candidates were eligible. The staff at the pain center were educated on RFA indications and procedural process. A pain management physician performed the procedure with the RN assisting by monitoring the vital signs and performing motor safety checks during genicular nerve stimulation. Dr. Kaufman proposed stimulating the genicular nerves with a threshold of 0.15V, which is a lower sensory threshold test for capture of the nerves as well as a change in the targeted temperature of 60° Celsius and time of 120 seconds for efficacy. Patients were contacted at 3 and 6 months post-procedure to obtain Visual Analogue Scale (VAS) pain scores, and ability to perform activities of daily living.

Results
A total of 30 patients underwent the procedure over 12 months. No long-term side effects were noted with only one patient reporting transient numbness of the affected knee. Of the 30 patients, 21 were contacted for follow up at 3 months, 73% reported greater than 55% reduction of their pre-procedure knee pain. 18 of those initial 21 patients were contacted at the 6-month mark, 67% described continued pain relief of 51% of baseline.

Conclusions
In this investigation, genicular nerve ablation was found to be safe and effective in controlling chronic osteogenic knee pain and should be considered as a treatment option for this population.

92 Rescue medication usage by patients with osteoarthritis of the knee treated with triamcinolone acetonide extended-release (FX006): a post hoc, pooled analysis of three randomized controlled clinical trials

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Purpose
Osteoarthritis (OA) of the knee is a painful condition that contributes to reduced mobility and impaired quality of life. Inflammation is a key pathology of OA joint disease and pain processes. Intra-articular (IA) injections of anti-inflammatory corticosteroids are frequently utilized to manage pain associated with OA with modest effect, but the analgesic effect of these injections is of limited duration. Rapid egress of corticosteroid from the joint space following injection may be responsible for this characteristic. Triamcinolone acetonide (TA) is currently injected as a crystalline suspension (TACs). A novel triamcinolone acetonide extended-release (TAER) formulation for intra-articular injection (FX006) embeds the same active ingredient (TA) in poly(lactic) co-glycolic acid (PLGA) microspheres. In Phase 2/3 clinical trials, FX006 demonstrated differential pharmacology and clinical efficacy compared to TACs in patients with OA of the knee: plasma and synovial fluid sampling demonstrated increased joint residency time and decreased systemic exposure following injection of FX006, and FX006 demonstrated sustained, clinically meaningful pain relief compared with saline-placebo and TACs.1,2

It is common in clinical trials of analgesic agents to issue rescue medication to patients at the beginning of the study to use as needed to manage pain. Assessment of the impact of the study medication on rescue medication utilization can provide important information on the robustness of the overall analgesic effect. We examined rescue medication usage in patients with knee OA treated with FX006.

Methods
A post hoc, pooled analysis of three Phase 2/3 double-blind, randomized, placebo-controlled clinical trials (NCT01487161, NCT02116972, and NCT02357459) was conducted. Patients with OA of the knee (American College of Rheumatology diagnostic criteria; Kellgren-Lawrence (K-L) grade 2/3 radiographic severity) and baseline Average Daily Pain (ADP)-intensity score ≥5 to ≤9 (0–10 Numerical Rating Scale) were enrolled. Patients received a single IA injection of FX006 32 mg or saline-placebo. ADP-intensity was assessed daily for 24 weeks (NCT02116972, NCT02357459) or 12 weeks (NCT01487161). Rescue medication (acetaminophen/paracetamol 500 mg tablet) was issued to patients at the beginning of the study to utilize on an as-needed basis to manage uncontrolled index knee pain or any other type of pain. Consumption of rescue medication was monitored through a daily diary reporting system, and pill counts were confirmed at the clinical site. Effect of the IA injection treatment on rescue medication use (mean number of daily rescue medication tablets in each weekly interval) was measured by least-square-mean (LSM) change from baseline (Day –7 to –1) to each week through Week 12 for FX006 vs saline-placebo, analyzed with mixed-effects model for repeated measures methodology on observed data with no imputation for missing data.
Results

The analysis included 586 patients (FX006, n=324; saline-placebo, n=262). Baseline demographic characteristics were well balanced: in the FX006 vs saline-placebo groups, most patients were female (57% vs 60%) and white (83% vs 86%), with a mean (standard deviation [SD]) age of 60.5 (9.2) vs 61.4 (8.7) years; the percentage of patients with K-L grade 2/3 OA of the knee was 39%/61% vs 40%/60%, and mean (SD) time since diagnosis was 7.1 (6.7) vs 6.5 (5.8) years. Rescue medication use was statistically significantly lower (p<0.05) with FX006 compared with saline-placebo at each of Weeks 1–12. At Week 12, mean number of daily rescue medication tablets taken (LSM [standard error, SE]) was 0.86 (0.099) for FX006 compared with 1.23 (0.11) for saline-placebo; LSM-difference (95% confidence interval) was −0.37 (−0.63, −0.11), p=0.0052.

Conclusions

In patients with painful knee OA, reduced rescue medication use following treatment with FX006 vs saline-placebo further supports the analgesic efficacy of FX006 through 12 weeks post-IA injection. Reducing the use of concomitant analgesic medications in this patient population (NSAIDs, opioids) may be a potential benefit of FX006 treatment.

References


93 The “Kleenex” Effect: Misidentification of Branded Pain Reliever Medications in an Enriched Sample of Abusers

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Purpose

There are significant public health concerns with improper consumption of prescription opioid pain relievers, both in the short-term (e.g., overdose, toxic exposure), and long-term (e.g., thrombotic thrombocytopenic purpura). The health risks vary by type of medication, such as active pharmacological ingredients, excipients, formulation, dosages, and the user’s preferred route of administration. Recall of the brand or trade names are typical methods that consumers use as an aid in presenting their medication utilization to clinicians, or other public health officers. Yet, surprisingly little is known regarding how well patients can identify various brands of medications. Understanding these features and which types of patient characteristics are associated with better reporting would help clinicians while assessing patient history during the clinical evaluation.

Methods

The current study conducted a self-reported survey of past-year opioid abusers in ten geographic areas around the United States (n=1,862) among persons aged 18 or older. Abusers were those reporting any extra medical use without a prescription or purely for the euphoric feelings of “getting high.” The inclusion criteria were restricted to those reporting abuse of prescription opioids in the past 12 months. Data were collected in 2015 between March and October. The participants were recruited via online advertisements and street intercept methods. The survey took about 30 minutes to complete. Pictures of eight of the most common branded opioid medications were provided to the respondent, and each was asked to identify the medication from a list of ten branded names. Descriptive analyses were used to provide information on the sample and validation data from the 2015 National Survey on Drug Use and Health. Descriptive data were also used to present information on the correct identification of each drug. Multivariable regression models were used to formulate predictors of the total number of correct responses. Finally, Item Response Theory (IRT) was used to examine which drugs exhibited the best ability to discriminate underlying ability to identify different prescription drugs.

Results

The sample of past-year opioid abusers were highly comparable to data from the National Survey of Drug Use and Health, with the composition being mostly male (68%), white (72%), and between the ages of 18-20 (40%). Insurance coverage was varied, between private (44%), public (32%) and none (23%). The lifetime abuse rates were highest for the original OxyContin (OP) at 44%. The reformulated rate was slightly lower at 40%. Vicodin™ (hydrocodone) and Generic Percocet were the most commonly endorsed medication for abuse at 46% and 45%, respectively. Those abusing generic Percocet were the most likely to correctly identify the drug from the pill picture (62%), followed by OxyContin (OC) at 54% and Zohydro™ (extended release hydrocodone) at 51%. OxyContin OC and OP were the most commonly endorsed drug when the index drug was incorrectly reported. The mean number of correct items was four out of eight. Statistically significant predictors of the total score correct were female sex, no insurance coverage, never married persons, employed, and persons with a high-school education or greater and stable housing. More recent use was associated with a high probability of correct identification. The psychometric properties, as measured by the IRT models, indicated that Opana™ was the most difficult item to identify, whereas Percocet and original OxyContin (OC) was the easiest to identify.

Conclusions

Using an enriched sample of prescription opioid abusers provides a unique opportunity to understand medication identification. Abusers are a good benchmark, given their regular usage of a diverse range of medications and even preference for different types of drugs due to their features (e.g., immediate versus extended release). Higher education and greater experience...
were associated with an increased chance of correctly identifying the drug of interest. Overall, these findings call attention to the need for pain management specialists to recognize that even the most experienced patients may mis-report or mis-identify their medications.

94 Ambulatory Stride Variability Measured by a Wearable Device is a Biomarker for Chronic Pain Severity
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Purpose
A biomarker is a measurable indicator of the severity or presence of a disease. Chronic pain is a complex biopsychosocial phenomenon that is difficult to manage, primarily due to the lack of practical biomarkers to individualize treatment. Physiologic functions such as sleep, autonomic regulation and gait can be quantitatively measured and are altered by chronic pain, and therefore represent potential biomarkers. However, single measurements at clinic visits are inadequate for this purpose due to lack of specificity and high variability.

Wearable technology has emerged over the past decade to provide convenient tracking of fitness and health parameters, primarily in the form of pedometers worn on the wrist. Recently, monitoring capabilities have expanded to include more complex functions such as sleep time and quality, heart rate variability and gait characteristics such as stride variability. By providing nearly continuous physiologic tracking, these wearable technologies may have a role as practical chronic pain biomarkers. However, the clinical utility of real-world biometric measurements, as opposed to their traditional acquisition in research settings, is an open question.

In this study, we evaluated the utility of stride variability, obtained in a real-world setting with a wearable device, as a biomarker for chronic pain severity.

Methods
This study retrospectively evaluated users of a wearable device to treat chronic pain (Quell®, NeuroMetrix, Waltham, MA) during a 6-month period (1/2017-6/2017). The device delivers high-frequency TENS and with a companion smartphone app collects demographic data, clinical information, and biometrics. Subjects rated 24-hour pain intensity and interference with activity, sleep and mood on an 11-point scale. Interference was analyzed as a composite average. Inclusion criteria were (i) demographic and clinical information, (ii) ≥5 days gait and pain data, and (iii) consent to use data.

The device is worn on the upper calf and has an accelerometer that monitors leg movement. Stride time is the interval between sequential toe-off events and stride variability is the ratio between the standard-deviation and mean stride time, expressed as percentage. Stride variability is calculated for each segment of ≥30 consecutive strides and is defined per 24-hour period as the minimum. Users with low mobility or who use device only while resting do not generate gait data.

For each subject, pain intensity, interference and stride variability were defined as the median over the study period. Subjects were stratified into low (≤3%), intermediate (3-5%) and high (>5%) stride variability groups. Differences among the groups for age, gender, BMI, pain intensity, interference, health conditions, sites, and duration were evaluated by one-way ANOVA and two-sample t-test for post-hoc analyses. The effect size was quantified by Cohen’s d.

Results
932 device users met the inclusion criteria. The age was 56±14 years (19-96), 56% female, and BMI was 30±6 kg/m². The number of painful health conditions was 3.5±2.0, with arthritis (64%) and back injury (42%) most frequently reported. The number of pain sites was 4.8±2.4, with low back (80%) and legs (73%) most frequently reported. Most subjects (71%) reported chronic pain for ≥3 years.

The number of pain ratings was 19±19 and number of stride variability measurements was 23±20 per subject. The stride variability was 3.3±0.9% (1.6-7.4%). Among all subjects, 43% were in the low variability group, 52% intermediate variability and 5% high variability. There were no statistically significant differences in BMI or pain duration. Subjects with high stride variability were older, more likely to be female, and had more painful health conditions and sites than subjects with low variability.

Pain intensity was 5.2±2.0 for the low variability group, 5.5±2.0 for intermediate variability, and 6.0±2.2 for high variability. There was a statistically significant difference by one-way ANOVA (p=0.0052). In post-hoc analyses, statistically significant differences were identified between the low and intermediate groups (p=0.0126) and low and high groups (p=0.0178). Cohen’s d was 0.40.

Composite pain interference was 4.5±2.4 for the low variability group, 4.8±2.4 for intermediate variability, and 5.3±2.6 for high variability. There was a statistically significant difference by one-way ANOVA (p=0.0145). In post-hoc analyses, statistically significant differences were identified between the low and intermediate groups (p=0.0275) and low and high groups (p=0.0317). Cohen’s d was 0.36.

Conclusions
Gait is a complex neurological phenomenon mediated by automated control circuits and high level cognitive processes, particularly executive functions. Chronic pain interferes with both automated and cognitive aspects of gait. This study demonstrated that stride variability, measured with a wearable device in a real-world setting, is a biomarker for chronic pain severity in a heterogenous population. High stride variability (≥5%) identified subjects with statistically and clinically significant increases in the number of painful health conditions, number of pain sites, pain intensity and pain interference compared to subjects with low stride variability (≤3%).
95 Self-Reported Weather Sensitivity Stratifies Subjects with Chronic Pain

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Purpose

Weather and chronic pain have long been thought to be related, with Hippocrates describing a connection in 400 BC. Weather is reliably forecast and available on mobile platforms. If a relationship between weather and chronic pain exists, it may be possible to predict chronic pain changes to optimize pain control. These relationships may also inform travel and geographic preferences by people with chronic pain. Moreover, an understanding of the interplay between weather and chronic pain may advance scientific understanding and lead to novel therapeutic approaches.

Contemporary studies have evaluated the relationship between weather and various forms of chronic pain. A consistent finding is that people with chronic pain believe that weather influences their pain. By contrast, objective studies have been mixed. Some identified meaningful statistical and clinical associations, whereas others did not. One explanation for these discrepancies is that self-reported weather sensitivity is a manifestation of confirmation bias; namely the tendency to recall instances of worsening chronic pain and certain weather patterns and ignore different pairings. Alternatively, scientific studies may have failed to uncover associations due to small sample sizes, insensitive outcome measures, complex relationships between weather and pain, and incorrect quantification of the weather exposure.

In this study, we analyzed a large heterogeneous chronic pain database to better understand demographic, clinical and physiological differences between subjects with and without self-reported weather sensitivity.

Methods

This study retrospectively evaluated users of a wearable device to treat chronic pain (Quell®, NeuroMetrix, Waltham, MA) during a 9-month period (10/2016-6/2017). The device delivers high-frequency TENS and monitors physiologic functions. The device and its smartphone app collect and store demographic data, clinical information, and biometrics. Subjects reported if they were weather sensitive, insensitive or unsure using the app. Weather sensitive subjects further identified one or more triggers among precipitation, cold, hot, humid, cloudy and windy. Subjects rated 24-hour pain intensity and interference, several painful health conditions, multi-site pain, and worst pain in the morning or all day. The sensitive group was characterized by greater pain intensity and interference, several painful health conditions, multi-site pain, and worst pain in the morning or all day. The insensitive group had lower pain intensity and interference, was less medically and anatomically complex, and was associated with worst pain overnight and during activity.

Results

4131 device users met the inclusion criteria. Weather sensitivity prevalence was 50.0%, 26.7% reported lack of weather sensitivity and 23.3% were unsure. Subsequent analyses excluded unsure subjects, leaving 3170. The common triggers were precipitation (77.4%), cold (69.5%) and humidity (31.3%). Weather sensitive subjects were younger (54.2±14.1 vs. 58.4±13.3 years, p<0.0001), had higher BMI (30.4±7.2 vs. 28.9±6.2 kg/m², p<0.0001) and were more likely female (62.5% vs. 39.6%, p<0.0001).

Weather sensitive subjects had more pain characteristics (3.6±2.1 vs. 2.5±1.7, p<0.0001) and pain sites (5.0±2.5 vs. 3.2±1.9, p<0.0001). Weather sensitivity (vs. insensitivity) was associated with high RR for fibromyalgia (3.5, 30.7% vs. 8.7%, p<0.0001), headaches/migraine (2.0, 29.7% vs. 14.8%, p<0.0001), head pain (2.8, 20.2% vs. 7.3%, p<0.0001), arm pain (2.4, 29.1% vs. 12.1%, p<0.0001) and hand/wrist pain (2.0, 46.1% vs. 22.7%, p<0.0001).

Weather sensitive subjects had greater pain intensity (5.9 ±2.0 vs. 5.4±2.0, p<0.0001), greater interference with activity (5.9±2.5 vs. 5.1±2.6, p<0.0001), sleep (4.8±2.7 vs. 3.9±2.7, p<0.0001) and mood (5.6±2.6 vs. 4.7±2.8, p<0.0001) and longer duration (77.0% vs. 57.2% >3 years, p<0.0001). Weather sensitivity was associated with a RR >1 for worst pain in the morning (1.4, 13.0% vs 9.2%, p=0.0017) and all-day pain (1.3, 49.3% vs. 38.9%, p<0.0001) and a RR <1 for worst pain at night/sleeping (0.7, 9.7% vs 13.9%, p=0.0004) and worst pain when active (0.7, 18.5% vs 27.7%, p<0.0001).

Conclusions

This study identified differences between subjects with chronic pain according to self-reported weather sensitivity. The sensitive group was characterized by greater pain intensity and interference, several painful health conditions, multisite pain, and worst pain in the morning or all day. The insensitive group had lower pain intensity and interference, was less medically and anatomically complex, and was associated with worst pain overnight and during activity. These results suggest that certain chronic pain cohorts may be most sensitive to weather and represent an enriched population for objective studies evaluating the relationship between chronic pain and weather.

96 Physician Practice Patterns and Treatment Challenges in Acute Postoperative Pain Management

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Purpose

Between 2% to 58% of patients experience moderate to severe postoperative pain. Managing postoperative pain can be challenging as many patients experience poorly controlled pain.
and/or analgesic medication-related adverse events (AEs). In relation to acute pain management, intravenous (IV) opioids remain a foundation of multimodal analgesic therapy and are highly effective in managing moderate to severe pain for many patient types and procedures. However, a difficult balance exists between achieving postoperative pain control and subsequent conventional IV opioid-related AEs, which may be dose-limiting, thereby resulting in a narrow therapeutic window and adversely affecting patient care. To better understand the challenges of acute postoperative pain management in the context of the increasing complexity of patients and procedures in acute care settings, a physician survey was conducted to gain insights into physician practices, treatment patterns, and the different factors that drive their therapeutic decisions.

**Methods**

An online survey of US-based surgeons, anesthesiologists, and critical care/emergency medicine physicians was conducted. Participants were identified from an opt-in healthcare database. Eligible physicians had prescribed an IV pain medication within the past month, had completed ≥ 1 of 27 surgical procedures in 6 surgical categories (general or bariatric, cardiovascular, colorectal, orthopedic or neurosurgery, plastic or cosmetic, or vascular), and practiced in an academic medical center, community hospital, or ambulatory care center. Surgical categories were chosen based on clinical assessment of those surgical categories most likely to experience moderate to severe pain and requiring IV pain medications following surgery. The survey contained questions about the types of medications they prescribe for patients following surgery to manage pain, the factors that influence their post-surgical pain medication regimens, the challenges they face when treating acute postoperative pain, and their perceptions of unmet needs with current therapies. The survey also included demographic questions including physicians’ primary practice setting, years in clinical practice, and geographic location.

**Results**

Of 501 physicians who completed the survey, 60% were surgeons. Nearly 60% of physicians reported that they had been practicing for > 10 years. The top 3 most prescribed pain medications were opioid agonists (95.6%), COX-2 inhibitors or NSAIDs (73.7%), and IV acetaminophen (60.5%). In the postsurgical setting, the main factors determining the choice of pain medications were patient risk factors such as age, comorbidities or prior surgeries (77.2%), post-surgical mobility (75.6%), avoidance of pain medication AEs such as nausea, vomiting, and respiratory depression (RD; 75.2%), and better control of patient-reported pain levels (74.5%). Past clinical experience (81.6%), surgery type (78.2%), onset of analgesic effect (67.1%) and better dose titratability (48.9%) were the main factors driving prescription decisions in a hospital setting. With respect to patient characteristics, physicians were most concerned about pre-existing RD (64.3%), a history of chronic opioid use (55.7%), age > 75 years (55.5%), and respiratory comorbidities (54.7%). The most important factors to physicians regarding patient recovery were well-controlled pain (61.3%) and post-surgical mobility (50.9%). The most common challenges physicians faced with postoperative pain management were nausea (76.2%), constipation (67.3%), and vomiting (60.3%). Physicians believed that the top unmet needs for acute postoperative pain management were a requirement for more medications associated with fewer side effects such as nausea, vomiting and RD (80.7%), and an ability to avoid or reduce unwanted pain medication-related AEs (64.9%). Practitioners were also asked to rate various characteristics of conventional parenteral opioids (including fentanyl, hydromorphone, and morphine which were the most commonly prescribed medications) on a scale of 1 (least preferred) to 10 (most preferred). No opioid rated above a 7.7 for any drug characteristic. The lowest scoring drug characteristics, which were therefore deemed to have the greatest room for improvement, were the occurrence of adverse events and use in high-risk patients.

**Conclusions**

The survey findings suggest that opioid-related AEs, such as nausea, vomiting and RD, remain a common challenge in postoperative pain management and play a key role in influencing treatment decisions, particularly in high-risk patients. Given the analgesic needs in acute surgical settings, opioids such as fentanyl, hydromorphone, and morphine are commonly prescribed, but their use appears limited by the risk of AEs and their safety profile in these high-risk cohorts. Overall, these findings highlight the need for medications that give rise to fewer side effects, which physicians recognized as being the a major unmet need in postoperative pain management.

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**97 Automated PaperSpray sample preparation using a robotic autosampler for clinical research**

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**Purpose**

PaperSpray ionization is a powerful tool, enabling rapid analysis of a wide variety of samples in minutes. However, current PaperSpray mass spectrometry workflows are reliant on manual spotting of samples onto the PaperSpray cartridge. This may be suitable for small numbers of samples, but can be a substantial limitation in high throughput applications. Fortunately, a suitable automation platform is readily available in the form of the robotic autosampler commonly used for LC- or GC-MS sample introduction, with the simple addition of an adapter plate to properly position the cartridges. With some straightforward modifications, the autosampler system may also be adapted to work with whole blood, directly from sample collection tubes, eliminating multiple stages of sample handling.

**Methods**

A PAL3 autosampler system (CTC Analytics AG, Zwingen, Switzerland), equipped with a dilutor tool, mixing unit, FastWash...
station, and three position tray holder was used for automated preparation of paper spray samples. A custom 3D-printed adapter plate was used to position Prosolia paper spray cartridges in the tray holder for spotting using the PAL3 autosampler. Samples were prepared in Vacutainer-type sample tubes and aspirated directly from these vials using a dilutor tool equipped with an extended sampling needle. Cartridges prepared manually were spotted using a 2-20 µL adjustable volume pipette. Mass spectrometry analysis was performed using a Prosolia™ Velox 360™ PaperSpray ion source coupled to a Thermo Scientific™ LTQ-XL ion trap mass spectrometer.

**Results**

A modified PAL3 autosampler system was evaluated as an automated sample preparation platform for PaperSpray ionization. Preliminary investigation was performed using ink and blood to visually confirm spotting position and spot size reproducibility with various needles and instrument parameters. Optimal spotting parameters for both conventional Hamilton point type 3 and type 5 (side-port) needles were determined. Even using a side-port needle, the automated system achieved highly symmetrical, reproducible spotting performance, significantly better than free-hand spotting with an adjustable volume pipette. The autosampler system was also adapted to aspirate samples directly from sealed Vacutainer-type blood collection vials, improving user safety by eliminating the possibility of sample aerosolization during vial opening and sample aspiration.

Cyclosporine A, acetaminophen, and everolimus were employed as research analytes to assess the performance of the automated spotting system when coupled to PaperSpray mass spectrometry. The reproducibility and signal intensity in samples applied using the autosampler was consistently equivalent or better than in samples applied by a skilled operator using a hand-held pipette, for both blood and water matrices. Additionally, when working with donated whole blood the automated method yielded more consistent spot position and diameter.

Carryover in sample spotting was assessed using cyclosporine A in water, alternating between spotting the cyclosporine solution and a solvent blank. The observed ms/ms signal from blanks spotted after an application of cyclosporine using the automated spotting system was not appreciably different from blanks spotted manually or cartridges to which no sample had been applied. In all cases, the automated spotting system yields equivalent or better performance than manual pipetting while providing enhanced user safety (by eliminating the need to open sample vials and aspirate potentially hazardous samples) and an overall streamlined PaperSpray-mass spectrometry workflow for clinical research reducing hands-on time for each sample.

**Conclusions**

Automated platform for PaperSpray sample spotting, eliminating manual pipetting of potentially hazardous samples and streamlining PaperSpray workflow.

98 Motivation for Change in Route of Administration during the Course of Opioid Abuse

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**Purpose**

Misuse and abuse of prescription opioids is a public health crisis. Oral ingestion of intact pills is the most frequently reported route of misuse and abuse for many prescription opioids, but alternative routes of administration (RoA) such as insufflation and intravenous injection are also common. Traditionally, the opioid misuse or abuse pathway has been described as follows: an initial oral opioid exposure in a genetically susceptible person induces a “high” or euphoric feeling, which may then trigger a desire to intensify subsequent opioid-related experiences through chewing pills, snorting, or injecting the opioid. However, the natural history of opioid abuse, such as changes in routes of abuse (RoA) or motivation for the changes overtime has not been well studied. Although several studies have explored motivations for misuse and for initiating opioid abuse, to our knowledge no research has specifically evaluated the reasons motivating change in RoA over the course of opioid abuse. Recently, this group conducted a study with adult patients entering an opioid abuse treatment center with the purpose of understanding the natural history of opioid abuse and motivation for changes in RoA. Previously reported data from the study revealed that there was no clearly defined “pathway” of abuse. However, 75% of the patients began prescription opioid abuse by swallowing pills intact, and 80% of those patients progressed to chewing, snorting, or injecting during the course of their abuse. The data regarding motivations for changing RoA are presented here.

**Methods**

Adult patients were recruited from a buprenorphine naloxone medication-assisted treatment clinic in western Kentucky. Semi-structured, one-hour interviews were conducted at the clinic and focused on capturing the natural history of patients’ opioid abuse and motivations for changing RoAs over the course of their abuse. These interviews were transcribed and “motivational statements” (instances where patients discussed motivation for changing RoA) were identified. A codebook of motivational factors was developed by a team of doctoral-level experts (n=5). The final codebook included 8 motivations: (1) Medication Specific Factors, (2) Social Influences: Pressures/Encouragement; (3) Social Influences: Avoid Social Consequences; (4) Health Related Reasons; (5) Achieve Desired Effect; (6) Prevent Negative Effects; (7) Abuse-Deterrent Properties Related; and (8) Aversion to Specific RoA. Two raters independently coded the motivational statements using the codebook and achieved 91% agreement. Both qualitative and quantitative exploratory analyses were conducted to identify patterns in
the motivation data within and across participants. First, the frequency of various motivations was calculated. Second, the relationship between motivations and specific changes in RoA was explored. Demographic information provided by participants was used to conduct exploratory analyses. For purposes of this study, swallowing opioid tablets intact was considered the least dangerous RoA, followed by chewing, snorting, and injecting.

Results
Seventeen of the 20 patients interviewed as part of the natural history study discussed motivation for changing RoA and were included in the analysis. The majority of participants identified as White/Caucasian (94.1%) and male (58.8%). The mean (SD) age of the sample was 35 (9.6) years. Approximately half (47.1%) of participants reported that they began abusing opioids after receiving an opioid prescription to treat pain from a physician (termed "pain patients"), and 70% reported using non-opioid substances prior to prescription opioid abuse. From these 17 patients' interviews, 34 "motivation statements" were identified. The most frequently cited motivation was Achieve Desired Effects (38.2%), followed by Social Influences: Pressure/Encouragement (17.6%). Although 6 patient interviews contained two or more motivation statements each, no between-participant patterns emerged. The majority (83.0%) of Social Influences: Pressure/Encouragement motivation statements were associated with transitioning to a more dangerous RoA, and most (80.0%) patients reporting this motivation began their abuse as "recreational abusers" (i.e., without a legitimate prescription written for them by a physician). Nearly all (92.3%) Achieve Desired Effect motivation statements were associated with a progression from swallowing to a more dangerous RoA. Both Health-Related Reasons motivation statements pertained to concerns about bodily harm resulting from injection. The two Abuse-Deterrent Properties Related motivation statements were related to an extended-release oxycodone product with AD properties, and both patients who discussed this motivation continued using the same opioid formulation, but reported increased effort to manipulate the drug for abuse.

Conclusions
Consistent with previous literature indicating that euphoria is a popular motive for initiating opioid abuse and misuse, these data suggest that euphoria motivated RoA transitions from swallowing pills intact to more dangerous RoAs. Based on these findings, it is possible that if patients are presented with a barrier to abuse by their preferred RoA, they might be disincentivized to begin or continue misusing/abusing prescription opioids. Social pressures also motivated the progression to more dangerous RoAs, highlighting the potential utility of social interventions in combating the prescription opioid crisis. These data support the need for further research in this area.

99 Development of a brief version of the Current Opioid Misuse Measure (COMM): The COMM-9
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Purpose
The Current Opioid Misuse Measure (COMM; Butler et al., 2007) is a commonly used self-report instrument to identify and monitor aberrant opioid-related behavior in chronic pain patients on opioid therapy. Multiple studies have shown that the COMM can accurately identify patients who are engaging in aberrant opioid-related behavior (including medication misuse, abuse, addiction, diversion, and opioid-seeking behaviors) with approximately 80% accuracy (Butler et al., 2007; Butler et al., 2010). The COMM's concurrent validity has been established with patients from pain management centers as well as pain patients in primary care settings (Meltzer et al., 2011). However, the length (17 items) of the COMM may limit its clinical utility. In its present form, the COMM is completed by paper-and-pencil and requires hand scoring by medical staff, which increases paperwork and staff burden. Therefore, the current study presents development of the "COMM-9," a brief electronically-administered 9-item form of the COMM.

Methods
Five hundred and seventeen patients with chronic noncancer pain on opioid therapy from pain treatment centers in five states completed the COMM. Adult (≥ 18 years) patients were eligible for participation if they were currently prescribed opioids for chronic pain. Patients were classified as either being positive or negative for aberrant drug-related behavior (the "Aberrant Drug Behavior Index" [ADBII]) based on: (1) data from a structured interview (42-item self-report Prescription Drug Use Questionnaire; PDUQ), (2) physician-report data (Prescription Opioid Therapy Questionnaire; POTQ), and (3) a urine toxicology screen. A patient was classified as positive for aberrant drug-related behavior if they were positive on the (1) PDUQ and/or (2) POTQ + urine screen. The optimal subset of COMM items that most strongly predict current aberrant drug-related behavior were identified using the LASSO method as the selection criterion in conjunction with the leave-one-out cross-validation (LOOCV) method as the stop criterion in SAS. Logistic regression was utilized to predict probabilities of positive ADBI from the subset of COMM items using all data (validation) and LOOCV (cross-validation). To compare the accuracy of the brief COMM vs. the full COMM in predicting aberrant opioid-related behavior, receiver operating characteristic curves (ROC) were generated for the (1) model predicted probabilities from the subset of COMM items using all data, (2) model predicted probabilities from the subset of COMM items using the LOOCV, and (3) the sum of the 17 COMM items (COMM raw total score).
Results

Five hundred and seventeen patients provided complete data and were included in the analyses. Most participants identified as Caucasian/White (85.3%) and slightly over half identified as female (52.8%). The mean age of participants was 50.7 years (SD = 12.2). Thirty-seven percent (N=189) of participants were classified as being positive on the ADBI. Nine items were identified before the selection method stopped, and content experts agreed that these items were satisfactory. ROC analyses revealed areas under the curve (AUC) of .79, .77, and .78 for the COMM-9 using all data, COMM-9 using the LOOCV, and the COMM total score, respectively. That is, in the current study the COMM-9 exhibited greater overall accuracy than the full 17-item COMM. Next, cut-points were identified to classify patients as having No/Low Risk, Moderate Risk, and High Risk. A cut-point of .28 was identified as having sensitivity of .77 and specificity of .65; patients who scored below this cut-point were classified as having No to Low levels of risk (less than 28% chance of aberrant opioid-related behavior). Patients whose score exceeded the cut-point of .50 were classified as having High Risk, and were more likely than not to engage in aberrant opioid-related behavior. This cut-point, identified to maximize specificity (i.e., raising the “bar” to reduce the rates of false positives—patients mistakenly identified as engaging in aberrant opioid-related behavior), corresponds with a specificity of .89, which naturally sacrifices sensitivity (47), but ensures that patients identified as high-risk are true positives. Patients whose score fell between these cut-points were classified as having Moderate levels of risk.

Conclusions

This study presents the successful development of a brief screener for current aberrant opioid-related behavior for pain patients. Despite reducing length of the instrument by nearly 50%, the COMM-9 maintains overall accuracy, sensitivity, and specificity of the full COMM. As each COMM-9 item’s response options contributes differentially to the COMM-9 score, the COMM-9 is administered on a computer, tablet, or smartphone. The COMM-9 is automatically scored by the computer, which integrates results into the electronic medical record (EMR) and generates an interpretive report for the provider, reducing both patient and staff burden.

100 Reality and Responsibility Revisited: Stakeholder Accountability in the Effort to Develop Safer Opioids

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Purpose

There are many stakeholders in the search for safer pain treatments in general, and safer opioid therapy in particular. Stakeholder groups include patients, healthcare practitioners, payors, industry, regulators, government, and media. Nearly a decade ago, stakeholder responsibility with respect to responding to the opioid crisis was first delineated (Passik, Heit, and Kirsh 2006). The various stakeholder groups’ responses have been of varying degrees of effectiveness. Since then, much attention has been paid to the science, potential utility, and the current state of the art of abuse deterrent formulations (ADFs) of opioid analgesics. This expert commentary aims to 1. Evaluate the present status of aspirations delineated since the publication of the original stakeholder responsibility manuscript, and 2. Discuss stakeholder roles and responsibilities in assuring that ADFs have a fair evaluation of their impact on curtailing misuse, abuse, addiction, and overdose.

Methods

Expert commentary

Results

Despite a changed climate regarding opioids, there remain many stakeholders with an interest in increasing the safety and ensuring the continued availability of opioid therapy for those who need it. Some progress has been made in new approaches to safeguard opioid therapy, for example, the development of multiple abuse-deterrent formulations. However, these contributions bring with them new responsibilities, and few stakeholders seem willing to support, economically and otherwise, either partial and incremental advances meant to provide a more balanced opioid environment.

Conclusions

Stakeholders must face the realities of our dual public health crises and live up to our responsibilities to the public health. This poster is based on a paper that will be part of an upcoming supplement devoted to ADFs in the Journal of Opioid Management.

101 A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Titration-to-Effect Study of Orally Administered CR845 in Patients with Osteoarthritis of the Hip or Knee

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Purpose

CR845 is a selective kappa opioid receptor agonist with a peripheral mechanism of action, a greater than 30,000-fold selectivity over mu and delta opioid receptors, and no known activity at other non-opioid receptors, ion channels, or transporters. It is currently being developed as a novel therapeutic agent for the treatment of acute and chronic pain. Its unique peptidic structure significantly differs from that of small molecule kappa opioid agonists developed to date, which, for the most part, are active within the central nervous system (CNS). Due to its hydrophilic tetrapeptide structure, CR845 has limited membrane permeability by passive diffusion that limits its access to the CNS. Thus, the compound preferentially activates kappa opioid receptors located outside the CNS (e.g., in peripheral sensory nerves and ganglia).
Findings from nonclinical pharmacological studies in rodents have indicated that CR845 can decrease pain, decrease itch, and reduce the production and release of pro-inflammatory mediators. As of July 2017, more than 1600 healthy volunteers and patients across 20 clinical studies have received CR845; 976 have been exposed to the intravenous (IV) formulation and 626 have been exposed to an oral (PO) formulation (capsules or tablets). Overall, CR845 has been shown to be safe and well tolerated when administered in both single and multiple IV or PO dose forms. Here we report preliminary results from a Phase 2b study designed to characterize the analgesic efficacy of orally administered CR845 in patients with osteoarthritis (OA) of the hip or knee (ClinicalTrials.gov NCT02944448).

Methods

476 male and female patients (ages ≥25 years) with moderate to severe pain (numeric rating scale [NRS] ≥5) associated with OA of the hip or knee were enrolled at 33 sites in the US. Following a 14-day screening period, patients were randomized in a 2:1 ratio to active vs placebo, respectively. CR845 (1.0, 2.5, or 5.0 mg enteric coated tablets) or placebo (similar appearing tablets) were provided for BID dosing for a total of 8 weeks, with each dose administered at least 2 hours prior to or after a meal. Each patient was started on a 1 mg dose of CR845 or matching placebo. During the initial 4-week post-randomization titration period, the dose of study drug was increased to 2.5 or 5.0 mg to effect in a double-blind fashion. Patients were then maintained for 4 weeks on the final individualized effective dose. The primary outcome measure was the change in pain at the index joint achieved with CR845 compared to placebo at Week 8/Day 57 from baseline as measured by the NRS. Secondary outcome measures included differences between CR845 and placebo in the Western Ontario and McMaster Osteoarthritis Index (WOMAC) total score and subscores for pain intensity, joint function, and stiffness and in the Patient Global Impression of Change scale (PGIC). Safety and tolerability measures over the 8-week treatment period include capturing of detailed medical and surgical history and monitoring of vital signs and treatment-emergent adverse events (AEs).

Results

CR845 efficacy was assessed in 118 patients with hip OA (CR845, n=78; placebo, n=40) and 358 with knee OA (CR845, n=238; placebo, n=120). The primary efficacy results comparing CR845 (all doses) vs placebo were not statistically significant. Patients titrated to 5.0 mg (n=289) exhibited a 35% reduction in mean joint pain score which didn’t reach statistical significance (p=0.111 vs placebo). However, patients with hip OA maintained on 5.0 mg (n=66) exhibited a statistically significant 69% reduction in mean joint pain score over placebo (p=0.043). The reduction in pain score in this subgroup was accompanied by a reduction in mean rescue medication of 41% at Week 8 vs placebo. For patients maintained on the 5.0 mg dose, there was a statistically significant increase in proportion of patients whose OA pain was “very much improved” or “much improved” as indicated by PGIC score in all patients (p<0.005 vs placebo) and in patients with hip OA (p<0.006 vs placebo). WOMAC scores for the 5.0 mg hip patients improved to 62% of baseline over the 8-week treatment period (p=0.116 vs placebo). Patients maintained on the 1.0 and 2.5 mg doses did not exhibit significant reductions in mean joint pain scores compared to placebo nor did patients with knee OA at any dose, possibly due to a larger placebo effect observed in this subgroup. All doses were generally well tolerated with no drug-related serious AEs. For all doses of CR845, the most common AEs at a ≥5% incidence level were constipation (13%), dizziness (8%), and dry mouth (6%). Importantly, there were no clinically significant changes in serum sodium levels observed during the 8-week treatment period for any dose group.

Conclusions

Post-hoc analyses demonstrated that hip OA patients who titrated to CR845 5.0 mg had a significant pain reduction compared to placebo patients. The PGIC measure of pain in hip and knee patients combined also showed significant benefit of 5.0 mg CR845 while other pain measures showed improvement but not statistical significance. The observed beneficial effects combined with a positive safety profile warrant a further trial, exploring a different design to assess the potential efficacy advantages offered by a longer treatment duration and/or higher doses of CR845.

102 A Systematic Review of Randomized Controlled Trials on Acupuncture Treatment for Low Back Pain Based on FEAS

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Purpose

About 85% of people in developed countries are to experience low back pain at some point throughout their lifetime. Therefore, low back pain has become one of the most frequent reasons for visiting practitioner or emergency departments in the United States.

At present, the management of low back pain comprises a variety of different intervention strategies, such as oral drugs, surgery, physiotherapy, behavioral therapy, exercise therapy, massage and acupuncture.

Among these strategies, acupuncture has become a popular non-surgical treatment method for relieving low back pain and improving functional disabilities because of its simplicity and good efficacy.

Despite of its wide use, the detailed intervention of acupuncture treatment may varies among practitioners. Therefore the standard model of acupuncture treatment is required.

The purpose if this article is to review RCTs on acupuncture treatment for low back pain in order to establish a standard acupuncture treatment model in treating low back pain.
Methods

RCT articles on acupuncture treatment for low back pain were searched through various online databases using keyword ‘acupuncture’, ‘electroacupuncture’ and ‘low back pain’. Additionally, references of recent review articles and meta-analysis were also examined.

Study quality of each paper was assessed using the FEAS (The Influencing Factors which Affect the Effectiveness of Acupuncture Scale).

Results

Ten out of the one hundred six articles searched were appropriate to the criteria of this study. (acupuncture treatment group n=332, compare group n=401)

Among the ten articles reviewed, two articles compared acupuncture treatment with non-penetrating sham acupuncture, and other two articles compared acupuncture treatment with placebo stimulation. Three articles compared acupuncture treatment with non-acupoint stimulating acupuncture, and the others compared acupuncture treatment with trigger-point stimulation, TENS, electroacupuncture and massage.

Eight articles mentioned ‘de-qi’ which refer to patient’s sensation and reaction toward acupuncture treatment. The number of acupuncture needles used to treatment was from two to twenty-six. The needle retention time was from ‘immediate removal of needles’ to half an hour. All studies used sterile disposable stainless steel needle, with length of 40mm to 70mm and diameter of 0.18mm to 0.3mm.

Conclusions

The ideal acupuncture treatment model for low back pain was obtained as follows. A sterile disposable stainless steel (0.30mmx40mm) should be inserted to more than six acupuncture points on the BL, GV and GB meridians such as acupoints BL23, BL25, BL40, BL60, GV4 and GB30. Needle handling method to obtain ‘de-qi’ is recommended and repeated stimulation during the 20 minute retention time is necessary. Ideal treatment frequency would be more than once a week for about 7 weeks.

103 Profiling non-medical use of tapentadol products among recreational drug abusers

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Purpose

Prescription opioid misuse and abuse is a public health epidemic in the United States (ONDCP 2015) and a growing source of morbidity, mortality, and substance abuse treatment admissions (SAMHSA 2015, SAMHSA 2014, Okie 2010, and Dart 2015). It is crucial to evaluate and characterize the abuse profiles associated with specific opioid compounds and formulations so that prescribers, payers, and patients can make informed decisions regarding pain treatment with opioid medications. Tapentadol is a centrally acting analgesic with two mechanisms of action: μ-opioid receptor agonism and noradrenaline reuptake inhibition (Tzschentke 2013, Kress 2010). Tapentadol has a lower affinity to the μ-opioid receptor compared to morphine and its noradrenaline reuptake inhibition may not be significantly rewarding compared to other opioids, suggesting an opioid-sparing effect and lower abuse potential for tapentadol products (Terlinden 2007, Raffa 2012). Previous literature suggests that the prevalence of non-medical use (NMU) of tapentadol is relatively low compared to other prescription opioid compounds (Butler 2015, Cepeda 2013). However, little has been published on the profile of those who use tapentadol products non-medically, including their motivation for use, methods of administration, tampering efforts, opinions, and experiences with tapentadol products. The Tapentadol Use Internet Survey and follow-up semi-structured online interviews were developed to describe and characterize NMU of tapentadol products (i.e., Nucynta® and Nucynta ER®) among a community of recreational drug abusers frequenting the online discussion forum website Bluelight.org.

Methods

A mixed-methods qualitative study was conducted via a survey and in-depth active online interviews to better understand NMU of tapentadol. NMU was defined as use of prescription opioids “in a way not prescribed,” including: 1) taking a medication not prescribed to you, 2) taking a medication for reasons other than what it was prescribed for, and/or 3) using a medication in a way not intended (e.g., taking more than prescribed, using an unintended route of administration, or tampering with the product). Participants for the survey and interviews were recruited from January through May 2017. To participate, individuals must have met the following conditions: ability to read/understand English; visited Bluelight.org; consented to participate; at least 18 years of age; resided in the United States; and reported NMU of Nucynta and/or Nucynta ER. Survey participants were asked if they were interested in a follow-up active online interview and, if so, were prompted to provide contact information (Bluelight.org username or email address). Eligibility requirements included the ability to use an online chat program and consent to participate. The survey was administered using the online data collection software Qualtrics. Survey data was analyzed using SAS® statistical software, with descriptive statistics reported using frequencies and percentages for binary/categorical variables and calculated means, medians, and ranges for continuous variables. Interviews were conducted using Cryptocat, a free, open-source, encrypted online chat program (Cryptocat, 2017). Interview transcripts were qualitatively evaluated by multiple reviewers using a modified Grounded Theory approach.

Results

Seventy-eight adults completed the survey, eight of whom completed a follow-up interview. Most survey participants were under 35 years old, male, White, and completed at least some college. Over half indicated opioids were their
preferred recreational substance. A similar demographic profile was noted among the subset (n=8) who completed the follow-up interview.

Among survey participants, NMU of Nucynta IR (n=67) was indicated more frequently than Nucynta ER (n=30) (19 used both formulations). Oral routes were the most common route for both products. Compared to Nucynta IR, a greater proportion of Nucynta ER users indicated tampering with the product. Motivations for NMU of tapentadol included enhanced pain relief, self-medication of anxiety/depression, alleviation of withdrawal, experimentation, and/or to get high. Most who indicated NMU of Nucynta ER and IR no longer used these products at the time of survey completion (73.3% and 82.1%), citing lack of access, better options, ineffective or unpleasant high, and/or negative side effects. The highest median NMU desirability ratings were given to oxymorphone (ER and IR), oxycodone (ER and IR), and morphine IR. Median desirability ratings were comparatively low for tapentadol products and desirability of tapentadol IR was greater than that of tapentadol ER.

Among interview participants (n=8), all reported NMU of Nucynta IR and half indicated NMU of Nucynta ER. Most used tapentadol orally, and those who had used both formulations of Nucynta typically preferred the IR version. Interview participants shared that tapentadol was a rare, unique opioid that was not well known among recreational drug abusers. While some interviewees experienced no high when using tapentadol, others experienced recreational effects along with hallucinations and/or other atypical effects at higher dosages. Opinions of tapentadol were influenced by opioid tolerance and individual preferences.

Conclusions
This mixed methods study contributes valuable qualitative information on NMU of tapentadol products. Tapentadol was characterized as a unique opioid with atypical effects, including hallucinations at a high milligram dosage. Nucynta products were typically used via oral routes, and tampering was more common with the ER formulation. Desirability ratings were low for tapentadol relative to other opioid compounds. These data suggest that, among this community of recreational drug abusers, tapentadol may be less attractive for NMU compared to other prescription opioid compounds, and the ER formulation of Nucynta is less attractive for NMU compared to the IR version.

104 Improving Chronic Pain Care and Opioid Safety in VA Primary Care: Implementation and Evaluation of the Integrated Pain Team Clinic

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Purpose
Chronic pain and the increase in opioid prescribing is a national public health problem which has led to a sharp uptick in opioid-related morbidity, mortality, substance use disorder treatment admission, and tragically, overdose deaths. Recent national guidelines for prescribing opioids for chronic pain (Department of Veterans Affairs and the Department of Defense and the Centers for Disease Control and Prevention) recommend engaging patients in interdisciplinary care and providing multimodal therapies to improve pain care and opioid safety. The San Francisco Veterans Affairs Health Care System (SFVAHCS) Integrated Pain Team (IPT) clinic, which is embedded within primary care, integrates and co-locates pain-trained primary care providers (PCPs), psychologists, and pharmacists to provide interdisciplinary, biopsychosocial pain care for patients with complex chronic pain and aberrant opioid use. PCPs refer patients via consult, and IPT providers assume short-term responsibility for pain care. Patients are offered a variety of multi-modal services, including behavioral therapies (i.e., mind body skills, cognitive behavioral therapy), non-opioid medication optimization, non-pharmacological pain management strategies (i.e., exercise, yoga acupuncture), opioid safety monitoring via urine drug screening and tapering when indicated, opioid overdose education, and naloxone kits for overdose reversal. IPT ultimately conducts a warm hand-off back to the PCP for long-term pain management. We matched patients with chronic pain enrolled in IPT to similar patients receiving usual primary care to compare changes in daily prescription opioid dose.

Methods
This was a prospective matched cohort design conducted October 2015 through December 2016 at SFVAHCS. Using a VA clinical performance dashboard, patients with chronic pain and prescribed chronic opioids (≥90 days dispensed in the past 120 days) at baseline were matched to similar patients receiving usual primary care. Patients prescribed opioid agonist treatment with methadone or buprenorphine/naloxone for opioid use disorder were excluded. Patients were matched on: age (<55 or ≥55), gender (male or female), psychiatric diagnoses (posttraumatic stress disorder, depression, bipolar disorder, and/or other psychiatric diagnosis), and baseline daily opioid dose (<100 or ≥100 MEDDD). Patients were assessed at 3-months (n=162) and 6-months (n=82). Primary outcome was between-group difference in change in mean morphine equivalent daily dose (MEDDD) at follow-up. We used Wilcoxon signed-rank test in descriptive analysis and examined Average Treatment Effect (ATE) in mixed-effects linear regression analysis.

Results
A total of 162 veteran patients were followed for 3-months: 81 enrolled in the IPT clinic versus 81 in usual primary care. Among these, 82 patients (41 pairs) were followed for 6-months. After 3-months, mean MEDDD decreased by 41.2mg (Std: 99.2mg) in the IPT group compared to 24.8mg (Std: 76.9mg) in usual care. This represents 61% (95% CI: 18%-104%) greater MEDDD reduction in the IPT group when adjusted for demographics and baseline MEDDD (p=0.006).
addition, twice as many patients in IPT compared usual care (38 vs. 19 patients) reduced MEDD by ≥50% at 3-months, and patients in the IPT group had a 2.6-fold higher odds of achieving ≥50% reduction in opioid use than usual care (p=0.004). At 6-months, mean MEDD decreased by 57.8mg (Std: 78.0mg) in the IPT group compared to 14.2mg (Std: 99.9mg) in usual care, representing 103% (95% CI: 21%-185%) greater MEDD reduction when adjusted for demographics and baseline MEDD (p=0.015). Furthermore, the IPT group had a 3.6-fold higher odds of achieving ≥50% reduction in MEDD than usual care (p=0.005).

Conclusions
Compared to usual primary care, the IPT clinical model led to significantly greater daily prescription opioid dose reductions at 3-months, with further reductions achieved by 6-months. An interdisciplinary biopsychosocial pain care team, embedded in primary care, decreases opioid use and improves opioid safety in veterans with chronic pain and opioid misuse. Implementation and dissemination of IPT-like models in other VA facilities and healthcare systems may lead to system-wide improvements in opioid risk reduction.

105 Medication Use among Patients Diagnosed with Headache and Migraine in a Large National Commercial Payer Database: A Retrospective Study
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Purpose
Characterize medication use among patients diagnosed with headache (H) and/or migraine (M)

Methods
Retrospective study of 547,558 adult patients diagnosed with H or M in the HealthCore Integrated Research Database between 1Jan07-31Jul15. H or M diagnosis was defined as presence of ≥2 claims associated with an ICD-9-CM or ICD-10-CM diagnostic code for H or M, with ≥1 claim occurring ≥30d after first observed claim (index date). Patients had ≥12mo pre-index enrollment. Five mutually exclusive diagnosis-based cohorts: H only (N=365,091), M only (N=94,492), H/M on same day (H/M, N=7,461), H then M (H-M, N=46,656) and M then H (M-H, N=33,858) were assessed for demographics, comorbidities, medication prescriptions, proportion of days covered (PDC)≥80% and persistence defined as no ≥30-day gap in preventive medication supply.

Results
Cohort mean (SD) age was 46(15.5)y, 72% female, and were followed for 3.6(2.5)y after index. The diagnoses of H and M, respectively, were made by: family practice (27%, 33%), internal medicine (20%, 20%), emergency medicine (10%, 5%), neurology (5%, 16%), and other/missing (37%, 26%). Approximately 11% of patients with a first diagnosis of H had a subsequent M diagnosis, and 25% of patients with a first diagnosis of M had a subsequent H diagnosis. Median time between diagnoses for H-M was 231d vs. 252d for M-H. The H only group had higher rates of vascular comorbidities compared with other groups (hypertension or dyslipidemia 32% vs. 19-24%; ischemic heart disease 7% vs. 2-3%; cerebrovascular disease 4% vs. 2%). Triptan use was low in those with H only (4%) but fairly similar in those with any M diagnosis [M (46%), H/M(47%), H-M (46%) and M-H (50%)]. Opioid use was fairly high in all groups [H (61%), M (57%), H/M (74%), H-M (71%) and M-H (74%)]. Triptan and opioid use between diagnoses among H-M was 18% and 56%, respectively, and among M-H 38% and 56%, respectively. Roughly half of the cohort had at least one prescription for a preventive medication after last diagnosis [H (47%), M (49%), H/M (65%), H-M (69%) and M-H (68%)]. The top choice of preventives following last diagnosis varied by group [H (ACE inhibitors, 18%), M (beta-blockers, 17%), H/M (antiepileptics, 31%), H-M (antiepileptics, 33%) and M-H (antiepileptics, 33%)]. OnabotulinumtoxinA use was rare (<1%). Proportion of patients, respectively, with PDC≥80% and persistent to preventive medications following final diagnosis was low [H (22%, 2%), M (20%, 2%), H/M (13%, 2%), H-M (16%, 1%) and M-H (17%, 3%)].

Conclusions
Many patients have multiple headache diagnoses and a higher percentage of patients have the more specific diagnosis (M) before a less specific diagnosis (H) than those diagnosed with H before M. Regardless of diagnosis, there is a high rate of opioid prescribing in the population, even in the population with only a migraine diagnosis; indeed, opioid use is higher than triptan use. There is substantial variation in use of preventive medications, which could be due to comorbidities, and PDC ≥80%, a marker of adherence, was consistently low. As such, there are opportunities to optimize therapy among H and M patients.

106 The positive impact of a North Carolina state-wide medicine disposal initiative on the DEA National Take Back Day program
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Purpose
Opioid abuse is one of the most pressing public health issues in the United States today. Opioid overdose is now the leading cause of death among individuals under the age of 50, with nearly half of those deaths attributed to prescription opioids. Nearly two-thirds of opioids misused and abused are diverted from legitimate pain patients, predominantly family and friends. The Drug Enforcement Administration (DEA)
designated April 29, 2017 as the 13th National Drug Take Back Day. Every state participates in takeback events, and the DEA reports the weight of the collections retrieved.

In 2002, the North Carolina Division of Public Health recommended the establishment of community based overdose prevention programs to address opioid overdose from prescription medications. Operation Medicine Drop (OMD), Safe Kids NC, Project Lazarus, the North Carolina Department of Insurance, the State Bureau of Investigation, and local police/sheriff departments have executed medicine disposal initiatives through medicine take back events and the installation of permanent disposal receptacles in police stations, hospitals, clinics and health department and pharmacies across North Carolina. OMD and Project Lazarus have coordinated with the twice annual DEA National Drug Take Back Day events, originally started in 2010, as well as various other events throughout the year.

Methods

Purdue Pharma L.P. collaborated with Project Lazarus to create the North Carolina Disposal Initiative (NCDI) research program. The goal of NCDI is to assess the effectiveness of drug takeback programs and drop boxes in removing scheduled substances (including opioids, benzodiazepines and stimulants) from circulation, and the impact of that removal on important public health outcomes: opioid overdose deaths, hospitalizations, and calls to poison control hotlines. NCDI supported Project Lazarus and OMD, specifically by funding local organizations to execute medicine take back events during the spring of 2017, including the weighing and counting of medications, the installation of new drop boxes, and increased community awareness of events. This included Purdue representatives providing healthcare and pharmacy professionals more than 60,000 tear sheets to distribute to patients to identify the location and time of local take back events and drop boxes.

We examined data published by the DEA that recorded amount of the collections in pounds and the number of national participating take-back sites for each state during National Drug Take Back Day. We compared data from April 30, 2016 and April 29, 2017 to examine year-over-year changes in North Carolina compared to all other states.

Results

From 2016 to 2017, North Carolina increased the total weight of collections from 15,449 pounds to 26,420 pounds, an increase of 10,971 pounds (71%). In 2017, North Carolina collected, on average, 440 pounds of collections per site. North Carolina ranked second in total increased weight of collections, fourth in relative increased weight of collections, and second in amount collected per site compared to the remaining 49 states, Washington DC, and Puerto Rico in 2017.

Nationwide, DEA’s numbers show a 1% increase in weight of collections from 2016 to 2017; from 893,498 pounds to 900,386 pounds. Year over year changes in the weight of collections at the state-level ranged considerably, from a relative decrease of -94% to an increase of 216%.

At 71%, North Carolina’s increase in from 2016 to 2017 was significantly higher than all surrounding states, including: Virginia (-13%), West Virginia (-32%), South Carolina (11%), Georgia (9%), Kentucky (17%) and Tennessee (16%).

The DEA also reported that North Carolina increased the number of participating take-back sites from 38 sites in 2016 to 60 sites in 2017, an increase of 22 sites (58%), placing North Carolina in the top 10 ranking of states that increased take-back sites in terms of both absolute number of additional sites and relative increases in take-back events.

Conclusions

NCDI showed a positive impact on the amount of take back medicines collected in North Carolina. The partnership between pharma, state government, and community based organizations is a model that could be replicated in other states. North Carolina showed substantial increases in the number and success of take back events, higher than national levels and surrounding states, which cannot be attributed solely to secular national or state changes. Additional research is ongoing to quantify the proportion of opioids collected and to assess the impact of the disposal initiatives on public health outcomes such as overdose mortality, hospitalizations, and poisonings.

107 Respiratory Effects of the Treatment of Chronic Pain with Buprenorphine when Administered as BELBUCA®

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Purpose

Opioid-induced respiratory depression is a serious and potentially fatal side effect of opioid use. With the growth of opioid use and misuse, the incidence of opioid-related adverse events (AE) has increased dramatically. Buprenorphine is a partial agonist at the opioid mu receptor. It has been shown to have a ceiling effect that limits respiratory depression in humans who were administered IV doses ranging from 0.05 mg to 0.6 mg. This respiratory ceiling effect could result in a lower incidence of respiratory depression with the use of buprenorphine than that caused by other opioids, notably those classified as CII (e.g. morphine). BELBUCA® (buprenorphine) buccal film delivers buprenorphine transmucosally via a novel bi-layered buccal film. BELBUCA is approved 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. Safety data from BELBUCA clinical trials conducted to support FDA approval and from spontaneous post-marketing Adverse Drug Experience (ADE) Reports are available to evaluate the incidence of respiratory adverse effects that may have been related to respiratory depression.

Methods

A retrospective and systematic review of the AE data from the 16 clinical trials (2474 subjects) that comprised the
BELBUCA NDA and supported its approval was performed. The AE databases from 9 Phase I, 2 Phase II, and 5 Phase III clinical research studies were searched for all terms within the MedDRA System Organ Class (SOC) or High Level Group Term (HLGT) that included “Respiratory, Thoracic, and Mediastinal”. All terms which could be considered possibly related to respiratory depression were identified. These AE terms were reviewed by a clinical team (nurse, physician, clinical scientists) for relevancy, with a subset of terms at the subject level evaluated further for a possible relationship to respiratory depression. Additionally, the post-marketing safety database was searched in a similar manner (search date, 16 July 2017). This database contains every ADE that has been spontaneously reported since approval of BELBUCA in October 2015.

Results

There were no AEs of respiratory depression reported in any of the 16 clinical trials supporting the BELBUCA NDA. Twenty-three AEs of potential concern, that were possibly related to respiratory depression, were identified and investigated further. Of these 23 events, 14 were considered relevant and evaluated at the subject level. These events were: dyspnea (4 total: Phase I = 3; Phase II = 1), shortness of breath (5 total: Phase III = 5), acute respiratory failure (1 total: Phase III = 1), respiratory insufficiency (1 total: Phase III = 1), hypoxia (2 total: Phase II = 1; Phase III = 1), and hypoventilation (1 total: Phase I = 1). Most AEs were reported as either mild or moderate and resolved without sequelae. The AE of acute respiratory failure occurred in a subject with ongoing pneumonia at the time of the event. Because the subject was hospitalized, the event was considered serious; causality was assessed by both the investigator and sponsor as unlikely related to study drug treatment. The AE of respiratory insufficiency occurred in a subject with a history of asthma, concomitant upper respiratory tract infection, and pneumonia. This event was considered moderate in severity, was assessed by the investigator as not-related to study drug treatment, and it resolved without treatment after 3 days. Spontaneous post-marketing ADE reports included 12 events that were considered relevant and warranted further investigation: 11 cases of dyspnea and 1 case of respiratory depression. The serious event of respiratory depression occurred in a female patient with a history of COPD. The event resulted in hospitalization during which time treatment with BELBUCA was stopped and Norco was restarted. The event resolved without sequelae. No additional information, including the severity of the event, was reported and repeated attempts to obtain more details were unsuccessful.

Conclusions

Respiratory depression was not induced following the administration of BELBUCA to 2474 subjects involving all NDA studies, which supports buprenorphine’s ceiling effect on respiratory depression as described in scientific literature. The two AEs of respiratory failure and respiratory insufficiency which occurred during Belbuca’s clinical development were both related to pneumonia and neither was considered to be related to buprenorphine treatment. Furthermore, the receipt of only one post-marketing case of respiratory depression, in a patient with COPD, continues to support this reassuring profile. The benign outcome of these searches should be considered when prescribing opioids for the treatment of pain.


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Purpose

Since 2000, deaths from prescription opioid overdose in the United States have increased, prompting action from clinicians, policymakers, and payers to address the epidemic. The Centers for Disease Control and Prevention report that in 2014, there were 28,647 opioid prescription and nonprescription overdose deaths, accounting for 61% of all drug overdose deaths. Patient and prescription factors related to misuse and risk of overdose include comorbid mental illness, non-opioid substance use disorders, previous hospitalizations, high morphine milligram equivalent (MME) daily dose and concurrent use of benzodiazepines. Reports suggest that the Medicaid population is uniquely vulnerable to opioid overdose. However, little is known about patterns of pharmacy and medical utilization prior to death in this population. The objective of this study was to describe demographic and clinical characteristics, medical utilization, opioid use, concurrent use of benzodiazepines, and substances involved in death in the year prior to overdose for Oklahoma’s Medicaid members who died of unintentional opioid prescription drug poisoning from 2012-2016. An additional objective was to identify risk factors associated with fatal unintentional prescription opioid overdose for this population.

Methods

Oklahoma Medicaid’s pharmacy and claims data were linked with medical examiner (ME) data for unintentional prescription overdose deaths through a member’s unique identifier and subsequently de-identified. Cases were members who were Medicaid eligible during year of death and had at least one prescription opioid claim between January 2012 and June 2016. Death date listed on ME data was defined as index date. Controls were Medicaid members with at least one opioid prescription claim and had not died during the study period. Dummy index dates were imputed for controls by adding the median time-to-event from first opioid claim to death date in cases to first opioid claim in controls. Propensity scores (PS) were generated through logistic regression using age, sex, race, Charlson Comorbidity Index, and number of opioid prescription claims with death as the outcome.

Dyspnea = 1. Most AEs were reported as either mild or moderate and resolved without sequelae. The AE of acute respiratory failure occurred in a subject with ongoing pneumonia at the time of the event. Because the subject was hospitalized, the event was considered serious; causality was assessed by both the investigator and sponsor as unlikely related to study drug treatment. The AE of respiratory insufficiency occurred in a subject with a history of asthma, concomitant upper respiratory tract infection, and pneumonia. This event was considered moderate in severity, was assessed by the investigator as not-related to study drug treatment, and it resolved without treatment after 3 days. Spontaneous post-marketing ADE reports included 12 events that were considered relevant and warranted further investigation: 11 cases of dyspnea and 1 case of respiratory depression. The serious event of respiratory depression occurred in a female patient with a history of COPD. The event resulted in hospitalization during which time treatment with BELBUCA was stopped and Norco was restarted. The event resolved without sequelae. No additional information, including the severity of the event, was reported and repeated attempts to obtain more details were unsuccessful.

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Methods

Oklahoma Medicaid’s pharmacy and claims data were linked with medical examiner (ME) data for unintentional prescription overdose deaths through a member’s unique identifier and subsequently de-identified. Cases were members who were Medicaid eligible during year of death and had at least one prescription opioid claim between January 2012 and June 2016. Death date listed on ME data was defined as index date. Controls were Medicaid members with at least one opioid prescription claim and had not died during the study period. Dummy index dates were imputed for controls by adding the median time-to-event from first opioid claim to death date in cases to first opioid claim in controls. Propensity scores (PS) were generated through logistic regression using age, sex, race, Charlson Comorbidity Index, and number of opioid prescription claims with death as the outcome.
Controls were matched 3:1 to cases on PS using a greedy algorithm. Demographics, comorbidities, pharmacy, and medical utilization were examined in the 12 months prior to index date for each group and compared by univariate analyses. Medications were concomitant if days’ supply and dates of service overlapped on calendar day. Comorbidities included those related to opioid abuse (eg, mental health disorders, non-opioid substance use disorders) and chronic pain diagnoses, which were defined as ≥2 claims ≥90 days apart with the same International Classification of Diseases pain code sets. Prevalence of substances attributed to death listed in the cause of death field in ME data were reported as frequencies.

Results

Of the 639 unintentional prescription opioid deaths observed, 321 had at least one prescription opioid claim between January 2012 and June 2016; these cases were matched to 963 controls. Similar to controls, cases averaged 44.5 (±11.2) years of age, 64.2% were female, 80.7% self-identified as white, and mean Charlson Comorbidity Index score was 1.5±2.0. Around 54.5% of controls and 83.2% of cases (p<0.05) had any mental health disorder. The most common chronic pain types were neck/joint pain (26.4% controls; 32.4% cases; p<0.05) and low back pain (26.6% controls; 43.6% cases; p<0.05). Compared to controls, cases had greater amounts of opioids in terms of mean daily morphine milligram equivalent doses (47.2±50.9 mg in controls vs. 67.22±74.4 mg in cases; p<0.05) and higher usage of long-acting opioids (15.9% in controls vs. 28.7% in cases; p<0.05). Concomitant opioids and benzodiazepines were seen in 35.9% of controls and 70.4% (p<0.05) of cases. Among those with opioid/benzodiazepine overlap, the mean length of overlap was greater among cases (134.3±115.8 days in controls vs. 169.2±121.9 days in cases; p<0.05). Further differences (p<0.05) were seen at 30-89 days (8.2% controls; 16.8% cases), 90-179 days (6.5% controls; 11.2% cases), and at least 180 days (12.5% controls; 33.3% cases) of overlap. The top substances involved in death included opioids alone (28.7%), opioids in combination with other opioids (15.3%) and in combination with benzodiazepines (29.3%). Six (1.9%) deaths involved cocaine and two (0.6%) deaths involved heroin.

Conclusions

Nearly half of Oklahoma Medicaid members who had a fatal unintentional prescription opioid overdose did not have an opioid prescription claim. Of those who had a prescription, most were middle-aged, female, and white. Chronic pain and comorbid mental health disorders were common. Cases had greater exposure to opioids, even when adjusting for number of claims. Concomitant exposure to benzodiazepines was also prevalent. Cocaine and heroin were implicated in a small proportion of deaths, suggesting additional illicit drug use. Future research should further assess the magnitude of these factors and develop predictive models to identify members at risk.

109 Effects of Naldemedine, a Peripherally Acting μ-Opioid Receptor Antagonist, on Inhibition of Large Intestinal Transit Induced by Morphine in Rodent Models

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Purpose

Opioids are widely prescribed for patients suffering from moderate-to-severe chronic pain, owing to their potent analgesic effects. However, opioid-induced constipation (OIC) often occurs due to the action of opioids on μ-opioid receptors in the enteric nervous system. Naldemedine (S-297995), a peripherally-acting μ-opioid receptor antagonist, was developed as a potential treatment for OIC. In this study, the effect of the μ-opioid receptor agonist morphine on small and large intestinal contractions was evaluated. Additionally, inhibitory activity of naldemedine to reverse the effect of morphine on large intestinal transit was evaluated.

Methods

Two experimental methods were used. 1) Isometric recordings: small and large intestines were isolated from mice and dissected histologically to jejunum, ileum, proximal-, transverse-, distal-colon, and rectum. The effect of morphine on circular muscle contractile responses was measured using isometric transducers. 2) Gastrointestinal Motility Monitor (GIMM): guinea pig distal-colon was isolated for an in-vitro assay measuring propulsive motility. The effect of naldemedine on morphine-induced inhibition of colonic transit was recorded in video and quantitatively evaluated.

Results

Isometric recordings identified different effects of morphine along different sections of small and large intestine. Strong contraction was detected in the rectum, distal- and transverse-colon; weak contraction was detected in the proximal-colon, jejunum and ileum. Video recordings from GIMM showed that morphine inhibited feces propulsion in a dose-dependent manner, and significant delay in propulsive velocity was observed at 3 μM of morphine. Naldemedine dose-dependently reversed the morphine-induced propulsive suppression (IC₅₀ > 0.31 μM). The highest dose of naldemedine alone (1 μM) had no effect on propulsion.

Conclusions

A differential effect of morphine on the circular muscle contractions of the small and large intestines with strong contraction on the anal side detected. Video analysis demonstrated that naldemedine potently reversed the
delay of colonic propulsion by morphine. Since the effect of morphine on intestinal smooth muscle contraction results in reduced peristaltic movement, leading to OIC, naldemedine may restore the propulsion by reversing such effect on contractions. These data suggest that naldemedine may be an effective treatment for OIC due to its effect in both the small- and large-intestines, as previously demonstrated.

110 A Novel Cancer Therapy using Gold Nano Particles for Plasmonic Photo-Thermal Ablation for Targeted Pancreatic Cancer Therapy
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Purpose
Pancreatic cancer is one of the most lethal cancers, with a 5-year survival rate of less than 7%. This form of cancer is notoriously dangerous as 64% of pancreatic cancer patients are diagnosed with Stage 3 or Stage 4. Due to their lack of tumor targeting, radiation and chemotherapy attack normal cells as well as malignant cells, leading to more complications or death.

Gold nanoparticles can be used to target cancer cells after being tipped with Polyethylene Glycol (PEG). Since tumor cells have increased vascularity, lower blood drainage, and have a distinct negative charge, the cancer cells will have a higher intake of the positively charged PEG gold nanoparticles. After being exposed to near-infrared (NIR) lasers, the nanoparticles heat up, leading to increased intracellular temperature and cell death.

Gold nanoparticles are a suitable treatment for targeted cancer therapy. Gold Nano particles are particularly useful due to unique optical properties, non-toxic nature, and relatively simple preparation and functionalization. AuNP’s can be produced in large quantities with defined shapes and sizes.

The depth of penetration of NIR lasers is up to 10cm which is effective in treating inoperable deep cancers such as pancreas, prostate, and neck and throat cancers which are otherwise inaccessible.

Nano technology is being investigated as an innovative therapeutic tool to improve cancer treatment. The purpose of this research is to study the efficacy of GNR and GNS and NIR laser in causing selective cancer cell death in pancreatic cancer cells.

Methods
Normal Non-Malignant epithelial cell cultures (THLE-3 (ATCC® CRL-11233™) were cultured in Dulbecco’s modified Eagle’s Medium (DMEM) and 5% bovine serum at 37°C under 5% CO2 for 3 days.

Pancreatic cancer cell cultures (MIA PaCa-2 (ATCC® CRL-1420™) were cultured in similar fashion. Both cells were cleaved by trypsin and replated onto in a 12-well tissue culture plate and grown for 3 days.

Aspirate 1ml of cell cultures, rinse with PBS buffer, and then immerse with 1ml PEG coated gold Nano rod and sphere solution each for 30 minutes.

Use 3 wells with cells are then exposed to NIR laser at 800 nm on 1mm diameter spot on the sample for 5 minutes at a power density of 30mW, 60mW and 90mW respectively.

The cells are then washed with 2 mL 0.4% trypan blue to identify dead cells which appear blue vs viable cells which appear intact and clear.

Pipette 20μL of solution on a glass slide. Place slide in Nexcelom automatic cell counter and the number of viable cells counted and documented. The process was repeated with Pancreatic cancer cells.

Cell count documented in 5 different trials with both non-malignant cells and cancer cells. The data analyzed by one-way ANOVA for statistically significant p values. While comparing Non-Malignant cells to Pancreatic cancer cells with Gold Nano rods and Gold Nano Sphere solutions at each one of the NIR power densities such as 30mW, 60mW and 90mW.

Results
Gold Nano-rods were significantly more effective in killing cancer cells while preserving non-malignant cells. For example, when comparing the effect of the 90 mW with each Nano-particle, the Gold Nano-rods eradicated 28% of the cancer cell population in 5 minutes while the Gold Nano-spheres killed 12.7% of the malignant cell population. At 30mW and 60mW the Nano-rods killed 7.4 and 12.1% while the Nano-spheres killed 4.9 and 6.5% of cancer cells.

The Nano-spheres have better absorption spectra at 580-600nm wavelength while Nano-rods shows greatest absorption at the 800nm NIR frequency. The optimization of absorption by Nano-rods, the depth of penetration of tissue to greater than 10cm and better conversion to heat inside the cancer cells, make Nano-rods an optimal agent for Photothermal therapy of deep tissue cancer such as Pancreatic cancer.

The optimal goal would be to kill the most cancer cells with least damage to the non-cancer cells. Though Gold Nano Rods at 90mW killed 28% of cancer cells vs 5.5% of non-malignant cells at 60mW the Gold Nano Rods killed 12.1% of cancer cells to 1.3% of non-malignant cells. This data conveys that for the 90 mW laser, for every 5 cancer cell deaths, there is one non-cancer cell death (5:1 ratio). Conversely, for the 60 mW laser, there are 9 cancer cell deaths for every one non-cancer cell death (9:1 ratio). This indicates that the 60 mW laser is a safer yet more effective type of Gold Nano-rod therapy.

While the Gold Nano rods are by far more effective agents for photo-thermal therapy, the NIR power at 60mW may be more effective to produce best cancer survival with least damage to non-malignant tissue.

Conclusions
Pancreatic cancer is one of the hardest cancers to treat with high morbidity and mortality. The targeted tumor therapy will greatly improve outcomes by targeting cancer cell death,
while minimizing normal cell death. Gold nanorods with PEG functionalization causes selective uptake by tumor cells and when exposed to NIR laser at 800nm at 60mW laser strength cause maximal tumor cell death by increased intracellular temperature.

NIR laser with GNR is optimal for deep tissue cancer targeting, while GNS are effective in targeting superficial cancers. Tumor targeting minimizes pain experienced during therapy by patients with advanced invasive Pancreatic cancer.

111 Platelet-Rich Plasma Injections for Adults with Cervical Facet Joint Mediated Pain: A Retrospective Analysis

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Purpose

Neck pain is considered one of the most common chronic pain conditions with an estimated lifetime prevalence of 67%, point prevalence of 22.2% and 14% prevalence of high pain intensity with disability in the Canadian population. Cervical facet joints have been identified as a common source of neck pain, with an estimated prevalence of 60%. Commonly, intra-articular lidocaine and corticosteroid injections are used to confirm diagnosis and relieve facet joint mediated pain. However, research demonstrates limited long-term efficacy.

Despite evidence-based conservative management, many patients with cervical spine pain report ongoing pain and disability over the long-term. As a result, there is growing interest in using platelet-rich plasma (PRP) injections as a treatment for those with persistent spinal disorders. The goal of PRP injections is to promote tissue repair and maximize the local environment for regeneration. PRP is thought to reverse the underlying pathophysiology of certain pain conditions, possibly eliminating the need for recurrent injections and treatments.

The purpose of this study was to determine the effect of PRP injections on self-reported pain intensity and patient satisfaction in adults with cervical facet joint mediated pain. The results of this study will inform a prospective trial that is currently in the development phase.

Methods

In this retrospective analysis, consecutive patients from our interventional pain management practice that have undergone cervical facet joint PRP injections in the years 2016 and 2017 were contacted by telephone to determine their self-reported outcomes pertaining to cervical spine pain intensity (within one month and their current status) and satisfaction (Modified McNab questionnaire) post-PRP injections. Patients were included in the study if they reported at least 80% relief in familiar pain intensity following comparative medial branch blocks, and they demonstrated history and physical exam findings consistent with facet joint pain. Exclusion criteria were other potential spine/referred pain generators, BMI >35 and major psychiatric disorders.

After informed consent, the PRP injection involved the following: 30 cc of autologous blood was obtained resulting in 4-6 cc of PRP. 1cc of PRP solution was injected into each joint with confirmed intra-articular position using standard fluoroscopic approach. Patients participated a rehabilitation program for 8 weeks post-injection.

Results

Seven patients (ages 35-64 years) treated with PRP injections for persistent cervical facet joint pain were reviewed. The median pain intensity (on a Numeric Pain Rating Scale (NPRS)). and duration of pain prior to the injections was 7/10 (range 4-9) and 84 months (range 36-360) respectively. The follow-up period ranged from six months to 52 months. There was a statistically significant reduction in self-reported cervical spine pain intensity at one month and in the current period post-PRP injections (p<0.05). There was a clinically relevant reduction (²2 points on a NPRS) in self-reported cervical spine pain intensity reported for the current time period (up to 52 months post-injection) in six out of the seven patients. All seven patients reported at least fair to excellent satisfaction with the PRP intervention. Five out of the seven patients reported procedural discomfort, but no seriously adverse events were noted.

Conclusions

This retrospective study provided data suggesting that PRP injections for cervical facet joint mediated pain may be effective in reducing pain intensity and preserving patient satisfaction. A prospective study incorporating a larger sample is necessary to validate these findings.

112 Retrospective analysis of the co-prescription of benzodiazepines with chronic opioid therapy in US private payers’ adherent population for the observation period of 2011-2016

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Purpose

Chronic pain is commonly associated with anxiety, depression and insomnia. Pain relief is not the only outcome of long-term opioid treatment, but also should be improved quality of life. This often requires concomitant prescription
of benzodiazepines in order to achieve improvement of patients' status, but could also represent potential abuse of opioid treatment when benzodiazepines (BZDs) are taken to enhance euphoria (Jones et al, Gudin et al) resulting from opioid intake and could be an additional burden for total health care cost.

The aim of this study was to compare co-prescription of benzodiazepines among long acting opioid (LAO) chronic pain patients, receiving tapentadol Extended Release (TapER) and oxycodone Extended Release (OxnER), during the time period of January 2011 - June 2016, using private insurance claims analyses.

**Methods**

Using data from the IBM Truven Health MarketScan® Commercial Claims and Encounters Database, patients who were older than 18, had insurance coverage for at least 3 months before index date and through the treatment period and were adherent to long-acting opioid treatment (PDC≥0.8) for the treatment period of minimum 90, 180 and 365 days, were included in the analysis. The number of patients prescribed concomitant benzodiazepines were compared between comparators, depending on duration of opioid treatment. Additional sub-analyses were conducted on patients who did not have a diagnosis of depression, anxiety or insomnia during opioid treatment with concomitant BZDs fills in order to identify patients recreationally using BZDs during analgesic treatment (not due to their primary indication).

**Results**

TapER patients had lower prevalence of concomitant benzodiazepines than OxnER patients, during first 90 days of treatment (36.81% vs. 42.81%, p<0.001). Similar results were observed for opioid treatment lasting 180 days with TapER versus OxnER (40.55% vs. 47.35%, p<0.001). Observing 365 days of LAO treatment, Tap ER remained with lower prevalence of patients receiving concomitant benzodiazepines, versus patients on OxnER (45.40% vs. 51.66%, p<0.001). In the subgroup of patients without diagnosis of depression, anxiety or insomnia, patients on TapER had statistically lower prevalence of BZDs dispensed during 90 days opioid therapy when compared to OxnER (29.4% vs. 36.7, p<0.001). Similar results were observed for 180 days of opioid treatment with TapER versus OxnER (30.7% vs. 39.0, p<0.001). At one year of opioid treatment, TapER had statistically lower % of patients using benzodiazepine, compared to OxnER (33.0% vs. 40.6, p<0.001).

**Conclusions**

Patients on TapER patients had the lowest incidence of concomitant BZD during treatment lasting 90, 180, 365 days. In the subgroup of patients who did not have any diagnosis related to a primary indication for benzodiazepines utilization, patients treated with TapER also had the lowest incidence of concomitant BZD. Further study of the impact of concomitant BZD utilization with LAO on potential of the respiratory depression effect is recommended.

113 Characterization of Abdominal Pain Response in Patients With Diarrhea-predominant Irritable Bowel Syndrome Treated With Rifaximin

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**Purpose**

Irritable bowel syndrome (IBS) is characterized by recurring abdominal pain associated with defecation or changes in bowel habits. IBS is further divided into subcategories based on the predominant bowel habit of a patient (eg, constipation-predominant IBS; diarrhea-predominant IBS [IBS-D]). Irritable bowel syndrome is estimated to affect approximately 11% of the global adult population. Abdominal pain is a key symptom in the diagnosis of IBS; it is also the most common reason why individuals see a healthcare provider. The nonsystemic antibiotic rifaximin is approved in the United States for the treatment of adults with IBS-D. The efficacy of rifaximin may be related to its beneficial effects on the gut microbiota. The aim of this study was to characterize the impact of a 2-week course of rifaximin on abdominal pain symptoms in patients with IBS-D.

**Methods**

A post hoc analysis of a phase 3 re-treatment trial was performed. Adults with IBS-D (meeting Rome III criteria) with a mean abdominal pain score of at least 3, after a screening phase with placebo, received open-label rifaximin 550 mg three times daily for 2 weeks. Abdominal pain scores were assessed by patient response to the question “In regards to your specific IBS symptom of abdominal pain, on a scale of 0–10, what was your worst IBS-related abdominal pain over the last 24 hours? ‘Zero’ means you have no pain at all; ‘ten’ means the worst possible pain you can imagine.” Abdominal pain responders were defined as patients with at least a 30% improvement in the weekly mean abdominal pain score during at least 2 weeks of the first 4 weeks post-treatment. Time to abdominal pain recurrence (defined as less than 30% improvement in weekly mean abdominal pain score for at least 3 weeks during a rolling 4-week consecutive period (additional 18 weeks of follow-up)) was assessed. Results were analyzed using an observed case method (patients were excluded if they had insufficient data to determine efficacy).

**Results**

A total of 2579 adults (mean age [SD], 46.4 [13.7] y; 68.2% female; mean daily abdominal pain score [SD] 5.5 [1.7]) were treated with rifaximin. The mean abdominal pain score (SD) at 4 weeks post-treatment for all enrolled patients was 3.6 (2.4), with a change from baseline of -1.9. A total of 1384 (56.8%) of 2438 evaluable patients
were abdominal pain responders. During up to 18 weeks of additional follow-up (ie, 22 weeks posttreatment), 382 (35.6%) of 1384 patients did not experience recurrence and maintained abdominal pain response. The median time to abdominal pain relapse was 14.0 weeks. In abdominal pain responders, mean change from baseline in mean daily abdominal pain scores, assessed weekly, ranged from an improvement of -3.3 to -2.7 during the additional 18 weeks of follow-up.

Conclusions
A short (2-week) course of rifaximin 550 mg improved abdominal pain symptoms in adults with IBS-D and provided durable response for a median of 3.5 months posttreatment. Thus, rifaximin relieves abdominal pain in patients with IBS-D.

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