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Efficacy and safety of NP-1998, a novel topical liquid formulation of capsaicin, in patients with postherpetic neuralgia: results of a phase 2, multi-center, placebo-controlled trial

Mark Wallace[1], Charles Argoff[2], Sunita Babbar[3], Mathews Adera[4], Enrique Carrazana[4]
[1]University of California, San Diego, La Jolla, CA, USA, [2]Albany Medical Center, Albany, NY, USA, [3]NeurogesX, San Mateo, CA, USA, [4]Acorda Therapeutics, Inc., Ardsley, NY, USA

Purpose

Qutenza® (capsaicin) 8% patch is approved in the US for the management of neuropathic pain associated with postherpetic neuralgia (PHN). A single 60-minute application of Qutenza has been shown to provide 12 weeks of pain relief in people with PHN. Reduction in and defunctionalization of epidermal nerve fibers is the presumed basis for the therapeutic effect of capsaicin in peripheral neuropathic pain syndromes. A prior 2-week phase 1 study conducted in healthy volunteers demonstrated that NP-1998 (10%) capsaicin liquid formulation treatment for 5 minutes reduced epidermal nerve fiber density by a similar proportion as a 60-minute Qutenza patch treatment. The current study was performed to verify whether the 5-minute application of NP-1998 would be efficacious in pain reduction in patients with PHN. The objectives of the study were: to determine the optimal duration of pre-treatment with a local anesthetic; to assess safety and efficacy of 5-minute applications of two concentrations of topical capsaicin solution (10% and 20% NP-1998) in patients with PHN; and to assess systemic exposure to capsaicin following 5-minute applications of 10% and 20% NP-1998.

Method

This was a phase 2, multicenter, randomized, double-blind, placebo-controlled trial conducted in 2 stages in patients with PHN. In stage 1, patients (n=39) were pre-treated with lidocaine (2.5%)/prilocaine (2.5%) for 0, 15, or 30 minutes prior to a 5-minute NP-1998 application (10% or 20%); lack of tolerability was defined as a request by the patient for removal of the study drug within 4 minutes of application. A total of 164 patients (20 from stage 1) with PHN were randomized to receive a single 5-minute application of study treatment in a 2:2:1 ratio [10% (n=66):20% (n=65): placebo (n=33)], and were followed for 12 weeks. The primary efficacy endpoint was mean percent change from baseline in "average pain for the past 24 hours" as measured by the Numeric Pain Rating Scale (NPRS) at week 8 following treatment. Secondary efficacy variables were mean percent change from baseline in NPRS score at week 12 following treatment, and the proportion of patients with ≥ 30% reduction in NPRS score compared to baseline by week 12. Additionally, pharmacokinetics for systemic exposure was assessed in a subset of patients in both stage 1 and stage 2. Safety was assessed through monitoring of adverse events (AEs) and clinical laboratory tests, vital signs, and physical examination. Analysis of safety parameters included all patients enrolled in both stage 1 and stage 2.

Results

All of the patients in stage 1 tolerated a 5 minute application of NP-1998 10% or 20% for all time points tested. Pre-treatment with a local anesthetic did not confer a tolerability advantage; therefore, stage 2 was conducted without pre-treatment with local anesthetic. The primary efficacy endpoint showed a dose-response in percent change in NPRS score during weeks 2-8 (Least squares [LS] means of -17.6%, -22.1%, and -25.4% in placebo, 10% and 20% treatment groups, respectively). A dose-response relationship was also observed in percent change in NPRS score during weeks 2-12 (LS means of -16.6%, -22.2%, and -26.0% in placebo, 10% and 20% treatment groups, respectively). The proportion of patients with at least a 30% decrease in NPRS score for weeks 2-8 were 33.3%, 27.3%, and 36.9%, for placebo, 10%, and 20% treatment groups, respectively. For weeks 2-12, the proportion of patients with at least a 30% decrease in NPRS score were 27.3%, 28.8%, and 41.5%, for placebo, 10%, and 20% treatment groups, respectively. The changes between the NP-1998 treatments and placebo were not statistically

significant. Pharmacokinetic analyses of 200 plasma samples (36, 80, and 84 for placebo, 10%, and 20% treatment groups, respectively), collected from 34 patients showed that of the patients treated with NP-1998, only one had detectable levels of capsaicin at the time points studied. Overall, NP-1998 treatment was tolerated and no patients terminated prematurely due to an AE. The most frequently occurring AEs were application site pain (15%, 76%, and 85% in the placebo, 10% and 20% treatment groups, respectively) and application site erythema (22%, 74%, and 86% in the placebo, 10% and 20% treatment groups, respectively).

Conclusions

Topical application of 10% or 20% of NP-1998 for 5 minutes was tolerated without the need for pre-treatment with local anesthetic. The pharmacokinetic analysis suggested that administration of NP-1998 resulted in minimal systemic exposure to capsaicin. Of the 2 formulations tested, NP-1998 20% had a greater effect on pain reduction over a 12-week period, suggesting that a 5 minute application of NGX-1998 20% may provide a convenient option to patients with PHN.

2

Automation of Luminex® xTAG® CYP2D6 and CYP2C19 RUO Assays

Aaron Benfield, Shoba Ananthanarayanan, Kim Anderson
Luminex Corporation, Austin, Texas, USA

Purpose

Pharmacogenetics is the study of the influence of genetic variation on drug response. For example, variations in the cytochrome *P450-2D6* (*CYP2D6*) gene have been shown to be a major cause of variability in drug response to pain medications such as tramadol, acetaminophen and several codeine-derivatives. In fact, specific mutations within the *CYP2D6* gene can result in reduced *or* increased 2D6 enzyme activity for specific drugs, leading to altered drug responses. For example, reduced 2D6 activity decreases the efficacy of codeine for pain management, whereas increased activity (i.e. ultra-rapid metabolizer) can result in severe or life-threatening toxicity.[1] In a similar manner, the P450-2C19 gene can affect the drug response of proton pump inhibitors, antiepileptics, antidepressants, antibiotics, antifungals, and anticancers.[2] Therefore, identification of patient CYP2D6 and CYP2C19 genotypes can help physicians tailor drug treatment by selecting the appropriate drug and dosage. The Luminex® xTAG® CYP2D6 v3 and xTAG® CYP2C19 v3 RUO assays can be run on the Luminex 100/200™ instrument to identify CYP2D6 and CYP2C19 genotypes within an 8-hour time frame. Laboratories offering pre-emptive genotyping often look to automation to minimize hands-on time and obtain maximum throughput. Here, we compared assay turnaround time, hands-on time, performance, and reagent overage between manual and automated workflow for specific steps performed as part of the CYP2D6 and CYP2C19 assay procedures.

Method

We performed the 2D6 and 2C19 RUO assay kits per the manufacturer's guidelines, using both manual and automated workflow for 48 sample batches. The following procedural steps were evaluated for automation: master mix aliquoting, addition of template, and bead hybridization setup. Differences between manual and automated workflow were measured for assay time, hands-on time, raw signal (i.e. median fluorescence intensity (MFI)), and genotype calling.

Results

Hands-on time was reduced by up to 75% when workflow was automated. No significant difference was observed between automated and manual workflow when we assessed assay time, raw signal, or genotype calling.

Conclusions

Our results indicate that the Eppendorf ep*Motion*® liquid handler can reduce hands-on time by up to 75%, while assay time and performance (i.e. raw signal and genotype calling) are not affected significantly. We believe the e*pMotion* is an excellent solution for laboratories running Luminex 2D6 and 2C19 assays in large batches. Benefits to automating the workflow not only result in significantly reduced hands-on time, but reduce the risk for the potential of human-error as well.

3

Efficacy of Dorsal Column Stimulators and Long Term Benefits in Patients with Chronic Pain

Vijayasree Arvind[1], Lisa Cano-Patino[1], Kavya Arvind[1], Anup Arvind[1]
[1]Cardinal Pain Center, Dallas, USA, [2]Clinical Research Institute at Methodist Medical Center, Dallas, USA

Purpose

At present, the indications of SCS are being revised constantly. Failed back surgery syndrome (FBSS) is the most common indication for SCS, whereas, the complex regional pain syndrome (CRPS) is the second one. Further indications may be phantom limb pain, chronic intractable pain located in the head, face, neck, or upper extremities, spinal lumbar stenosis in patients who are not surgical candidates, and others.

The mechanism of action of SCS would be based on the antidromic activation of the dorsal column fibers, which activate the inhibitory interneurons within the dorsal horn. The International Neuromodulation Society established that: Neuromodulation is defined as, "the therapeutic alteration of activity in the central, peripheral or autonomic nervous systems, electrically or pharmacologically, by means of implanted devices". Low frequency electrical stimulation has an excitatory effect, whereas, high frequency stimulation is applied to produce neuronal inhibition. At present, neuromodulation is used for several neurological conditions such as epilepsy, movement disorders, psychiatric disease, spasticity and pain. With regard to pain treatment, low frequency is applied to activate dorsal spinal tracts, periaqueductal gray matter, and motor cortex, while inhibitory stimulation is utilized for peripheral nerve, thalamic, and hypothalamic modulation. Spinal cord stimulation is a technique of neuromodulation, which consists of placing leads in the epidural space of the spinal cord, as a method to treat numerous types of disturbances.

Method

Patients who had undergone either a Dorsal Column Stimulator Trial or Implant in the past 5 years were interviewed after an informed consent was obtained. The issues addressed included efficacy of the trial and implant in reducing their pain, improvement in medication usage, improvement in activities of daily living and sleep.

Results

Over the 5 years, 58 patients had undergone trials of Dorsal Column Stimulators. 50% of the trial patients proceeded to having implantation. On analyzing the responses to the questionnaire, the Dorsal Column Stimulator reduced the VAS Score on an average by 40%. It reduced the intake of pain pills by 25% and improved activities of daily living to a moderate extent. It increased the number of hours the patients slept by 10%. There was one patient with severe neurological complications.

Conclusions

Pain attributable to failed back syndrome, reflex sympathetic dystrophy, and peripheral neuropathy responded favorably to spinal cord stimulation. The successful patients reported improvements in daily living as well as a decrease in analgesic usage.

In patients who have undergone previous surgical procedures, the shorter the duration of time to implantation, the greater the rate of success. SCS in both cases brought a reduction of the level of pain and an improvement to quality of life. Careful selection of candidates both for Dorsal Column stimulator trial and implant is crucial for long term success.

4

Safety and Tolerability of Extended-Release Oxycodone/Acetaminophen Tablets in Phase 3 Clinical Trials

Thomas Barrett[1], Kenneth Kostenbader[1], Srinivas Nalamachu[2], Wendy Toler[1]
[1]Mallinckrodt Pharmaceuticals, Hazelwood, MO, USA, [2]International Clinical Research Institute, Overland Park, KS, USA

Purpose

To characterize the safety and tolerability of extended-release (ER) oxycodone (OC)/acetaminophen (APAP) (XARTEMIS™ XR, formerly MNK-795; Mallinckrodt Brand Pharmaceuticals, Inc., Hazelwood, MO) using pooled data from 2 phase 3 clinical trials. ER OC/APAP is approved for the treatment of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate. ER OC/APAP 7.5/325-mg tablets have a biphasic formulation providing immediate release of 25% of the OC and 50% of the APAP for acute analgesia and extended release of 11.25 mg OC/325 mg APAP over a 12-hour period for sustained analgesia. Coadministration of OC with APAP has an opioid-sparing effect, demonstrating effective analgesia with a lower OC dose and improved tolerability compared with a higher OC dose alone. APAP has dose-related adverse events (AEs) such as liver toxicity; hence, the approved daily dose of 2 ER OC/APAP 7.5/325-mg tablets twice daily delivers an APAP dose (1300 mg) well below the US Food and Drug Administration-recommended daily maximum of 4000 mg.

Method

Adult (≥18 years) men and women who provided written informed consent enrolled in 2 phase 3 clinical trials. Study I was a multicenter, open-label safety trial in which patients (n=376) with moderate to severe chronic pain caused by osteoarthritis of the knee or hip or chronic low back pain received 2 ER OC/APAP tablets (total dose, 15/650 mg) every 12 hours for ≤35 days. Study II was a multicenter, randomized, double-blind, placebo-controlled, parallel-group safety and efficacy trial (RCT) with a 14-day open-label safety trial extension (OLE) in a model of acute postoperative pain. Before surgery, patients consented either to the RCT alone (n=329) or to both the RCT and OLE (n=146). In the RCT, on the first postoperative day following routine perioperative intravenous analgesia, patients received a 2-tablet dose of placebo control or ER OC/APAP (total dose, 15/650 mg) administered every 12 hours for ≤48 hours. All patients in the OLE received a 2-tablet dose of ER OC/APAP (total dose, 15/650 mg) administered every 12 hours until no longer needed for ≤14 days.. Safety was assessed, with clinically significant abnormal laboratory values, vital signs, pulse oximetry, and electrocardiogram abnormalities reported as AEs.

Results

In total 607 patients (mean age, 48.2 years) received ≥1 dose of ER OC/APAP; 68.5% were women, and the majority were white (62.9%) and not Hispanic or Latino (81.9%). A total of 488 (80.4%) patients who received ER OC/APAP completed their respective on-study treatment, and 86 (14.2%) discontinued treatment because of AEs. A total of 163 patients received placebo during the study II RCT (mean age, 44.6 years; 82.8% women; 63.2% white; 73.0% not Hispanic or Latino); of these, 142 (87.1%) completed placebo treatment and 2 (1.2%) discontinued placebo treatment because of AEs. Overall, mean exposure to ER OC/APAP in study I and the study II RCT and OLE was 20.3 days (range, 1-42 days); mean exposure to placebo in the study II RCT was 2.8 days (1-3 days). The integrated summary of AEs showed at least 1 AE was reported by 55.9% of patients (ER OC/APAP, 60.8%; placebo, 21.5%). The most frequent AEs in patients treated with ER OC/APAP were nausea (25.7%), dizziness (13.0%), and vomiting (12.9%); the most frequent AEs with placebo were nausea (5.5%) and headache (4.9%). Liver function test (LFT) abnormalities were recorded in 12 patients treated with ER OC/APAP, of whom 6 discontinued the study as a result. All LFT abnormalities resolved spontaneously; none met Hy's Law criteria for drug-induced liver injury. Most AEs were mild or moderate in severity. Eight serious AEs were reported, of which 2 in the ER OC/APAP group (abdominal pain, gastroesophageal reflux) and 1 in the placebo group (hypersensitivity) were considered treatment related. Only

the hypersensitivity reaction necessitated treatment discontinuation. Vital signs and pulse oximetry results were consistent with those reported for opioid/APAP combination drugs. No respiratory depression or clinically meaningful electrocardiogram abnormalities were reported.

Conclusions

In patients treated with ER OC/APAP, the most common AEs (nausea, vomiting, and dizziness) were consistent with the AE profile of other opioid/APAP combination drugs. Most AEs were mild or moderate in severity. Abnormalities in LFTs were infrequent and resolved spontaneously. Vital signs, pulse oximetry, and electrocardiogram findings were unremarkable. These results support the safety of administration of ER OC/APAP for ≤35 days in adult patients with moderate to severe pain.

5

Respiratory Rates and O_2 Saturation After Administration of Oxycodone/Acetaminophen Extended-Release Tablets

Thomas Barrett, Kenneth Kostenbader, Jeannie Montgomery, Wendy Toler
Mallinckrodt Pharmaceuticals, Hazelwood, MO, USA

Purpose

Respiratory depression is a known, potentially fatal, dose-related risk associated with opioids. Extended-release (ER) oxycodone (OC)/acetaminophen (APAP) (XARTEMIS™ XR, formerly MNK-795; Mallinckrodt Brand Pharmaceuticals, Inc., Hazelwood, MO) is a fixed-dose combination analgesic with biphasic immediate-release (IR) and ER characteristics, indicated for acute pain severe enough to warrant treatment with an opioid analgesic and for which alternative treatment options are inadequate. This post hoc analysis evaluated respiratory rates and oxygen (O_2) saturation following single-dose administration of ER OC/APAP, IR OC/APAP, and placebo in participants who were experienced recreational users of prescription opioids.

Method

This study was a post hoc analysis of a single-center, randomized, single-dose, double-blind, double-dummy, active- and placebo-controlled, 7-way crossover design. Participants included healthy adult (aged 18-55 years) male and female nondependent recreational opioid users. Participants underwent an initial naloxone challenge test to confirm a lack of physical dependence on opioids and a drug discrimination test to determine that they could detect the subjective effects of OC. During double-blind treatment, participants received each of 7 treatments: intact tablets of ER OC/APAP 15/650 mg, intact tablets of IR OC/APAP 15/650 mg, intact tablets of ER OC/APAP 30/1300 mg, intact tablets of IR OC/APAP 30/1300 mg, overencapsulated crushed tablets of ER OC/APAP 30/1300 mg, overencapsulated crushed tablets of IR OC/APAP 30/1300 mg, and placebo tablets. There was a 72-hour washout between treatments. Vital signs and pulse oximetry were assessed. Qualitative (summary) statistical analysis was performed. The study received institutional review board approval, and all subjects provided written informed consent.

Results

Of 107 participants who entered the study, 61 met inclusion criteria, passed the naloxone challenge and drug discrimination tests, and entered the treatment phase (received ≥1 study dose; safety population). Participants had a mean age of 25.8 years, 73.8% were men, and the majority were white (83.6%) and not Hispanic or Latino (86.9%). Overall, changes in respiratory rate and pulse oximetry were small and not considered clinically significant. Mean (SD) changes in respiratory rate (breaths/minute) from baseline to 2 hours postdose were 0.0 (2.7) for placebo, 0.5 (2.3) and -0.8 (2.8) for 15/650 mg and 30/1300 mg intact ER OC/APAP, 0.0 (2.5) and 0.0 (2.7) for 15/650 mg and 30/1300 mg intact IR OC/APAP, and 0.4 (2.4) and 0.8 (2.6) for 30/1300 mg crushed ER and IR OC/APAP, respectively. Mean (SD) changes in O_2 saturation from baseline to 2 hours postdose were 0.5% (2.0) for placebo, -0.7% (1.7) and -0.5% (1.8) for 15/650 mg and 30/1300 mg intact ER OC/APAP, -0.6% (1.6) and -1.5% (1.6) for 15/650 mg and 30/1300 mg IR OC/APAP, and -0.5% (1.6) and -1.5% (1.8) for 30/1300 mg crushed ER and IR OC/APAP, respectively. No events of respiratory depression were reported.

Conclusions

In this study of recreational opioid users, there was no evidence of respiratory depression with ER OC/APAP (15/650 mg intact and 30/1300 mg intact and crushed), IR OC/APAP (15/650 mg intact and 30/1300 mg intact and crushed), or placebo.

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Opioid Abuse/Dependence Symptoms and Gender

Elizabeth Baumgartner[1,2], Angela DeVeaugh-Geiss[1], Howard Chilcoat[1]
[1]*Purdue Pharma LP, Stamford, CT, USA,* [2]*Wesleyan University, Middletown, CT, USA*

Purpose

Prior research has described differences in drug and alcohol abuse among men and women. One study utilizing 2006 National Survey on Drug Use and Health (NSDUH) data found that although more men reported lifetime or past year nonmedical opioid use, there was no difference in current opioid abuse/dependence by gender among past year nonmedical users. To further examine gender differences in opioid abuse/dependence, we sought to explore the symptom profiles of men and women who met criteria for opioid abuse/dependence in the 2012 NSDUH survey.

Method

Data from respondents in the 2012 NSDUH survey who met criteria for past year opioid abuse or dependence (n=616) were included in the analyses. The proportion endorsing the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for opioid dependence (tolerance, withdrawal, used more/longer than intended, inability to cut down, great deal of time spent on substance-related activities, neglect of important activities due to use, or psychological/physical problems associated with use or continued use) or opioid abuse (failure to fulfill obligations, hazardous use, use-related legal problems, or social/interpersonal problems) were calculated. Additionally, demographics, past year abuse/dependence of other disorders (alcohol, cocaine, hallucinogens, heroin, marijuana, sedatives, stimulants, tranquilizers), as well as proportion with past year treatment for opioid analgesic abuse/dependence, the proportion having ever injected, and the distribution of days used in the past year (categorized as 1 day, 2-9 days, 10-19 days, 20-49 days, 50+ days) were described. All results were stratified by gender. Because of the complex sampling design of the NSDUH survey, all analyses utilized the sample weights.

Results

In 2012, 616 individuals met criteria for opioid abuse/dependence, including 313 men and 303 women; approximately three quarters met criteria for opioid dependence (78% of men; 74% of women). A greater proportion of women were in the youngest age category (12-17 years of age: 13% vs. 4% of men), while a greater proportion of men were in the oldest age category (26-64 years of age: 64% vs. 55% of women). The most common dependence symptoms were tolerance and time spent in substance activities; both criteria were endorsed by a similar proportion of men and women (tolerance: 78% and 76%, respectively; time spent: 74% and 73%, respectively). Among dependence symptoms, women were more likely to endorse withdrawal (57% vs. 49%) and using more/for longer than intended (43% vs. 30%), while men were more likely to report inability to cut down (36% vs. 25%), neglect of activities (55% vs. 44%), and psychological/physical problems associated with use (55% vs. 49%). The proportion of men endorsing abuse was higher across 3 of the 4 symptoms, with the greatest difference observed in use-related legal problems (24% of men vs. 9% of women) and social/interpersonal problems (51% of men vs. 41% of women). Men were more likely (≥5% difference) to have cocaine abuse/dependence (18% vs. 4% of women), heroin abuse/dependence (19% vs. 4% of women), and stimulant dependence (16% vs. 10% of women), while women were more likely to report sedative abuse/dependence (7% vs. 1% of men) and tranquilizer abuse/dependence (21% vs. 16% of men). Men were more likely to have ever injected prescription drugs (37% vs. 12% of women) and reported more frequent past-year nonmedical opioid use (68% of men reported >50 days/past-year vs. 57% of women). Nine percent (9%) of men and 7% of women reported past-year treatment for opioid analgesics use.

Conclusions

In the 2012 NSDUH survey, men with opioid abuse/dependence were more likely to report use/continued use despite substance-related problems with their health (psychological/physical problems), relationships/work (interpersonal/social problems, neglect of important activities), and legal problems. Additionally, men were generally more likely to meet abuse/dependence criteria for other substances, with the exception of sedative or tranquilizer abuse/dependence which were more common in women. In both men and women, past-year treatment for opioid use was low (<10%). Understanding gender differences in opioid abuse/dependence could inform and improve education, intervention, and treatment efforts.

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Outcomes associated with treatment of chronic pain with tapentadol prolonged release compared with morphine controlled release (CR) and oxycodone CR: a UK primary-care observational study

Christopher Morgan, Garth Baxter, Sara Jenkins-Jones, Craig Currie, Dieter Schultewolter
Pharmatelligence, Cardiff, UK

Purpose

Chronic pain is estimated to affect approximately eight million people in the UK. As well as having an impact upon individuals' daily functioning, sleep patterns and mental health, chronic pain also places a large burden on health services, accounting for an estimated 20% of UK primary-care workload. Whilst many treatment options are available, for those in uncontrolled severe pain, strong opioids such as morphine or oxycodone may be prescribed. However, opioids can be associated with side effects such as constipation and nausea, which may in themselves result in excess health-service utilisation. Tapentadol is a novel centrally acting analgesic with μ-opioid receptor agonist and noradrenaline reuptake inhibitor (MOR-NRI) activities. It is available in two forms in the UK: tapentadol (Palexia) tablets and tapentadol prolonged-release (Palexia SR). Tapentadol prolonged release is licensed for use in adults with severe chronic pain that can only be adequately managed with opioid analgesics. In phase III trials, tapentadol prolonged release has been shown to be effective in the management of moderate to severe chronic pain with superior gastrointestinal tolerability compared with oxycodone controlled release (CR). There were also significantly fewer discontinuations for patients prescribed tapentadol prolonged release compared with oxycodone CR. The purpose of this study is to determine whether similar findings are observed in routine practice and their impact on healthcare utilisation, based on a UK observational dataset.

Method

Data were sourced from the Clinical Practice Research Datalink (CPRD): a database derived from 650 primary-care practices in the UK. Patients prescribed tapentadol prolonged release (PR) were selected from launch (May 2011) to February 2014. Baseline characteristics were extracted and a prior pain pathway estimated. Underlying pain diagnosis was ascertained from associated clinical Read codes. Index date was defined as date of first tapentadol prescription. Patients with prescriptions for oxycodone CR or morphine CR since 2011 were extracted as potential controls and pain pathways were estimated. Controls were matched (1:1) on gender, age and pain duration, site and aetiology. Pattern of tapentadol prescription was described. Endpoints for the comparative analyses were rates of adverse gastrointestinal events associated with opioid use: constipation, nausea and vomiting and the time to discontinuation, defined as cessation of target therapy followed by the addition of an alternative strong opioid. Patients were followed from index date to date of discontinuation or censorship (earliest of: end of pain episode, the patient's last contact or last data-collection point). Crude rates were compared by Fisher test. Kaplan-Meier curves were presented and Cox proportional hazards model created. Additional covariates were age, gender, duration of pain episode (to index date) and comorbidity represented by the Charlson index. Rates and costs of health-service utilisation per person year were calculated and compared between cases and controls using the Mann-Whitney *U*-test.

Results

816 patients with a prescription of tapentadol PR were identified; 760 (93.1%) had a pain diagnosis. Mean pain episode duration was 3.4 (sd 4.4) years. 400 (52.6%) patients had a pain diagnosis with no location or aetiology recorded. 129 (17.0%) had a musculoskeletal diagnosis and 124 (16.3%) had back pain. 521 (68.6%) patients had progressed along the WHO pain ladder from non-opioids to weak opioids to strong opioids with tapentadol prescribed as either first (215 (28.3%)) or subsequent (306 (40.3%)) strong opioid. 595 (78.3%) and 498 (65.5%)

tapentadol PR patients were matched to an equivalent number of morphine CR and oxycodone CR patients respectively. Primary-care contacts in the year before initiation were similar: 16.3 (sd 13.7) versus 16.8 (13.8) for tapentadol and oxycodone and 15.7 (sd 12.6) versus 16.7 (12.9) for tapentadol and morphine. Charlson index was lower for tapentadol in both arms: 1.8 (sd 2.0) versus 2.3 (2.3) and 1.7 (1.9) versus 2.2 (2.3) respectively. Time to adverse events was significantly lower for tapentadol in both arms. Compared with oxycodone the adjusted hazard ratios were 0.492 (0.255-0.949) for nausea and vomiting, 0.463 (0.240-0.893) for constipation and 0.486 (0.302-0.782) for the combined endpoint. For morphine the respective adjusted hazard ratios were 0.506 (0.283-0.906), 0.456 (0.270-0.771) and 0.489 (0.326-0.732). There was no significant difference in discontinuation rates: adjusted hazard ratios for tapentadol were 0.826 (0.605-1.128) compared with oxycodone and 0.914 (0.694-1.204) compared with morphine. Tapentadol was associated with reduced resource use. Compared with oxycodone the relative rate of primary-care contact was 0.773 (0.740-0.808), accident and emergency attendance 0.689 (0.548-0.865), outpatient attendance 0.807 (0.740-0.879) and inpatient admission 0.713 (0.607-0.836). Compared with morphine the respective relative rates were 0.801 (0.770-0.834), 0.692 (0.560-0.855), 0.894 (0.823-0.971) and 0.982 (0.840-1.149).

Conclusions

Within this observational study based on early UK routine data, there were significantly fewer adverse gastrointestinal events associated tapentadol prolonged release use relative to both oxycodone CR and morphine CR. Whilst there was no significant differences in persistence rates between tapentadol prolonged release and either comparator there was significantly reduced primary- and secondary-care resource use associated with tapentadol prolonged release. As with all observational studies, potential bias due to issues of residual confounding and confounding by indication should be considered. However, the rates of adverse events that we report are broadly similar to those observed in randomised clinical trials.

8

Use of MDDScore for the Identification of Comorbid Major Depressive Disorder (MDD) in Patients with Chronic Pain

John Bilello[1], Linda Thurmond[1], Joseph Shurman[2], Forest Tennant[3]
[1]Ridge Diagnostics, Research Triangle Park, NC, USA, [2]Scripps Memorial Hospital, San Diego, CA, USA, [3]Veract Intractable Pain Clinic, West Covina, CA, USA

Purpose

The presence of comorbid MDD has a direct impact on chronic pain, associated with higher pain intensity and more comorbidities in those patients. Additionally, a serious problem in the treatment of pain is suicide, which is approximately 3-fold higher in pain patients with comorbid major depressive disorder. Current or traditional diagnostic systems have failed to adequately assess true MDD in patients with chronic pain. In particular it is difficult to apply assessment tools to segregate MDD from the demoralization or other changes in mood inherent in chronic pain states. MDDScore, a multi-analyte blood test for depression, has been shown to identify MDD patients and segregate them from non MDD patients in multiple prospective studies with 93% overall accuracy. The MDDScore test was applied to patients in multiple chronic pain states to aid in determination of treatment for co-morbid MDD or depressed mood.

Method

The three study groups analyzed included: (a) patients with centralized intractable pain (CIP) from the Veract Intractable Pain Clinic (n=93), (b) patients with chronic pain of diverse origin from the Scripps Pain Clinic (SPC) (n=20), and (c) a series of prospectively collected patients with comorbid arthritis and depressive symptoms (n=28). Each had a blood sample drawn for quantitation by immunoassay of 9 serum biomarkers (Alpha-1 Antitrypsin, Apolipoprotein C3, Brain Derived `Neurotrophic Factor, Cortisol, Epidermal Growth Factor, Myeloperoxidase, Prolactin, Resistin, and soluble TNF Receptor II). MDDScore was calculated using a proprietary algorithm and patients were scored from 1-9. MDDScores of ≥5 are indicative of a high probability of MDD, 93.7% of well characterized MDD patients had an MDDScore greater or equal to 5; 91.9% of control patients had scores of <5 (Bilello et al J Clinical Psychiatry in Press).

Results

A very distinct bi-modal pattern of MDDScore distribution was observed. Greater than 90% had scores at the low or very high end of the scale. Thus there was clear separation of 2 distinct groups. Eighteen of 28 patients with comorbid arthritis (64.2%) had MDDScores greater or equal to 5. Forty-nine of 93 CIP patients (52.7%) and 9 of 20 (45%) patients with chronic pain of diverse origin had scores of ≥ 5.

Conclusions

Early recognition and treatment of depression has been shown to improve the outcome in pain management. Our results indicate that MDDScore was able to segregate patients into two major groups based upon MDDScore. These data suggest we are able to identify chronic pain patients with a higher probability of comorbid major depression. Furthermore this study suggests that it is possible to readily identify and thus differentially treat pain patients with comorbid MDD.

9

The Durability of OnabotulinumtoxinA for the Treatment of Chronic Migraine: CLARITY Pilot Study

Andrew Blumenfeld[1], Andrew Inocelda[1], Christopher Purdy[2], Laura Dalfonso[2], Raf Magur[2]
[1]Headache Center of Southern California, Encinitas, CA, USA, [2]AHRM Incorporated, Buffalo, NY, USA

Purpose

Limited data exist on the durability of benefit of onabotulinumtoxinA for chronic migraine (CM) beyond 5 cycles. The objective of this analysis was to evaluate the durability of benefit of 7-9 cycles of onabotulinumtoxinA (BOTOX®) for patients with CM.

Method

Medical records for patients with CM per *International Classification of Headache Disorders, 3rd edition (beta)* (*ICHD-3b*) criteria (≥15 headache days/month) were reviewed. Inclusion required a baseline visit, ≥7 onabotulinumtoxinA injection cycles, 12 ± 2 weeks between injections, and 155-195U onabotulinumtoxinA dose using the PREEMPT injection paradigm.[1] Abstracted data included dose, headache days, Migraine Disability Assessment (MIDAS) test, Headache Impact Test (HIT-6), and adverse events.

Results

33 patients qualified (7 cycles, n=16; 8 cycles, n=7; 9 cycles, n=10). Mean headache days at baseline, cycle 7, and cycle 9 were 19.08, 6.25, and 6.57, respectively. Mean headache-free days at baseline, cycle 7, and cycle 9 were 10.92, 23.75, and 23.43, respectively. Proportion of patients considered incapacitated based on MIDAS scores at baseline and cycle 7 were 53% and 12%, respectively. Proportion of patients achieving >50% reduction in headache days at cycles 7 and 9 were 85% and 90%, respectively. 50% of patients had >5-point reduction in HIT-6 score by cycle 7. No serious adverse events were reported.

Conclusions

This series of patients demonstrated durable onabotulinumtoxinA benefit based on reduction in headache days after 7-9 treatments and long-term improvements in migraine-related disability as evaluated by MIDAS and HIT-6. Results warrant investigation in a larger study to better understand the durability of onabotulinumtoxinA benefit for CM in clinical practice.

Funding: Allergan, Inc.

Reference: 1. Blumenfeld A, et al. *Headache*. 2010;50(9):1406-1418.

10

More than 20 million patients used 5% lidocaine medicated plaster: an update on its safety profile

Irmgard Boesl, Simone Koenig
Global Innovation - Late Clinical Development, Grünenthal GmbH, Aachen, Germany

Purpose

5% lidocaine medicated plaster was prescribed worldwide to approximately more than 20 million patients between the first marketing authorization in 1999 and mid of 2014. This calculation is based on the assumption that patients applied on average 1.1 plasters per day and the average duration of treatment is about 3 months (1). Clinical data from more than 1400 patients were collected in clinical phase 1 to 3 trials. 5% lidocaine medicated plaster is indicated for the symptomatic relief of neuropathic pain associated with previous herpes zoster infection (PHN) and recommended in international treatment guidelines (2).

Method

The pooled dataset comprised overall 502 patients suffering from PHN coming from 4 clinical Phase III trials. Due to different methods of capturing adverse events datasets from three clinical Phase III trials in 394 patients were pooled to perform an integrated analysis of the safety profile (3). The dataset included also 249 patients from a one year long-term trial (4). The criteria for evaluation were frequency and type of adverse events (AEs) for safety analysis and demographic parameters including age, gender, ethnic group, duration of PHN, prior cardiac diseases, prior renal diseases and prior hepatic diseases. Adverse drug reaction (ADR) frequency was calculated.
Additionally, spontaneous safety reports from consumers and healthcare professionals were collected for approximately 20 million patients (as of July 2014) who had been prescribed the 5% lidocaine medicated plaster between 1999 and mid of 2014. Data include expected and unexpected ADRs.

Results

The pooled analysis revealed that more than 80% of the patients were older than 65 years. Mean PHN-duration was 3.0 years. Overall, 56.4% of the patients were females and 97.9% were Caucasians. Medical history revealed that frequency of cardiac diseases was 55.0%, renal diseases 6.4% and hepatic diseases 5.2%. Approximately 16% of patients experienced an ADR related to the skin, mostly of mild or moderate intensity. No specific ADR-onset or duration pattern was observed. No serious ADRs occurred.
Against a background of 20 million patients exposed, spontaneously reported adverse events were mainly skin reactions, application site reactions, or reports of drug inefficacy (for unapproved indications). The majority of ADRs were nonserious in nature. Post authorization experience appears to be in line with the safety profile identified from the clinical development program.

References
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Conclusions

The frequency of prior and concomitant cardiac-, renal- and hepatic diseases was representative for an elderly population. The pooled analysis of clinical trials showed that the 5% medicated plaster was well tolerated by the patients, also during long-term use for up to one year (5).
The topically active 5% lidocaine medicated plaster has been used in more than 20 million patients worldwide. The extensive post-marketing surveillance confirmed its favourable safety profile. These findings support its first line position in the treatment of localized neuropathic pain after herpes zoster infection.

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Relationship between Pain Relief, Sleep Improvement, and Overall Impression of Improvement in Patients with Postherpetic Neuralgia

Shay Bujanover[1], Neel Mehta[2], Rajiv Shah[2], Amitabh Gulati[3]
[1]Depomed, Inc., Newark, CA, USA, [2]Weill Cornell Medical College of Cornell University, New York, NY, USA, [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA

Purpose

Postherpetic neuralgia (PHN) is a chronic neuropathic pain syndrome that interferes with many aspects of patients' physical function and their quality of life. Because neuropathic pain tends to be worse during the night, sleep disturbance is one of the most common complaints among patients with PHN. Sleep disturbance may in turn lead to additional comorbid conditions such as anxiety or depression, and some studies suggest that shortened or disturbed sleep may lead to reduced pain tolerance. Consistent with these observations, there is evidence supporting a reciprocal relationship between pain and sleep in which pain disturbs sleep, and poor sleep enhances pain. Thus, improvement in sleep quality, in addition to control of neuropathic pain, may provide quality patient care and improve patients' overall quality of life.

To address these issues, we examined the relationship between changes in pain intensity and interference of pain with sleep in patients with PHN treated with gastroretentive gabapentin (G-GR; Gralise®, Depomed, Inc., Newark, CA). Furthermore, we characterize how changes in these measures contribute to patients' overall impression of improvement.

Method

Data from two Phase 3 (double-blind, randomized, placebo-controlled) and one Phase 4 (open-label, single-arm) clinical trial of patients with PHN who received G-GR 1800 mg once-daily (n=556) were integrated. Visual Analog Scale (VAS) on the 100-mm scale for pain intensity and Brief Pain Inventory (BPI) on the 0-10 numeric rating scale for sleep interference were completed at baseline and the end of study (Week 10 for Phase 3 and Week 8 for Phase 4). In accordance with the published literature and the consensus summary statement produced by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), reductions of ≥30% served as determinants of clinically important reductions from baseline in the VAS or BPI sleep interference scores. Patients' Global Impression of Change (PGIC) for overall improvement was completed at the end of study. Multiple logistic regression analyses were performed to examine correlations between VAS, BPI sleep interference, and PGIC. Safety assessments included the incidence of adverse events (AEs).

Results

The mean change from baseline in the VAS score was -24.6 and the mean change from baseline in the BPI sleep interference score was -2.3. Both changes were significant when compared with baseline values ($p<0.0001$). Forty-five percent of patients reported feeling "Much" or "Very Much" improved on the PGIC at the end of the G-GR treatment.

For most of PHN patients treated with G-GR, there was a positive correlation between clinically significant reduction in the VAS and BPI sleep interference sores. Likewise, "Much" or "Very Much" improvement on the PGIC was positively associated with percent reductions from baseline in both VAS and BPI Sleep Interference scores. Changes in VAS and BPI Sleep interference both significantly influenced overall improvements measured on the PGIC; however, the percent change in the VAS score had greater influence on the probability of being "Much" or "Very Much" improved on the

PGIC than did percent change in the BPI Sleep Interference score ($p<0.0001$ vs. $p=0.0063$). Consistent with this, the percent change in VAS had greater significance ($p<0.0001$ vs. $p=0.0082$) for independently predicting "Much" or "Very Much" improvement on the PGIC.

In total, 53.2% of patients reported any AE, and the incidence of all AEs decreased from 21.2% at Week 1 to 3.2% at Week 9. The incidence of somnolence, one of AEs, was low (4.9%), and it subsided quickly to sustained, low levels for the remainder of the treatment period (from 3.2% at Week 1 to no patients reporting somnolence by Week 7). This level was considerably lower than the proportion of patients who reported a clinically significant improvement in sleep quality (55%).

Conclusions

Both pain relief and sleep improvement were important for overall impression of improvement in PHN patients treated with G-GR, but pain relief was the stronger contributor. Because the proportion of patients reporting somnolence was much smaller than the proportion of patients reporting sleep improvement, the daytime somnolence that may occur as an AE and the direct effect of G-GR on improving sleep are distinct from one another. Pain and sleep qualities ultimately impact patients' overall sense of well-being, and such characterization of their complex interactions may result in better design of treatments for PHN, thus providing better outcomes for patients.

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Effects of Demographic and Socioeconomic Characteristics on Barriers to Chronic Migraine Consultation, Diagnosis, and Treatment: Results From the CaMEO (Chronic Migraine Epidemiology & Outcomes) Study

Dawn Buse[2,3], David Dodick[1], Richard Lipton[2,3], Michael Reed[4], Kristina Fanning[4], Aubrey Manack Adams[5], Adrian Holden[5]
[1]Department of Neurology, Mayo Clinic, Phoenix, AZ, USA, [2]The Saul R. Korey Department of Neurology, Albert Einstein College Of Medicine, Bronx, NY, USA, [3]Montefiore Medical Center, Bronx, NY, USA, [4]Vedanta Research, Chapel Hill, NC, USA, [5]Allergan, Inc., Irvine, CA, USA

Purpose

Effective medical care for chronic migraine (CM), at minimum, requires (1) medical consultation for headache (HA), (2) accurate diagnosis, and (3) an effective treatment plan. Failure at any stage makes acceptable patient outcomes unlikely. The American Migraine Prevalence and Prevention Study found that only 26.3% of episodic migraineurs received appropriate treatment.[1] Data on barriers to care for CM would help plan interventions to improve treatment outcomes. We estimated the rate of appropriate treatment among those with CM and determined the effect of demographic, socioeconomic, and HA variables on barriers to care in persons with CM in a naturalistic setting.

Method

The CaMEO Study recruited persons to complete a series of web-based surveys over 1 yr. The web-panel was constructed in an attempt to be demographically representative of the US. Of 16,789 respondents meeting modified *International Classification of Headache Disorders, 3rd edition, beta version* (*ICHD-3b*) criteria for migraine, 1,476 (8.8%) met study criteria for CM (modified *ICHD-3b* migraine diagnosis + ≥15 HA days/mo [previous 3-mo average]; *ICHD-3b* criteria A/B for migraine and C for CM not assessed). This analysis included self-reported demographic, socioeconomic, and HA-specific data for respondents who (1) met study CM criteria, (2) had Migraine Disability Assessment (MIDAS) grade ≥2, and (3) reported whether or not they had health insurance. Descriptive statistics were used to assess rates of receiving minimally appropriate treatment and logistic multivariate analyses assessed predictors of consulting patterns.

Results

Of those with CM, a MIDAS grade ≥2, and information on insurance status, only 512/1,254 (40.8%) respondents reported currently being managed or treated by a healthcare professional (HCP) for HAs (current consulters). Of current consulters, 126/512 (24.6%) reported receiving a diagnosis of CM (or transformed migraine) from an HCP. Of those diagnosed with CM, 56/126 (44.4%) received minimally appropriate treatment (acute + preventive therapies). In total, 4.5% (56/1,254) of the CM population passed all 3 barriers to care and received minimally appropriate care.

The odds of consulting an HCP increased with age (odds ratio [OR; 95% CI]: 1.02 [1.01-1.03]), were higher for those with vs without insurance (OR [95% CI]: 4.61 [3.05-6.96]), and increased with symptom severity (OR [95% CI]: 1.16 [1.11-1.22]) and disability (MIDAS; OR [95% CI]: 1.02 [1.00-1.04]). Among consulters, the odds of receiving a CM diagnosis from an HCP were higher for women (OR [95% CI]: 1.93 [1.03-3.61]), as symptom severity increased (OR [95% CI]: 1.25 [1.14-1.37]), and for those seeing an HA specialist (OR [95% CI]: 2.38 [1.54-3.69]). Possibly because of small sample size, none of the variables predicted receiving appropriate treatment among those diagnosed with CM.

Conclusions

Several barriers must be overcome for persons with CM to receive minimally appropriate treatment. Appropriate treatment is more likely with increasing age and among women, those with insurance, and those with greater migraine disability and symptom severity, although very few (4.5%) eligible respondents with CM actually received minimally appropriate treatment. Public health efforts should focus on improving consultation, diagnosis, and treatment of CM.

Reference: Lipton RB et al. *Headache*. 2013;53:81-92.

Funding: Allergan

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Family Burden of Chronic Migraine to the Migraineur: Results of the CaMEO (Chronic Migraine Epidemiology & Outcomes) Study

Dawn Buse[1,2], David Dodick[3], Aubrey Manack Adams[4]
[1]*The Saul R. Korey Department of Neurology, Albert Einstein College of Medicine, Bronx, NY, USA,* [2]*Montefiore Medical Center, Bronx, NY, USA,* [3]*Department of Neurology, Mayo Clinic, Phoenix, AZ, USA,* [4]*Allergan, Inc., Irvine, CA, USA*

Purpose

Chronic migraine (CM) is associated with significant personal disability,[1] but the effect of migraine on the lives of members of a migraineur's family is less well known. We assessed the perception among those with CM of the nature and extent of migraine burden on family activities and relationships.

Method

CaMEO recruited persons from a web-based panel, using quota sampling in an attempt to obtain a sample representative of US demographics, who completed web-based surveys over 1 year to characterize migraine. This analysis included data from respondents meeting study CM criteria (modified *International Classification of Headache Disorders, 3rd edition (beta)* [*ICHD-3b*] migraine diagnosis + ≥15 headache [HA] days/mo for past 3 months; *ICHD-3b* criteria A/B for migraine and C for CM not assessed). The proband's family burden survey (FBS) assessed several domains, including but not limited to overall burden, family activities missed, relationship impact, activities missed and interactions with partner/children, important family/life events, and vacations.

Descriptive statistics (count items: mean, SD; binary items: number, percent endorsing) and sex contrasts (count items: rate ratio [RR] from negative binomial regression model; binary items: odds ratio [OR] from binomial logistic regression model) were calculated.

Results

Of the 11,518 respondents with valid data for the proband FBS, 994 (8.6%) were classified as having CM and included in this analysis. 812 (81.7%) of the CM probands were women and 182 (18.3%) were men.

Probands experienced reduced enjoyment of family activities and reduced quality time with partner 6.9 and 6.6 days in the prior month, respectively. Most probands felt that HAs made them easily angry/annoyed with their partner (70.2%) and made their partner's life hard (64.1%). Many avoided sexual intimacy because of HAs (67.2%), felt they would be a better partner without HAs (72.5%), and felt guilty about how their HAs affected their partner (64.4%).

The odds of women reporting interictal stress in romantic relationships were 34% lower than that of men (OR [95% CI]: 0.66 [0.43-1.00]; P=0.049); similar interictal sex differences were seen in relationships with children (OR [95% CI]: 0.58 [0.35-0.99]; P=0.044). Respondents reported missing 20% of planned vacations because of HAs (no sex difference; P=0.88).

Women cancelled plans 23% less often than men (4.09 vs 5.28 times/mo; RR [95% CI]: 0.77 [0.61-0.98]; P=0.031). In the past year, women missed 49% fewer holidays/religious events (2.79 vs 5.49; RR [95% CI]: 0.51 [0.32-0.80]; P=0.003) and 52% fewer weddings/important events (2.46 vs 5.09; RR [95% CI]: 0.48 [0.30-0.79]; P=0.004) than men.

Conclusions

Most individuals with CM reported that migraine attacks have significant effects on family relationships and activities. Reduced enjoyment of activities was commonly reported. Women consistently reported lower rates of absenteeism because of HA than men across many activities. Reasons for this are unknown. The nature and severity of attacks may be qualitatively different between men and women, or women may feel more obligated to keep commitments despite a migraine attack.

Reference: 1. Buse DC, et al. *Headache*. 2012;52(10):1456-1470.

Funding: Allergan

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Development and Validation of a Screening Tool to Identify Chronic Migraine (ID-CM)

Richard Lipton[1,2], Daniel Serrano[1,3], Dawn Buse[1,2]
[1]Albert Einstein College of Medicine, Bronx, NY, USA, [2]Montefiore Headache Center, Bronx, NY, USA, [3]Vedanta Research, Chapel Hill, NC, USA

Purpose

Though screening is a common strategy for improving diagnosis, there are no validated screening tools for individuals with chronic migraine (CM). The goal of this study was to develop and validate a self-administered screening tool for CM.

Method

The item pool for the candidate screening tool was derived from review of existing instruments and expert input. A draft questionnaire was selected out of the initial item bank based on face validity and clinical judgment from a Delphi panel. Cognitive debriefing interviews were then
conducted among 10 CM patients to assess relevance and understandability of questions and response choices. The draft screening tool was subsequently administered online to respondents with self-identified "severe headache" in order to determine initial psychometric properties and screening tool composition. Unique item response theory (IRT) models were used to determine screening tool properties in addition to checking initial classification accuracy. In the final phase of the study, phone interviews were conducted by clinicians to compare ID-CM to the "gold standard" (ie, clinician diagnosis) in order to finalize the tool (ie, items and scoring). Analyses were conducted using M-plus version 7.1 (Los Angeles, CA) and SAS version 9.2 (Cary, NC).

Results

The candidate screening tool item pool contained 27 items. A draft questionnaire of 20 items
was selected based on face validity and clinical judgment from the Delphi panel. Cognitive debriefing interviews confirmed that the 20 items were well understood and considered relevant. The draft screening tool was administered to 1562 individuals, including CM (n=363), EM (n=416), and other severe headache (n=783). Based on IRT modeling, a two-stage screening process was determined to be suitable to detect cases using ID-CM: 1) screen for migraine among respondents with severe headache; 2) screen for CM among migraine cases. Items were reduced from the first stage questions but no items were reduced from the second stage questions. Initial classification accuracy was high. A total of 111 telephone interviews were completed to determine final screening tool composition. The final ID-CM tool consists of 12 questions, including 4 symptoms items, 2 headache frequency items, 2 disability items, 2 drug use items, and 2 planning items. ID-CM demonstrated a sensitivity and specificity of 82% and 87% respectively when compared to clinical interview classifications.

Conclusions

A self-administered screening tool has been developed through existing instrument review,
expert panel consensus, and psychometric work to screen for CM. The ID-CM has demonstrated high capability to accurately classify respondents into CM among individuals with headaches.

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Evaluation of abuse potential of a prescription opioid with limited market penetration: EXALGO® abuse among a sample of individuals evaluated for substance abuse treatment

Stephen Butler, Emily McNaughton, Ryan Black, Theresa Cassidy
Inflexxion, Inc., Newton, MA, USA

Purpose

Research has shown that in real-world settings, different opioid analgesic products have different abuse patterns, with some products more likely to be abused than others. Key factors related to abuse of prescription drugs include amount of a product's local availability, desirability of the particular product for purposes of abuse/misuse compared to available alternatives, the ability to abuse through alternate routes of administration (ROA) and the relative cost to obtain the drug for purposes of abuse. Evaluating abuse potential of a product that is new to the market or has relatively low prescription volume presents methodological challenges, since low abuse prevalence for a particular product may be related to limited availability or low desirability for the product or both. To help address this, we propose a multi-faceted approach including: (1) examination of abuse rates in a population of individuals likely to seek and abuse a highly desirable-for-abuse product, even with low prescribed availability (e.g., individuals in substance abuse treatment), (2) examination of abuse adjusted for prescription volume (dosage units dispensed), (3) selection of specific comparators including comparison to opioid products for active pharmaceutical ingredient (API), immediate-release (IR)/extended-release (ER) formulation, comparators with known route-of-administration profiles, and comparators that have similar prescription volume. For this study, we examine the abuse potential of EXALGO®, (an ER hydromorphone). EXALGO has relatively low prescribed availability, an API that is highly desirable for abuse, and has an ER OROS® Push-Pull® drug delivery system that may discourage abuse via alternate routes of administration (e.g., snorting or injection).

Method

A cross-sectional, observational surveillance study compared prevalence of overall and prescription-adjusted abuse for EXALGO since its market introduction (April 2010 through December 2013) as measured against selected comparators over the same time period in a sentinel sample of adults evaluated for substance abuse treatment drawn from the NAVIPPRO® surveillance system. Patients were evaluated using the Addiction Severity Index-Multimedia Version (ASI-MV®), a computer-administered, clinical interview that collects self-report of past 30-day drug abuse including specific prescription products. Patients differentiate abuse of prescription products using screen images. This study examined the relative prevalence of self-reported past 30-day abuse of EXALGO and seven selected comparators: hydromorphone IR as the API comparator, two products with relatively low prescription volume (KADIAN®, AVINZA®), as well as other morphine ER products, oxymorphone ER, oxycodone ER and tramadol ER. General estimating equations (GEE) log-Poisson models estimated: (1) product-specific prescription-unadjusted abuse prevalence, (2) prescription-adjusted abuse prevalence (e.g., number of abuse cases per 100 ASI-MV assessments per 100,000 dosage units), and (3) relative risk (RR) of past 30-day abuse (abuse of EXALGO relative to comparator). GEE log-Poisson regression models also estimated route-specific abuse (e.g., swallowed whole vs. other route and snorting and injection).

Results

From April 2010 through December 2013, 188,582 adults completed the ASI-MV at 756 treatment facilities in 41 states. Prevalence of past 30-day EXALGO abuse (cases per 100 ASI-MV assessments) was 0.02%, significantly lower ($p < 0.0001$) than all comparators. Thus, abuse prevalence was 77 times lower than the API comparator, hydromorphone IR, and the other ER opioid comparators (relative risk range: oxycodone ER, RR = 230.4 to AVINZA,

RR = 5.7). Prescription-adjusted RR for EXALGO abuse was significantly lower than all but one comparator ($p < 0.0001$). Products with prescribed availability closest to that of EXALGO were more likely to be abused (i.e., AVINZA RR= 3.0, KADIAN RR= 2.6 and tramadol ER RR=4.5). High prescription volume comparators had from 10 times (oxymorphone ER) to 65 times (oxycodone ER) EXALGO's prescription volume. The prescription-adjusted RR for EXALGO was significantly lower than all other comparators ($p < 0.0001$), with the exception of "other morphine ER" (RR = 0.71, $p = 0.0021$). Comparisons of ROA profiles, were conducted on the few (N = 42) who abused EXALGO. Use by ROA other than swallowing whole was reported significantly less than the API comparator, hydromorphone IR, and products known to have high injection and snorting rates (e.g., the morphine ER products and oxymorphone ER). Alternate route use was not different from oxycodone ER and occurred more often than tramadol ER. Snorting of EXALGO was reported less than hydromorphone IR, other morphine ER, oxymorphone ER and oxycodone ER, but was not significantly less than KADIAN, AVINZA or tramadol ER. EXALGO abuse via injection was significantly lower than comparators with known high injection: hydromorphone IR, other morphine ER products, KADIAN and AVINZA. Injection for EXALGO was not different from oxymorphone ER and oxycodone ER; and tramadol ER had less injection than EXALGO.

Conclusions

Abuse by adults evaluated for substance abuse treatment of a low prescription volume product was examined for EXALGO. EXALGO abuse rates unadjusted and adjusted for prescription volume are low relative to selected comparators, even after accounting for its low prescription volume. Prescription-adjusted abuse of EXALGO was less than individual products with similar prescription volume; lower than the API comparator and all but one of the high-volume ER comparators. ROA analyses should be interpreted cautiously given the few EXALGO cases observed. Examination of other data (e.g., Internet discussion) may allow assessment of whether desirability exists for a drug like EXALGO.

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Evaluation of Internet forum discussion to assess abuse potential of a prescription opioid with limited market penetration: EXALGO as a case study.

Emily McNaughton, Ryan Black, Taryn Dailey, Theresa Cassidy, Stephen Butler
Inflexxion, Inc., Newton, MA, USA

Purpose

Post-market evaluation of the abuse potential of newly marketed or low-volume prescription medications presents methodological challenges. While prevalence estimates provide an understanding of medication abuse within a population, in the case of low-volume medications, it is possible that even after accounting for prescription volume, observations of low prevalence rates of abuse may reflect factors other than a medication's recreational appeal. To understand whether observed low prevalence is truly related to a low level of availability or low level of desirability of the product, evaluation of data from recreational drug abuse Internet forums may be useful. Internet forums present an uncensored, "real-time" window into the interest in and sentiment expressed by those who post about recreational use of prescription medications. A product with high abuse potential may be discussed frequently and positively, despite limited availability. A drug with low abuse potential may be discussed less often and be more likely to be discouraged for abuse. Extended release (ER) hydromorphone (EXALGO®) was examined, given its relatively low prescribed availability, the high abuse potential of its active pharmaceutical ingredient (API), and its OROS® Push-Pull® technology, which may discourage abuse via alternative routes of administration. The extent to which online discussion of EXALGO by recreational abusers reflects interest in and desire to obtain and abuse the product was examined. Qualitative and quantitative methods developed over the past seven years as part of the NAVIPPRO® Web Informed Services (WIS®) program were used to evaluate the abuse potential of EXALGO relative to comparator analgesics.

Method

Messages posted on seven recreational drug abuse Internet forums between April 1, 2010 and December 31, 2013 were evaluated. To measure the overall level of interest in EXALGO within these communities, the proportion of posts (i.e., messages) and unique authors that mentioned EXALGO and seven comparator compounds - hydromorphone, KADIAN®, AVINZA®, morphine, oxycodone ER, oxymorphone, and tramadol - were calculated across the study period both unadjusted and adjusted for prescription volume using binomial logistic regression models. To assess the sentiment expressed by authors, all EXALGO-related posts written across the study period were qualitatively reviewed by trained coders and determined to be endorsing, discouraging, mixed, or unclear in nature and compared to previously coded posts for the following comparators: reformulated OxyContin®, morphine ER, oxymorphone, (original formulations), reformulated Opana® ER, tramadol, and Dilaudid®. Utilizing the qualitatively coded data, the degree to which each product/compound was endorsed for abuse was estimated using the Endorsement Ratio (ERo) methodology which employed a mixed effects multinomial logistic regression model. The sample of EXALGO-related posts was also qualitatively reviewed by trained coders for additional information that could be used to contextualize interest/disinterest in EXALGO abuse by the online community (e.g., what did individuals think about the OROS formulation?).

Results

Of 4,154,159 messages posted on the monitored web forums during the study period, 132,910 posts by 18,283 unique authors mentioned at least one of the products/compounds examined. Quantitatively, while the proportion of posts that mentioned EXALGO (pr = 0.000123) was significantly lower than each of the compound comparators evaluated (range OR from 45.4 for hydromorphone to 111.9 for morphine; all ps < 0.0001) and KADIAN (OR =

1.2; p =0.004), EXALGO was discussed significantly more frequently than AVINZA (OR = 0.51, p < 0.0001). When considering the proportion of unique authors, EXALGO was discussed by significantly fewer authors than the comparator compounds (range OR from 22.1 for oxymorphone to 61.2 for morphine; all ps < 0.0001) and by a greater number of authors than AVZINA (OR = 0.45, p < 0.0001), however, unlike posts, no significant difference was observed between unique authors posting about EXALGO and KADIAN (OR = 1.05, p = 0.50). No changes were observed when adjusting for prescription volume. Estimation of endorsement utilizing the qualitatively coded posts yielded an ERo for EXALGO of 1.84; significantly lower than Dilaudid (5.04), original oxymorphone (5.75), and original OxyContin (3.47), but significantly greater than reformulated OxyContin (0.93) and reformulated Opana ER (0.58). The ERo for EXALGO was lower, but not significantly different, than morphine ER (2.65) and tramadol (1.53). For contextualization, qualitative review of posts that endorsed EXALGO referenced efforts associated with tampering with the OROS system to extract hydromorphone for abuse while discouraging EXALGO posts mentioned the relative cost of the product, the idea that abusing the product was dangerous, displeasure associated with abusing the OROS delivery system, and overall difficulties tampering with the formulation.

Conclusions

Among hydromorphone-related posts, EXALGO is less frequently discussed and endorsed for abuse than IR hydromorphone. Whether this is due to EXALGO abuse-deterrent properties is unclear. Qualitative coding of the few EXALGO-related posts available may reflect limited experience with or unstable online opinion about a product that is not widely available. Efforts to defeat the OROS formulation were discussed, so the formulation may serve as a barrier to abuse. Given the desirability for abuse of the API, an unprotected and/or less costly version of hydromorphone ER may be more desirable for abuse than EXALGO. Further monitoring is warranted.

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Peripheral Edema and Weight Gain in Adult Patients with Painful Diabetic Peripheral Neuropathy (DPN) Receiving Gabapentin Enacarbil (GEn) or Pregabalin Enrolled in a Randomized Phase 2 Trial

Anne Calkins[1], Joseph Shurman[1,2], Mark Jaros[1,3], Richard Kim[1,4], Gwendoline Shang[1,4]
[1]New York Spine and Wellness Center, North Syracuse, NY, USA, [2]Scripps Memorial Hospital, La Jolla, CA, USA, [3]Summit Analytical, LLC, Denver, CO, USA, [4]XenoPort, Inc., Santa Clara, CA, USA

Purpose

GEn is an actively transported prodrug of gabapentin. In this 20-week, randomized phase 2 study in adult patients with neuropathic pain attributed to DPN, neither the GEn (1200 mg/day, 2400 mg/day, or 3600 mg/day) nor control (pregabalin 300 mg/day) arms differed from placebo with regard to the primary efficacy endpoint (change from baseline in the mean 24-hour average pain intensity score). GEn was well tolerated across dosages. The objective of this study was to examine the incidences of peripheral edema and weight gain in adult patients with painful DPN receiving GEn, pregabalin, or placebo in a phase 2 trial.

Method

The incidence of peripheral edema and weight gain by treatment groups, the proportions of patients with worsening pedal edema, weight gain ≥7% at any post-randomization visit and mean changes in body weight from baseline were explored in this analysis.

Results

The safety population comprised 420 patients. Compared with pregabalin, patients randomized to GEn experienced less peripheral edema and weight gain. The incidences for peripheral edema were: GEn, 3% (1200 mg), 0% (2400 mg), and 9% (3600 mg); pregabalin, 17%; placebo, 4%. The incidences for weight gain were: GEn, 0% (1200 mg), 4% (2400 mg), and 4% (3600 mg); pregabalin, 8%; placebo, 1%. The proportions of patients who experienced a ≥7% weight gain at any post-randomization visit were: GEn, 5% (1200 mg), 7% (2400 mg), and 10% (3600 mg); pregabalin, 15%; placebo, 3%. The mean (2SE) changes from baseline in weight gain at the end of the 12-week maintenance treatment phase were 1.22 (0.95), 1.71 (0.84), and 1.85 (0.77) kg for GEn 1200, 2400, and 3600 mg, respectively, 2.65 (0.92) kg for pregabalin, and -0.55 (0.72) kg for placebo.

Conclusions

In this phase 2 study in adult patients with painful DPN, GEn was associated with overall lower incidences of peripheral edema and weight gain than pregabalin; the weight gain in GEn-treated patients appeared to be dose-dependent. Data support examination in future clinical trials.

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Sensitivity Analyses of the Primary Efficacy Endpoint in a Phase 2 Randomized, Placebo-controlled Study of Gabapentin Enacarbil (GEn) in Adult Patients with Neuropathic Pain Associated with Postherpetic Neuralgia (PHN)

Anne Calkins[1], Jeff Gudin[2], Barry Gidal[3], Mark Jaros[4], Richard Kim[5], Gwendoline Shang[5]
[1]New York Spine and Wellness Center, North Syracuse, NY, USA, [2]Englewood Hospital and Medical Center, Englewood, NJ, USA, [3]University of Wisconsin, Madison, WI, USA, [4]Summit Analytical, LLC, Denver, CO, USA, [5]XenoPort, Inc., Santa Clara, CA, USA

Purpose

GEn is an actively transported prodrug of gabapentin. In this phase 2 randomized, placebo-controlled study in adult patients with PHN, GEn 1200 mg/day, 2400 mg/day, and 3600 mg/day demonstrated statistically significant differences compared with placebo with regard to the primary endpoint, change from baseline to end of maintenance treatment (EOMT; 1 week up-titration and 12 weeks maintenance) in mean 24-hour average pain intensity score. Our objective was to confirm the robustness of the results from the primary endpoint of this study using a prespecified sensitivity analysis.

Method

Adult patients with PHN were randomized (1:1:1:1) to GEn 1200 mg/day, 2400 mg/day, 3600 mg/day or placebo. In the primary analysis, comparisons between GEn treatment arms and placebo were made for the intent-to-treat population using an analysis of covariance (ANCOVA) model, using last observation carried forward (LOCF) for imputation of missing data. In addition to the LOCF method, here we report prespecified sensitivity analyses of the primary endpoint using the baseline observation carried forward (BOCF) imputation method and a mixed-effect model repeated measures (MMRM) analysis.

Results

All 3 GEn treatment groups demonstrated statistically significant differences in mean changes from baseline to EOMT relative to placebo using all 3 analysis methods. Mean differences (95% confidence interval) relative to placebo for the GEn 1200 mg, 2400 mg, and 3600 mg groups, respectively, were: LOCF, -0.81 (-1.40, -0.23; P=.007), -0.70 (-1.33, -0.07; P=.029), and -1.07 (-1.68, -0.45; P=.001); BOCF, -0.94 (-1.51, -0.36; P=.001), -0.65 (-1.27, -0.03; P=.040), and -0.68 (-1.28, -0.08; P=.027); and MMRM, -0.81 (-1.32, -0.31; P=0.002), -0.68 (-1.23, -0.14; P=.014), and -1.07 (-1.61, -0.54; P<.001). Although the study was not powered to detect differences between GEn doses, the greatest numerical difference vs placebo using the LOCF and MMRM methods was observed with GEn 3600 mg, while this was the case for GEn 1200 mg using the BOCF method.

Conclusions

Regardless of the analysis methodology, there were significant differences between all three doses of GEn and placebo with regard to the primary endpoint, confirming the validity of the primary analysis.

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Sensitivity Analyses of Secondary Pain Intensity Endpoints in a Phase 2 Randomized, Placebo-controlled Study of Gabapentin Enacarbil (GEn) in Adult Patients with Neuropathic Pain Associated with Postherpetic Neuralgia (PHN)

Anne Calkins[1], Jeff Gudin[1], Barry Gidal[1], Mark Jaros[1], Richard Kim[1]
[1]New York Spine and Wellness Center, North Syracuse, NY, USA, [2]Mt. Sinai University School of Medicine, Englewood, NJ, USA, [3]University of Wisconsin, Madison, WI, USA, [4]Summit Analytical, LLC, Denver, CO, USA, [5]XenoPort, Inc., Santa Clara, CA, USA

Purpose

GEn is an actively transported prodrug of gabapentin. In this phase 2 randomized, placebo-controlled study in adult patients with PHN, GEn 1200 mg/day, 2400 mg/day, and 3600 mg/day demonstrated statistically significant differences compared with placebo with regard to the primary endpoint (change from baseline to end of maintenance treatment [EOMT; 1 week up-titration and 12 weeks maintenance] in mean 24-hour average pain intensity score) and secondary endpoints (pain intensity scores according to daily eDiary assessments) (Zhang Pain J 2013). The objective of our study was to confirm the robustness of the primary analysis of the secondary pain intensity endpoints using a prespecified sensitivity analysis.

Method

Adult patients with PHN were randomized (1:1:1:1) to GEn 1200 mg/day, 2400 mg/day, 3600 mg/day or placebo. In the primary analysis, comparisons between treatment arms and placebo were made for the intent-to-treat population using an analysis of covariance (ANCOVA) model, using last observation carried forward (LOCF) for imputation of missing data. In addition to the LOCF method, here we report prespecified sensitivity analyses of secondary endpoints using the baseline observation carried forward (BOCF) imputation method and a mixed-effect model repeated measures (MMRM) analysis.

Results

Statistically significant differences in mean changes from baseline were observed for GEn 1200 mg relative to placebo using the LOCF, BOCF, and MMRM analysis methods, respectively, for the following endpoints: daytime average pain (-0.88, P=.004; -0.97, P=.001; -0.88, P<.001), nighttime average pain (-0.69, P=.022; -0.82, P=.006; -0.69, P=.009), daytime current pain (-0.96, P=.002; -0.92, P=.002; -0.97, P<.001), nighttime current pain (-1.00, P=.0015; -1.01, P=.001; -1.00, P<.001), daytime worst pain (-0.88, P=.009; -1.03, P=.002; -0.88, P=.002), and nighttime worst pain (-0.73, P=.028; -0.90, P=.006; -0.72, P=.013).

Conclusions

Results of the sensitivity analyses of the secondary efficacy measures were consistent with those in the primary analysis, showing statistically significant differences between GEn 1200 mg and placebo for all assessed pain endpoints; this confirms that the analysis methodology did not materially impact the results. Results for GEn 2400 mg and 3600 mg will be included in the full presentation.

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Reefer Madness: Policy Changes on a New (Old) Prescription Drug - Marijuana

Sara Calvin, Scott Novak
RTI International, Research Triangle Park, NC, USA

Purpose

With opiate addiction a serious concern among clinicians, alternative options for patient pain relief should be considered. Since the 1990s, marijuana has been an approved pain management treatment in certain states for patients with chronic pain and cancer-related pain in the United States. Marijuana use policies continue to change, and vary by state. Some states have decriminalized marijuana, legalized the use of medical marijuana, and/or legalized the recreational use of marijuana. Due to the recent marijuana legalization for all residents in two states, medical marijuana laws have received national media coverage and the public's interest. As more Americans learn of medical marijuana and legalization policies, and as patients continue to look to clinicians for guidance on pain treatment, it is important that clinicians understand how these policies can impact their prescribing approach. This study reviewed the state-level policies of when medical marijuana laws and marijuana decriminalization and legalization were implemented, as well as the differences in implementation. Regulations regarding registries and specific medical conditions, including chronic pain, within medical marijuana laws were reviewed. Clinical implications of medical marijuana use among patients, such as accidental exposure in children, are increasingly being published and were also included in this study. Additionally, state-level estimates of current marijuana use and substance abuse treatment admissions for marijuana are shown, giving clinicians a solid background on the current issues of abuse around marijuana in their state, as well as how these policies impact marijuana abuse and treatment needs.

Method

First, a literature review was performed to find relevant policy sources on current medical marijuana and marijuana decriminalization and legalization (e.g., PubMed, Library of Congress, Google Scholar). Second, Google searches were performed to find additional policy content. Third, a data review was performed to find nationally representative data on marijuana use and substance abuse treatment admissions for marijuana by state. State-level estimates of marijuana use from the National Survey on Drug Use and Health (NSDUH) and marijuana substance abuse treatment admissions from the Treatment Episode Data Set (TEDS) were provided on the Substance Abuse and Mental Health Data Archive (SAMHDA), sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA). Using these nationally representative data sets, current marijuana use and substance abuse treatment data among states with marijuana decriminalization, medical marijuana laws, and marijuana legalization were compared to states without those policies.

Results

Results from the literature review indicate that state-level medical marijuana policies were implemented in the United States as early as 1999 and as recently as 2014. Marijuana decriminalization was implemented in some states as early as 1974. Results of this literature review also found large variability in the passage and implementation of medical marijuana and marijuana decriminalization and legalization laws by state. In states with marijuana decriminalization policies, most (N=10) eventually implemented medical marijuana policies, although the majority of states with current medical marijuana laws did not have marijuana decriminalization laws in place beforehand (N=14). Four states with marijuana decriminalization still have not implemented medical marijuana or marijuana legalization policies. Having a well-established medical marijuana policy and infrastructure around that policy seem to be the best indicator for states adopting a marijuana legalization policy (N=2). This study also found that the implementation of marijuana laws varies considerably by state (e.g., dispensaries, specific medical conditions). Public

use NSDUH data, combining annual averages from 2002 to 2011, indicate that current marijuana use varies by state, as do TEDS substance abuse treatment admission data for marijuana from 1992 to 2012. Additional detail on the data and its relationship with state-level marijuana policy will be provided in the full presentation.

Conclusions

Opiate addiction continues to be a serious concern among clinicians treating patients with pain, and the use of medical marijuana may provide a favorable alternative. The findings of this review will give clinicians a better understanding of state-specific marijuana legislation and potential impacts of this legislation on marijuana use and associated treatment admissions among persons residing in each state.

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The changing abuse ecology: implications for evaluating the abuse pattern of extended-release oxymorphone and abuse-deterrent opioid formulations

Theresa Cassidy[1], Jared Beaumont[1], Veronica Urdaneta[2], Simon Budman[1], Stephen Butler[1]
[1]Inflexxion, Inc., Newton, MA, USA, [2]Endo Pharmaceuticals, Malvern, PA, USA

Purpose

FDA Guidelines released in January 2013 on evaluating abuse-deterrent formulations (ADFs) recommend direct comparison of prevalence of abuse for the ADF against historical baseline levels of non-ADF comparators. This analysis assumes a level of stability in the prescription opioid market prior to and following introduction of the ADF. However, introduction of ADF opioid products occurred in conjunction with the introduction of new non-ADF opioids (including brand and generic formulations) creating a dynamic landscape or "abuse ecology" in which abusers adapt and respond to new products as well as ADF vs. non-ADF alternatives for abuse. A reformulated version of extended-release (ER) oxymorphone designed to be crush-resistant (OPANA® ER - oxymorphone hydrochloride extended-release tablets; Endo Pharmaceuticals Inc., Malvern, PA) became commercially available in February 2012, concurrent with the cessation of production and diminishing supply of the original (non-ADF) brand formulation of this product. Existence of the original brand as well as new generic ER and immediate-release (IR) oxymorphone formulations offer potential non-ADF alternatives for abuse of oxymorphone ER. A simple pre-post comparison of abuse and route of administration (ROA) profiles assumes that abuse of the original product would remain unchanged in the time period following introduction of the ADF. To examine this assumption, we reviewed abuse and route of administration patterns for both original and reformulated ER oxymorphone, and generics after introduction of crush-resistant ER oxymorphone during an 18-month period (October 2012 through March 2014).

Method

Data were collected during October 2012 through March 2014 from a sample of 77,175 adults assessed for substance abuse problems and treatment planning at centers in the U.S. using surveillance data from the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®). Individuals were assessed using the Addiction Severity Index-Multimedia Version (ASI-MV®), a standardized clinical interview that collects self-reported data on past 30-day abuse of illegal substances and prescription medications from adults during treatment admission and planning. Estimates of abuse prevalence for reformulated crush-resistant oxymorphone ER and other categories of oxymorphone (both ER and IR formulations) were measured as the proportion of abuse reported within the past 30 days among the total study sample of those assessed for substance abuse treatment and adjusted for prescription volume. ROA patterns were examined via calculating the percentage of individuals who reported abuse via a specific ROA among only those individuals who reported past 30-day abuse of the product or compound of interest (i.e., reformulated oxymorphone ER, original oxymorphone ER, generic oxymorphone ER). Abuse was defined as any non-medical use of a prescription opioid product.

Results

During the 18-month period examined (October 2012 - March 2014), abuse of reformulated oxymorphone ER per assessments and per prescriptions dispensed was higher than historical baseline abuse for original oxymorphone ER (1.03 versus 0.81 cases per 100 assessments; 86.76 versus 70.84 cases per 100,000 prescriptions). After market

introduction of an ADF oxycodone ER product, abuse of original oxymorphone ER increased to a maximum of 1.94 cases per 100 assessments in Q4 2011 and then started to decline coinciding with introduction of reformulated oxymorphone ER. Also, during the past 18 months, abuse prevalence for reformulated oxymorphone ER was lower than generic formulations of oxymorphone ER (0.98 versus 1.03 cases per 100 assessments) and for any non-ADF brand or generic formulations of oxymorphone ER (1.44 cases per 100 assessments). Per prescriptions dispensed, abuse prevalence for reformulated oxymorphone ER (83.43 cases per 100,000 prescriptions dispensed) was lower than non-ADF generic formulations of oxymorphone ER (264.88 cases per 100,000 prescriptions dispensed) and any non-ADF brand and generic oxymorphone ER (336.03 cases per 100,000 prescriptions dispensed). ROA patterns indicate that reformulated oxymorphone ER was mostly abused via injection (64%) with lower percentages of oral abuse (22%) and snorting (21%) while non-ADF ER oxymorphone formulations (both brand and generic) indicated lower injection (36%) and a greater frequency of snorting (63%).

Conclusions

Evaluating the public health impact of ADFs should take into account the current market environment and dynamic "abuse ecology" for prescription opioids. Given market changes for oxymorphone products, comparison of abuse patterns of reformulated oxymorphone ER to historical baseline levels alone may not provide the most meaningful evaluation of abuse of this product. In the current environment, data indicate abuse of reformulated oxymorphone ER is lower than non-ADF oxymorphone ER formulations with changes in ROA patterns suggesting lower frequency of snorting but a higher percentage of abuse via injection for reformulated oxymorphone ER compared to other non-ADF oxymorphone ER products.

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Pharmacokinetics of Diclofenac Potassium for Oral Solution vs. Diclofenac Potassium Immediate-Release Tablets: Effect of Fed vs. Fasting

Alan, M. Rapoport[1], Shay Bujanover[2], Cuiping Chen[2]
[1]*The David Geffen School of Medicine at UCLA, Los Angeles, CA, USA,* [2]*Depomed, Inc., Newark, CA, USA*

Purpose

Diclofenac potassium for oral solution (Cambia®, Depomed, Newark, CA) is the only non-steroidal anti-inflammatory drug approved as a monotherapy for the acute treatment of migraine attacks with or without aura in adults 18 years of age or older. This solution formulation was developed to provide a more rapid rate of absorption, and thus a fast onset of action to relief migraine pain. The rapid rate of absorption was achieved through the dynamic buffering technology, which utilizes potassium bicarbonate as the buffering agent to increase the solubility of diclofenac potassium prior to and in the GI tract during the absorption. A 50-mg diclofenac potassium in such buffered formulation dissolves completely in 1 to 2 ounces (30 to 60 mL) of water prior to administration. The drug administration is not specified for fed or fasted conditions as the efficacy and safety studies were not conducted under these conditions. However, the fed condition typically leads to a slower GI emptying and motility, and changes in gastric pH, all of which may affect the absorption rate of diclofenac potassium, and thereby lead to possible changes in drug efficacy. Moreover, such effects may also depend on diclofenac dosage forms (e.g., solution vs. tablet).

The objective of this study was to compare the pharmacokinetics of diclofenac dosed as the oral solution vs. an immediate-release (IR) tablet, and examine the food effect on both formulations.

Method

This was an open-label, randomized, crossover pharmacokinetic (PK) study in healthy subjects between 18 and 45 years old. Subjects (n=36) were randomized to receive a single 50-mg dose of diclofenac potassium as a solution vs. IR tablets under fed (a high fat, high calorie breakfast) and fasting (no food for a minimum of 10 hours before dose) conditions, with a ≥7-day washout period. Blood samples for PK analyses were taken at pre-dose and at up to 12 hours post dose, and analyzed for diclofenac plasma concentrations. Maximal (or peak) concentration (C_{max}), time to C_{max} (t_{max}), overall systemic exposure measured as area-under-concentration time curve (AUC) from time 0 to last measurable concentration (AUC_t), and extrapolation to infinity (AUC_∞) were obtained using non-compartmental analysis. Comparative assessments for diclofenac systemic exposure (C_{max} and AUCs) were performed between the solution and IR tablets under fed and fasting conditions, and between fed and fasting conditions for both formulations. Equivalent systemic exposure (i.e., bioequivalence) between the solution and the IR tablets, or between fed and fasted conditions for either dosage was defined when geometric mean ratio for both C_{max} and AUCs and its 90% CI were within 80.0%–125.0%. Adverse events (AEs) were monitored throughout the study. Paired t-test was used to compare t_{max} and C_{max} between the formulations under same fed or fasted conditions, and between the fed and fasted conditions for both formulations. A p-value of ≤ 0.05 was considered statistically significant.

Results

Thirty six subjects (61% males, 91.7% white, 31.9 ± 7.6 years) were enrolled and randomized. Thirty three (91.7%) completed all treatments.

When taken under fed conditions, the solution resulted in approximately 80% faster t_{max} [median (range), hr: 0.17 (0.08–4.00) vs. 1.25 (0.33–8.00), p = 0.00015], and a 21% lower C_{max} (mean ± SD, ng/mL: 506 ± 305 v. 835 ± 449, p = 0.00061) compared with the tablets. AUCs were similar between the solution and the tablet formulations.

When taken under fasted conditions, the solution exhibited a 50% faster t_{max} [median (range), hr: 0.25 (0.17–0.67) vs. 0.50 (0.25–4.00), p = 0.00035] to achieve a 77% higher C_{max} (Mean ± SD, ng/mL: 1620 ± 538 vs. 1160 ± 452, p = 0.00032) compared with the tablets. AUCs were similar between the two formulations.

When taken under fed conditions, the solution resulted in a similar t_{max} [median (range), hr: 0.25 (0.17–0.67) vs. 0.17 (0.08–4.00), p = 0.185], but 64% lower C_{max} (Mean ± SD, ng/mL: 1620 ± 538 vs. 506 ± 305, p < 0.00001) compared with fasted conditions. In contrast, diclofenac IR tablets under fed conditions resulted in a more delayed t_{max} [median (range), hr: 0.50 (0.25–4.00) vs. 1.25 (0.33–8.00), p = 0.00143], and ~30% lower C_{max} (Mean ± SD, ng/mL: 1160 ± 452 vs. 835 ± 449, p = 0.00377). AUCs were similar between fasted and fed for both formulations.

The assessment of bioequivalence between the solution and the tablets under either fed or fasted conditions, or between fed and fasted for either formulation, revealed that the geometric mean ratio for C_{max} and its 90% CI were outside the 80.0%–125.0% range, while being within the range for AUCs.

Twelve (33%) subjects experienced ≥1 treatment-emergent AE during the study. All AEs were mild or moderate and none resulted in study discontinuation.

Conclusions

Diclofenac oral solution is not equivalent to diclofenac IR tablets. Fed condition had a greatest formulation-dependent effect on t_{max} and a smaller effect on C_{max} for the solution compared with the tablet, but had no formulation-dependent effect on AUCs. Under fasted condition, the solution formulation provided a more rapid rate of absorption as reflected by a consistently shorter t_{max} to a higher peak concentration compared with the tablet formulation. These data provide an important insight into the effect of food on the pharmacokinetic profiles of diclofenac solution compared with the tablet formulation, which may have clinical implications.

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Compounded preparations in the management of spinal related neuropathic pain: a two year follow up analysis

YUNG CHEN[1], HENRY TRUONG[1]
[1]SAN MATEO SPINE CENTER, SAN MATEO, CA, USA, [2]MARINER ADVANCED PHARMACY CORP, FOSTER CITY, CA, USA

Purpose

To evaluate the role and efficacy of topical compounded preparations in neuropathic pain treatment.

Method

Retrospective chart review at Private Practice Physiatry/Spine Center. Patients' electronic charts who visited the San Mateo Spine Center were retrospectively reviewed.
Inclusion Criteria:
MRI of lumbar or cervical findings
Positive electrodiagnostic findings
Age 18 years and older
Diagnosis of neuropathic pain (ICD code 723.X and 724.X)
Combination of various therapeutic agents such as NSAIDS, local anesthetic, anticonvulsant, NMDA receptor antagonist, anti-spasmodic and/or calcium channel blockers are prescribed in varying strengths

Results

Total number of spine patients with either lumbar sacral radiculopathy, cervical radiculopathy, spinal stenosis, and radiculitis diagnosis was 428.
222 females with an average age of 62
206 males with an average age of 58
Patients were prescribed varying preparations and were instructed to apply 1-2 grams topically to painful area three to four times daily as needed at onset of pain. Patient follow ups were conducted and 92% reported positive responses and 93% of San Mateo Spine Center patients were able to discontinue or taper off oral pain medications, including opioids, NSAIDS, and/or anticonvulsants medications.
Rare side effects were recorded; 0.01% of studied patients reported rash and 0.003% of patients reported dizziness. No other adverse effects were reported.

Conclusions

Topical compounded preparations appear to ameliorate neuropathic pain symptoms. 92% of the patients reported positive responses with the preparations and 93% of our patients were able to decrease their reliance on oral pain medications.
Larger controlled, double blinded, multicenter studies on the effectiveness of the topical pain preparations should be considered. Furthermore, a triad relationship involving trained compounding pharmacist is highly recommended in order to achieve maximal benefit and to ensure safe usage of compounded medications.

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A retrospective chart review of spinal patients treated with methylprednisolone versus prednisone

YUNG CHEN[1], HENRY TRUONG[1]
[1]SAN MATEO SPINE CENTER, SAN MATEO, USA, [2]MARINER ADVANCED PHARMACY CORP, FOSTER CITY, USA

Purpose

Sciatica (lumbosacral radiculopathy) is a common problem seen by spine specialists and is diagnosed in approximately 1% of all patients with acute lower back pain.[1] The mechanical and/or inflammatory events affect one or more lumbosacral nerve roots for which oral methylprednisolone or prednisone are commonly prescribed. Corticosteroid agents are known to reduce tissue damage by stabilizing cell membranes, reducing capillary permeability, and limiting release of proinflammatory substances.[2-3]

The purpose of this study is to determine if oral tapered methylprednisolone regimen is superior to prednisone

Method

In this study, the charts of 424 lower back pain patients who visited a private practice spine center were retrospectively reviewed. Data was collected based on the number of patients who were prescribed methylprednisolone, and prednisone, repeated spinal injection, and the outcome.

Results

Patients suffering from back and leg symptoms subsequent to failed back surgery, lumbar sacral radiculopathy, cervical radiculopathy, spinal stenosis, and/or radiculitis, were seen at San Mateo Spine Center. Patient's charts were retrospectively reviewed. This review included 406 patient electronic charts. A total of 424 patients who were diagnosed with intractable back pain; 218 females and 206 males with an average age of 62 and 64, respectively. Patients were either prescribed methylprednisolone or prednisone. The results showed that 76% of methylprednisolone treated spinal patients reported positive outcomes compare to 58% of prednisone treated spinal patients. In the former group, 68% of patients required additional spinal injection for pain control compares to 76% in the latter group.

Structural changes to corticosteroid molecules (Figure1) bring about changes in specificity and/or potency as a result of changes in affinity and intrinsic activity of corticosteroid receptors, alterations in absorption, protein binding (transcortin), rate of excretion and/or membrane permeability.
Prednisone and methylprednisone are derivatives of hydrocortisone as shown in Figure 1. Methylprednisolone (6α-methyl analog of prednisolone) is equally bioavailable but 2x the glucocorticoid receptor than prednisolone.[3] The metabolic pathway of methylprednisolone also yields 3 active metabolites that potentiate glucocorticoid activity.[3-5] We postulate that these differences may contribute to superiority of methylprednisone in spine patients.

Conclusions

The response to each corticosteroid agent is highly variable. In our experience, most of the patients who switched to methylprednisolone were less likely to require repeated injections. While not all patients with lower back pain require oral corticosteroid as an initial pharmacologic intervention, methylprednisone may be more favorable for back and leg pain with lumbosacral radiculopathy.

The weakness of our review is limited by our method of review due to simple logistic difficulties. The use of a single center is consistent but labor intensive.

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Physical therapy utilization and recovery after lumbar spinal injections for 1600 patients with spine related disorder

YUNG CHEN
SAN MATEO SPINE CENTER, SAN MATEO, CA, USA

Purpose

Physical therapy (PT) has been advocated as an effective treatment for lower back pain secondary to spine disorder, though disagreement exists regarding its benefits, and international guidelines contain conflicting recommendations for manipulation and exercise therapy.1-3 In the cooperative spine care settings, physical therapy and rehabilitation interventions are often overlooked and underutilized, despite high level of functional deficiency experienced at San Mateo Spine Center. As a result, little is known about the value of physical therapy interventions.

The primary goal of this review was to evaluate PT utilization with respect to functional gain of patients with spinal related disorder. Our hypothesis was that proper PT intervention would be associated with decreases in the subsequent rates of lumbar surgery, lumbosacral spinal injections, and oral pain medication needs.

Method

Retrospective chart review of 1600 patient charts (782 female, mean age 66 and 818 male, mean age 62) diagnosed with lumbar sacral radiculopathy, spinal stenosis, and radiculitis who visited San Mateo Spine Center over 24-month period for treatment. A review of functional improvement, repeated spinal injections, and oral medication usage were assessed at the six-month follow up visit.

Results

During the six-month follow up, assessment of functional gain were found in 92% of patients with PT versus 52% without PT. A repeat of spinal injection was given to 68% versus 30% of the patients who used PT and did not use PT, respectively. It was also observed that patients who utilized physical therapy showed a decrease in oral medication; roughly about 60% less. Prospective trials of PT in spine-related patients are needed to better define response rate and predictors of response. This study supports the importance of physical therapy after spinal injections for patients suffering back pain.

Conclusions

PT may play an integral part in a collaborative environment in which referred patients underwent a standardized evaluation by PT to determine their movement dysfunctions and musculoskeletal impairments. A treatment program was then customized including manual therapy techniques (joint and soft tissue mobilizations, passive stretching), modalities (interferential stimulation, cold laser, ultrasound), therapeutic exercises (lumbosacral stabilization and LE strengthening), and home exercises including ergonomics and postural training. PT compliant patients were observed to require less visits, interventions, and/or prescription drugs.

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Single-Dose Pharmacokinetics of 2 or 3 Tablets of Extended-Release Hydrocodone Bitartrate/Acetaminophen (MNK-155) Under Fed and Fasted Conditions

Narayan P. S. Cheruvu, Kenneth Kostenbader, Michael J. Giuliani, Jim L. Young, Krishna Devarakonda
Mallinckrodt Pharmaceuticals, Hazelwood, MO, USA

Purpose

A biphasic extended-release (ER) fixed-dose combination opioid analgesic, ER hydrocodone bitartrate (HB)/acetaminophen (APAP) 7.5/325-mg tablets (MNK-155, Mallinckrodt Pharmaceuticals, Hazelwood, MO), is in development for the management of moderate to severe acute pain. ER HB/APAP tablets are formulated with gastroretentive ER drug delivery technology (Acuform®, Depomed, Inc., Newark, CA) that has been associated with clinically meaningful food effects in other approved products. We report 2 phase 1 studies in healthy adult volunteers evaluating the effect of fed (high- and low-fat meals) versus fasted conditions on single-dose pharmacokinetics (PK) and bioavailability following administration of ER HB/APAP 7.5/325-mg tablets.

Method

These were phase 1, single-center, open-label, randomized, single-dose, 3-period crossover studies in healthy volunteers 18 to 55 years of age. Participants were randomly assigned to 1 of 6 treatment sequences, receiving ER HB/APAP under fed conditions (high- and low-fat meal) and fasted conditions. In study 1, ER HB/APAP was administered as a single 2-tablet dose, and in study 2 it was administered as a single 3-tablet dose. Blood samples were collected for plasma analysis of hydrocodone and APAP. Area under the curve (AUC) from time 0 to the last quantifiable concentration (AUC_{0-t}) and from time 0 extrapolated to infinity (AUC_{0-inf}) and maximum observed plasma concentration (C_{max}) of hydrocodone and APAP were compared across the 3 treatments (high-fat meal, low-fat meal, and fasting) using analysis of variance. A 90% CI of the geometric least squares mean ratio fully contained within 80% to 125% indicated no difference between treatments. Safety and tolerability were also assessed.

Results

In study 1 and 2, 48 and 30 participants, respectively, were enrolled and 40 and 21 completed the study. Plasma hydrocodone and APAP concentrations rose rapidly following administration of a single 2-tablet or 3-tablet dose of ER HB/APAP. In both studies, under fed (high- or low-fat meal) versus fasted conditions, 90% CIs for AUC_{0-t} and AUC_{0-inf} for both hydrocodone and APAP were entirely contained within the bioequivalent range (80%-125% of fasted-state value), indicating that the high- and low-fat meals did not affect the extent of exposure. In addition, in both studies, a high-fat meal did not affect the C_{max} for hydrocodone. A low-fat meal did not affect peak exposure of hydrocodone in study 1, whereas it increased peak exposure by approximately 19% in study 2. With regard to APAP, compared with the fasted condition, a high-fat meal decreased peak exposure by approximately 20% (study 1) and 13% (study 2), and a low-fat meal decreased peak exposure by 22% (study 1) and 21% (study 2). This decrease in peak exposure ~ 20% for APAP is comparable to the reported food effects for other APAP-containing products. The rate of ≥1 treatment-emergent AE (TEAE) was 54.2% in study 1 and 50.0% in study 2, with no notable difference between treatment groups. There were no serious AEs or deaths. The most common TEAEs were nausea (study 1, 25.0%; study 2, 36.7%), vomiting (12.5%; 26.7%), and dizziness (20.8%; 20.0%).

Conclusions

PK and safety findings were overall comparable between treatment groups, demonstrating a minimal food effect, and the safety profile of ER HB/APAP was consistent with expectations for a low-dose opioid treatment. These findings

suggest that ER HB/APAP can be safely and effectively administered under fed (high- or low-fat meals) or fasted conditions when used as directed.

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Comparison of Subjective Drug Effects of Orally Administered MNK-155 Extended-Release Hydrocodone Bitartrate/Acetaminophen Tablets Versus Immediate-Release Hydrocodone Bitartrate/Acetaminophen Tablets in Recreational Users of Prescription Opioids

Narayan P. S. Cheruvu[1], Krishna Devarakonda[1], Kenneth Kostenbader[1], Yanping Zheng[1], Jeannie B. Montgomery[1], Thomas Barrett[1], Jim L. Young[1], Lynn R. Webster[1]
[1]Mallinckrodt Pharmaceuticals, Hazelwood, MO, USA, [2]PRA Health Sciences, Salt Lake City, UT, USA

Purpose

To evaluate the relative abuse liability of single, equal, intact, and crushed doses of extended-release (ER) hydrocodone bitartrate (HB)/acetaminophen (APAP) tablets (MNK-155, Mallinckrodt Pharmaceuticals, Hazelwood, MO), immediate-release (IR) HB/APAP tablets, and placebo by measurement of positive subjective drug effects in nondependent experienced recreational users of prescription opioids. ER HB/APAP is under development for the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate. ER HB/APAP 7.5/325-mg tablets are formulated to provide immediate release of 25% of the HB and 50% of the APAP and extended release of the remainder over a 12-hour dosing interval. Fast onset of effect has been identified as a factor that makes an opioid more attractive for abuse.

Method

This was a single-center, randomized, double-blind, double-dummy, active- and placebo-controlled, 7-way crossover study in healthy nondependent recreational users of prescription opioids 18 to 55 years of age with a body mass index 18 to 33 kg/m^2. During double-blind treatment, participants received each of 7 treatments: intact tablets of ER HB/APAP 22.5/975 mg, IR HB/APAP 22.5/975 mg, ER HB/APAP 45/1950 mg, IR HB/APAP 45/1950 mg; overencapsulated crushed tablets of ER HB/APAP 45/1950 mg, IR HB/APAP 45/1950 mg, and placebo tablets (intact or overencapsulated). There was a 72-hour washout between treatments. Subjective drug effects included drug liking, high, and good drug effects, which were each assessed on a 100-point visual analog scale (VAS) at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 hours postdose.

Results

A total of 52 participants who received all 7 treatments were included in the analysis. Mean VAS scores for drug liking, high, and good drug effects were lower for intact ER HB/APAP 45/1950 mg and crushed ER HB/APAP 45/1950 mg compared with intact IR HB/APAP 45/1950 mg. Median maximum effect (E_{max}) for drug liking, high, and good drug effects was significantly lower for intact ER HB/APAP 45/1950 mg and crushed ER HB/APAP 45/1950 mg versus intact IR HB/APAP 45/1950 mg ($P<0.0001$). Median time to E_{max} for drug liking, high, and good drug effects was significantly longer for intact ER HB/APAP 45/1950 mg versus intact IR HB/APAP 45/1950 mg ($P<0.0001$) and for crushed ER HB/APAP 45/1950 mg versus intact IR HB/APAP 45/1950 mg ($P<0.0001$), indicating a longer period of time to reach E_{max}. For intact ER HB/APAP 45/1950 mg versus intact IR HB/APAP 45/1950 mg, approximately 49% and 28% of subjects had a ≥30% and ≥50% reduction, respectively, in drug-liking E_{max}, 62% and 48% for high E_{max}, and 50% and 38% for good drug effects E_{max}. For crushed ER HB/APAP 45/1950 mg versus intact IR HB/APAP 45/1950 mg, approximately 71% and 46% of subjects had a ≥30% and ≥50% reduction, respectively, in drug-liking E_{max}, 85% and 68% for high E_{max}, and 70% and 58% for good drug effects E_{max}.

Conclusions

In this population of recreational prescription opioid users, single, equal, orally administered doses of ER HB/APAP showed lower positive subjective effects than IR HB/APAP, whether intact or crushed.

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Influence of Pharmacokinetic Differences on Pharmacodynamic Measures of Abuse Liability: Comparison of MNK-155 Extended-Release Hydrocodone Bitartrate/Acetaminophen Tablets and Immediate-Release Hydrocodone Bitartrate/Acetaminophen Tablets in Recreational Users of Prescription Opioids

Narayan P.S. Cheruvu[1], Krishna Devarakonda[1], Kenneth Kostenbader[1], Yanping Zheng[1], Jeannie B. Montgomery[1], Jim L. Young[1], Lynn R. Webster[1]
[1]Mallinckrodt Pharmaceuticals, Hazelwood, MO, USA, [2]PRA Health Sciences, Salt Lake City, UT, USA

Purpose

To correlate pharmacodynamic (PD) and pharmacokinetic (PK) measures associated with abuse liability after administering extended-release (ER) and immediate-release (IR) hydrocodone bitartrate (HB)/acetaminophen (APAP) fixed-dose combination (FDC) analgesics and placebo to healthy adult nondependent recreational users of prescription opioids. Patient-reported PD measures of positive subjective drug effects (eg, visual analog scales [VAS] of drug liking, high, good drug effects) are accepted surrogates of abuse liability; opioid PK parameters of high peak plasma concentration (C_{max}) and/or short time to C_{max} (t_{max}) are associated with high PD measures of abuse liability. Conversely, studies have shown that lower C_{max} and delayed t_{max} are associated with lower positive subjective PD effects. drug liking, drug high, good drug effects, and lower abuse liability. Opioid abusers may crush, chew, or otherwise manipulate ER formulations to release the opioid with a faster t_{max} and higher C_{max} and may manipulate IR or ER formulations to facilitate alternate routes of administration. Human abuse liability studies are an important tool for the United States Food and Drug Administration to assess the relative abuse potential of a new, potentially abuse-deterrent formulations. ER HB/APAP 7.5/325-mg tablets (MNK-155; Mallinckrodt Pharmaceuticals, Hazelwood, MO) are being developed for the management of moderate to moderately severe acute pain and feature biphasic delivery of 25% of the HB and 50% of the APAP from an IR layer for rapid onset of effect and delivery of the remainder from an ER layer for 12-hour dosing.

Method

This single-center, randomized, double-blind, active- and placebo-controlled, 7-way crossover study enrolled healthy adult men and women who were nondependent, experienced recreational users of prescription opioids. Patients received a challenge test to confirm a lack of physical dependence, and a drug discrimination test to confirm their ability to detect subjective effects of hydrocodone. Participants were assigned in an order determined by the randomization scheme to receive each of 7 treatments, consisting of single doses of intact ER and IR HB/APAP 22.5/975 mg, intact ER and IR HB/APAP 45/1950 mg, crushed ER and IR HB/APAP 45/1950 mg, and placebo. Measures of PD (drug liking, high, good drug effects) and PK were assessed predose and up to 24 hours postdose, and correlation coefficients between PK and PD data were calculated. Each treatment was separated by a 72-hour washout period. Blood samples for analysis of individual hydrocodone plasma concentrations were collected predose and up to 24 hours after dosing. Hydrocodone PK parameters (area under the plasma concentration-time curve [AUC], C_{max}, and t_{max}) were analyzed by standard noncompartmental methods using WinNonlin®, version 6.2 or higher, for each study participant. Drug liking, high, and good drug effects were measured on 100-point VAS and summarized as maximum drug effects (E_{max}), time to E_{max} (t_{Emax}), and area under the drug effects curve (AUE). Correlation coefficients between PK and PD outcomes were calculated using SAS®, version 9.1 or higher. Adverse events were recorded.

Results

Of 55 participants randomized to treatment, 52 completed all 7 periods. Intact ER HB/APAP produced lower C_{max} and longer t_{max} for hydrocodone compared with equal doses of IR HB/APAP. The C_{max} was 26.0 ng/mL and 60.5

ng/mL for ER and IR HB/APAP, respectively, at the 22.5-mg dose, and 53.5 ng/mL and 114.3 ng/mL for intact ER and IR HB/APAP at the 45-mg dose. The median t_{max} was 2.6 hours and 1.1 hours for ER and IR HB/APAP, respectively, independent of dose. Crushed ER HB/APAP 45/1950 mg produced a lower C_{max} (58.5 vs 101.1 ng/mL) and longer t_{max} (4.1 vs 1.1 hours) for hydrocodone than crushed IR HB/APAP 45/1950 mg. ER HB/APAP 45/1950 mg produced similar hydrocodone C_{max} levels for the intact (53.5 ng/mL) and crushed (58.5 ng/mL) formulations. However, crushing ER HB/APAP significantly reduced the IR characteristic of the drug; t_{max} was delayed by 1.5 hours, representing a 58% longer over intact ER HB/APAP. In addition, crushed ER HB/APAP produced considerably lower hydrocodone levels (2.6 vs 19.5 ng•h/mL) soon after dosing (eg, AUC_{0-1}) than intact ER HB/APAP 45/1950 mg. Drug liking and drug high were greater for all IR HB/APAP compared with ER formulations. In addition, crushing ER HB/APAP delayed, but did not increase positive subjective effects, and produced lower ratings of drug liking and high than the same dose of IR HB/APAP. Comparisons of PD and PK parameters showed that higher concentrations of hydrocodone (C_{max}, AUC) were more rewarding than lower concentrations and appeared to be dose proportional. Plots of E_{max} versus C_{max} and AUE versus AUC showed strong correlation between the PK and PD parameters.

Conclusions

ER HB/APAP tablets produced lower C_{max}, longer t_{max} and lower positive subjective PD effects compared with IR HB/APAP tablets when orally administered as single equal doses, whether intact or crushed. Counterintuitively, crushing ER HB/APAP tablets caused marked delay of t_{max}, possibly because hydrocodone from the IR layer was captured in the polymeric matrix of the ER layer, diminishing the IR characteristics of the formulation. The study of PK and PD outcomes suggests ER HB/APAP tablets have less abuse liability compared with IR HB/APAP tablets, intact or crushed.

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Trends in abuse and diversion in multiple surveillance systems three years after introduction of reformulated OxyContin

Howard Chilcoat, Paul Coplan
Purdue Pharma, Stamford, CT, USA

Purpose

In August 2010, Purdue Pharma introduced reformulated OxyContin, which was intended to deter abuse through routes that require tampering, such as snorting or injecting. Previous findings showed declines in abuse and diversion across multiple surveillance systems in the first one to two years after reformulation. This study extends these findings to 3 years and beyond. In addition to examining abuse via any route, changes in rates of abuse through oral and non-oral routes were estimated.

Method

Quarterly data from four on-going major surveillance systems were examined: 1) Intentional abuse exposures in the RADARS® System Poison Center (PC) program and 2) National Poison Data System (NPDS); 3) Assessment of individuals in substance abuse treatment through the NAVIPPRO ASI-MV system and 4) reports by law enforcement officials participating in the RADARS System Drug Diversion program. The rates of abuse and diversion for OxyContin and comparator opioids in the 3 years after reformulation (Jan 2011 to Dec 2013) were compared to the average rate in the year prior to reformulation (Jul 2009 to Jun 2010). Rates of abuse and diversion were estimated adjusted by population and number of prescriptions.

Results

Population-adjusted rates of intentional abuse exposures for OxyContin reported in the RADARS PC program and NPDS declined steadily in the three-year post-reformulation period relative to the one-year period prior to reformulation. For each of these systems, rates declined approximately 20% in the first quarter in the post-reformulation period (1Q2011), to more than a 70% decline by the end of the 3-year follow-up (4Q2013). On average, intentional abuse exposures declined 52% and 53%, in RADARS PC and NPDS respectively, in the three years after reformulation compared to the year prior to reformulation. Among opioid abusers assessed in the NAVIPPRO system, rates of abuse of reformulated OxyContin were 48% lower in the post- relative to the pre-reformulation period. OxyContin drug diversion rates declined more than 70% in the third year after compared to the year before reformulation. In all surveillance systems, reductions in rates of abuse were observed for both oral and non-oral routes of administration although the magnitude of decline was larger for abuse through non-oral routes. In general, decreases in measures of abuse and diversion of OxyContin across multiple studies/populations were observed soon after reformulation and the magnitude of these decreases were larger for OxyContin than for comparator opioids.

Conclusions

These findings indicate that declines in abuse and diversion of OxyContin after reformulation have persisted up to three years post-reformulation and declines were larger for routes that required tampering, consistent with the design of the reformulation. Additional follow-up is needed to assess whether these trends continue.

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Detection of buprenorphine, fentanyl, their corresponding metabolites and the designer drug analogue acetyl fentanyl in urine and blood with newly developed enzyme-linked immunosorbent assays

L. Stewart, R. Acheson, J. Darragh, M.E. Benchikh, D. Chung, M.L. Rodriguez, R.I. McConnell, S.P. FitzGerald
Randox Toxicology Limited, Crumlin, UK

Purpose

Purpose. Buprenorphine and fentanyl are opioid analgesics. Buprenorphine, a partial agonist of the μ-opioid receptor, is used for treating pain and opiate addiction. It is a beneficial medication when used as prescribed, it has however abuse liability. Fentanyl is used in medicine as an intravenous anaesthetic/analgesic and in pain management as transdermal patches and lozenges. Buprenorphine is a Schedule III narcotic and fentanyl is Schedule II under the Controlled Substances Act. The two compounds are extensively metabolized in humans and the primary route for both is N-dealkylation to the metabolites norbuprenorphine and norfentanyl respectively. In addition the use of a designer drug analogue, acetyl fentanyl has increased since 2013 with confirmed fatalities and non-fatal overdoses. Immunoassays enabling the detection of all these compounds facilitate the screening of samples in the drug testing process.

The aim of this study was to evaluate the analytical performance of two newly developed enzyme-linked immunosorbent assays (ELISAs) one for the detection of buprenorphine and metabolites and the other for the detection of fentanyl, metabolites and the designer drug analogue acetyl fentanyl in urine and blood. These ELISAs represent useful screening tools for monitoring the use or misuse of these compounds.

Method

Competitive colorimetric immunoassays were employed. The corresponding capture antibodies were immobilised and stabilised on the respective 96-well microtitre plate surface. The analyte, if present in the sample, competes with the horseradish peroxidase labelled conjugate for antibody binding sites on the microtitre plate. Absorbances were read at 450 nm. The signal is inversely proportional to the concentration of drug in the sample.

Results

The buprenorphine ELISA was standardised to buprenorphine and the metabolites norbuprenorphine and norbuprenorphine-3β-D-glucuronide were detected with cross-reactivity of 499% and 139% respectively. The limit of detection values were 0.75 ng/ml (urine) and 0.57 ng/ml (blood). The intra-assay precision (n=12), expressed as mean %CV, was <3.0% for different concentration levels. The percentage recovery from fortified urine and blood samples with a HPLC assigned stock ranged from 111% to 128% (urine) and from 95% to 117% (blood). A collection of blood samples with buprenorphine values assigned by GC/MS were assessed and an agreement of >90% was obtained.

The fentanyl ELISA was standardised to norfentanyl, the parent compound was detected with cross-reactivity of 790% and benzylfentanyl, thienylfentanyl, acetyl fentanyl, ω-hydroxyfentanyl, (+) cis-3-methylfentanyl and α-methylfentanyl were also detected with cross-reactivity ranging from 134% to 20%. Heroin, morphine, 6-monoacetylmorphine elicited negative response at 250 ng/ml. The limit of detection values were 0.51 ng/ml (urine) and 0.67 ng/ml (blood). The intra-assay precision (n=12), expressed as %CV, was <5.0% for different concentration level. Assessment of 20 urine samples and 20 whole blood samples with this ELISA and gas chromatography mass spectrometry (GC/MS) showed 100% agreement (cut-off 1 ng/ml).

Conclusions

The results indicate that with these ELISAs buprenorphine, fentanyl, their corresponding metabolites and the designer drug analogue acetyl fentanyl can be detected in urine and blood. The limits of detection in urine (0.75 ng/ml for buprenorphine and 0.51 ng/ml for fentanyl) were below the minimum performance limit recommended by the Society of Forensic Toxicologists (SOFT) (1 ng/ml buprenorphine and fentanyl). In blood the limits of detection were 0.57 ng/ml and 0.67 ng/ml respectively. These ELISAs are useful screening tools for monitoring the use or misuse of these compounds.

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Oral Abuse Potential Study of a Once-Daily, Single-Entity, Extended-Release Hydrocodone Tablet (Hysingla™ ER) in Recreational Opioid Users

Stephen Harris[1], Salvatore Colucci[1], Allesandra Cipriano[1], Pierre Geoffroy[2], Talar Hopyan[2], Naama Levy-Cooperman[2]
[1]Purdue Pharma L.P., Stamford, CT, USA, [2]INC Research Toronto, Toronto, ONT, Canada

Purpose

A once-daily, single-entity, extended-release hydrocodone bitartrate tablet (HYD; Hysingla™ ER) has been formulated using a proprietary extended-release technology that provides physicochemical attributes intended to impart abuse deterrent properties. The oral abuse potential of chewed HYD and of milled HYD (using an industrial mill) were compared to intact HYD, immediate release (IR) hydrocodone solution, and placebo.

Method

Study design, conduct, analysis and interpretation followed FDA's Jan-2013 draft guidance, *Abuse-Deterrent Opioids - Evaluation and Labelling*. Healthy subjects with a history of recreational opioid use who were not physically dependent on opioids were enrolled. Eligible subjects successfully completed a blinded qualification evaluation confirming that they could tolerate a 60 mg IR hydrocodone dose and could adequately differentiate the effects of hydrocodone from placebo. Subjects (N=40) then received the 5 treatments in a randomized, double-blinded, quadruple-dummy fashion (7-day washout between treatments): intact HYD 60 mg tablet, milled HYD 60 mg tablet, chewed HYD 60 mg tablet, 60 mg hydrocodone IR oral solution, and placebo. Abuse potential was evaluated using subjective pharmacodynamic (PD) assessments. The primary measures were 'at the moment' Drug Liking visual analog scale (VAS) and 'High' VAS. Secondary measures included: Overall Drug Liking VAS, Take Drug Again VAS, Subjective Drug Value, Good and Bad Effects VASs. Pupillometry was included as an objective measure of opioid effects. Plasma samples were collected to characterize hydrocodone and metabolite pharmacokinetics (PK), and safety was assessed.

Results

Primary PD findings for IR solution vs. placebo confirmed study validity. Mean Emax values for positive PD measures were greatest for IR solution, followed in descending order by milled HYD, chewed HYD, intact HYD, and placebo. Statistical analysis of PD measures indicated that chewed HYD had lower abuse potential than IR solution. PK results were generally consistent with the PD findings. Study treatments were well-tolerated.

Conclusions

Overall, the study results support the conclusion that HYD has meaningful abuse-deterrent physicochemical properties.

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Crushing and Extraction Resistance of EG-001, an Abuse-Deterrent ER Morphine in Clinical Development

Edward J. Cone[1], August R. Buchhalter[1], Karsten Lindhardt[2], Torben Elhauge[2], Nikolaj Skak[2]
[1]PinneyAssociates, Bethesda, MD, USA, [2]Egalet Corporation, Wayne, PA, USA

Purpose

Prescription opioid abuse is a major public health problem, with more than 6.8 million Americans abusing prescription opioids on an annual basis. The introduction of abuse-deterrent (AD) opioid analgesic formulations is intended to reduce manipulations (tampering) by abusers and to improve patient safety. There is currently no AD morphine product available on the market. Frequently, the first steps taken by individuals interested in abusing opioids by different routes of administration (eg, oral, rectal, insufflation, and injection) are particle size reduction (crushing to a fine powder), followed by solvent extraction. An extended-release (ER) oral morphine formulation, EG-001 (Egalet Corporation, Wayne, PA), has been developed based on a proprietary AD drug delivery system (Guardian™ Technology), which has physical and chemical barriers intended to deter common methods of abuse. This formulation demonstrates substantial hardness intended to resist crushing and powdering for insufflation. In addition, the tablet forms a gel when hydrated and resists extraction. The purpose of this study was to perform a comprehensive laboratory assessment of physical and chemical challenges with EG-001. The study was designed based on Category 1 procedures presented in the United States Food and Drug Administration's (FDA) 2013 Draft Guidance for Industry Abuse-Deterrent Opioids - Evaluation and Labeling.

Method

Physical manipulation studies were conducted by a third-party laboratory (DrugScan, Horsham, PA). These manipulations included a range of mechanical and electrical household tools frequently used in tampering methods to overcome tablet hardness. EG-001 tablets were tested with and without various heat pre-treatments. MS Contin® (Purdue Pharma, Stamford, CT) was the comparator in all procedures. Each physical manipulation procedure was standardized for a specific tool to achieve optimum particle size reduction. Two endpoints were used in evaluating the results following each manipulation: 1) the use of an equivalent amount of time and effort with EG-001 tablets as required for comparator failure (ie, reduction to a fine, uniform powder) and 2) the use of up to 5× the time and effort employed with the comparator in attempts to overcome the hardness of EG-001 tablets. Resulting powders were characterized for particle size (sieving and imaging), morphine uniformity in different particle size fractions, percentage of weight recovery, and dose recovery.

Extraction studies were conducted with a variety of common household solvents (eg, water, vinegar, and ethanol) and toxic solvents (eg, acetone and methylene chloride). Per FDA Category 1 recommendations, the solvents had relevant characteristics (pH, polarity, and protic and aprotic properties) for extraction. The effects of agitation, heat, and time of extraction on extraction efficiency were evaluated.

Results

Untreated EG-001 tablets were highly resistant to grinding attempts under all conditions that successfully reduced the comparator to a powder and also with 5× the time/effort expended with the comparator. Unsuccessful manipulations involved spoons, a hammer, mortar and pestle, pill crusher, and a foot file. Only minor tablet deformations occurred with these manipulations. Grating and filing produced only a minor (less than 10%) amount of tablet particles that could be insufflated. Grinding with electrical tools (spice grinder and coffee grinder) also resulted in the production of minor amounts of powdered material (ie, less than 5% of particles smaller than 500 µm). Pre-treated EG-001 tablets displayed similar hardness and resistance to cutting, crushing, and grinding as untreated tablets. Because of the

extreme hardness of the tablets, electrical instruments frequently became overheated and were damaged (broken grinder blades and cracked container vessels) during these manipulations. In contrast, the comparator was easily ground to a fine powder with all household tools.

Extraction efficiencies varied with conditions, but were equivalent to or lower than those obtained with the comparator product under identical conditions. Extraction studies encompassed a wide range of solvent types, temperatures, and times. Extraction recoveries were frequently low (eg, <20%) over the first 2 hours. Depending upon conditions, extending the extraction time through 8-24 hours resulted in only slightly enhanced recoveries. These data demonstrated that EG-001 tablets continued to resist extraction for intact, sliced, and powdered tablets under many conditions.

Conclusions

EG-001 tablets displayed extreme resistance to crushing and grinding with all household tools, whereas the comparator was easily converted to a fine powder. Pre-treatment of EG-001 by thermal stressing did not alter its resistance to physical manipulation. EG-001 tablets resisted all extraction attempts and maintained ER characteristics throughout the studies. Although no AD formulation may be expected to prevent all forms of abuse, EG-001 may present significant barriers to physical and chemical manipulations for the purposes of extraction and insufflation of morphine. Based on these data, EG-001 has the potential to fill the need for an AD morphine product.

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Comparison of Abuse Rates of Buprenorphine Patch versus other Extended-release Opioid Analgesics in the National Poison Data System Database

Paul Coplan, Nelson Sessler, Hrishikesh Kale, Jerod Downing
Purdue Pharma L.P., Stamford, CT, USA

Purpose

Butrans®, a once-weekly buprenorphine transdermal system (ie, patch) introduced in 2011, is the only product containing buprenorphine approved for pain treatment in the United States. Buprenorphine is a partial μ-opioid receptor agonist with high receptor affinity and slow receptor dissociation, which provides effective analgesia. Buprenorphine is a Schedule III prescription opioid, a category of drugs that has less potential for abuse than Schedule II, drugs such as the full mu agonists of morphine, oxycodone, and fentanyl, according to the Controlled Substances Act. Opioid analgesics provide analgesic benefits for pain when other options are not effective or inappropriate, but can be intentionally abused; reduction of abuse while preserving analgesic benefits of opioids is an important goal. To date, there are few published data comparing the rate of abuse of the buprenorphine transdermal system to other opioids. The purpose of this study is to compare the rate of abuse of the buprenorphine transdermal system (Butrans) to several other extended-release (ER) opioid products in the United States (US). Calls to poison centers are strongly correlated with poisoning mortality as identified on death certificates for opioids and may be used for timely surveillance of mortality, as well as with emergency room visits recorded in the Drug Abuse and Warning Network (DAWN). Therefore, calls to poison centers reporting abuse of an opioid were used to compare rates of abuse of different opioid types used to treat chronic pain.

Method

The National Poison Data System is a poisoning exposure surveillance database maintained by the American Association of Poison Control Centers that captures 99.8% of poison exposures reported to all poison centers in the US. Calls received at poison centers are managed by healthcare professionals who have received specialized training in toxicology and managing exposure emergencies. Opioid exposures reported to poison centers are classified into reasons, including intentional abuse, unintentional therapeutic errors, unintentional general exposures, and adverse reactions. The extensive network of poison centers reporting into NPDS allows nationally representative coverage. Surveillance data on drug abuse are limited in the US. Poisoning data from NPDS can provide a unique and important proxy measure of opioid abuse, as well as outcomes affecting patients and those accidentally exposed to opioids. The primary outcome for the study was abuse exposures reported to poison centers in 2013, two years after buprenorphine transdermal system became available for use in the US. Opioids evaluated included buprenorphine transdermal system, fentanyl transdermal system, ER oxymorphone, ER oxycodone and methadone. Intentional abuse was defined as an exposure resulting from the intentional, improper, or incorrect use of a substance in order to gain a high, euphoric effect or some other psychotropic effect. The numbers of intentional abuse exposure cases were divided by the number of prescriptions obtained from IMS Health to provide prescription-adjusted rates that account for availability of opioids in the community. Using buprenorphine patch as the reference category, rate ratios, 95% confidence intervals (CI) and p-values were calculated.

Results

In the National Poison Data System during 2013, there were 4 abuse exposures per 506,647 prescriptions for buprenorphine patch, 361 abuse exposures per 6,835,562 fentanyl patch prescriptions, 230 abuse exposures per 6,058,158 OxyContin prescriptions, 96 abuse exposures per 959,557 ER oxymorphone prescriptions, and 982 abuse exposures per 4,016,702 methadone prescriptions. The rate of abuse calls to poison centers per million prescriptions

was 8 for buprenorphine transdermal system, 53 for fentanyl transdermal system, 38 for reformulated OxyContin, 100 for ER oxymorphone, and 244 for methadone. The rate of abuse exposures per 10,000 prescriptions dispensed in the United States was approximately 7-fold lower for buprenorphine patch versus fentanyl patch (rate ratio = 0.15, 95% CI: 0.06- 0.40, p= 0.0002). The abuse rate for buprenorphine patch was 5-fold lower than OxyContin (rate ratio = 0.21, 95% CI: 0.08-0.56, p= 0.0018); 13-fold lower for ER oxymorphone (rate ratio = 0.08, 95% CI: 0.03-0.21, p= <.0001); and 31-fold lower than methadone (rate ratio = 0.03, 95% CI: 0.01-0.09, p= <.0001).

Conclusions

Calls to poison centers involving intentional abuse in 2013 were significantly lower for buprenorphine patch versus fentanyl patch, OxyContin, ER oxymorphone, and methadone, both in absolute number and prescription-adjusted rates. These results suggest that the buprenorphine transdermal system, while still abused, is less abused than other opioid transdermal patches and extended-release opioids approved for the treatment of chronic pain.

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Is the Buprenorphine Patch associated with Lower Overdose rates than other Opioid Analgesics among Pain Patients?

Paul Coplan[1], Nelson Sessler[1], Chuck Wentworth[1], Howard Chilcoat[1], Louis Alexander[1], Jerod Downing[1]
[1]Purdue Pharma L.P., Stamford, CT, USA, [2]Analytic Consulting Solutions, Inc., Wakefield, RI, USA

Purpose

The study objective was to compare opioid overdose rates, particularly at higher dosage strengths and among elderly patients, among patients prescribed the buprenorphine transdermal system (patch) and the two most commonly prescribed extended-release (ER) opioids in the UK: ER morphine tablets and fentanyl patch. This study was conducted in the UK because an electronic medical record database is available, buprenorphine patch use for pain started in 2005 (versus 2011 US start), and buprenorphine patch maximum dosage strength in the UK is 168 mg morphine-equivalent dose {MED} versus 48 MED in US, allowing for the exploration of the impact of higher doses. Reduction of overdoses while preserving analgesic benefits of opioids is an important goal. Buprenorphine is a partial μ-opioid receptor agonist with high receptor affinity and slow receptor dissociation, which provides effective analgesia equipotent to fentanyl. Buprenorphine administered intravenously in animals and healthy human volunteers has a ceiling effect for respiratory depression, which may be associated with lower risk of unintentional overdose than full opioid agonist opioids (eg. morphine, fentanyl) though there are sparse data evaluating this hypothesis. We stratified the comparison of overdose risk for buprenorphine patch and other opioids by single versus multiple concomitant opioid use because risks of opioid overdose can be substantially higher when multiple opioids are used concomitantly. We also stratified by age ≥65 years of age because older patients may be more vulnerable to overdose effects of opioids interacting with polypharmacy from multiple drugs.

Method

This was a retrospective cohort study of patients prescribed select ER opioid analgesics who were treated in general practices participating in THIN, an anonymized patient record database , between January 2003 and August 2012. Incidence rates of unintentional (ie, excluding suicides) overdose events per 100 patient-years of treatment were calculated for patients age 18 or greater prescribed buprenorphine patch, fentanyl patch, or extended-release morphine tablets. Overdose events were ascertained from diagnostic Read codes. Episodes of time on an opioid of interest by "use" were calculated for each patients with overdose incidence stratified into 3 USE categories: single opioid use (only drug of interest prescribed), multiple opioid use concomitantly, and all opioid use combining single and multiple opioid use. The calculated daily dose of opioid of opioid of interest (buprenorphine patch, fentanyl patch, and morphine ER tablets) first required estimation of total days' supply from the prescription quantity (total units) divided by the prescribed number of units/day followed secondly by conversion to morphine equivalents using published conversion factors. Episodes of time on an opioid of interest by MED were calculated for each patient with overdose incidence stratified into four MED categories (1-19, 20-49, 50-99, and ≥100 mg/day). Poisson regression controlling for opioid dosage and potency, age, gender, cancer, mental illness, chronic disease score, and central nervous system drug use was used to calculate adjusted relative risks (aRR) of overdose. The model included daily dose of all opioid tablets, capsules, and transdermal patches calculated similar to that for the opioids of interest.

Results

A total of 102,527 subjects were prescribed an opioid of interest between 2003 and 2012. The unadjusted incidence of unintentional overdose was 0.49% per year of use among 41,703 patients (147 overdoses) prescribed buprenorphine patches, 0.82% among 32,146 patients (198 overdoses) prescribed fentanyl patches, and 1.10% among 43,652 patients (370 overdoses) prescribed ER morphine tablets. The risk of overdose among patients ≥18 years of age was 40% higher among patients prescribed fentanyl patch versus buprenorphine patch (aRR= 1.40,

95% CI: 1.13–1.75) and 70% higher for morphine ER tablets versus buprenorphine patch (aRR= 1.70 (95% CI: 1.40–2.08). In the patient subset ≥65 years of age, the overdose risk was higher for fentanyl patch (RR = 1.52, 95% CI: 1.06–2.18) and ER morphine (RR = 2.35, 95% CI: 1.70-3.24) versus buprenorphine patch. The risk of opioid overdose was higher for multiple opioid use versus single opioid use for ER morphine (0.88% versus 1.45% per year of use) and fentanyl patch (0.67% versus 1.05%), but not for buprenorphine patch (0.50% versus 0.48%). Among patients using multiple opioids concomitantly, overdose risk was substantially higher for ER morphine than buprenorphine patch (aRR = 2.42, 95% CI: 1.75-3.36) and for fentanyl versus buprenorphine (aRR= 1.87 95% CI: 1.30 – 2.70). Patients ≥65 years of age using multiple opioids had nearly 5 times greater overdose risk when prescribed morphine ER versus buprenorphine patch (aRR = 4.95, 95% CI: 2.64–9.28). To assess whether overdose risk differs between the 3 ER opioids at higher daily opioid doses, we used buprenorphine patch at 20-49 MED as the reference category. Buprenorphine patch use at >100mg MED had a similar risk (aRR = 1.22, 95% CI 0.71-2.10) but fentanyl patch use at >100mg MED had a greater overdose risk (aRR= 1.88, 95%CI 1.39-2.53) as did morphine ER (aRR = 2.80, 95%CI 2.10-3.73).

Conclusions

Results from this study indicate that buprenorphine patches are associated with a lower risk of opioid overdose than fentanyl patches or ER morphine tablets, especially among the elderly using multiple opioids concomitantly. In addition, the risk of overdose increased moderately above dosage strengths above 100 mg/day for other opioids but did not increase for buprenorphine. The lower risk of opioid overdose associated with buprenorphine use as compared to other commonly used ER opioids was particularly apparent when multiple opioids were used concomitantly.

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Decrease in Diagnosed Opioid Abuse, Addiction, or Poisoning after OxyContin® with Abuse Deterrent Characteristics was introduced in a Commercially Insured Population

Paul Coplan, Aditi Kadakia
Purdue Pharma L.P., Stamford, CT, USA

Purpose

This study assessed the effect of reformulating OxyContin with abuse-deterrent characteristics on diagnosed opioid abuse, addiction and poisoning/overdose in a commercially insured population. Abuse of prescription opioids is a serious public health problem. However, opioid analgesics are recommended for treatment of serious, persistent pain after non-pharmacologic therapies and non-opioid medications have been used. The US FDA has stated "Encouraging the development of opioids with abuse-deterrent properties is just one component of a broader approach to reducing abuse and misuse, and will better enable the FDA to balance addressing this problem with meeting the needs of the millions of people in this country suffering from pain". OxyContin is an extended-release (ER) oxycodone analgesic that was reformulated in August 2010 with physicochemical barriers to breaking, crushing, or dissolving intended to deter abuse by tampering. Post marketing studies have reported reductions in abuse of reformulated OxyContin among individuals assessed in substance abuse treatment centers, in exposures reported to poison centers, in overdose fatalities reported to the manufacturer, in doctor-shopping, and reductions in OxyContin abuse in a cohort of OxyContin abusers in Kentucky. The objective of the study was to assess changes in rates of diagnosed opioid abuse, addiction or poisoning associated with OxyContin in the year before versus the year after its reformulation, stratified by whether a single opioid or concurrent multiple opioids were used. Changes in rates among patients dispensed OxyContin were compared to three opioid comparator groups to differentiate between secular trends affecting all opioids versus changes specific to OxyContin.

Method

A retrospective cohort study was designed using MarketScan Commercial data. The cohort included patients (≥18 years) who were incident or prevalent users of OxyContin or 3 comparator opioids (IR SE oxycodone, ER oxymorphone, ER morphine); separate cohorts were included for each drug. The study period was divided in three time frames: 1 year before reformulation of OxyContin (August2009- July2010), 3 months of transition period (August2010-October2010) after its reformulation, and 1 year after reformulation (November2010-October2011). Opioid exposure was defined as episodes of continuous duration of drug use using a 15 day allowable gap between subsequent prescriptions. Person time in years was calculated for each episode, summed across all episodes and for all individuals. Person time was further stratified into different cuts based on concomitant drug use during an episode. Person time ended at the occurrence of an event or at the end of an episode; whichever came first. The event of interest was opioid abuse, addiction or poisoning, whichever occurred first, and was defined using ICD9CM codes (304.0x, 304.7x, 305.5x, 965.00, 965.02, 965.09). Patients who were diagnosed with an event were classified into various drug categories based on drugs used in 30-day window prior to the event. Incidence rates per 100 person years were calculated for each drug overall and also for various categories, and were expressed as % of patients per year of use. Changes in rates from 1 year before to 1 year after reformulation were calculated.

Results

Diagnoses for opioid abuse, addiction or poisoning decreased by -12% (95% CI -17% to -7%) for OxyContin from the year before to the year after reformulation, from 8.4% to 7.4% per year of use. Among patients prescribed a single opioid, abuse/addiction/poisoning for OxyContin decreased -29% (95%C I-38% to -18%, p<.0001), from 4.3% to 3.1%. Among patients prescribed multiple opioids including OxyContin, abuse/addiction/poisoning

decreased -10% (95% CI-16% to -5%, p=.0005), from 11.1% to 9.9%. For the 3 opioid comparator groups, abuse/addiction/poisoning increased 3% (95%CI: -2% to 8%, p=0.2079) for IR SE oxycodone, decreased -3% (95% CI -13% to 8%, p=0.5632) for ER oxymorphone, and decreased -5% (95%CI: -11% to 1%, p=0.1218) for ER morphine compared to -12% decrease for OxyContin pre- to post-reformulation. Among patients dispensed a single opioid, abuse/addiction/poisoning increased 15% (95%CI: 5%, 26%, p=0.0024) for IR SE oxycodone, increased 29% (95% CI: -4%, 74%, p=0.0883) for ER oxymorphone, and increased 8% (95%CI: -9% to 28%, p=0. 3743) for ER morphine compared to -29% decrease for OxyContin. The decrease for OxyContin was significantly greater than changes for IR SE oxycodone (<0.001), ER oxymorphone (p=0.003) and ER morphine (p=0.0002). Among patients dispensed multiple opioids, abuse/addiction/poisoning rates increased 3% (95% CI: -2%, 10%, p=0.2599) for IR SE oxycodone, decreased -7% (95% CI: -17%, 5%, p=0.2442) for ER oxymorphone, and decreased -8% (95% CI: -15% to -1%, p=0.0215) for ER morphine compared to -10% decrease for OxyContin. Abuse/addiction/poisoning with single opioid use was 3.1%, 6.2%, 7.1%, and 3.3% for OxyContin, IR SE oxycodone, ER oxymorphone and ER morphine, respectively, per year of use. With multiple concomitant opioid use, abuse/addiction/poisoning was 9.9%, 12.8%, 16.5%, and 9.6% for OxyContin, IR SE oxycodone, ER oxymorphone and ER morphine, respectively. Addiction (dependence), abuse, and poisoning comprised 83%, 4% and 13% of abuse/addiction/poisoning diagnoses.

Conclusions

Abuse/addiction/poisoning rates were 2 to 3 times higher among patients dispensed two or more opioids concurrently versus one opioid. There was a significant decrease in abuse/addiction/poisoning diagnoses for OxyContin from the year before to the year after reformulation, with no significant change for IR SE oxycodone, ER oxymorphone or ER morphine simultaneously. The decrease for OxyContin was greatest among patients dispensed OxyContin only, while abuse/addiction/poisoning increased for the 3 comparators when dispensed alone. These results indicate that the abuse-deterrent characteristics of reformulated OxyContin led to significant decreases in abuse/addiction/poisoning that did not occur with comparator opioids in the same period.

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Using audience response systems to enhance chronic, non-cancer pain knowledge acquisition among veterans

Elizabeth Simmons, David Cosio, Erica Lin
Jesse Brown VA Medical Center, Chicago, IL, USA

Purpose

Educating patients on factual information related to chronic pain and self-management improves knowledge, pain outcomes, and compliance. Without proper pain education, patients may be misinformed or maintain unrealistic expectations regarding their pain prognosis and treatment. In addition, patients who maintain impractical beliefs and attitudes about their pain are less likely to engage in self-management behaviors and more likely to seek more potent medications and risky interventions for pain relief. Therefore, understanding patients' pain knowledge and determining ways to enhance accurate knowledge acquisition has become a focus of chronic pain research.

Many education programs, including health education programs, deliver information via traditional lecture-based classes-a process characterized as passive learning. The Cone of Learning Model emphasizes the usefulness of incorporating more active learning strategies to enhance learning and knowledge retention. Active learning strategies have been associated with increased pupil engagement, improved performance on assessments, and increased motivation.

Past research has utilized different types of technology-assisted education systems in order to promote a more active learning environment and simultaneously obtain additional measurements of change in knowledge. Audience response systems (ARSs) have been shown to improve participant engagement and attention; increase attendance; reinforce key information; become a conduit for communication between pupil and instructor to improve instruction; and improve learning performance and retention of presented material.

The current study assessed changes in pain knowledge among veterans who attended a 12-week "Pain Education School" and examined whether or not the addition of ARSs leads to greater increases in pain knowledge.

Method

A sample of 102 veterans aged 24 to 84 years old who elected to participate in the 12-week "Pain Education School" program was evaluated. The program was developed in November 2009 at a Midwestern VA medical center using the Agency for Healthcare Research and Quality's principles and the VA's National Center for Health Promotion and Disease Prevention's manual. The program consisted of an introduction class followed by 11 weekly one-hour classes that were led by guest speakers from 23 different disciplines within the facility. Providers from each discipline shared information about chronic, non-cancer pain from their perspective, what treatments were available in their service, and how to access their respective clinics. The use of an ARS was employed in the current study to facilitate more active learning among participants (N= 69) at the main VA hospital, but not at the affiliated community outpatient clinics. The technology utilized was TurningPoint® from Turning Technologies, LLC. The ARS software is an interactive application that offers a simple interface for polling in Microsoft® PowerPoint®. Participants' knowledge of concepts was obtained before and after each presentation weekly; thus changes in understanding of information were assessed at numerous time-points. A 2x2 repeated measures analyses of variance was conducted to examine pre- to post-test changes on the Readiness Questionnaire (stage of readiness to adopt a self-management approach), the Pain Information and Beliefs Questionnaire, and the Patient Health Questionnaire-2 (depressive symptoms) and to explore the impact of ARS use on pain knowledge acquisition.

Results

A 2x2 RM MANOVA with "Intervention Condition" (VA hospital vs. affiliated outpatient clinics) as the between-subjects factor and "Time" (pre- vs. post-test scores) as the within-subjects factor was computed. The analyses found a significant multivariate "Condition x Time" interaction, Wilks' $\lambda = 0.89$, $F(4, 90) = 2.81$, $p = 0.03$. Post hoc univariate ANOVA revealed that veterans who used the ARS at the main VA hospital (Mpre = 13.20, Mpost = 13.98) yielded significantly greater increases in knowledge scores than veterans at the affiliated community outpatient clinics (Mpre = 14.10, Mpost = 13.83), $F(1, 93) = 5.29$, $p = 0.02$. In fact, pain knowledge decreased among those who did not have access to the ARS at the affiliated community outpatient clinics, but this difference was not statistically significant ($t(28) = 0.69$, $p = 0.50$). Post hoc univariate ANOVA also revealed that veterans at the affiliated community outpatient clinics (MPre = 2.59, MPost = 3.86) had significantly greater increases in readiness to adopt a self-management approach than veterans at the main VA hospital (MPre = 3.03, MPost = 3.64), $F(1, 93) = 4.90$, $p = 0.03$. No significant differences were found for "Intervention x Time" on pain beliefs, $F(1, 93)= 0.07$, $p= 0.79$), nor depression, $F(1, 93)= 0.67$, $p= 0.42$).
The results of the RM MANOVA also indicated main effects for "Time," Wilks' $\lambda = 0.63$, $F(4, 90) = 13.03$, $p = 0.00$. Post hoc univariate tests revealed significant main effects for "Time" on pain beliefs, $F(1, 93)= 4.50$, $p= 0.04$; stage of readiness to adopt a self-management approach, $F(1, 93)= 38.68$, $p= 0.00$; and depressive symptoms, $F(1, 93)= 14.06$, $p= 0.00$. No significant main effect was found for "Time" on pain knowledge, $F(1, 93)= 1.23$, $p= 0.27$).

Conclusions

The current study yielded additional data supporting the effectiveness of VA pain education programming in increasing readiness to adopt a self-management approach, improving pain beliefs, and decreasing depression scores among veterans. Furthermore, the study highlighted the benefits of incorporating innovative technology to improve knowledge acquisition among veterans. The use of an ARS allowed for an active learning approach to pain education. Additionally, this technology helped presenters become aware of and subsequently clarify any misinformation regarding chronic pain and its self-management at the completion of each class. Other key variables that impact knowledge outcomes should be further evaluated.

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Using Patient Pain Education to Increase Complementary & Alternative Treatment Utilization in Veterans with Chronic, Non-Cancer Pain

David Cosio, Erica Lin
Jesse Brown VA Medical Center, Chicago, IL, USA

Purpose

Due to the dramatic rise in opioid prescriptions and overdose deaths among pain populations, the pendulum of care appears to be swinging back towards the side of caution when prescribing opioids. Veterans have voiced their dissatisfaction with prescription medications through their pursuit of CAM modalities. Their perception tends to be that the current U.S. medical care system is lacking in "holism." The goal of chronic pain management should be to integrate mainstream and CAM therapies for which there is some high quality scientific evidence.
Past research has shown that veterans are active consumers of CAM. Past findings have indicated that chiropractic care was the least preferred, while massage therapy was the most favored among veterans with chronic, non-cancer pain. The 2002 Healthcare Analysis and Information Group Study on VA CAM Utilization indicated that 84% of facilities provided some form of CAM. The most common modalities offered included acupuncture, biofeedback, chiropractic care, hypnosis, music therapy, and relaxation techniques. Most CAM modalities were provided by conventionally trained practitioners and were typically integrated into treatment plans.
Past studies have shown that more than 75% of veterans who are non-users of CAM would utilize these treatment options if available at the VA. This finding suggests that veterans are not fully aware of the CAM options available to them. The current study tested the hypothesis that veterans would report an increase in CAM utilization after completing a formal pain education program in a VA medical center.

Method

A sample of 243 veterans enrolled in the "Pain Education School" program at a Midwestern VA Medical Center program between November 4, 2011-October 26, 2012. The "Pain Education School" was developed in November 2009 at a Midwestern VA medical center using the Agency for Healthcare Research and Quality's principles and the VA's National Center for Health Promotion and Disease Prevention's manual. Each veteran in this sample completed an introduction class and was subsequently scheduled for eleven weeks of one-hour classes led by guest speakers from 23 different disciplines within the facility. The topics included information about 13 different CAM modalities offered at the VA. Nearly half (42%; N=103) of the sample who completed the pre-education assessment also elected to complete the post-education assessment, and their responses were included in the current study. The assessment included questions adapted from the Complementary and Alternative Medicine Questionnaire©, SECTION A: Use of Alternative Health Care Providers (California Health Interview Survey, 2003). The 13 modalities inquired included ACT/mindfulness, acupuncture, aromatherapy, biofeedback/relaxation, chiropractor, healing (therapeutic) touch, hypnosis, massage therapy, movement (yoga, Tai Chi), music/art therapy, osteopathic manipulation, spirituality/religion, and traditional healer (such as a "Curandero" or Native American "Medicine Man").

Results

At baseline, the five most used CAM modalities among this sample of veterans with chronic, non-cancer pain were the chiropractor (31%), massage therapy (28%), spirituality/religion (18%), biofeedback/ relaxation (16%), and acupuncture (14%). The five least utilized CAM therapies were hypnosis (3%), aromatherapy (3%), healing (therapeutic) touch (5%), ACT/mindfulness (6%), and traditional healers (8%). Female veterans were more likely to seek biofeedback/relaxation, music/art, aromatherapy, and acupuncture than their male counterparts. Past research has shown that women are more likely than men to use any form of health care, a tendency reflected when

considering CAM. Caucasian veterans were more likely to utilize aromatherapy and a chiropractor then veterans from minority groups. Veterans who identified as Hispanic were more likely to seek hypnosis then their non-Hispanic counterparts. Veterans who live in rural areas (nonmetropolitan areas of the US that are communities of 50,000 residents or fewer) were more likely to seek chiropractor services then veterans who live in urban populations. Current findings also suggested that there were differences in majority racial groups in different areas (Caucasians more in rural and African Americans more in urban areas). This pattern of racial distribution across areas is consistent with demographic data from the U.S. Census. The evidence concerning race/ethnicity and CAM use is complex and general trends are difficult to ascertain. However, research seems to suggest that people from racial/ethnic minorities tend to use CAM less than their Caucasian counterparts. Paired-samples t-tests were conducted to evaluate the impact of the program on veterans' utilization of CAM after completing a pain education program. There was a significant difference between the pre-test (M=1.65, SD=2.22) and post-test (M=2.64, SD=2.54) measures of use of alternative health care providers of CAM; t (102)=4.190, p=.000.

Conclusions

Veterans with chronic, non-cancer pain tend to be active consumers of CAM. They prefer chiropractic care above all other modalities currently offered in the VA system. Veterans also tend to use the power of prayer/spirituality which explains how it has been the #1 CAM modality used in the US. It is not surprising to find that the least utilized modalities identified were the ones that tend to have controversies surrounding them. The current study has found that veterans with chronic, non-cancer pain will increase their utilization of CAM if additional education is provided about their availability.

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Lubiprostone Therapy Increases Spontaneous Bowel Movement Frequency in Patients with Opioid-Induced Constipation Patients Regardless of Gender, Age, or Race: Pooled Analysis of Three Well Controlled 12-Week Studies

Byron Cryer[1], Shadreck Mareya[2], Taryn Losch-Beridon[2], Gayle Dolecek[2]
[1]University of Texas Southwestern Medical School, Dallas, TX, USA, [2]Sucampo Pharma Americas, LLC, Bethesda, MD, USA

Purpose

The goal of this study was to assess the influence of gender, age, and race on the overall frequency of spontaneous bowel movements (SBMs) in response to 12 weeks of therapy with oral lubiprostone (24 mcg BID) in patients with chronic non-cancer pain and opioid-induced constipation (OIC).

Method

Three multicenter, randomized, placebo-controlled, double-blind trials, assessed the efficacy of lubiprostone therapy in treating OIC (i.e., <3 SBMs/wk) in adult patients using opioids to treat chronic non-cancer pain. Patients were randomized to receive lubiprostone 24 mcg (n=659) or placebo (n=641) BID for 12 weeks. Pooled data from these trials was examined to assess change from baseline (CFB) in SBM frequency across the entire treatment period for the overall pooled population and for subgroups defined by gender, age, and race.

Results

The study population had a mean age of 50.5 years (range: 20-89). Most patients were women (62.5%), and 82.1% were white. Twelve weeks of lubiprostone therapy increased SBM frequency to a significantly greater extent than placebo in the overall population (CFB 2.8 vs 2.2 SBMs/wk, respectively; $P<0.001$). Similar statistically significant improvements in SBM frequency with lubiprostone treatment were also seen in subgroup analyses of men and women ($P\leq0.004$ for both populations). Statistical significance was not achieved in the subgroup of elderly patients (≥65 years), likely due to the small size of this population (n=110). However, the absolute treatment difference between the lubiprostone and placebo arms in the elderly group was identical to that in the non-elderly population (+0.6 SBM/wk treatment advantage for lubiprostone vs placebo in both age subsets; $P<0.001$ for non-elderly). For the same endpoint, the treatment difference between lubiprostone therapy and placebo was greater in non-white patients (3.2 vs 2.5 SBMs/wk; n=224) than in white patients overall (2.7 vs 2.2 SBMs/wk), though statistical significance was achieved only in the white population (n=1027; $P<0.001$).

Conclusions

Lubiprostone (12-week treatment) consistently increased SBM frequency more than placebo regardless of patient gender, age, or race. Lubiprostone achieved statistical separation from placebo overall, and for subgroups of men, women, white patients, and adult patients (age <65 years). Non-white patients and elderly patients (≥65 years) showed equivalent or better response to lubiprostone therapy than white and non-elderly patients, although these differences did not reach statistical significance due to limited patient numbers in these groups. This research was funded by Sucampo Pharma Americas, LLC, Bethesda, MD, and Takeda Pharmaceuticals International, Inc., Deerfield, IL.

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Safety and effectiveness of higher vs. lower doses of single-entity hydrocodone extended-release

Sharon M. Weinstein[1], Carol Curtiss[2], Cynthia Y. Robinson[3], Bradley S. Galer[3], Errol Gould[3], Arnold Gammaitoni[3]
[1]University of Utah Huntsman Cancer Institute, Salt Lake City, UT, USA, [2]Tufts University School of Medicine, Boston, MA, USA, [3]Zogenix, Inc., Emeryville, CA, USA

Purpose

The use of higher doses of opioids in patients with severe chronic pain conditions has recently raised potential safety concerns. Current guidelines on the use of opioids to treat chronic pain suggest that the use of higher doses requires caution because of the potential for higher incidence of adverse events and an increased risk of accidental overdose. The purpose of this study was to compare the effectiveness and safety of single-entity hydrocodone extended-release (HC-ER) titrated to doses ≥100 mg/d vs <100 mg/d for the treatment of chronic pain in opioid-experienced patients.

Method

Subjects with a diagnosis of moderate-to-severe chronic painful conditions who were currently treated with an opioid were enrolled in this multicenter, 12-month, open-label safety study. Eligible subjects were converted to HC-ER (dosed every 12 hours [q12h]) at a daily dose 20%-30% less than the equivalent dose determined from the Opioid Conversion Table. During the 6-week conversion/titration (C/T) period, the dose was titrated in increments of 20 mg/d (ie, 10 mg q12h) every 3-7 days until a stable dose was established. Subjects demonstrating a stable dose during the C/T phase continued in a 48-week treatment period during which further dose adjustments (up or down) were allowed to achieve an optimal balance of effectiveness and tolerability. Subjects were categorized by their most commonly used dose during the treatment period. Brief Pain Inventory (BPI) and Hospital Anxiety and Depression Scale (HADS) scores were taken at screening, the end of the C/T period, and at 12 study visits during the treatment period. Adverse events (AEs) were assessed continuously during the study. No statistical analysis was performed for this posthoc study.

Results

A total of 638 subjects enrolled in the study, and 424 (66%) achieved clinically meaningful control of pain with a stable dose during the C/T period and continued in the treatment period. The patients entering the treatment period had a mean age of 51 years, 44% were male, 80% were White, and 18% were Black or African-American. The principal chronic painful conditions were low back pain (46.7%) and osteoarthritis (22.9%). Other conditions were noted by 32.8% of patients. During the treatment period, 317 subjects received higher doses (≥100 mg/d) and 107 received lower doses (<100 mg/d) to control their pain. Reductions in BPI "average pain" score from screening to the end of the C/T period were similar in both dose groups (5.85±1.75 [mean±SD] to 3.43±1.49 and 6.22±1.57 to 3.36±1.29 for the <100 mg/d and ≥100 mg/d dose groups, respectively) and were maintained through the end of the study. Both subgroups demonstrated comparable improvements in BPI pain interference and HADS scores throughout the treatment period. The overall incidence of opioid-related AEs was similar in both dose groups. The incidence of treatment-related severe and serious AEs were greater in the higher dose (2.8%, 0.6%) than in the lower dose group (0.9%, 0%). The incidence of common treatment-emergent opioid-related AEs was similar in both groups (nausea, 11.2% and 9.5% in the <100 mg/d and ≥100 mg/d groups, respectively; constipation, 10.3% and 13.2%; vomiting, 7.5% and 10.4%; diarrhea, 3.7% and 4.1%; somnolence, 6.5% and 3.5%). Four patients in the higher dose group died during the study, but none of the deaths were considered to be related to the study drug.

Conclusions

The effectiveness and safety profiles of the higher and lower dose subgroups of HC-ER were comparable. This study demonstrates that with careful titration and monitoring, subjects with moderate-to-severe chronic pain can achieve clinically meaningful pain relief with generally good tolerability whether on higher or lower doses.

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Impact of a Nurse Pain Champion Program on Surgical Inpatient Units

Sarah Derman, Brenda Poulton
Fraserhealth, Surrey BC, Canada

Purpose

The purpose of this study was to examine the effect an intensive pain management nursing mentorship program would have on 1) the nurses involved in the program; 2) nurse colleagues who were not a part of the program; 3) pain documentation; and 4) patient experiences. In a collaborative effort between PainBC and Fraser Health, 17 registered nurses from surgical inpatient units at 4 hospitals participated in a 1 year intensive mentorship education project. PainBC is a nonprofit society working toward reducing the burden pain through engagement, education and advocacy. Fraser Health is one of the largest and fastest growing health authorities in Canada; providing healthcare to 1.6 million people through 12 acute care hospitals, residential, community and public health services.

The Intensive nursing mentorship model of care has been shown to beneficially impact pain management including increasing the knowledge and skill of the nurses who were mentored (McMillan, Tittle, Hagan, & Small, 2005), improving awareness and increasing practice of patient centered care (Holley, McMillan, Hagan, Palacios, & Rosenberg, 2005), reduced staff turnover amongst those involved in the program, improving patient satisfaction with pain control, decreasing the prevalence of pain, (Grant, Ferrell, Hanson, Sun, & Uman, 2011; Paice, Barnard, Creamer, & Omerod, 2006) and improving pain documentation (Binhas, et al., 2011).

However little has been published regarding the impact of such a program on patient satisfaction/ patient reported pain; and the perception on pain management from colleague nurses (i.e. nurses not participating in the program).

Method

This was a small pilot pre-test post-test study with multiple data sources, examining the impact of a Nurse Pain Champion program on surgical inpatient units. A year long mentorship program with 17 registered nurses, from the surgical inpatient units at 4 hospitals in Fraser Health was implemented in 2013/2014. Through 4 sources of data collection: 1) Pain Champion nurse knowledge and skill pretest and posttest, 2) non Pain Champion nurse survey, 3) patient satisfaction survey and 4) chart audit we examined the changes that occur as a result of this program.

Data was collected at three time points, pre, mid and post implementation of the mentorship program

Tools:

The "Knowledge and Attitudes Survey Regarding Pain" developed by Betty Ferrell, & Margo Mcaffery in 1987 and revised in 2012 was utilized for assessing the Pain Champion nurses pre and posttest.

To assess the perspectives of the non-Pain Champion nurses, we used "the Strategic and Clinical Quality Indicators in Post-Operative Care," a validated and reliable tool developed by Idvall, Hamrin, Sjostrom & Unosson, (2001).

Post-operative Patient Charts (Day 1 to Day 3 post surgery) were audited for: frequency pain scores were documented, frequency of pain scores at 5/10 or greater; and frequency of pain reassessment after pain medication was provided.

Patient perspective was obtained using a Patient Post-operative Pain Management Survey that was adapted from the Revised American Pain Society Patient Outcome Questionnaire (Gordon et al., 2010).

Results

17 nurses began the project, but unfortunately due to illness, maternity leaves, and job changes only 12 nurses completed the full project. Of the 12 nurses who completed the project 100% scored the same or improved on the Knowledge and Attitudes Survey, with 92% (11 nurses) improving. All feedback from the pain champion themselves indicated a high level of satisfaction with the project.

Data Collection:

Knowledge and attitudes survey of pain champion nurses: 17 pretest surveys and 12 posttest surveys.

Strategic Clinical Quality Indicators of Post op care of non-pain champion nurses: 90 pretest surveys and 77 posttest surveys.

Chart Audit: 55 charts pre project, 55 charts mid project and 55 charts post project.

Patient survey: 61 surveys pre project and 50 surveys post project.

Data analysis is currently underway, and preliminary descriptive statistics will be presented in poster format at Painweek2014.

Conclusions

Pain management is a complex multidimensional experience that is unique to each patient, and can be highly influenced by health professionals' beliefs, attitudes and knowledge; practice changes are particularly challenging requiring more than purely education. Through an in depth frontline nursing mentorship model, hoping to have influenced a culture change, we examined how the nurses themselves, their colleagues, their patients and pain documentation was affected.

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Exploring Hemodialysis Patients' Understanding and Beliefs about Their Chronic Pain: Preliminary Findings

Alexandra Kruthaup-Harper, Sarah Derman, Sony Sekhon, Savita Korpal, Marianne Mamaed
Fraserhealth, Surrey, BC, Canada

Purpose

A team of frontline hemodialysis nurses with a keen interest in chronic pain participated in a Point of Care Research Challenge. The purpose of the Point of Care Research Challenge was to support first-time researchers at the point of care (providing direct care) in developing a research proposal, applying for a grant, and conducting a small local research project that was relevant to nursing care at Fraser Health. Fraser Health is one of the largest and fastest growing health authorities in Canada; providing healthcare to 1.6 million people through 12 acute care hospitals, residential, community and public health services.

Problem Statement

Identifying and understanding patients' pain beliefs had not been explored in the context of End Stage Renal Disease (ESRD) or specifically for those patients receiving Hemodialysis treatment. Exclusion of renal patient involvement in many studies may in part be due to this population's complex healthcare needs and multiple co-morbidities.

Research question

What are hemodialysis patients' beliefs and understanding of their chronic pain?

Method

The study used a qualitative descriptive design with semi-structured interviews and qualitative content analysis. Qualitative description aims to capture participants in their natural state, describing an experience or event in everyday terms using their language with no pre-selection or manipulation of variables (Sandelowski, 2000). It is an effective approach in health care research with the findings providing a good basis for concept clarification, instrument development and an entry point for further study (Sandelowski, 2000; Neergaard, et al., 2009)

Convenience and purposive sampling strategies were used to recruit participants with chronic pain, end stage renal disease and receiving regular hemodialysis. Each participant was interviewed for 1 to 1.5 hours with semi-structured interviews focussed on pain beliefs and understandings.

The data were analyzed using qualitative content analysis. The researchers remained close to the data, minimizing their interpretation of it though a small amount is inevitable. The risk of interpretation was managed by the use of reflexive journaling. As data was collected, it was concurrently analyzed, enabling the researchers to continuously adapt their treatment of the data to permit new data and new insights to immerge. Comparing patient responses enabled the researchers to search for conflicting evidence, negative cases, and find contradictions that were then clarified with other participant interviews. Data from interviews, observations and notes were coded to identify similar phrases, patterns, and themes that were compared and contrasted. The outcome was a descriptive summary of the participants' viewpoint organized in a way that best fit the data (Sandelowski, 2000).

Results

Seven participants (3 women and 4 men) receiving long term hemodialysis treatments were recruited from an in-centre hemodialysis unit located in a tertiary hospital. They ranged in age from 67-93 yrs old and were receiving hemodialysis for 1.4 - 8.5 yrs

The study participants' stories and experiences of living with chronic pain included: 1) multiple pain management strategies trialed over the years; 2) their understanding of the types and sources of pain they have; 3) the medications they take with the accompanying side effects and; 4) their verbalized or implied pain beliefs. Three central themes that emerged and can be categorized as three belief statements: 1) The pain is unfixable; 2) I am so complex and pain is just one part of it and 3) No one wants to hear about pain.

The first theme was the hopeless, unchangeable state of their chronic pain; the belief that the pain was "unfixable". Subconcepts of this belief include: desperation; constancy and chronicity of the pain; and failure. However there was also a sense of hope and desire for a cure, with language usage that indicated a belief that a cure is something to hold onto but not expect.

The second theme was an understanding that pain management was hindered by co-morbidities and further confounded by dialysis treatment. One participant described this as, *"having so many [health problems] compounding on each other."* He further describes this as "*I'm very complicated or you know my problems are very complicated but they're all banging into each other, you know."*

The third theme was a lack of attention given to the subject of chronic pain, by healthcare professionals. The participants expressed the belief that healthcare professionals did not want to hear about chronic pain experiences.

Conclusions

The preliminary findings from this study demonstrate how 7 participants living with chronic pain, ESRD and receiving HD treatment have learned to endure the multiple challenges and complexities of their current health. Their stories indicate a resignation to the notion of there being no cure and only possible temporary relief. These experiences reflect a great deal of stoicism in which they have learned to endure. A silent suffering they purposefully hide from others, rather wearing a mask of stoic determination. These preliminary findings provide a beginning look into complex medical patients understanding of their chronic pain.

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Population Pharmacokinetics of Oxycodone and Acetaminophen Following a Single Oral Dose of Extended-Release Oxycodone/Acetaminophen Tablets

Ryan Franke, Terri Morton, Krishna Devarakonda
Mallinckrodt Pharmaceuticals, Hazelwood, MO, USA

Purpose

To evaluate the single-dose population pharmacokinetics (PK) and the effects of a meal on the single-dose PK of extended-release oxycodone/acetaminophen tablets (ER OC/APAP; XARTEMIS™ XR, Mallinckrodt Brand Pharmaceuticals, Inc., Hazelwood, MO), a fixed-dose combination (FDC) analgesic approved for the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate. ER OC/APAP employs biphasic immediate-release for acute pain and ER delivery for infrequent dosing. Clinically, population PK is important in determining whether dose adjustments are necessary based on patient-specific factors such as body weight, age, sex, and race.

Method

This was a pooled analysis of data from 4 randomized, single-dose crossover trials enrolling healthy participants or nondependent recreational opioid users aged 18 to 55 years with a body mass index (BMI) of 19 to <30 kg/m^2 and a body weight ≥60 kg. In studies 1 through 3, healthy adults or healthy adult nondependent, recreational opioid users received single doses of 1, 2, or 4 intact ER OC/APAP 7.5/325-mg tablets (total doses: 7.5 mg/325 mg, 15/650 mg, and 30/1300 mg, respectively). In study 4, healthy adults received 2 ER OC/APAP 7.5/325-mg tablets (total dose 15 mg/650 mg) after a high-fat meal (1000±100 calories), a low-fat meal (800±80 calories), or under fasted conditions. Doses administered under fasted conditions in study 4 were pooled with data from studies 1 through 3 for the assessment of population PK, which examined the effects of 6 variables (sex, race, age, weight, height, and BMI). In each study, participants were scheduled to receive each treatment separated by a 6- to 7-day washout period. Blood samples were collected for up to 48 hours after dosing. OC and APAP concentrations were measured by using high-performance liquid chromatography with tandem mass spectrometry. Single-dose population PK was analyzed using first-order conditional estimation methods. Food effects were analyzed using first-order conditional estimation with interaction methods. Adverse events were recorded.

Results

A total of 128 participants completed all assigned treatments and were included in the analysis; 31 participants from study 4 completed all assigned treatments and were included in the analysis of food effects. Under fasted conditions, average estimates for OC were 92.4 L/h for total clearance (CL), 772 L for volume of distribution (V), and 1.15 h^{-1} for absorption rate constant (Ka). Body weight and race were statistically significant sources of variability in the CL and V of OC. There was a positive correlation between body weight and OC PK parameters, such that every 10% change in body weight was accompanied by approximately a 7.5% change in both CL and V. Black participants had 17.3% lower CL and 16.9% lower V compared with white participants. Body weight was the only factor associated with significant variability in APAP CL and V. For every 10% change in weight from the median value of 73.5 kg, a 7.5% change occurred in CL and V. In the food analysis, the Ka of OC and APAP decreased by 39% and 20%, respectively, with the low-fat, low-calorie meal and by 48% and 18% with the high-fat, high-calorie meal.

Conclusions

Body weight and race were associated with statistically significant changes in the single-dose PK of ER OC/APAP. Because ER OC/APAP tablets are available only in a 7.5/325-mg unit dosage and are recommended for administration as a 2-tablet dose, it is only possible to raise or lower the dose by a 50% increment. Thus in clinical practice, dose adjustment may be necessary for extremely underweight or overweight patients but not for race. Food also had a significant effect on Ka, but overall exposure to OC and APAP was not changed. Therefore, ER OC/APAP may be administered without regard to food intake.

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Population Pharmacokinetics of Oxycodone and Acetaminophen Following Multiple Oral Doses of Extended-Release Oxycodone/Acetaminophen Tablets

Terri Morton, Ryan Franke, Krishna Devarakonda
Mallinckrodt Pharmaceuticals, Hazelwood, MO, USA

Purpose

To determine population pharmacokinetics (PK) of oxycodone (OC) and acetaminophen (APAP) in healthy adult volunteers administered extended-release oxycodone/acetaminophen (ER OC/APAP; XARTEMIS™ XR, Mallinckrodt Brand Pharmaceuticals, Inc., Hazelwood, MO). ER OC/APAP 7.5/325-mg tablets have a novel biphasic delivery system providing immediate release of 25% of the OC and 50% of the APAP and ER of the remainder over a 12-hour dosing interval, and are approved for the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate. It is important for prescribers to know whether the novel ER OC/APAP formulation leads to unexpected clinically relevant variability in PK based on population characteristics such as sex, race, age, body weight, height, and body mass index (BMI).

Method

This post hoc analysis pooled data from 2 phase 1 single-center, open-label, randomized, multiple-dose studies (with 3- or 4-period crossover design). Participants aged 18 to 55 years had a BMI of 19 to <30 kg/m^2 and a minimum body weight of 130 pounds. Exclusion criteria included electrocardiogram abnormalities (eg, atrioventricular and bundle branch blocks, QT_c prolongations); pulse oximetry readings <95% in the awake state; use of nicotine-containing products within the previous 6 months; and a history of drug or alcohol abuse, psychiatric disorders, gastrointestinal disease, seizures, or malignancy. Participants received 2 tablets of ER OC/APAP 7.5/325 mg (total dose, 15/650 mg) administered orally under fasted conditions every 12 hours for 4.5 days (9 doses). Plasma samples were obtained before dosing and at multiple time points for up to 7 days. The levels of OC and APAP in plasma were measured using high-performance liquid chromatography with tandem mass spectrometry detection. An exponential error model was used to describe interindividual variability, whereas a proportional error model was used for residual variability. The influence of 6 covariates (sex, race, age, body weight, height, and BMI) on total body clearance (CL), volume of distribution (V), and absorption rate constant (Ka) was examined. The primary population for all PK analyses was completers, defined as participants who completed all periods of the study. Adverse events were recorded.

Results

Fifty-seven of 96 (59.4%) enrolled participants completed all periods of the study; the majority of the completers were men (65%) and white (67%). Representation of races other than black and white was inadequate for comparisons. Age comparisons were limited by the study inclusion criteria of ages 18 to 55 years, and the study exclusion criteria limited the range of body weight and BMI comparisons. Using first-order conditional estimation with interaction methods, the PK of OC was best described by a 1-compartment model. In the final model, the average estimates of CL, V, and Ka for OC were 75 L/h, 756 L, and 0.581 h^{-1}, respectively. Body weight was a significant source of variability in V for OC at steady state. Similar to OC, the PK of APAP was also best described by a 1-compartment model. The Ka was fixed at a value (5.51 h^{-1}) observed in the base model. In the final model, the average estimates of CL and V for APAP were 25 L/h and 119 L, respectively. Sex was identified as a significant source of variability in CL and V, with predicted APAP CL values of 25 L/h in men and 21 L/h in women. Body weight had an effect on the variability in V, with predicted V values of 193 L/h in men and 174 L/h in women for a 72-kg participant under steady-state conditions.

Conclusions

At steady state, body weight was a significant source of variability in V for both OC and APAP, and women had lower APAP CL and V compared with men. Because ER OC/APAP tablets are available only in a 7.5/325-mg unit dosage and recommended for administration as a 2-tablet dose, it is only possible to raise or lower the dose by a 50% increment. Thus, in clinical practice, dose adjustment may be necessary for extremely underweight or overweight patients, but not for men versus women.

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Single- and Multiple-Dose Pharmacokinetics of Extended-Release Hydrocodone Bitartrate/Acetaminophen (MNK-155) Compared With Immediate-Release Hydrocodone Bitartrate/Ibuprofen and Immediate-Release Tramadol HCl/Acetaminophen

Krishna Devarakonda, Narayan P. S. Cheruvu, Kenneth Kostenbader, Michael J. Giuliani, Jim L. Young
Mallinckrodt Pharmaceuticals, Hazelwood, MO, USA

Purpose

To evaluate the single- and multiple-dose pharmacokinetics (PK) and bioavailability of 3 fixed-dose combination (FDC) analgesics: extended-release (ER) hydrocodone bitartrate (HB)/acetaminophen (APAP) 7.5/325-mg tablets (MNK-155; Mallinckrodt Pharmaceuticals, Hazelwood, MO), immediate-release (IR) tramadol HCl/APAP 37.5/325-mg tablets, and IR HB/ibuprofen 7.5/200-mg tablets. ER HB/APAP is being developed for the management of moderate to severe acute pain for which nonopioid analgesics are inadequate. ER HB/APAP has a biphasic formulation with an IR layer delivering 25% of the HB and 50% of the APAP for rapid pain relief and an ER layer delivering the remainder of the HB/APAP over a 12-hour dosing period.

Method

This was a phase 1, open-label, randomized, 4-period crossover study with a single-dose phase and a multiple-dose phase. Healthy men and nonpregnant, nonlactating women aged 18 to 55 years, weighing ≥130 lb (men) or ≥110 lb (women), with a body mass index 19 to 30 kg/m^2 enrolled with written informed consent. For the single-dose phase, participants (n=30) received each of 4 treatments in cross-over fashion: ER HB/APAP 7.5/325 mg 2 tablets administered at hour 0 (initial dose), ER HB/APAP 7.5/325 mg 3 tablets administered at hour 0, IR HB/ibuprofen 7.5/200 mg 1 tablet administered at hour 0 and hour 6, and IR tramadol HCl/APAP 37.5/325 mg 1 tablet administered at hour 0 and hour 6. For the multiple-dose phase, participants (n=29) received each of 4 treatments in cross-over fashion: 2 ER HB/APAP 7.5/325-mg tablets every 12 hours (q12h; total of 8 doses); ER HB/APAP 7.5/325 mg, 3 tablets administered at 0 hours followed by ER HB/APAP 7.5/325 mg, 2 tablets q12h (total of 8 doses); IR HB/ibuprofen 7.5/200 mg, 1 tablet every 6 hours (q6h; total of 16 doses), and IR tramadol HCl/APAP 37.5/325 mg, 1 tablet q6h (total of 16 doses). Plasma samples were taken for up to 156 hours after the initial dose to assess hydrocodone and APAP PK parameters (eg, half-life [$t_{½}$], peak plasma drug concentration [C_{max}], time to C_{max} [t_{max}], area under the concentration versus time curve from time 0 to infinity [$AUC_{0\text{-}inf}$]). Adverse events were recorded.

Results

Single-dose hydrocodone PK for ER HB/APAP demonstrated a longer mean $t_{½}$ (7.32 hours, 2 tablets; 7.08 hours, 3 tablets) and shorter median t_{max} (3.00 hours, both doses) compared with IR HB/ibuprofen (5.74 hours, 8.00 hours, respectively); however, t_{max} for IR HB/ibuprofen followed the tablet administered at hour 6. Hydrocodone mean C_{max} for IR HB/ibuprofen (25.46 ng/mL) approximated that for 3 tablets of ER HB/APAP (26.34 ng/mL), and the mean dose normalized AUC values were comparable to IR HB/ibuprofen. For single-dose APAP, mean $t_{½}$ was longer for ER HB/APAP (7.93 hours, 2 tablets; 8.26 hours, 3 tablets) compared to IR HB/APAP (5.74 hours), and median t_{max} for ER HB/APAP was similar (0.63 hours, 2 tablets; 0.50 hours, 3 tablets) compared with the values for IR tramadol HCl/APAP (0.53 hours). In addition, for APAP the dose normalized mean C_{max} and AUC for IR tramadol HCl/APAP (5145 ng/mL) were similar to that for 3 tablets of ER HB/APAP (5719 ng/mL), but mean $AUC_{0\text{-}inf}$ for IR tramadol HCl/APAP similar to both 2 and 3 tablets of ER HB/APAP (5719 ng/mL). Steady-state hydrocodone PK was reached by day 2 for ER HB/APAP and IR HB/ibuprofen. Steady-state hydrocodone exposure ($AUC_{0\text{-}12h}$, average plasma drug concentration, peak plasma drug concentration) for IR HB/ibuprofen and ER HB/APAP (with and without a loading dose) was similar. Steady-state APAP PK was achieved in 1 day for ER HB/APAP (no loading dose) and in 2 days for

IR tramadol/APAP and for ER HB/APAP with a loading dose. Steady-state APAP exposure ($AUC_{0\text{-}12h}$, average plasma drug concentration, peak plasma drug concentration) for IR tramadol/APAP and ER HB/APAP was similar. Adverse events were typical of FDC opioid analgesics.

Conclusions

Consistent with its biphasic design, ER HB/APAP had a longer $t_{1/2}$ than either IR formulation. At steady state, peak and total HB and APAP exposure after administration of ER HB/APAP was similar to that of the IR comparators.

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Single- and Multiple-Dose Pharmacokinetics of Extended-Release Hydrocodone Bitartrate/Acetaminophen (MNK-155) Compared With Immediate-Release Hydrocodone Bitartrate/Acetaminophen

Krishna Devarakonda, Narayan P. S. Cheruvu, Jim L. Young
Mallinckrodt Pharmaceuticals, Hazelwood, MO, United States Minor Outlying Islands

Purpose

Extended-release (ER) hydrocodone (HB)/acetaminophen (APAP) 7.5/325-mg tablets (MNK-155, Mallinckrodt Pharmaceuticals, Hazelwood, MO) are being developed for management of moderate to severe acute pain for which nonopioid analgesics are inadequate. ER HB/APAP is a biphasic release formulation, with an immediate-release (IR) layer delivering 25% of the HB and 50% of the APAP for rapid pain relief and an ER layer delivering the remainder of the HB/APAP over a 12-hour dosing period. This abstract presents data from 2 phase 1 clinical trials evaluating the single-dose and steady-state pharmacokinetics (PK) of the hydrocodone and APAP components of ER HB/APAP and IR HB/APAP 7.5/325-mg tablets in healthy adult participants (18-55 years).

Method

Study 1 was a single-center, open-label, randomized, 3-period crossover study of single-dose and steady-state PK under fasted conditions. In the single-dose portion of the study, participants were administered 1 or 2 tablets of ER HB/APAP or 1 tablet of IR HB/APAP. In the multiple-dose portion of the study, participants were administered ER HB/APAP given as 1 and 2 tablets every 12 hours (q12h) and IR HB/APAP administered as 1 tablet every 6 hours (q6h) for 4.5 days. Study 2 was a single-center, open-label, randomized, 2-period crossover study of steady-state PK following administration of ER HB/APAP given as 2 tablets q12h for 4.5 days with a loading dose of 3 tablets compared with IR HB/APAP administered as 1 tablet q6h for 4.5 days under fasted conditions. Blood samples were obtained for PK assessments, which were compared between treatments using analysis of variance; a 90% CI of the geometric least squares (LS) mean ratio fully contained within 80% to 125% indicates no difference between treatments. AEs were assessed throughout both studies.

Results

In study 1, 48 participants enrolled and 44 (91.7%) completed the study; in study 2, 26 participants enrolled and 19 (73.1%) completed the study. In study 1, the 90% CIs of the LS mean ratios for hydrocodone and APAP exposure (area under the curve [AUC] from time 0 to time t [AUC_{0-t}], AUC from time 0 extrapolated to infinity [AUC_{0-inf}], and steady-state AUC from time 0 to 12 hours postdose [AUC_{0-12h}^{ss}]) and for APAP maximum observed plasma concentration (C_{max} and steady-state C_{max} [C_{max}^{ss}]) were entirely contained within the bioequivalent range (80%-125%), indicating no difference between treatments. Hydrocodone C_{max} and C_{max}^{ss} were comparable for both ER HB/APAP treatments; C_{max}^{ss} values for ER HB/APAP and IR HB/APAP were also equivalent, whereas the single-dose C_{max} for ER HB/APAP was 26% (1 tablet) and 28% (2 tablets) lower compared with IR HB/APAP. In study 2, the 90% CI for the LS mean ratio for the total exposure and the average steady state concentration of hydrocodone and APAP PK parameters was within the bioequivalent range. Rates of ≥1 treatment-emergent AE (TEAE) in the overall patient population were 68.8% in study 1 and 57.7% in study 2. There were no severe or serious TEAEs in either study. The most common TEAEs in patients treated with ER HB/APAP were headache, nausea, and dizziness (study 1) and nausea, dizziness, and vomiting (study 2).

Conclusions

In 2 clinical studies, total exposure as estimated by the AUC of hydrocodone and APAP was equivalent for ER HB/APAP and IR HB/APAP. TEAEs were comparable across treatment groups and typical of low-dose opioid treatment.

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Predictors of long-term immediate-release hydrocodone/acetaminophen use among a commercially insured population

Angela DeVeaugh-Geiss, Paul Coplan, Aditi Kadakia
Purdue Pharma LP, Stamford, CT, USA

Purpose

Most patients are prescribed immediate-release (IR) hydrocodone/acetaminophen for short-term treatment (<14 days), however, evidence suggests that some patients receive long-term, higher dose hydrocodone/acetaminophen treatment. For example, among opioid treatment patients in Group Health Cooperative and Kaiser Permanente (Northern California) IR hydrocodone combination products were the most commonly prescribed opioids across acute, episodic, and long-term episodes. Furthermore, an FDA drug utilization review found that one-tenth of all patients prescribed hydrocodone/acetaminophen (approximately 1.6 million out of 16 million) received >109 days of treatment. Our prior research suggests that though the proportion of patients continuing long-term IR hydrocodone/APAP patients is low (<1%), the number of patients receiving long-term hydrocodone/APAP is at least 3 times the number on long-term extended-release (ER) morphine. The number on long-term therapy increased further when longer allowable gaps in therapy were utilized to identify long-term users, likely reflecting the identification of another patient sub-type - those treated with intermittent long-term hydrocodone/acetaminophen. Given the risks associated with acetaminophen use, particularly long-term and/or high-dose, it is important to understand patterns of prescription hydrocodone/acetaminophen use, including predictors of long-term use.

Method

Using a national commercial insurance database (MarketScan; January 2008 through September 2013), patients ≥18 years old with a new IR hydrocodone/acetaminophen prescription and 12 months insurance enrollment (6 months before and 6 months after index prescription) were identified. Existing users were excluded to include a baseline period for identification of diagnoses and to standardize the follow-up period after the first (index) prescription for calculation of continuous use. The primary objective of the study was to identify predictors of long-term IR hydrocodone/acetaminophen use. Long-term use was defined as >90 days of continuous therapy. Continuous therapy was defined as no gaps in supply ≥15 days; once the patient exceeded this allowable gap, their period of continuous use ended. Because the pharmacy claims do not include an indication, pain diagnoses were temporally linked to prescriptions by identifying pain diagnoses that occurred in the one month prior to or following the first prescription. Baseline indicators (including non-pain diagnoses) were defined as events in the claims records (eg, prescriptions dispensed, medical claims filed) in the 6 months preceding the first prescription. Predictors included in the logistic regression model included patient demographics (age, sex) and clinical characteristics (cancer, pain, depression and substance abuse diagnoses; initial IR hydrocodone/acetaminophen dose; prior use of other IR opioids; prior use of ER/long-acting opioids; other psychotropic or pain medication). Depression was identified based on diagnostic codes and antidepressant prescriptions. All drugs and diagnoses were modeled as presence of the condition/prescription vs. no diagnostic codes/prescriptions; categories were not mutually exclusive.

Results

In the MarketScan Commercial database covering 100 million insured individuals, there were 7.7 million patients initiating IR hydrocodone/acetaminophen. The median and mean daily hydrocodone dose at the first IR hydrocodone/acetaminophen prescription (index) were 33 mg/d and 42.3mg/d, respectively, and 15% received >4g of acetaminophen at the first prescription. Though only a small percentage of IR hydrocodone/acetaminophen users continued use for more than 90 days (0.76%), the number of patients meeting this criterion was large (n=58,445).

Patients who continued on long-term IR hydrocodone/acetaminophen were less likely to have index acetaminophen doses exceeding 4g than those who used for <90 days (4.4% vs. 15.0%, respectively). In the final regression model, the characteristics most strongly predicting long-term IR hydrocodone/acetaminophen use were: prior use of long-term IR opioids (vs. short-term IR use; OR=3.17, 95%CI 3.07, 3.29), any prior use of ER/LA opioids (vs. none; 1.63, 95%CI 1.56, 1.71), back/neck pain (vs. no back/neck pain; 2.59, 95%CI 2.54, 2.63), fibromyalgia (vs. no fibromyalgia; 1.55, 95%CI 1.49, 1.62), osteoarthritis (vs. no osteoarthritis; 1.80, 95%CI 1.75,1.85), rheumatoid arthritis (vs. no rheumatoid arthritis; 1.93, 95%CI 1.82, 2.05), baseline substance abuse disorders (vs. no substance abuse disorder; 2.00, 95%CI 1.90, 2.11), baseline chronic obstructive pulmonary disease (vs. no COPD; 1.96, 95%CI 1.88, 2.05), and baseline gabapentin prescriptions (vs. no gabapentin prescriptions; 1.52, 95%CI 1.47, 1.58). Other factors significantly associated with long-term IR hydrocodone/acetaminophen use included: gender (male), lower hydrocodone doses at index, neuropathic pain, baseline depression, baseline cardiovascular disease, and baseline medication prescriptions (atypical antipsychotics, sedative/hypnotics, muscle relaxants, pregabalin). There was no significant association between long-term IR hydrocodone/acetaminophen use and prior use of NSAIDs. Patients with doses of acetaminophen >4g at baseline, no prior IR opioid exposure, and patients with dental pain, fracture, or abdominal pain were significantly less likely to continue hydrocodone/acetaminophen long-term.

Conclusions

Though only a small proportion of IR hydrocodone/acetaminophen users continued treatment >90 days, the number of patients was large (n=58,445). Characteristics most strongly predicting long-term IR hydrocodone/acetaminophen use included: prior long-term use of other IR opioids (vs. <90 days of IR opioid use in the baseline period), a back/neck pain diagnosis, baseline substance abuse disorders, and baseline COPD. Understanding characteristics predictive of long-term IR hydrocodone/acetaminophen use could help to inform treatment decisions, including initiation of new opioid therapy or switching from one opioid to another (ie, opioid rotation), particularly for patients who are at greater risk of acetaminophen-related toxicity.

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Routes of administration and frequency of abuse of OxyContin® and immediate-release oxycodone in a rural Kentucky county following introduction of reformulated OxyContin

Angela DeVeaugh-Geiss[1], Jennifer Havens[2], Carl Leukefeld[2], Hrishikesh Kale[1], Paul Coplan[1], Howard Chilcoat[1]
[1]Purdue Pharma LP, Stamford, CT, USA, [2]University of Kentucky, Lexington, KY, USA

Purpose

Prescription opioid abuse is a significant public health problem in the United States. One strategy to reduce the impact of prescription opioid abuse is the development of formulations that are more difficult to manipulate for purposes of abuse, particularly through routes that require tampering including intranasal and intravenous routes. OxyContin (oxycodone HCl controlled-release) was reformulated to render it more difficult to manipulate for purposes of intentional abuse. In August 2010, shipments of original OxyContin stopped and reformulated OxyContin started; in 2013, the FDA approved revisions to the prescribing information based on evidence from the abuse-deterrence and liking studies. There is emerging evidence on the impact of such formulations in national surveillance systems; however, these surveillance systems utilize cross sectional national averages and do not provide detailed measures of abuse or individual changes in abuse patterns. Additional post-marketing studies have also been conducted, including a cohort study of individuals who had abused original OxyContin in rural Kentucky. In this cohort, there was less abuse of reformulated OxyContin as compared to concurrent reports of immediate-release (IR) oxycodone and retrospective reports of abuse of original OxyContin in August 2010 (prior to the introduction of the reformulation). At 6-month follow-up interviews, the prevalence and frequency of reformulated OxyContin abuse remained low. The current study describes results of a second follow-up interview, conducted in the sample of OxyContin abusers originally recruited and assessed in 2010-2011.

Method

Structured follow-up interviews were conducted approximately 2.5 years after the initial post-reformulation interview (August 2013-April 2014) (n=138, 73% of original sample) in a cohort of individuals who abused original OxyContin prior to August 2010 in rural Kentucky. The interviews assessed opioid abuse, including past 30-day routes of administration (ROA) and frequency of abuse (days per month among those reporting abuse), as well as preferred opioid before and after the reformulation. Individuals were originally interviewed 4-13 months after the introduction of the reformulation between December 2010-September 2011 (n=189) and in the first follow-up interview approximately 6-months after the initial post-reformulation interview (August 2011-April 2012) (n=164, 85% of original sample).

Results

Of the original 189 individuals recruited and assessed in 2010-2011, 138 completed the second follow-up interviews conducted between August 2013 and May 2014 (73%). Most participants (78%) selected original OxyContin as their preferred opioid prior to the reformulation, though none selected reformulated OxyContin as their current preferred drug. The most common preferred drugs at the second follow-up interview were: IR oxycodone (43%) Suboxone®/Subutex® (32%) methadone (11%). Only two individuals (1.4%) reported abuse of reformulated OxyContin - one reported abuse via swallowing whole (2 days/month) and one reported abuse via chewing (4 days/month). Additionally, one individual reported abuse of original OxyContin via injecting (2.0 days/month); this individual also reported injecting IR oxycodone (30 days/month). Overall, there was a decline in the prevalence of IR oxycodone abuse (51%) compared to the initial post-reformulation and the 6-month follow-up interviews (85% and 96%, respectively), though frequency of IR oxycodone abuse remained high among those reporting abuse (mean days/month: 22.2, 95% CI 19.5, 24.9). The prevalence of abuse of any opioids declined from over 90% to 78% at

the second follow-up interview, though frequency of abuse of any opioids also remained high among those who abused (mean days/month: 26.8, 95%CI 25.4, 28.1). There was an increase in the number and proportion of participants reporting medical use of methadone or buprenorphine - 15 participants reported their major source of buprenorphine was a clinic or treatment facility (2 reported buprenorphine was prescribed for pain) and 11 reported their major source of methadone was through a treatment facility Few respondents (4%) reported attempting to manipulate reformulated OxyContin for purposes of abuse and 14% reported that they had friends, family, or dealers who had attempted to manipulate reformulated OxyContin for purposes of abuse.

Conclusions

While original OxyContin was retrospectively reported to be the preferred drug for the majority of individuals before introduction of reformulated OxyContin, none reported preferring reformulated OxyContin at the follow-up interviews, and only 2 individual reported abuse of reformulated OxyContin in the past 30-days. The low prevalence and frequency of reformulated OxyContin abuse suggest that the reformulation has deterred OxyContin abuse in this community more than 2 years after the first post-reformulation interviews (and ~3 years after the introduction of the reformulation).

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Multiplexing LC-MS/MS Forensic Methods for High-Throughput Urine Screening to detect Buprenorphine and Ethanol Use

Joseph Di Bussolo[2], Kristine Van Natta[1], Marta Kozak[1]
[1]Thermo Fisher Scientific, San Jose, CA, USA, [2]Thermo Fisher Scientific, Franklin, MA, USA

Purpose

Many forensic laboratories need to analyze many urine specimens to screen for buprenorphine as well as ethanol use. The sample load for one forensic screening method may be similar to or greater than the other. This LC-MS/MS forensic method to measure buprenorphine/norbuprenorphine (Bup/Norbup) in urine, which has a total run time of 4 minutes and a data window of 1.5 minutes, can be multiplexed on a 4-channel LC system to achieve a maximum throughput of 39 injections per hour. There may be less demand to run a forensic method to measure ethyl glucuronide and ethyl sulfate (EtG/EtS), which also has a total run time of 4 minutes and a data window of 1.5 minutes. Since both methods share common MS source parameters, the EtG/EtS batch can run on one channel of system to fit 13 injections per hour while 26 injections from a larger Bup/Norbup batch can be done on two other channels. Using the 4th channel would not increase the total hourly throughput (e.g., 19 Bup/Norbup + 19 EtG/EtS injections) but would ensure that nearly all specimens would get analyzed even if one channel stops because it exceeds maximum pressure. We will present data that prove equivalence between channels and demonstrate the accuracy, repeatability, robustness and ruggedness of these forensic methods when multiplexed.

Method

A four-channel UHPLC system interfaced to a tandem mass spectrometer was used to multiplex two LC-MS/MS methods that utilized reversed-phase chromatography eluting into a heated electro-spray ionization source. One method measured buprenorphine and norbuprenorphine (Bup/Norbup) in hydrolyzed urine specimens and the other measured ethyl glucuronide
and ethyl sulfate (EtG/EtS) in diluted urine specimens. Each method had a data window of 1.5 minutes within a total run time of 4 minutes.

Results

Either method multiplexed across all four channels had a throughput of 39 injections per hour. Multiplexing one method across two channels and the other across the remaining two channels allowed an hourly throughput of 19 Bup/Norbup and 19 EtG/EtS injections per hour. To satisfy different throughput demands for the two methods, it was most efficient to multiplex the larger
Bup/Norbup batch across two channels to achieve 26 injections per hour while using one other channel to run a smaller batch of EtG/EtS to achieve 13 injections per hour. Injections of quality control samples demonstrated an accuracy within 10% of verified values across all channels for either method and coefficients of variation of less than 3% for chromatographic peak retention times and less than 20% for peak area counts.

Conclusions

We demonstrated equivalence between channels of a four-channel UHPLC system to justify multiplexing Bup/Norbup and EtG/EtS methods to achieve maximum sample throughputs as demands for each change. Since the data window in both methods was more than 1/4th of the
total run time, only three channels were needed to maximum total throughput. However, using the 4th channel

ensured productivity as nearly all specimens would be analyzed even if one channel stopped because it exceeded maximum pressure.

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Abuse-resistant, Extended-release Morphine is Resistant to Physical Manipulation Techniques Commonly Used by Opioid Abusers

Ray DiFalco[1], Eric R. Kinzler[2], Carmela Pantaleon[2], Stefan Aigner[2]
[1]Cerovene, Valley Cottage, New York, USA, [2]Inspirion Delivery Technologies, LLC, Valley Cottage, New York, USA

Purpose

The misuse and abuse of prescription opioids is a major public health problem in the United States. Nonmedical use usually begins with oral administration of intact tablets; however, as recreational opioid abusers become more experienced with misuse, they commonly manipulate (crush) extended-release (ER) formulations to circumvent their ER characteristics, induce "dose dumping," and increase the opioid's bioavailability. Nonmedical users then self-administer the manipulated high-dose tablets via the oral, intranasal, or intravenous routes to induce a rapid euphoric high. Abuse-deterrent formulations of ER opioids that incorporate barriers to physical manipulation may, therefore, deter abuse via any route that first requires crushing or grinding. An investigational formulation of ER morphine using abuse-resistant, extended-release (ARER) technology has been developed to increase the hurdles required for physical manipulation; retain the formulation's ER characteristics, even if the product is manipulated; and form a non-syringeable viscous material if the tablet is manipulated and prepared for intravenous administration. As a first step toward obtaining regulatory approval, the "FDA Draft Guidance on Abuse-Deterrent Opioids-Evaluation and Labeling" recommends that rigorous laboratory-based in vitro testing on the ability to physically crush, cut, grate, or grind the product using readily available household tools be performed first, as the results of these experiments influence the design of further in vitro and in vivo human abuse liability studies. Here, the physical abuse-deterrent properties of Morphine ARER were characterized with tools readily available to abusers to manipulate prescription opioids.

Method

The ability to physically manipulate (crush) Morphine ARER 100-mg tablets (Inspirion Delivery Technologies, LLC) and controlled-release morphine sulfate 100 mg (CR-morphine) was assessed by using a variety of common household instruments that included: a hammer, spoon, knife, grater, mortar and pestle, pill crusher, and a coffee grinder. Manipulations were repeated 5 times for each instrument with a maximum manipulation time of 5 minutes. Difficulty in manipulation of each tablet was recorded using a 10-point rating scale where 1 = "very easy" and 10 = "impossible" to manipulate, and an average difficulty score was calculated. Because opioid abusers commonly heat or cool currently available formulations to facilitate dose dumping, physical manipulation of Morphine ARER with each instrument was also performed after tablets were placed in a microwave oven for 1 minute, a standard kitchen freezer for 30 minutes, and a conventional oven for 30 minutes. Particle size of manipulated Morphine ARER tablets was assessed with a mechanical tray sieve using a descending order of screen mesh filter sizes from 2000 µm to 425 µm to 150 µm to determine which method produces the smallest, homogenous particle size distribution to use in downstream studies.

Results

CR-morphine tablets were easily manipulated with all tested household instruments requiring minimal effort (mean difficulty = 1) and time (mean time 5 to 43 seconds). Each household tool easily produced a fine, homogenous particulate weighing approximately 150 mg when CR-morphine tablets were crushed. In contrast Morphine ARER tablets could not be easily manipulated (mean difficulty = 7.4 to 10; mean time 49 seconds to 5 minutes) with all but 1 of the household instruments tested. Only when Morphine ARER tablets were manipulated with a coffee grinder was a relatively small, homogenous particle size distribution produced, with the resulting crushed material weighing more

than 600 mg. Greater than 50% of the crushed material from Morphine ARER tablets that were manipulated using a mortar and pestle (53%), hammer (70%), knife (76%), grater (77%), pill crusher (98%), or spoon (100%) was retained on the large 2000-µm or 425-µm–sized filters. Pretreatment of Morphine ARER tablets in the microwave, freezer, or oven did not alter particle size distribution.

Conclusions

In contrast to CR-morphine tablets, Morphine ARER tablets are hard, making them resistant to physical manipulation; pretreatment did not substantially alter particle size with any tool, and only the coffee grinder produced small, homogenous particles. The large volume of material produced when a Morphine ARER tablet is crushed may itself be a deterrent to abuse. Taken together, these data suggest that the abuse-deterrent properties of Morphine ARER provide marked impediments for adulteration into homogenous, small particles and may, therefore, deter abuse via routes of administration that first require crushing of the tablet into a powder.

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Patient Characteristics and Prescription Opioid Utilization Among Chronic Pain Patients Treated with Tapentadol ER or Oxycodone CR

Jacqueline Pesa[1], Rachel Halpern[2], Jessica Lopatto[1], Mike Durkin[1], Stephanie Korrer[2], Damon Van Voorhis[2]
[1]Janssen Scientific Affairs, LLC, Titusville, NJ, USA, [2]Optum, Eden Prairie, MN, USA

Purpose

Chronic pain affects approximately 100 million persons in the United States; direct and indirect expenditures associated with chronic pain are estimated to be $560 to $635 billion per year (Institute of Medicine, 2011). Included in the direct expenditures are costs associated with utilization of prescription opioid therapy, which plays a prominent role in the treatment of chronic pain. The purpose of this study was to describe observed characteristics of chronic pain patients who initiated therapy with tapentadol extended release (TAP-ER) or oxycodone controlled release (OXY-CR) and to compare daily average consumption (DACON) and use of short-acting opioids (SAOs) between matched cohorts of TAP-ER and OXY-CR chronic pain patients.

Method

Retrospective pharmacy and medical claims data from a large US health plan were analyzed for adult patients with ≥1 Rx for OXY-CR or TAP-ER between 9/1/2011 and 9/30/2012. Patients had 6 months of continuous enrollment before and after the date of first observed claim for the index product (index date), no pre-index claims for the index product, and ≥ 90 days supply of any opioid(s) in the study period to focus on chronic pain patients. Patients in the TAP-ER and OXY-CR cohorts were propensity score matched in a 1:2 ratio (TAP-ER: OXY-CR) with unconditional logistic regression controlling for demographics, insurance type, and pre-index pain medications, healthcare costs, and clinical conditions. Match quality was assessed by comparing attributes between pre-match cohorts and between post-match cohorts with chi-square tests for categorical variables and student t-tests for continuous variables, and by visual inspection of propensity histograms. Index product DACON (quantity dispensed/days supply) was measured for the matched cohorts over the first 30 days post-index and from day 31 to day 180, then stratified by continuous use (≥25 days supply of index product [day 1-30], ≥125 days supply [day 31-180], no claims for the opposite index product) or non-continuous use. Patients with ≥2 post-index SAO fills were identified. The difference in SAO use between the matched cohorts was tested with Rao-Scott chi-square; the difference in mean DACON between the subsets of the matched cohorts categorized as continuous or non-continuous users was tested with a student t-test. No adjustment was made for multiplicity.

Results

In the pre-index period, age, gender, geographic region, insurance type, Charlson comorbidity index score, prevalence of pain conditions, healthcare costs, and opioid use differed ($P<0.001$) between the unmatched OXY-CR (N=11,511) and TAP-ER (N=1,148) cohorts. The pre-match OXY-CR cohort was older, more likely to be male, had a higher mean Charlson score and higher mean healthcare costs, and was more likely to have pre-index cancer or musculoskeletal pain other than back or neck pain; the pre-match TAP-ER cohort was more likely to have pre-index back, neck, and neuropathic pain and pre-index short-acting opioid and benzodiazepine use (all $P<0.05$). The matched cohorts of 1,120 TAP-ER and 2,240 OXY-CR patients appeared well matched by both statistical tests (no covariate P-values <0.05) and visual evaluation of propensity score histograms. In the 6 months post-index, the OXY-CR and TAP-ER cohorts displayed significantly different DACON patterns. For continuous users, the mean DACON over the first 30 days was 2.38 in the OXY-CR cohort (n=560) and 2.13 in the TAP-ER cohort (n=224) ($P<0.001$). The mean DACON for continuous users during the last 150 days post-index was 2.35 and 2.02 for those subsets of the OXY-CR and TAP-ER cohorts, respectively ($P<0.001$). Among non-continuous index product users, TAP-ER was

also observed to have lower mean DACON in both time periods (both P<0.001). In addition, 90.6% of OXY-CR patients had ≥2 post-index SAO fills compared with 81.0% of TAP-ER patients (P<0.001).

Conclusions

The characteristics of chronic pain patients treated with TAP-ER differed significantly from those among patients treated with OXY-CR; TAP-ER patients were younger on average, more likely to be female, more likely to have back, neck, and neuropathic pain, and more likely to have used opioids before initiating the index product. When those differences were removed through propensity score matching, TAP-ER patients had lower mean DACON and were less likely to use an SAO after initiating therapy compared with their matched OXY-CR counterparts.

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What do we know about the withdrawal of, dependence on and addiction to Tapentadol compared to Morphine and Oxycodone- At five years post approval?

Gary Eichenbaum[1], Hany Rofael[2], Jeffrey Gudin[3], Mila Etropolski[4], Thomas Tzschentke[5], Ilona Steigerwald[5], Ute Richarz[6], Gary Vorsanger[1]
[1]Janssen Research and Development, Raritan, NJ, USA, [2]Janssen Scientific Affairs, Titusville NJ, USA, [3]Englewood Hospital and Medical Center, Englewood, NJ, USA, [4]Janssen Research and Development, Titusville, NJ, USA, [5]Grunenthal, Aachen, Germany, [6]Janssen Global Services, Zug, Switzerland

Purpose

Withdrawal avoidance (negative reinforcement), pleasure-seeking and finding (positive reinforcement) and "wanting" (incentive sensitization) are key contributors leading to dependence, addictive behaviors and abuse[1,2]. Pharmacological differences in the extent of mu opioid receptor (MOR) agonism and mu opioid induced changes in noradrenergic and dopaminergic activity may result in differences between opioids with respect to negative reinforcement, positive reinforcement, "wanting" and addictive behaviors. Tapentadol is a newer analgesic for the treatment of moderate to severe pain that has lower potency at the MOR compared to Schedule II mu opioids like oxycodone and morphine. In addition, unlike oxycodone and morphine, tapentadol directly inhibits the norepinephrine reuptake transporter. Therefore, it is of interest to compare the extent of withdrawal, behaviors in non-clinical models of abuse, and actual rates of abuse of tapentadol to that of standard MOR agonists such as oxycodone and morphine. The purpose of this poster is to present non-clinical and clinical data evaluating the physical and psychological dependence potential of tapentadol compared to that of morphine or oxycodone, as well as to present post-marketing data evaluating abuse, misuse and diversion patterns for tapentadol since its launch in 2009 compared to those of other Schedule II opioids. We also discuss the pharmacological basis for potential differences in its withdrawal, addiction and abuse profile.

Method

- ***Preclinical Studies*** - Data from a self-administration study in monkeys, naloxone-precipitated and non-precipitated withdrawal after chronic subcutaneous administration in rats[3] and mice[4] (precipitated only) and a behavioral abuse liability model in rats[5,6] will be presented.
- ***Clinical Studies*** - Results from a drug liking study in opioid-experienced, as well as the Clinical Opiate Withdrawal Scale (COWS) and the Subjective Opiate Withdrawal Scale (SOWS) data from pooled Phase 2/3 clinical studies with tapentadol Immediate-Release (IR)[7] and Extended-Release (ER)[8] will be presented.
- ***Post-marketing Results*** - Surveillance data on abuse, misuse and diversion of tapentadol collected using Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) are reported[9]. Street price data were obtained from 1,080 questionnaires collected during 11 quarters from 2010 through 2012. The mean prices were computed per milligram for the targeted prescription opioids in order to make standardized price comparisons across the drug classes.[10]

Results

Available nonclinical and clinical data suggest that tapentadol has a low incidence of withdrawal and dependence, despite showing comparable frequency of self-administration in opioid addicted animals and drug liking in opioid-experienced subjects. In non-clinical models of withdrawal, the severity and frequency of withdrawal symptoms was significantly lower for tapentadol than morphine, and some differences between the two drugs were observed in a conditioned place preference model that are suggestive of reduced abuse potential of tapentadol. In Phase 2 or 3 clinical studies, subjects receiving tapentadol IR or ER had a low incidence of mild to moderate withdrawal symptoms

assessed with the COWS (secondary endpoints). From 2 to 4 days post cessation of treatment the rates of mild to moderate withdrawal were numerically less for subjects receiving tapentadol IR (17% [n=306]) compared to oxycodone IR (29% [n=66]) and on day 5 they were comparable for tapentadol IR (8% [n=183]) and oxycodone IR (9% [n=43]). From days 2 to 4 post cessation of treatment, mild to moderate withdrawal rates were comparable for tapentadol ER (14% [n=635]) and oxycodone ER (15% [n=244]) but on day 5 they were numerically lower for tapentadol ER (5% [n=1145]) vs oxycodone ER (13% [n=447]). Post-marketing data generally show lower rates of abuse, misuse and diversion compared to other Schedule II mu opioids. In the five years since the introduction of tapentadol to the US market, prospective monitoring for abuse using well accepted independent surveillance methodologies has consistently shown, in general, a low and stable incidence of abuse, misuse and diversion compared to other Schedule II opioids. In addition, the mean street price for tapentadol is the lowest compared to other Schedule II opioids[10].

Conclusions

Taken together, the available data and inherent differences in the pharmacological activity of tapentadol relative to that of other Schedule II opioid analgesics suggest that there may be potential differences in the extent of withdrawal, dependence and abuse and support further hypothesis testing.

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Does tapentadol affect sex hormone concentrations differently than morphine and oxycodone? An initial assessment and possible implications for OPIAD

Gary Eichenbaum[1], Mila Etropolski[2], Karen Gohler[3], Ilona Steigerwald[3], Joseph Pergolizzi[4], Myoung Kiim[5], Gary Vorsanger[6]
[1]Janssen Research and Development, Raritan, NJ, USA, [2]Janssen Research and Development, Titusville, NJ, USA, [3]Grunenthal, GmbH, Aachen, Germany, [4]Temple University School of Medicine, Department of Pharmacology, Philadelphia, PA, USA, [5]Johnson and Johnson, Epidemiology and Health Economics, New Brunswick, NJ, USA, [6]Janssen Scientific Affairs, Titusville, NJ, USA

Purpose

Opioid-induced androgen deficiency (OPIAD) affects patients treated with opioid analgesics. Symptoms of OPIAD include reduced libido, erectile dysfunction, fatigue, hot flashes, depression, anemia, decreased muscle mass, menstrual irregularities, vasomotor instability, weight gain, and osteoporosis[1]. The biochemical pathways by which μ-opioid receptor (MOR) agonism cause OPIAD are not fully understood. However, there is clinical and nonclinical evidence showing that MOR agonism may result in a reduction in LH and testosterone by directly inhibiting hypothalamic gonadotropin-releasing hormone (GnRH) secretion[2]. MOR agonists have also been shown to reduce noradrenergic activity[3], which may then indirectly further reduce GnRH output[4]. Since GnRH and consequently sex hormone concentrations may decrease under conditions of reduced noradrenergic activity and may be elevated in the presence of increased noradrenergic activity[4], it is of interest to evaluate whether tapentadol (a centrally acting analgesic with MOR agonist and norepinephrine reuptake inhibition [NRI] activities that showed increased brain norepinephrine levels in preclinical studies[5]) and reduced MOR agonism (i.e. affinity and functional activity) has less impact on sex hormone concentrations than other Class II opioid analgesics such as morphine and oxycodone (MOR agonists without NRI activity). The objectives of this poster are to: (1) Present a post-hoc analysis of results on the effects of tapentadol (NUCYNTA® and NUCYNTA ER®) on sex hormone concentrations from 3 clinical studies; and (2) evaluate if the data are consistent with the mechanistic hypothesis that tapentadol's lower potency at the MOR and its NRI activity may have less impact on androgen concentrations than morphine or oxycodone

Method

Three clinical studies were conducted: Study 1 (single-dose comparison study vs. morphine and placebo in healthy volunteers), Study 2 (single-dose escalation study in healthy volunteers without an active comparator), and Study 3 (multiple-dose study vs. oxycodone in patients with osteoarthritis). Studies 1 and 2 were conducted at medical research centers in Germany and the United Kingdom; Study 3 was conducted at primary and secondary care centers and medical research centers in the United States. All three studies were randomized, double-blind, and placebo-controlled. Concentrations of testosterone, luteinizing hormone (LH), and follicle stimulating hormone (FSH; Study 3 only) were evaluated at 6 and 24 hours post-dose in Studies 1 and 2, respectively, and at varying times of day post-dose in Study 3. It should be noted that the study populations, dosing regimens, and durations of treatment administration differed for Studies 1, 2, and 3 and the analyses of sex hormone concentrations were not the primary objectives of these studies.

Results

In Study 1, mean serum total testosterone concentrations in healthy male volunteers were similar at baseline for all treatment periods (Mean ± SD of 14.7-14.8 ± 5.4-6.1 nMol/L); 6 hours after dosing, mean concentrations were comparable between placebo (8.6 nMol/L) and tapentadol IR (43 mg, 8.8 nMol/L; 86 mg, 9.3 nMol/L), but were lower following administration of morphine IR 30 mg (5.4 nMol/L). In Study 2, there were no or minimal changes in

testosterone in the therapeutic dose range with tapentadol (75-100 mg IR) and there was a modest decrease (-7.4 ± 6.12 nMol/L at 150 mg and -6.3 ± 4.03 nMol/L at 175 mg) that appeared to level off in the supratherapeutic range (125-175 mg IR); mean testosterone and LH concentrations with all doses remained within normal ranges (testosterone, 4.56-28.2 nMol/L; LH, 2.9 to 4.6 U/L). In Study 3, the mean (SD) decrease in the testosterone concentration from baseline to endpoint for male patients receiving tapentadol ER (100 mg, -1.9 [0.71] nMol/L; 200 mg, -2.1 [0.93] nMol/L) was numerically smaller compared to oxycodone CR (20 mg, -2.7 [0.93] nMol/L) but higher compared to placebo (-0.3 [1.62] nMol/L). The data in Studies 1 and 3 (only studies with active comparators) indicate that tapentadol may have a reduced effect on sex hormone concentrations compared with morphine (Study 1) or oxycodone (Study 3).

Conclusions

The results from the three clinical studies are consistent with the proposed mechanistic hypothesis that as a consequence of its reduced MOR agonism and NRI activities, which result in elevated CNS concentrations of norepinephrine, tapentadol may have a lesser effect on sex hormone concentrations compared with other Class II opioid analgesics such as morphine and oxycodone. The data provide justification for conducting additional hypothesis testing studies and are not intended to be used towards clinical decision making. Future studies may help to elucidate if the observed trends are clinically significant and would translate into a reduced incidence of OPIAD.

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Mu Opioid Analgesics and Mood: Importance of Receptor Pharmacology

Gary Eichenbaum[1], Dawn Baumgardner[1], Susan Serpico[2], Erica Elefant[2], Gary Vorsanger[2]
[1]Janssen Research and Development, Raritan, NJ, USA, [2]Janssen Scientific Affairs, Titusville, NJ, USA

Purpose

There is a high comorbidity of chronic pain and mood disorders and one may impact the other. Based on their mechanism of action, MOR analgesics may impact mood due to and independent of their analgesic properties[1]. Chronic administration of MOR analgesics are associated with adaptive changes[2] in endogenous norepinephrine[3], dopamine[4], glutamatergic[5] and cannabinoid[6] signaling, brain morphology[7] and endocrine homeostasis[8]. However, the extent to which different MOR analgesics, themselves, directly alter mood, independent of their analgesic effect, is difficult to evaluate due to challenges distinguishing their mood altering effects from those due to chronic pain or the analgesia that they provide. This is further complicated by inherent differences in their receptor pharmacology at the MOR and other receptors[9]. Other confounding factors include patient differences such as: age, genetics, psychosocial characteristics, treatment history, concomitant medications, and comorbidities, all of which contribute to the differences in sensitivity of patients to different MOR analgesics[9]. This poster evaluates some of the potential direct and indirect pharmacological effects of chronic MOR analgesic drug use on mood, and how fundamental differences in receptor pharmacology may differentially impact mood. It also highlights the need for the development and application of new nonclinical and clinical approaches to compare how MOR analgesics may directly affect mood. These new approaches could help to inform clinical study design, serve to differentiate and guide selection of opioid analgesics, as well as enable evaluation of potential differences and benefits of novel pain therapies.

Method

A targeted review of the literature was performed on the topic of management of chronic pain using MOR analgesics, pharmacologic activity and co-morbid mood disorders in PubMed/MEDLINE and Google Scholar. The databases were searched from database inception to June 2014. Search terms were used individually and in combination. No formal analysis of the level of evidence presented in the manuscripts reviewed was done; the goal was to identify published studies regardless of the design type.

Results

There is preclinical and clinical evidence that opioid drugs directly impact mood in a manner that is independent of their analgesic affect. Chronic administration of MOR analgesics has been shown to produce distinct changes in noradrenaline levels[3], serotonin[10], dopamine signaling[4], mu opioid receptor expression[2], glutamatergic signaling[5], cannabinoid signaling[6], and sex hormone levels (e.g. testosterone and LH)[8]. Furthermore changes in these biochemical parameters have been shown to affect mood. Reduced norepinephrine and dopamine signaling are observed in depressed patients and elevation of norepinephrine levels has been shown to ameliorate symptoms of depression. Wider fluctuations in these neurotransmitters, which can occur on withdrawal from, or with intermittent MOR analgesic use, are associated with increased anxiety[11]. Changes in norepinephrine and dopamine signaling are also associated with withdrawal symptoms[11], "liking" (positive reinforcement), and "wanting" (incentive salience)[4], which may also contribute to changes in mood. Additionally the reduction in testosterone and LH, which may be associated with chronic MOR analgesic therapy, can result in symptoms of opioid-induced androgen deficiency (OPIAD), which may include a significant impact on mood[8]. Most of the clinical studies reviewed highlighted challenges with distinguishing direct effects of the MOR analgesics from indirect effects (e.g., changes in quality of life or other chronic pain related factors). In addition, despite clear differences in the receptor pharmacology of different MOR analgesics, there have been limited head-to-head comparisons on their chronic effects on mood, making it difficult to determine their long

term clinical impact. Based on these results, important factors to incorporate in future nonclinical and clinical chronic assessments of MOR analgesics in the treatment of pain include: evaluation of receptor pharmacology through biomarker evaluation and functional imaging, pain pathophysiology, patient-specific attributes, and comprehensive mood assessments.

Conclusions

There is a need to develop and implement research models and clinical practices to better evaluate the mood altering effects of MOR analgesics on patients with chronic pain. The results of these models and practices will guide application of more suitable treatment regimens for chronic pain patients that take into account potential differences between drugs with respect to their receptor pharmacology and effects on mood; and will also provide a basis of comparison for, and differentiation of, new therapies

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An Evaluation of the Bioavailability and Dose Linearity of BEMA® Buprenorphine Buccal Film in Healthy Subjects

Andrew Finn[1], Stephen Bai[2], Steve Xiang[3]
[1]BDSI, Raleigh, NC, USA, [2]former employee of Endo Pharmaceuticals Inc., Malvern, PA, USA, [3]Endo Pharmaceuticals Inc., Malvern, PA, USA

Purpose

The purposes of this study were to determine the relative bioavailability of buprenorphine from single buccal doses of BEMA Buprenorphine formulations (F14 and F24), plasma buprenorphine pharmacokinetics (dose proportionality), and to determine the absolute bioavailability of buprenorphine from single doses of BEMA Buprenorphine.

Method

This was an open-label, randomized, single-dose, 5-sequence, 5-period, crossover study in healthy male and female subjects, between 18 and 55 years of age. Based on the assigned treatment sequence, each subject was randomly assigned to receive a single dose of BEMA Buprenorphine 75 mcg, 300 mcg (2 different formulations), 1200 mcg and intravenous buprenorphine 300 mcg, over the 5 periods. Each dose was administered under fasted conditions and was separated by at least a 7-day washout period. The treatments are identified as follows:

A. BEMA Buprenorphine 75 mcg (Formulation F24)

B. BEMA Buprenorphine 300 mcg (Formulation F24)

C. BEMA Buprenorphine 300 mcg (Formulation F14)

D. BEMA Buprenorphine 1200 mcg (Formulation F14)

E. Buprenorphine Injection 300 mcg, injected over 2 min.

Approximately 25 subjects were randomized to ensure that at least 20 subjects completed all 5 periods of the study.

Blood samples were collected for determination of buprenorphine and norbuprenorphine plasma concentrations predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, and 48 hours after each dose.

Subjects were confined to the clinical research facility beginning on the day prior to dosing (Day 0) until the morning of Day 3 (48 hours post-dose) during each of the 5 periods.

All subjects were administered 50 mg naltrexone, 12 and 0.5 hours prior to and 12 and 24 hours after each treatment of buprenorphine.

Results

Twenty-five subjects were dosed with buprenorphine in Period 1. Twenty completed all 5 periods of the study. Data from all 25 subjects were analyzed.

Bioavailability of buprenorphine from the 2 formulations (F24 and F14) of BEMA Buprenorphine films was comparable after the 300 mcg doses. The ratio of F24 to F14 formulation geometric least squares mean (90% CIs) values was: 93.6% (74.9-117.1) for C_{max}; 102.5% (86.0-122.0) for AUC_{last}; and 102.9% (89.2-118.6) for AUC_{inf}. The mean absolute bioavailability of buprenorphine across the 75 mcg to 1200 mcg BEMA Buprenorphine soluble buccal doses ranged from 0.46 to 0.51. The 95% CIs were all within 0.38 to 0.58.

Power model analysis indicated that the pharmacokinetic parameters C_{max}, AUC_{last}, and AUC_{inf} were linearly related to dose and the 90% CIs about the slope ranged between 0.81 and 1.18.

The 90% CIs for the slopes of C_{max} (0.81-0.97) and AUC_{last} (1.05-1.18) did not include unity, indicating that C_{max} increased less than proportionately with dose and AUC_{last} increased more than proportionately with dose. The 90% CI for AUC_{inf} (0.97-1.09) indicated that AUC_{inf} increased proportionately with dose. Dose proportionality of systemic exposure to buprenorphine was supported by the similarity of the mean bioavailability of buprenorphine from 75 mcg to 1200 mcg doses of BEMA Buprenorphine buccal soluble film.

Maximum concentrations of norbuprenorphine after administration of BEMA Buprenorphine were one tenth that of buprenorphine.

No deaths or SAEs occurred during the study. Treatment related TEAEs occurring in >2 subjects were nausea, decreased appetite, and dizziness.

Conclusions

Buprenorphine bioavailability from the 2 BEMA Buprenorphine formulations was comparable and systemic buprenorphine exposure increased in a linear manner from 75 mcg to 1200 mcg. Systemic buprenorphine exposure (AUC_{inf}) from BEMA Buprenorphine was proportional to the dose. BEMA Buprenorphine was well tolerated at all doses when administered to naltrexone blocked healthy subjects.

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An Evaluation of the Pharmacokinetics, Safety, and Tolerability of BEMA® Buprenorphine Following Multiple Dose Administration to Healthy Subjects

Andrew Finn[1], Stephen Bai[2], Steve Xiang[3]
[1]BDSI, Raleigh, NC, USA, [2]former employee of Endo Pharmaceuticals Inc., Malvern, PA, USA, [3]Endo Pharmaceuticals Inc, Malvern, PA, USA

Purpose

Opioids are typically titrated to an effective and well-tolerated dose over a period of days or weeks. Buprenorphine is a partial mu agonist with poor oral bioavailability that requires transmucosal, transdermal or parenteral administration for analgesia. BEMA Buprenorphine is a mucoadhesive polymer film product designed for buccal delivery of buprenorphine. Following single-dose administration of BEMA Buprenorphine, the buprenorphine elimination half-life was found to range from 11 to 23 hours. Based on these results, a 12-hour dose interval was chosen and it was estimated that the plasma concentration versus time profile would approach steady-state within 6 doses. To investigate this hypothesis, a multiple-dose pharmacokinetic study was performed with BEMA Buprenorphine administered at a dose range of 60 to 240 mcg twice a day.

Method

This was an open-label, dose-escalating, multiple-dose study in healthy male and female subjects, of any race, between 18 and 55 years of age.

Ten (10) healthy volunteers were administered 24 doses of BEMA Buprenorphine at 12 hour intervals. Oral naltrexone was co-administered to reduce the incidence of nausea and vomiting as well as the risk of respiratory depression. All subjects were administered 6 of each of the following 4 doses of BEMA Buprenorphine in a dose escalating manner: 60, 120, 180, and 240 mcg. Subjects were confined to the study unit beginning on the day prior to dosing (Day -1) until the morning of Day 13 (12 hours after the last dose; 72 hours after the first 240 mcg dose). They returned to the clinic on Days 14 and 15 for collection of the last 2 pharmacokinetic samples.

Blood samples for determination of buprenorphine and norbuprenorphine plasma concentrations were collected according to the following schedule for each dose level:

- 60 mcg/12 h: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 60, 61, 62, 63, 64, 68;
- 120 mcg/12 h: 0, 24, 48, 60, 61, 62, 63, 64, 68;
- 180 mcg/12 h: 0, 24, 48, 60, 61, 62, 63, 64, 68;
- 240 mcg/12 h: 0, 24, 48, 60, 61, 62, 63, 64, 68, 72, 96, 120.

The 0 h sample for 120 mcg/12 h, 180 mcg/12 h and 240 mcg/12 h was the 72 h sample for 60 mcg/h, 120 mcg/12 h and 180 mcg/12 h, respectively.

Results

Buprenorphine plasma concentrations could not be quantified in every subject for the full 12-hour dosing interval after the 1st and 6th 60 mcg doses (until 8 or 12 hours). Buprenorphine was quantified for the full 12-hour dosing interval, in every subject, after the 6th 120, 180, and 240 mcg doses.

Apparent steady state plasma buprenorphine concentrations were reached by the fourth dose (i.e., within 48 hours) in each dose level. Steady state C_{max} (ss) and $AUC_{0-\tau}$ values for buprenorphine increased linearly with an increase in BEMA Buprenorphine dose.

For the 60-, 120-, 180- and 240 mcg doses, the mean C_{max} (ss)values were 0.076, 0.156, 0.216 and 0.364 ng/mL, respectively, and the respective mean $AUC_{0-\tau}$ values were 0.49, 0.97, 1.36 and 2.34 ng·hr/mL. The median Tmax values at steady state ranged from 2.0 to 3.0 hrs across the 4 BEMA Buprenorphine dose levels.

Eight of the 10 subjects enrolled received all 24 study doses, and 2 subjects who experienced nausea received 23 of the 24 study doses. There were no deaths or serious adverse events (AEs) and no subjects were withdrawn from the study. All of the AEs, which were mild to moderate in severity, were considered by the Investigator to be possibly related to study drug.

Conclusions

Apparent steady-state plasma buprenorphine concentrations were reached within 48 hours following BEMA Buprenorphine administration at 12 hour dosing intervals. At doses up to 240 mcg, steady-state C_{max} and $AUC_{0-\tau}$ values for buprenorphine increased in a near dose proportional manner with transmucosal delivery from the BEMA film. BEMA Buprenorphine was generally well tolerated in this healthy population receiving concurrent naltrexone. There were no deaths or serious AEs and no subjects were withdrawn from the study.

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Differentiating the effect of an opioid agonist on cardiac repolarization from μ-receptor mediated, indirect effects on the QT interval

Borje Darpo[1], Meijian Zhou[1], Stephen Bai[2], Steve Xiang[3], Andrew Finn[4]
[1]iCardiac, Rochester, NY, USA, [2]former employee of Endo Pharmaceuticals Inc, Malvern, PA, USA, [3]Endo Pharmaceuticals Inc., Malvern, PA, USA, [4]BDSI, Raleigh, NC, USA

Purpose

Methadone and other opioids cause QTc prolongation and potentially fatal proarrhythmias in susceptible subjects. Evaluation of an opioid's QT effect is confounded by indirect effects induced by nausea, vomiting and sleepiness. We therefore conducted a thorough QT study in healthy volunteers with a supratherapeutic dose of BEMA buprenorphine under naltrexone coverage.

Method

This was a randomized, 4-way cross-over thorough QT study conducted in 58 healthy volunteers to evaluate the effect of buprenorphine administered through a buccal soluble film (BEMA buprenorphine) at a supratherapeutic dose. Buprenorphine was administered in combination with naltrexone. Since the QT effect of naltrexone is not known, a naltrexone-alone treatment period was included, as well as a positive control, 400 mg oral moxifloxacin. Subjects received 3 mg BEMA buprenorphine with concomitant naltrexone, placebo, 400 mg moxifloxacin and naltrexone-alone in separate treatment periods and ECGs and PK samples were collected serially before and after dosing.

Results

Treatment with 3 mg BEMA buprenorphine resulted in a small, not clinically relevant effect on the QTc interval with the largest mean placebo- and naltrexone-corrected, change-from-baseline QTcF (ΔΔQTcF) of 5.2 ms at 6 hours and 5.8 ms at 8 hours with an upper bound of the 90% confidence interval of 7.0 and 7.5 ms, respectively. Exposure response analysis using a linear model demonstrated a shallow and statistically significant relationship between plasma levels of buprenorphine and ΔΔQTcF with an estimated population slope of 0.65 msec per ng/mL (90% CI: 0.22 to 1.08). The study's ability to detect a small QTc effect was confirmed by the effect of moxifloxacin. Naltrexone alone did not have an effect on ΔΔQTcF.

Conclusions

The study demonstrated that a supratherapeutic dose of 3 mg BEMA buprenorphine did not cause a QTc effect exceeding 10 msec, the level of clinical and regulatory concern.

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Evaluating the Pain Management Learning Needs of Pharmacists Versus Physicians?

Robert Forbes[1], Joe Duz[2], Sol Stern[3], Michael Boivin[4]
[1]Johnson & Johnson Inc., Markham, ON, Canada, [2]CTC Communications, Mississauga, ON, Canada, [3]Argus Medical Group, Oakville, ON, Canada, [4]COMMPHARM, Barrie ON,, Canada

Purpose

The management of patients with Chronic Non Cancer Pain (CNCP) is often stated as an area that continues to need improved Health Care Professional (HCP) education. Vadivelu (2013), noted 20-30% of Americans experience pain and is amongst the most frequent reasons for visiting a physician. The Canadian Community Health Survey (2007) found 1 in 10 Canadians (age 12-44) experienced chronic pain. In 2012 The American Geriatrics Society (AGS) published their BEERS Criteria for Potentially Inappropriate Medication use in Older People. The paper (AGS 2012) cited that 27% of adverse drug events (ADE's) in primary care and 42% in long-term care were preventable. Whether elderly or not, HCP's continue to seek quality educational programming aimed at enhancing their knowledge, skills and improved attitudes towards managing this complex issue. An innovative web based, learning program was designed to allow both physicians and pharmacists to explore new and current information in CNCP and apply that learning in live patient encounters.

The program contains 2 distinct and independent components:

1) A facilitator led, live case - building session

2) A self-directed live patient component conducted as web based learning.

Both programs allow the learner to apply skills and knowledge gained through participating in them, thus improving their ability to manage CNCP.

Method

The physician accredited facilitator module was developed to allow a "Pre Built" case to be explored allowing for a high degree of interaction between the facilitator and participants. The pre-built standard case was a mock patient presenting with some common pain related complaints. The physician program also contained a separate blank case that was to be developed through the course of the educational interaction. The pharmacist accredited program contained only a blank case to be built through the live facilitator-led exercise. Both programs also afforded the HCP to return to their practice and engage subsequent patients (live face to face visits with real CNCP patients) and explore building an online case with patient details as they were presented through that specific patient encounter.

Continued learning occurs through an interactive and dynamically generated tool that presents patient specific steps at each part of the CNCP patient interview. The program generates relevant details surrounding patient examination, history, diagnoses, treatment plans as information is entered by the HCP. At the end of each patient interview, a PDF could be transferred into the patient's electronic medical record (EMR) for the physician and in the case of the pharmacist program, a PDF could be printed with an outline of the interaction between the pharmacist and the patient. This abstract looks at the self-scores of six specific physician and pharmacist questions completed before and after the live, facilitator led accredited event. The questions were completed to identify the HCP's perceived knowledge of various pain management issues.

Results

The results show what the physicians (n=175) and pharmacists (n= 204) rated themselves on, regarding the specific question both before and immediately after the educational session.

Q1: Rate your confidence to: Understand the importance of diagnosing comorbidities that may be impacting the ability to effectively manage chronic pain.

Physicians before / after and change: 55%, 96% and 41%. Pharmacists before / after and change: 32%, 83% and 51%.

Q2: Rate your confidence to: Accurately assess the level of risk associated with prescribing opioids to a patient with chronic pain

Physicians before / after and change: 52%, 93% and 41%. Pharmacists before / after and change: 29%, 79% and 50%.

Q3: Rate your confidence to: Accurately conduct a thorough assessment of a patient's chronic pain

Physicians before / after and change: 47%, 89% and 42%. Pharmacists before / after and change: 20%, 80% and 60%.

Q4: Rate your confidence to: Effectively initiate a non-pharmacologic management plan for a patient with chronic pain

Physicians before / after and change: 55%, 88% and 33%. Pharmacists before / after and change: 26%, 72% and 46%.

Q5: Rate your confidence to: Differentiate the different mechanisms of action of the agents that are utilized to treat chronic pain

Physicians before / after and change: 48%, 88% and 40%. Pharmacists before / after and change: 44%, 75% and 31%.

Q6: Rate your confidence to: Integrate the clinical data associated with the various options in terms of efficacy, impact on function and side effects

Physicians before / after and change: 43%, 87% and 44%. Pharmacists before / after and change: 28%, 73% and 45%.

MEAN CHANGES: Physicians before / after and change: 50%, 90% and 40%. Pharmacists before / after and change values are: 30%, 77% and 47%.

Conclusions

- The marked difference in pharmacists scoring occurred due to significant lower initial self-assessed CNCP knowledge. This may point to a large education gap in the understanding of CNCP management.
- Learning needs may be different for both health care groups.

- Interactive web based and live interactive case focused educational programs may be effective tools in raising confidence levels of both physicians and pharmacists in managing chronic pain
- Both physician and pharmacist programs produced similar increases in self-score after the events.

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Additional Clinical Oversight of Urine Drug Testing of Injured Workers Reduces Medication Utilization and Risk Factors Associated with Misuse of Opioids

Matthew Foster[1], Mueller Brooke[1]
[1]Helios, Tampa, FL, USA, [2]University of Florida College of Pharmacy, Gainesville, FL, USA

Purpose

The use of opioid medications to treat pain associated with workplace injuries is prevalent. There has been an increased national awareness of opioid use over the past several years due to the fraud, abuse, addiction, and cost associated with these medications. A need exists for a service that identifies high risk claimants, facilitates the urine drug testing process, and provides interpretation and recommendations for action to clients based on the results.
The Helios Drug Testing and Monitoring (DTM) service deters diversion and drug abuse while promoting appropriate use of opioid medications by facilitating urine drug testing at the prescriber level. This service ensures that an on-going monitoring program is in place for injured workers at risk for fraud, waste, and abuse. The DTM service utilizes a proprietary application to identify injured workers in need of additional monitoring for their chronic opioid therapy and engages a Helios clinical pharmacist to work in conjunction with the urine drug testing laboratory and the injured worker's prescriber.
A comprehensive study was performed to assess the impact of additional clinical pharmacist oversight of the Helios Drug Testing and Monitoring service.

Method

This study was conducted by analyzing the outcomes of DTM results and clinical interventions for injured workers identified and subsequently enrolled in the Helios DTM service between March and May 2013 secondary to an inconsistent urine drug test result.
The impact of enrollment into the DTM service was determined by calculating change in medication utilization and high risk therapeutic issues. The categories measured for utilization changes included total medications, opioid analgesics, controlled substances, and benzodiazepines. Utilization was determined based on the days of supply of the medication being evaluated. Opioids were converted to a standard morphine equivalent (MED) for the purpose of evaluating the change in average MED.

Results

335 injured workers enrolled in the DTM service were evaluated for changes in utilization during the course of their annual enrollment. The average age of the patient was 49 years old, with an injury age of 7.8 years.
Changes included reductions in utilization of opioids (-34.2%), benzodiazepines (-44.4%), and carisoprodol (-40.9%). The average baseline MED was 145 mg, which dropped to 100 mg by the end of the enrollment period. In fact, at the end of enrollment, 30.1% of claimants had no opioid use based on MED. Reductions were also seen in high risk therapeutic concerns, including decreases in multiple prescribers of opioids (-39%), use of three or more concurrent opioids (-46%), and concurrent use of stimulants and sedatives (-25%).

Conclusions

By providing prescribers with additional information regarding unexpected drug test results, the DTM service has successfully driven down injured worker utilization for controlled substances and other medications, as well as, decreasing therapeutic risks associated with the treatment of chronic pain.

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Methadone Policy Development and Computerized Decision Support Promoting Safe Inpatient Methadone Use

Maria Foy
AbingtonHealth, Abington, PA, USA

Purpose

Methadone is a strong mixed opioid analgesic generally indicated for detoxification and maintenance of opioid addiction and abuse. In recent years, methadone use for moderate to severe pain has increased due to an effort to recognize and treat chronic pain. Insurance plans embraced the use of methadone as an inexpensive alternative to other long acting opioids such as oxycodone sustained release. Over the last 10-15 years, methadone use has increased by 700 percent, leading to a five-fold increase in deaths associated with drug. Methadone has distinct pharmacokinetic properties and individual patient response to therapy that can lead to harm if not used appropriately. Recognizing the dangers of inappropriate methadone use, our institution developed a methadone policy and order set to guide physicians on the appropriate use of methadone for addiction maintenance, pain, and prevention of withdrawal in a heroin abuser admitted for a medical diagnosis other than detoxification.

Method

An interdisciplinary committee with representatives from psychiatry, pharmacy, nursing and medicine was formed to develop an institution specific policy for methadone use to ensure a safe and proper process of ordering, dispensing and administering methadone. Since our institution is not a licensed detoxification facility, methadone cannot be used solely for an opioid withdrawal indication. Ordering procedures and dispensing processes based on the drug indication were outlined in the policy. Restrictions were placed on use of methadone for analgesia. Practitioners from the pain, palliative care, and oncology teams who were trained on the unique dosing and monitoring of methadone were the services allowed to order methadone for pain unless the patient was receiving the medication prior to admission. An order set was then developed that provided decision support on the use of methadone based on the indication chosen from a drop down list on initial ordering. Dosing recommendations were provided for prevention of withdrawal based on a recommendation from psychiatry. Once the indication was chose, a customized order screen subsequently directs the practitioner to correctly dose methadone based on indication. If addiction maintenance is chosen, verification of methadone dose and last dispense from the clinic is required before the order can be processed. Education to the pharmacy staff was conducted on appropriate methadone use.

Results

Monitoring for accurate methadone dosing is reviewed on initial order by the pharmacy staff. Assessing for appropriate use based on approved indications and restrictions outlined in the methadone policy is also routinely reviewed by the pain management pharmacist. A medication use evaluation is to be presented to the Pain Management and the Pharmacy and Therapeutics Committees on a yearly basis as a quality assurance measure for the institution.

Conclusions

Development of an institutional methadone policy and order set with decision support has promoted safe and effective use of methadone at our institution.

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Single-entity, extended-release hydrocodone bitartrate: sustained effective pain relief throughout the 12-hour dosing interval

Srinivas Nalamachu[1], Oscar A. deLeon-Casasola[2,3], Cynthia Y. Robinson[4], Bradley S. Galer[4], Errol Gould[4], Arnold Gammaitoni[4]
[1]International Clinical Research Institute, Overland Park, KS, USA, [2]State University of New York at Buffalo, Buffalo, NY, USA, [3]Roswell Park Cancer Institute, Buffalo, NY, USA, [4]Zogenix, Inc., Emeryville, CA, USA

Purpose

Extended-release (ER)/long-acting opioids are formulated to provide sustained delivery of medication which may improve pain control by providing reduced variability of plasma concentrations. In addition, these formulations reduce dosing frequency, and therefore may decrease dosing errors and dosing error-associated adverse events. However, these formulations vary in providing adequate pain relief throughout the entire dosing interval, and many chronic pain patients require more frequent dosing of long-acting opioids than is recommended by the product's manufacturer. Single-entity, hydrocodone (HC)-ER is formulated for 12-hour dosing. In a multiple-dose pharmacokinetic study, HC plasma concentrations were stable at steady state as demonstrated by minimal peak-to-trough variation, suggesting it has the ability to provide consistent pain relief throughout the 12-hour dosing interval. This study evaluated the durability of pain relief of this new formulation of HC-ER throughout the 12-hour dosing interval by examining patterns of rescue medication utilization in patients with chronic low back pain.

Method

This multicenter, enriched enrollment, randomized withdrawal study began with an open-label, conversion/titration (C/T) phase (≤6 weeks) in which subjects (N=510) with moderate-to-severe chronic low back pain were converted from their current opioid to individualized doses (20-100 mg) of HC-ER dosed every 12 hours (q12h). The appropriate starting dose was chosen at the discretion of the investigator and was about 20%-30% less than the dose determined from the Opioid Conversion Table based on the current total daily opioid dose. During the C/T phase, the dose was increased by 20 mg/day (ie, 10 mg q12h) every 3-7 days to a maximum of 200 mg daily or until a stabilized dose was attained. Subjects who failed to attain a stabilized dose were withdrawn from the study. After the C/T phase, subjects were randomized in a double-blind fashion to HC-ER or placebo for the 12-week treatment phase. During the treatment phase, rescue medication (hydrocodone 5 mg/acetaminophen 500 mg) was permitted up to twice daily and usage was determined by analysis of subjects' electronic diaries. Rescue medication taken by the placebo group was not included in this analysis. Pain was assessed using a numerical rating scale (NRS; 0=no pain, 10=worst pain imaginable) at screening, weekly during the C/T phase, and at each of the 5 study visits during the treatment phase.

Results

A total of 151 subjects completed the C/T phase and were randomized to HC-ER. The average age was 50.4 years, 38.4% of subjects were male, 81.5% were White, and 17.2% were Black or African-American. Average pain score declined from 7.0 at screening to 3.0 at the end of the C/T phase and remained reduced compared with screening throughout the treatment phase (NRS=3.8 at study end). During the treatment phase, no definitive pattern or end of dose failure was observed with regard to rescue utilization after the morning or evening dose of HC-ER. During the majority of dosing days (76.7%), rescue medication was not needed after the evening dose of HC-ER. Subjects did not need rescue medication on 36.0% of the dosing days after the morning dose of HC-ER. Time distribution of rescue medication use showed that 79.3% of all doses were administered following the morning dose of HC-ER, with the peak usage (46.2%) occurring 4-8 hours after dosing of HC-ER, followed by 18.7% and 14.4% rescue medication usage 0-4 and 8-12 hours post-dose, respectively. Only 20.7% of all rescue medication doses occurred following the

evening dose of HC-ER, and the dosing frequency of rescue medication for the three 4-hour post-dose periods following the evening dose of HC-ER was similar to one another. Analysis of the percentage of days on which rescue medication was used showed a similar temporal pattern, with peak use occurring most often at 6-8 hours following the morning dose of HC-ER (10.7% to 12.4% of days). No similar hourly pattern of rescue medication used was observed following the evening dose of HC-ER.

Conclusions

These data indicate that end of dose analgesic failure did not occur with HC-ER. Low use of rescue medication following the evening dose of HC-ER suggests patient sleep was not interrupted due to pain. The need for rescue medication in the middle of the day for some patients was possibly due to increased activity. HC-ER demonstrates low peak-to-trough fluctuation at steady state which translated to effective pain relief throughout the entire 12-hour dosing interval without end of dose failure. New single-entity HC-ER provides an effective option for patients using immediate-release HC/acetaminophen chronically who are at risk for acetaminophen-induced hepatic injury.

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Trends in opioid prescribing from 2008-2013 based on morphine equivalent dosing

Daniel Garcia, Mancia Ko, Michael DeGeorge, Pat Woster
Ameritox, Baltimore, MD, USA

Purpose

The use of morphine equivalent dosing (MED) has been a standard in pain management when adjustments are made to total dose or when changing from one compound to another. A few states have adopted dose limits using morphine equivalents in their efforts to curb the rising trend of opioid abuse. There is evidence suggesting that hazard ratios increase substantially above 100 mg MED/day[1]. Other studies have shown that a drug overdose risk is associated with doses as low as 40-50 MED/day[2, 3]. Washington State employs a standard of 120 mg MED while Ohio uses 80 mg MED as its threshold. Indiana recently enacted emergency rule Title 844, section 9 requiring a face-to-face review of the treatment plan when MED exceeds 60 mg. The majority of states have not adopted any MED standards.

The goal of this study is to compare total MED prescribed for patients across a six year period with respect to geographic area, age, gender, payor, and combination therapy to determine significant variations and trends

Method

The study population included over 2 million samples from individuals on known stable doses of prescribed opioid therapy. Patients' prescriptions were identified from the medication records provided by their clinician. The total daily dose was calculated by multiplying dose per pill by number of pills per dose and by dosing frequency per day and converted to a daily morphine equivalent reported in milligrams. The total daily dose included different formulations of the same compound. Extended release and immediate release formulations were combined for a total dose. Samples were excluded if the prescription was written for use on an as-needed (prn) basis. Prescriptions selected for the analysis included hydrocodone, hydromorphone, oxycodone, oxymorphone and morphine. Analyses were performed for all samples, and then sub-categorized for each compound, for those on a single compound, and for those on two or more compounds. Generalized linear models were used to calculate adjusted MED effect sizes and 95% CI. Variables in the model included: year of sample collection, age, gender, medication prescription history, dosing regimens, concomitant medication, payor, geographic region and concomitant benzodiazepine prescription.

Results

For all samples, the mean MED was approximately 100 during the years 2008 – 2011, and then declined to 94.5 and 85.7 in 2012 and 2013, respectively (adjusted change 2008 to 2013, -10.6; 95% CI, -11.6 to -9.5). On analysis by compound sub-category, the mean MED varied widely by category with a range from a low MED of about 30 for hydrocodone and a high of about 200 for those on two or more compounds. Oxycodone was the only compound for which MED changed substantially over time. Oxycodone mean MED was stable at about 160 for 2008 to 2010, but then decreased to about 150, 140 and 130 in 2011, 2012, and 2013, respectively (adjusted change 2008 to 2013: -24.7; 95% CI, -27.2 to -22.3). No other category of compound showed an adjusted MED change from 2008 to 2013 of seven or greater. Other variables associated with a difference in adjusted MED included: gender (females vs, males) adjusted MED -19.5; 95% CI, -19.8 to -19.1), age (age 60+ vs age 19-39, adjusted MED -8.5; 95% CI, -9.0 to -8.0), region (compared to states in the South U.S. region, adjusted MED was 65.7 and 44.0 in the Northeast and West, respectively), payor (self-pay vs commercial insurance, adjusted mean MED 17.3;, 95% CI, 16.7 to 17.9; and Medicaid vs commercial insurance, adjusted mean MED -9.8; 95% CI, -10.3 to -9.2), and concomitant benzodiazepine prescription (with vs without benzodiazepine prescription, mean MED 14.6; 95% CI, 14.3 to 15.0).

Conclusions

Although there have been increased opioid sales, drug-related overdose deaths and substance abuse treatment admission in the past decade[5], the overall total MED prescribed to pain patients have only shown minimal reductions.

Opioids are often prescribed with benzodiazepines for various indications. Despite the fact that the labels of numerous approved opioid products recommend a reduced opioid dose when prescribed in conjunction with a CNS depressant, including benzodiazepines[4], this study showed that this combination is associated with higher MED.

Efforts to reduce the amount of MED prescribed have had minimal impact on reducing the MED prescribed to pain patients.

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The Biopsychosocialspiritual Impact of Chronic Pain in Adolescence: A Proposed Model for Psychotherapeutic Intervention

Melissa Geraghty
Rago & Associates, Naperville, IL, USA

Purpose

It is estimated by the American Pain Association that 15 to 20% of people 19 years of age and under live with chronic pain (Painaction, 2012). Many adolescents report pain of some degree, and for a "minority of adolescents the pain can persist for over three months to become chronic pain, with 8% reporting their chronic pain as severe" (Eccleston, Jordan, & Crombez, 2006, p. 684). Furthermore, it is known that many adults with chronic pain first experienced unceasing pain as an adolescent or child.

Despite the prevalence of chronic pain in adolescence, studies are primarily limited in the literature to preliminary studies and studies that intertwine findings with pediatric and adult populations. These studies do not lend specific information on how to provide evidence-based treatment for the adolescent in chronic pain. This is a limitation as adolescents have different intellectual understanding, emotional regulation, conceptualization of problems, and coping skill capacity than pediatric and adult populations.

Adolescence itself is a diverse age group due to differences in biology, psychological functioning, social interactions, and spirituality, thus resulting in three theoretical subgroups of age: 10 to 12 years, 13 to 15 years, and 16 to 18 years. This study focused on late adolescence (i.e., ages 16 to 18). A psychotherapeutic program stemming from the biopsychosocialspiritual model, with a concentration on the role of the clinical health psychologist, was developed.

Method

A literature review was conducted to analyze the effects of chronic pain on an adolescent's quality of life. This literature review provided an overview of the chronic pain literature in general and outlined the statistical data of chronic pain prevalence. It further discussed distinctions between chronic illness/condition, chronic disability, and chronic pain, and included a brief discussion of chronic pain experiences throughout the different age groups. Various aspects of disability (e.g., type or time of onset, type of course, degree of visibility, prevalence, degree of prejudice, and stigma) were also covered. Each component of the biopsychosocialspiritual model was discussed in order to further understand the complexity of an adolescent in chronic pain (e.g., neural and cognitive processes, fear-avoidance, peer group, spiritual pain and uncertainty, etc.).

A proposed psychotherapeutic program model was then presented, with a focus on the adolescent subgroup aged 16 to 18. This model was heavily influenced by acceptance-based treatment, mindfulness, and mind-body interventions. The theoretical orientation that supported the proposed model was Acceptance and Commitment Therapy (ACT), which focuses on values, goal setting, mindfulness, behavioral change, and acceptance of pain. The biopsychosocialspiritual model was incorporated into the initial conceptualization of the client. It is this author's hope that clinical health psychologists who utilize this model will be able to guide their clients in learning how to live a fulfilling and valued life despite unyielding pain levels

Results

The findings of this study indicated that the inclusion of adolescents in research and psychotherapeutic interventions with pediatric and adult populations, does not serve the adolescent population well. It is this author's opinion that such

limitations diminish the difficulties and capabilities of the adolescent in chronic pain, making psychotherapeutic intervention that is empirically sound more difficult to find and consequently implement.

The literature review discussed the impact of chronic pain on all facets of an adolescent's life. It is the health psychologist's role to understand all components of the biopsychosocialspiritual model in order to assist and advocate for his or her clients. Specifically, the older adolescent (i.e., ages 16 to 18) has several developmental tasks to focus on as he or she emerges into adulthood with a disability--learning how to live with and manage the disability, concerns about acceptance by peers, concerns about body image and identity, exploration of sexual identity, and adjusting to interdependence. Adolescents of this age begin to develop a more cohesive sense of identity, which can be profoundly impacted by chronic pain.

The proposed psychotherapeutic program model that was presented included interventions such as the integration of an interdisciplinary team, psychoeducation and acceptance of pain, exploration of values and the creation of goals, mind-body techniques, creating an energy conservation plan, and learning how to speak at the level of an adolescent. This program model included various examples of evidence-based techniques. Further, it was founded that clients working within an acceptance-based model with the incorporation of mindfulness engage in more value driven behaviors, thus increasing their overall quality of life. In contrast, research has shown that maladaptive efforts to decrease, avoid, and control pain serve to exacerbate pain, which increases levels of disability and heightens emotional suffering.

Conclusions

This study has shown that adolescents in chronic pain must have treatment that is tailored to their biopsychosocialspiritual needs. Both psychological and medical sciences, along with the components of social support and spirituality, can improve quality of life and overall physical functioning. Through psychotherapy, clients can learn how to live a rich and meaningful life despite pain levels. The behavioral processes of acceptance and mindfulness have been found to be crucial components of well-being for those in chronic pain. Overall, it is important to challenge clients to start thinking differently about their relationship with pain through acceptance-based methods.

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In vitro Assessment of the Effects of Alcohol on the Release Rate of Hysingla™ ER, a Once-daily, Single-entity, Hydrocodone Bitartrate Formulation

Jennifer Giordano, Hugh Huang, Jenny Kianto, Shefali Das
Purdue Pharma L.P., Cranbury, NJ, USA

Purpose

Extended release opioid formulations are designed to maintain a specific drug plasma concentration-time profile over many hours. Some patients purposefully or inadvertently co-administer alcoholic beverages with medications. Due to additive CNS depressive effects of opioids and alcohol, co-administration of ethanol and opioids is dangerous. In some cases, the controlled release mechanisms of these formulations are vulnerable to increased rates of drug release in the presence of alcohol (ethanol). Hysingla™ ER (once-daily, single-entity hydrocodone bitartrate) is a novel drug product formulated with the intent to be abuse-deterrent, including resistance to 'dose dumping' in alcohol, and 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. Some controlled release opioid formulations have reported an increase in release rates (in vitro or in vivo) in the presence of ethanol. Designing a product without ethanol liability was an important criterion for development of Hysingla™ ER.

Method

The rate controlling polymer of Hysingla™ ER tablets facilitates the controlled slow diffusion of drug from the tablet matrix. This in vitro dissolution study evaluated the effects of varying ethanol concentrations on the drug release rate controlling mechanism. The lowest and highest tablet strengths (20 mg and 120 mg) were studied at 1, 2, 4, 8, 12, 18 and 24 hours in the absence (0%) and presence of 4%, 10%, 20% and 40% (v/v) ethanol in Simulated Gastric Fluid (SGF). SGF has been used as media for in vitro modeling and prediction of in vivo tablet dissolution. These media were chosen to mimic and bracket the potential ethanol concentration of the stomach when alcoholic beverages such as beer, wine, or distilled spirits are co-administered with Hysingla™ ER. The f_2 similarity factor was used to statistically compare dissolution profiles where applicable. An f_2 metric value >50 indicates similarity. In addition, another hydrocodone extended release formulation (twice daily Zohydro™ ER) was analyzed in a similar manner.

Results

There was no evidence of rapid or unexpectedly high rate of hydrocodone release for Hysingla™ ER tablets in the presence of ethanol. On the contrary, the presence of ≥10% ethanol decelerated the release of hydrocodone consistently over 24 hours. Conversely, the presence of 10% ethanol in SGF increased the rate of release of hydrocodone from Zohydro™ ER tablets and resulted in dissimilar dissolution profiles (f_2 similarity values for 10 mg and 50 mg were 45 and 44; respectively). Increasing ethanol content resulted in corresponding increases in the rate of hydrocodone release. Ethanol concentrations ≥20% resulted in near complete release of hydrocodone from Zohydro™ ER tablets in one hour.

Conclusions

The Hysingla™ ER in vitro data indicate that there is no obvious potential for increased rate of hydrocodone release, or 'dose dumping,' in the presence of up to 40% ethanol therefore demonstrating the ruggedness of the formulation. Conversely, Zohydro™ ER is not resistant to 'dose dumping;' exposure to certain concentrations of ethanol significantly accelerated the release of hydrocodone.

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REMEDIES in Chronic Pain-Risk Evaluation and Mitigation Strategies: An Employer-Driven CME Initiative for Efficacy and Safety

Kurt Boyce[1], Amanda Glazar[2]
[1]*Applied Clinical Education, New York, New York, USA,* [2]*Global Education Group, Littleton, Colorado, USA*

Purpose

The ongoing educational initiative entitled *REMEDIES in Chronic Pain-Risk Evaluation and Mitigation Strategies: An Employer-Driven CME Initiative for Efficacy and Safety* (REMEDIES) has 6 primary goals:

1. Educate health care professionals on all elements of the FDA *Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics*
2. Deliver content in 3 hours or less using a Primary Curriculum
3. Reinforce learning with a Supplementary Curriculum
4. Reach 10,000+ members of intended audiences (primary care physicians, pain specialists, nurse practitioners, physician assistants, and other professionals involved in the management of pain)
5. Achieve Levels 1-7 educational outcomes as defined by the revised Moore Scale
6. Provide non-certified online educational resources for both professionals and patients.

The curriculum consisted of the following elements:

- Resource Center (Patient and Professional)
- 3 Live Sessions
- 2 Monographs
- 2 Webcasts
- 2 Patient Simulations
- 2 DecisionPoints
- 1 Performance Improvement Program
- 3 Patient Screenings/Seminars

Educational Partners included:

- Global Education Group: CME provider and statistical analysis partner
- Applied Clinical Education: joint provider and distribution partner
- American Society of Pain Educators (ASPE): education and distribution partner
- National Association of Managed Care Physicians (NAMCP): education and distribution partner
- Intelligent Medical Decisions (IMD): performance improvement partner
- MedMatRX: education and employer liaison
- RealCME: technology and outcomes partner

Method

To accomplish its goals, REMEDIES incorporates a blend of learning methods. These include live symposia, interactive web-based activities, a 3-stage performance improvement program, and a series of 3 patient screening and education activities. These varied formats provide valuable tools that help learners navigate the clinical challenge of opioid prescribing in their practices.

Participation, engagement, learner scores, evaluation data, learner feedback, question and response distribution (Levels 1-4) are collected via the RealCME Reporting Tool.

Level 5 outcomes for all certified live and online activities are captured and analyzed via the RealMeasure Platform in which learners are presented with pre- and post-test and evaluation questions that measure knowledge, competence, confidence, and current practices. All participants receive postcurriculum assessments 6 to 8 weeks after completion of their latest intervention.

Patient health (Level 6) is measured directly through the PI-CME initiative, which uses a 3-stage process of review, analysis, and application.

Community health (Level 7) is measured through de-identified insurance claims data provided by participating employer health networks. Data was provided for a period encompassing 12 months before delivery of the patient screenings and the professional education and again 6 to 8 months after delivery.

Outcomes measurements were designed to measure the effect of knowledge, competence, performance, and patient outcomes throughout all activities and to measure the reliability of self-reported changes in confidence and practice behaviors with actual patient outcomes.

Results

Results through July 31, 2014 indicate strong impact on 7 outcomes levels.

- Level 1 Outcomes: 21,000+ participants; 4,444 content completions; 4,139 evaluations and certificates; 24,178 resource center visits.
- Level 2 Outcomes: 4,139 evaluations; 98% *Agree* or *Strongly Agree* that the learning objectives were met; 97% *Agree* or *Strongly Agree* that the faculty was effective; 97% *Agree* or *Strongly Agree* that the activities were free from bias.
- Level 3 Outcomes: Pre- versus post-test comparison demonstrate a 39% increase in knowledge of the topics addressed in the curriculum.
- Level 4 Outcomes: Pre- versus post-participation analysis demonstrate a 43% increase in confidence/competence.
- Level 5 Outcomes: Pre- versus post-test analysis of the application of practice strategies demonstrates an average increase of 67% among learners.
- Level 6 Outcomes: 200 physicians enrolled in the program; 100 met the enrollment criteria for opioid prescribing; physician behavior has increased 96% from stages A to C; 300+ patients documented; program is ongoing.

Level 7 Outcomes: Variance from baseline to post-education data analysis indicates a 12.8% increase in employees seeking medical care for 1 of 20 identified pain conditions; an 8.3% decrease in payments across 20 ICD-9 codes; a collective savings of more than $58,000 among participants.

Conclusions

REMEDIES has demonstrated a high level of success in achieving its educational goals. Subjective and objective analyses indicate success at all levels of the Moore Scale of educational outcomes, and results remain consistently strong.

REMEDIES will complete its certification in October 2014, at which time a final outcomes assessment will be performed. Upon completion of the final analysis, Global and ACE will seek to have the results published for the CME community and the intended health care audiences.

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A Study of Mindfulness-Based Stress Reduction Virtual Reality (VR) for Chronic Pain Management

Diane Gromala, Chris Shaw, Xin Tong, Mehdi Karamnejad
Simon Fraser University, Surrey, BC, Canada

Purpose

Approximately 20 percent of people in North America suffer from chronic pain. Chronic pain is defined as pain that lasts more than 6 months and that persists beyond the healing of its putative cause. The cause of this disease is unknown and its complexity involves neurobiological, psychological and social dimensions; thus, there is no universal treatment for this disease. Pharmacological approaches for managing chronic pain are common, and are typically supported by a diversity of adjunct treatments. However, digital media has not been widely used as a method of treatment in conjunction with traditional pharmacological approaches. Researchers have proposed that immersive virtual reality (VR) can serve as an unusually powerful pain control technique. Provocative studies have demonstrated the efficacy of VR for reducing short-term acute pain, but applications of VR for long-term chronic pain have only just begun. In this research, we seek a novel approach for the management of chronic pain using a tripartite system of VR, biosensor technology, and the well-known mindfulness meditation technique of Mindfulness-Based Stress Reduction (MBSR). The goal was to help participants to regulate their physiological states by learning MBSR in VR.

Method

In this study, the three most commonly employed pain measurement tools to track chronic pain were planned to be used: the McGill Pain Questionnaire (MPQ), the Pain Disability Index and the 10-point Visual Analogue Scale (VAS). After patients rated their pain and its intensity in three tools, they were randomly assigned to either the control group or to the VR group to learn the MBSR protocol. Participants in the control group sat on a chair in a relaxing manner, were equipped with finger-mounted Galvanic Skin Response (GSR) sensors, and then listened to the MBSR narration. The MBSR protocol took twelve minutes for each participant. Immediately afterwards, the participants rated their pain using the same questionnaire used immediately prior to the session. The VR group was additionally exposed to VR for the twelve minutes. Participants' GSR data continuously updated the VR environment. After the session, the participants rated their pain experience again using the same three questionnaires.

Results

Patients self-reported their pain in the 10-point VAS before and after the session for each condition. For the 10-point scale, preliminary results suggest that on average, VR was more effective in reducing pain and its intensity (mean=4.71, SD=1.88) compared to the non-VR condition (mean=7.3, SD=2.73). In addition, we used the difference of the reported pain level before and after the trials to indicate the reduction in pain; i.e., the difference is the level of pain reduction. A one-way analysis of this difference was used to calculate the T-Test for the means of the pre-session and post-session pain level. There was a significant difference in the pain reduction for Control (M=0.16, SD=1.16) and VR (M=2.71, SD=1.88) conditions; $t(10)=2.96$, $p < 0.05$. Results suggest that VR and GSR had a positive effect on pain reduction for chronic pain patients.

Conclusions

The results suggested that VR could be potentially useful in helping chronic pain patients to manage (decrease) their pain. The method worked because VR, in conjunction with biofeedback and MBSR, enables patients to see a mirrored version of themselves in a 3D simulated environment, and learn the skill to self-modulate physiological states and pain levels.

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Effect of Dosing Interval on Pharmacokinetics and Safety of Fentanyl Pectin Nasal Spray

Anita Gupta[1], Shay Bujanover[2], Cuiping Chen[2]
[1]*Division of Pain Medicine and Regional Anesthesiology, Department of Anesthesiology and Perioperative Medicine, Drexel University College of Medicine, Philadelphia, PA, USA,* [2]*Depomed, Inc., Newark, CA, USA*

Purpose

Many patients with cancer experience a persistent pain, and despite the around-the-clock treatment, they can also experience sudden, short-lived, acute episodes of severe pain, known as breakthrough cancer pain. Fentanyl Pectin Nasal Spray (FPNS; Lazanda®; Depomed, Newark, CA) is a fentanyl citrate nasal spray approved for the treatment of breakthrough cancer pain. The nasal delivery allows direct and efficient absorption of fentanyl from the nasal mucosa into the systemic blood, and thus may permit rapid pain relief. In the FPNS formulation, pectin is used to control the release of fentanyl from the formulation, and it modulates fentanyl absorption via the nasal mucosa. This ultimately achieves an optimum balance between a fast rate of absorption without uncontrollable peak concentration and minimum dropping of the spray to the back of the throat following the drug administration. Also, unlike the delivery via the oral mucosal or traditional nasal spray, FPNS does not result in swallowing any portion of the administered dose, thus avoiding partial degradation to inactive metabolites and a later untimely peak arising from the swallowed portion.

Because breakthrough cancer pain may occur multiple times throughout the day, multiple doses of FPNS may be required to control pain. This study evaluated the effects of different FPNS dosing intervals on pharmacokinetics (PK), safety, and tolerability.

Method

This was an open-label, randomized study in healthy volunteers. Five treatments were administered to the right nostril of each subject, with a ≥3-day washout between treatments. These treatments were: A, 1 X 100 µg; B, 2 X 100 µg, 4-hr apart; C, 2 X 100 µg, 2-hr apart; D, 2 X 100 µg, 1-hr apart, and E, 8 X 100 µg consecutively. Each treatment was administered under a naltrexone block. PK blood samples were collected at pre-dose and 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 360, 480, 720, and 1440 minutes following the administration of treatments A and E. For the two-dose regimens (treatments B, C, and D), samples were collected in similar frequency to allow accurate characterization of the two peaks following two doses. Plasma samples were analyzed to determine fentanyl concentrations. PK parameters including peak concentration (C_{max}), time to C_{max} (t_{max}), and area under the concentration-time curve (AUC) were derived using non-compartmental model method. C_{max}, t_{max}, and AUC were normalized to a 100-µg dose, log-transformed, and compared between treatments using a mixed effects analysis of variance (ANOVA) model with treatment as a fixed, and subject a random effect.

For the two-dose regimens (treatments B, C and D), log-transformed C_{max} values were compared between the first and second doses using a paired t-test. t_{max} values were compared with non-parametric method. A p value of ≤ 0.05 was considered statistically significant.

Results

Thirteen subjects were enrolled and 10 completed the study. Time to peak (t_{max}) was consistently rapid, with a median value of 10–15 minutes post dose across all regimens. For the two-dose regimens, C_{max} (mean ± SD, pg/mL) was higher after the second than the first dose; the increase was statistically significant for the 1- and 2-hr, but not the 4-hr

intervals [4 h: 699 ± 246 vs. 643 ± 264; 2 hr: 688 ± 217 vs. 512 ± 246, p=0.001; 1 hr: 743 ± 178 vs. 513 ± 125, p=0.0001). There were no significant differences in AUC (mean ± SD; p·gh/mL) among 2-dose regimens [1 hr: 3160 ± 1100; 2 hr: 2830 ± 910; 4 hr: 3100 ± 799]. After eight consecutive 100-µg doses, the average C_{max} and AUC_{0-24} were approximately 5-fold of those for a single 100-µg dose (C_{max}, pg/mL: 2960 ±1500 vs. 572 ± 230; AUC, pg·h/mL: 6790 ± 2900 vs.1130 ± 454), suggesting a less than dose proportional increase in exposure.

No new adverse events (AEs) or safety signals were observed compared with those reported for other fentanyl formulations. Fifty-three percent of patients reported ≥1 AE, with dizziness (11.9%) and somnolence (4.9%) being most common. In total, 12.9% of patients discontinued due to AEs. All AEs rapidly decreased to sustained low levels after 4–5 weeks of treatment. There were no clinically significant safety issues with regards to physical examinations, clinical laboratory tests, vital signs, or ECG evaluations.

Conclusions

FPNS demonstrated a consistent, rapid rise to peak fentanyl plasma concentration across all doses. When the intervals between two doses were shorter, the C_{max} of the second dose was higher than the C_{max} of the first dose. However, both single- and multiple-doses of FPNS under naltrexone blockade were well tolerated. AUC values were independent on dosing intervals. C_{max} and AUC reached a plateau after 8 consecutive doses into the same nostril, suggesting an additional safety feature of the formulation. In summary, the PK profile of FPNS appears to match the pattern required for the treatment of breakthrough cancer pain.

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Low Risk of Aberrant Drug-Related Behavior Observed During a 12-Month Open-Label Study in Patients Taking an Extended-Release Hydrocodone Tablet, Formulated with Abuse-Deterrence Technology, for Chronic Noncancer Pain

Martin E. Hale[1], Thomas R. Zimmerman, Jr[2], Yuju Ma[2], Richard Malamut[2]
[1]Gold Coast Research, LLC, Plantation, FL, USA, [2]Teva Pharmaceuticals, Frazer, PA, USA

Purpose

To evaluate aberrant drug-related behaviors and addiction after treatment with an extended-release (ER) hydrocodone tablet formulated to provide sustained pain relief with dosing every 12 hours. This formulation employs Teva abuse-deterrence technology, which provides resistance against rapid release of the active moiety when the tablet is manipulated or taken with alcohol.

Method

In this 12-month, phase 3, open-label study, eligible patients had either previously completed a 12-week, randomized, placebo-controlled study of ER hydrocodone or were newly enrolled with chronic (≥3 months) noncancer pain; excluded were those taking oxycodone 135 mg/day (or equivalent) for 14 days or with recent history/current substance/alcohol abuse. After titrating ER hydrocodone (15-90 mg every 12 hours) to an analgesic dose, patients received up to 52 weeks of open-label treatment. Aberrant drug-related behaviors or addiction were assessed using Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R), Addiction Behavior Checklist (ABC), and Current Opioid Misuse Measure (COMM) questionnaires. Study drug diversion and loss were monitored throughout the study.

Results

Of the 330 patients enrolled, 329 patients received ≥1 ER hydrocodone dose, 291 entered the open-label treatment period, and 184 completed the study. Mean age was 54.3 years, and 79% of patients were white. Primary chronic painful conditions were back/low back pain (66%), osteoarthritis (25%), diabetic peripheral neuropathy (4%), neck pain (3%), and traumatic injury, complex regional pain syndrome, rheumatoid arthritis, fibromyalgia, and knee pain (<1% each). At week 4, mean (standard deviation) SOAPP R total score was 6.7 (6.7) and 75% of patients had SOAPP-R scores <18 (indicative of patients with lower occurrence of aberrant drug use behavior). The majority of patients had ABC scores <3 at baseline (97%) and endpoint (99%) and COMM scores <9 at baseline (86%) and endpoint (91%); ABC scores ≥3 and COMM scores ≥9 are considered predictive of aberrant drug-related behavior. Eight (2.4%) patients reported study drug diversion, and 36 (11%) reported loss of study drug. No patients were withdrawn from the study due to diversion or loss of study drug.

Conclusions

The low occurrences of inappropriate opioid use, aberrant drug use behavior, and study drug diversion during this long-term safety study may support the potential abuse-deterrence properties of the new ER hydrocodone tablet formulated with abuse-deterrence technology.

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Evaluation of Work/School Productivity Following Treatment with an Extended-Release Hydrocodone Tablet Formulated with Abuse-Deterrence Technology: a 12-Month Open-Label Study in Patients with Chronic Pain

Martin E. Hale[1], Thomas R. Zimmerman, Jr[2], Yuju Ma[2], Richard White[2], Richard Malamut[2]
[1]Gold Coast Research, LLC, Plantation, FL, USA, [2]Teva Pharmaceuticals, Frazer, PA, USA

Purpose

To evaluate productivity at work and school after treatment with an extended-release (ER) hydrocodone tablet formulated to provide sustained pain relief with dosing every 12 hours. This formulation employs Teva abuse-deterrence technology, which provides resistance against rapid release of the active moiety when the tablet is manipulated or taken with alcohol.

Method

In this 12-month, phase 3, open-label study, eligible patients were rolled over from a previous 12-week, randomized, placebo-controlled study of ER hydrocodone or were newly enrolled with chronic (≥3 months) noncancer pain. After titrating ER hydrocodone (15-90 mg every 12 hours) to an analgesic dose, patients received up to 52 weeks of open-label treatment. Productivity was evaluated using the World Health Organization's Health and Work Performance Questionnaire-Short Form (HPQ-SF) and domains of the Sheehan Disability Scale (SDS).

Results

Of the 330 patients enrolled, 329 received ≥1 ER hydrocodone dose, 291 entered the open-label treatment period and were evaluable for productivity outcomes, and 184 completed the study. Mean age was 54.3 years, and 79% of patients were white. Primary chronic painful conditions were back/low back pain (66%), osteoarthritis (25%), diabetic peripheral neuropathy (4%), neck pain (3%), and traumatic injury, complex regional pain syndrome, rheumatoid arthritis, fibromyalgia, and knee pain (<1% each). Mean HPQ-SF absolute absenteeism scores decreased from 13.6 hours lost/month at baseline to 10.0 hours lost/month at endpoint, indicating an improvement in absenteeism from work. Mean HPQ-SF absolute presenteeism scores increased from 67.0 at baseline to 77.1 at endpoint, indicating a decrease in lost performance. Mean SDS score for work/school decreased from 5.0 at baseline to 2.8 at endpoint (score ≥5 indicates significant impairment). At baseline on the SDS, patients lost a mean of 4.9 days in the previous month because of their disability and were underproductive for a mean of 7.1 days. At endpoint, mean number of days lost in the previous month was reduced to 2.2 and mean number of underproductive days was reduced to 4.3. Sustained improvements in absenteeism, presenteeism, and productivity were reported throughout the study.

Conclusions

ER hydrocodone may help to improve productivity at work or school in patients with chronic noncancer pain.

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Evaluation of Quality of Life, Functioning, and Disability Following Treatment with an Extended-Release Hydrocodone Tablet Formulated with Abuse-Deterrence Technology: a 12-Month Open-Label Study in Patients with Chronic Pain

Martin E. Hale[1], Thomas R. Zimmerman, Jr[2], Yuju Ma[2], Richard Malamut[2]
[1]Gold Coast Research, LLC, Plantation, FL, USA, [2]Teva Pharmaceuticals, Frazer, PA, USA

Purpose

To evaluate quality of life, functioning, and disability after treatment with an extended-release (ER) hydrocodone tablet formulated to provide sustained pain relief with dosing every 12 hours. This formulation employs Teva abuse-deterrence technology, which provides resistance against rapid release of the active moiety when the tablet is manipulated or taken with alcohol.

Method

In this 12-month, phase 3, open-label study, eligible patients were rolled over from a 12-week, randomized, placebo-controlled study of ER hydrocodone or were newly enrolled patients with chronic (≥3 months) noncancer pain. After titrating ER hydrocodone (15-90 mg every 12 hours) to an analgesic dose, patients received up to 52 weeks of open-label treatment. Assessments included Clinician Assessment of Patient Function (CAPF), Patient Assessment of Function (PAF), Brief Pain Inventory-Short Form (BPI-SF) pain interference questions, 36-item Short-Form Health Survey (SF-36), and Sheehan Disability Scale (SDS).

Results

Of the 330 patients enrolled, 329 patients received ≥1 ER hydrocodone dose, 291 entered the open-label treatment period, and 184 completed the study. Mean age was 54.3 years, and 79% of patients were white. Primary chronic painful conditions were back/low back pain (66%), osteoarthritis (25%), diabetic peripheral neuropathy (4%), neck pain (3%), and traumatic injury, complex regional pain syndrome, rheumatoid arthritis, fibromyalgia, and knee pain (<1% each). Improvement in 5 areas of functioning evaluated by the CAPF (general activities, walking ability, ability to work/perform activities of daily living, relationships with others, and enjoyment of life) and 6 of 7 areas of functioning evaluated by the PAF (ability to go to and perform work, walk, exercise, socialize, have sex, and enjoy life) were reported for at least 49% of patients at week 4 and endpoint. A 2- to 3-point mean decrease was observed for each of the BPI-SF pain interference questions from baseline to week 4 throughout the study. Mean changes from baseline to endpoint in SF-36 subscales (bodily pain, general health, mental component summary, mental health, physical component summary, physical functioning, role emotional, role physical, social functioning, and vitality) ranged from 3.3 to 22.3. Mean SDS scores improved from moderate to mild disruption in work/school (5.0 to 2.8), social life (4.8 to 2.5), and family life (5.1 to 2.6; all $P<0.001$) from baseline to endpoint.

Conclusions

Patients who received ER hydrocodone showed early numeric improvement with increased functioning, with continued improvement throughout the 12 month open label study.

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Long-Term Safety and Maintenance of Analgesia with an Extended-Release Hydrocodone Tablet Formulated with Abuse-Deterrence Technology during a 12-month Open-Label Study in Patients with Chronic Pain

Martin E. Hale[1], Thomas R. Zimmerman, Jr[2], Yuju Ma[2], Richard Malamut[2]
[1]Gold Coast Research, LLC, Plantation, FL, USA, [2]Teva Pharmaceuticals, Frazer, PA, USA

Purpose

To evaluate the long-term safety of an extended-release (ER) hydrocodone tablet formulated to provide sustained pain relief with dosing every 12 hours. This formulation employs Teva abuse-deterrence technology, which provides resistance against rapid release of the active moiety when the tablet is manipulated or taken with alcohol.

Method

In this 12-month, phase 3, open-label study, eligible patients (aged 18-80 years) were rolled over from a previous 12-week, randomized, placebo-controlled study of ER hydrocodone or were newly enrolled with chronic (≥3 months) noncancer pain. After titrating ER hydrocodone (15-90 mg every 12 hours) to an analgesic dose, patients received up to 52 weeks of open label treatment. Safety assessments included adverse events (AEs), serious AEs, withdrawals, and deaths. Patient global assessment (PGA) of pain control was also evaluated (assessments collected before the first titration dose in the previous study were considered baseline for rollover patients).

Results

Of the 330 patients enrolled, 329 patients received ≥1 ER hydrocodone dose and were evaluable for safety, 291 entered the open-label treatment period, and 184 completed the study. Mean age was 54.3 years, and 79% of patients were white. Primary chronic painful conditions were back/low back pain (66%), osteoarthritis (25%), diabetic peripheral neuropathy (4%), neck pain (3%), and traumatic injury, complex regional pain syndrome, rheumatoid arthritis, fibromyalgia, and knee pain (<1% each). The analgesic dose of ER hydrocodone identified was 15 mg for 70 patients (24%), 30 mg for 77 patients (26%), 45 mg for 52 patients (18%), 60 mg for 52 patients (18%), and 90 mg for 40 patients (14%). A total of 88 patients (30%) required ≥1 dose adjustment; 77 patients (26%) had their dose of ER hydrocodone increased, and 11 patients (4%) had their dose of ER hydrocodone decreased. A total of 284 patients (86%) reported ≥1 AE, most commonly (>5%) constipation (26%), nausea (19%), headache (12%), somnolence (11%), vomiting (9%), and upper respiratory tract infection (8%). Twenty-seven (8%) patients experienced ≥1 serious AE (SAE); SAEs (>1 patient) included dehydration (n=2), deep vein thrombosis (n=2), renal failure (n=3), and pneumonia (n=3); none were considered treatment related. Sixty-two (19%) patients withdrew because of treatment-emergent AEs, most commonly nausea (5%) and constipation (3%). Two deaths were reported (cause unknown, n=1; cardiac arrest and hyperkalemia, n=1); neither was considered treatment-related. Good/excellent PGA responses were reported by 20% of patients at baseline, 81% at the beginning of open-label treatment, and 75% at endpoint (last observed postbaseline data).

Conclusions

ER hydrocodone demonstrated a safety profile consistent with the known safety profile of hydrocodone and other opioids and was well-tolerated up to 12 months in patients with chronic pain, with improvements in pain control observed early and maintained through the end of the study.

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Using the LIFE test to measure physical functioning in patients completing multidisciplinary treatment for chronic pain:

Paul Heideman, Ben Lexau, Chris O'Hotto, Rachel Peterson
Medical Advanced Pain Specialists, Minneapolis, MN, USA

Purpose

Multidisciplinary pain treatment programs have been shown to reduce patients' experience of pain and increase patients' ability to engage in physical activity (i.e., physical function). Outcome studies of multidisciplinary treatment programs have largely employed self-report measures of physical function (e.g., Oswestry Disability Index). Relatively few studies have employed standardized and objectively based measures of physical function to assess effectiveness. In the present study, an objective, standardized measure of physical functioning is used to assess the effectiveness of multidisciplinary pain treatment.

Method

Participants were 266 patients (73% female; mean age = 46 years; range 17-79 years) with chronic pain who completed a four week long, four hour per day multidisciplinary treatment program. The program included physical therapy, education, and relaxation response training. Patients carried a variety of pain diagnoses: 55% lumbar; 15% cervical; 1% thoracic; 28% multisite or widespread pain (e.g. fibromyalgia).

The Limited Inventory of Functional Endurance (LIFE) test is a composite measure of patient performance on ten physical tasks that represent activities of daily living. Tasks include lifting, carrying, walking, stair climbing, transfers, balance, and overhead endurance. The LIFE total score reflects physical performance across 10 Likert-type items (5 point response option). A maximum LIFE Test score is 100. A lower total score reflects greater physical limitation. The LIFE test was developed and standardized at Medical Advanced Pain Specialists.

Results

As hypothesized, there was a significant increase in LIFE scores from 52/100 at the time of admission to 69/100 at the time of discharge ($p < .001$). This suggests improvement in physical functioning. Similarly, patients showed a reduction in pain rating (6.2/10 vs. 5.2/10, $p < .001$), a reduction in Oswestry Disability Index (.46 vs. .40, $p < .001$), and a reduction in perceived neck disability (.38 vs. .34, $p < .001$).

Conclusions

The present study demonstrated benefits of multidisciplinary treatment for chronic pain. Subjectively, patients reported less pain and improved physical function. This study demonstrated that improvements in physical function could be measured with an objective standardized test. The LIFE test is an objective measure that can be used to assess treatment outcomes in patients with chronic pain. Further research is needed to validate the LIFE test.

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The Evolving Demographics of Opioid Addiction

Michael Higgins[1], Gianpietro Zampogna[2], Joseph V. Pergolizzi, Jr.[3,4], Jo Ann LeQuang[2]
[1]Highline Research Advisors, New York, NY, USA, [2]NEMA Research, Inc, Bonita Springs, FL, USA, [3]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA, [4]Department of Pharmacology, Temple University School of Medicine, Philadelphia, PA, USA, [5]Department of Anesthesiology, Georgetown University School of Medicine, Washington, DC, USA

Purpose

Opioid addiction presents the healthcare system with unprecedented new challenges. In 2012, 4.5 million Americans were reported to be addicted to opioids and 24 million admitted to having taken an illicit drug in the past month.[1]The face of addiction is changing with the fastest-growing population of opioid addicts individuals between the ages of 50 and 69.[1]Illicit drug use cost the U.S. $193 billion in 2007. [2]Today, about 90% of heroin users have migrated to the illicit drug after exhausting access to prescription opioids. [3]And contrary to many assumptions that drug abusers are uneducated "street people," over 30% of heroin addicts have attended or graduated from college. [4]

The purpose of our study was to investigate the recently reported statistics on opioid addiction in America, in particular, to determine if and how the demographics of opioid addiction have changed.

Method

Our report is based on recent available data from the medical literature, government and authoritative websites, and financial analysis. A list of key statistics was generated and then assessed by authors for relevance to describing the changing face of opioid addiction. Emphasis was placed on identifying data and trends that contradict the prevailing concept of opioid addiction today.

Results

Almost 24 million Americans (9.2% of the population) have used an illicit drug in 2012, up from 8.1% in 2008.[5]Estimates show that on a daily basis in 2012, about 7,900 Americans used an opioid agent non-medically for the first time.[1]Because most opioid addicts report marijuana as their first illicit drug, under the "gateway theory," the growth in opioid use will continue to increase, as it already has from 2010, when 14.5 million Americans reported using opioids "within the past month" to 18.9 million in 2012.

Poly-substance abusers are common: of 22.2 million substance abusers in 2012,[5] 4.5 million used a drug but not alcohol, 14.9 abused alcohol but not drugs, and 2.8 abused both drugs and alcohol. Of those patients, 1.0 million were treated for drug abuse (excluding alcohol) and 1.2 million were treated for drug-and-alcohol abuse. This is only a fraction of substance abusers. An estimated 1.9 million addicts in the U.S. prison system[6] are incorporated in these statistics.

Opioid addiction frequently occurs in the young, but those aged 50 to 69 years are the fastest-growing subpopulation. People ≥ 65 years who had at some point in their lives abused opioids increased significantly by 34% from 2011 to 2012.[1] The very young—ages 12 to 17—compose about 26% of opioid addicts.

Many heroin users (47%) and prescription drug abusers (45%) have graduated high school and 22% and 30%, respectively, have had some college. Ninety percent of heroin addicts are white, mean age 22.9 years, split evenly

between men and women, who started substance abuse with marijuana and progressed to prescription painkillers and finally heroin.[3] Most opioid abusers live in large urban areas (41%), then smaller urban areas, and finally rural areas. The abuse rate per person in rural areas is higher than large cities.

Conclusions

The number of opioid addicts in America is large and there is no reasonable expectation the trend toward increasing numbers of addicts will decrease. What has changed is the face of opioid addiction. Opioid addicts are typically younger, more educated than expected and many migrate to heroin when prescription opioid supplies are no longer available to them. Many opioid addicts are poly-substance abusers and only a small subset receive treatment. Surprising to many, there are an increasing number of 50-69 year old Americans that are abusing prescription opioids, which is an excellent example of the heterogeneity of today's opioid abuser.

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Opioid Conversion Applications for iPhone and Android Systems: Accuracy Determination and Comparison.

Nightingale Meyou[1], Danielle Chipchura[1], Renee Holder[1]
[1]*Roseman University of Health Sciences, Henderson, NV, USA,* [2]*Nathan Adelson Hospice, Las Vegas, NV, USA*

Purpose

Accurate equianalgesic conversion is an essential skill for healthcare practitioners in a variety of settings. Due to convenience, smart-device applications for medical professionals are becoming more prevalent, but their reliability can vary significantly due to lack of regulation. The purpose of this investigation was to determine the accuracy of opioid conversion applications (OCAs) for smartphones.

Method

Android and iPhone application stores were searched using the search terms "opioid conversion calculator," "opioid conversion," "opioid converter," "opioid calculator," and "opioid" to identify applications. Applications that advertised an opioid calculator or conversion tool, and converted among common opioids and routes (morphine enteral [E] and parenteral [P], hydromorphone E and P, oxycodone E, hydrocodone E, oxymorphone E and P, and fentanyl P) were included. Applications that offered only a conversion table, duplicate applications, or those that were not written in the English language were excluded. OCA accuracy was tested using the total daily dose (TDD) of nine randomly selected patients, each using one of the common opioids. Authors calculated and verified the TDD and opioid conversion values for each regimen using a conventional equianalgesia table. Each TDD and opioid was entered into the OCA, converted to the other common opioids, and recorded. All conversions were verified by at least one study author. Accuracy was defined as (1-[observed value - expected value]/expected value) x 100%. The primary outcome was overall mean conversion accuracy of an OCA. Secondary outcomes were mean conversion accuracy to and from each opioid, and comparison of overall accuracy of free versus paid applications.

Results

Eighty-eight potential OCAs were identified (68 Android, 20 iPhone). Eighty-five OCAs were excluded resulting in three evaluable OCAs. No iPhone OCAs met the full inclusion criteria. All three evaluable OCAs were free. Evaluable OCAs ranged in overall accuracy from 84.22 ± 32.2% to 87.71 ± 26.16%. The most accurate app was Opioid Converter. Converting from all opioids but fentanyl resulted in the highest accuracy of 95.06 ± 14.81%, while converting from fentanyl resulted in the lowest accuracy of 28.9 ± 26.66%. Converting to all opioids but fentanyl resulted in the highest accuracy 91.11 ± 26.67% while converting to fentanyl resulted lower than expected calculated doses and a low accuracy of 60.5 ± 14.81%.

Conclusions

Opioid Converter was the most accurate OCA identified. Based on accuracy rates for individual opioids, Opioid Converter may be a useful tool to determine equianalgesic doses of morphine E and P, hydromorphone E and P, oxycodone, hydrocodone, and oxymorphone E and P. Opioid Converter may result in inaccurate estimations of fentanyl equianalgesia, erring on the low side. Only free OCAs met the inclusion criteria; therefore, no comparison was made to paid OCAs. Given that equianalgesic doses serve as a guideline, clinical judgment using individual patient factors should not be eliminated from the equation when converting among opioids.

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Choosing the Best Urine Benzo Screen for Monitoring Adherence to Alprazolam or Clonazepam

Maggie L Hopkins, Elisabeth Malmberg, Bella Church, Gwendolyn A McMillin
University of Utah, Salt Lake City, Utah, USA

Purpose

The purpose of this study was to predict the detection rates of three common laboratory-based benzodiazepine immunoassays, using authentic patient urine that was confirmed positive for alprazolam or clonazepam.

There are a number of immunoassay platforms on the market for screening to detect benzodiazepines in urine. Despite the fact that the cutoff concentration for each assay may be the same, each immunoassay has a different sensitivity for individual analytes (parent drug and drug metabolites). This can lead to inconsistency between detection rates of individual immunoassays and drugs, which may lead to false-negative screen results. Many tests are ordered to gauge compliance for medication use. False negatives greatly disrupt the course of normal care for patients, resulting in investigations, medication refill delays and damage to the patient-provider relationship.

Method

De-identified urine drug testing results were obtained retrospectively according to protocols approved by the University of Utah Institutional Review Board. Results were generated for 18,502 urine samples submitted to ARUP Laboratories (SLC, UT) for quantitative benzodiazepine testing, by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). We chose two common benzodiazepine drugs, alprazolam and clonazepam, to further analyze. There were 5926 samples positive for alprazolam and/or the alprazolam metabolite alpha-hydroxyalprazolam. There were 4032 samples positive for clonazepam and/or the clonazepam metabolite 7-aminoclonazepam. The LC-MS/MS method included pre-analytical hydrolysis. The detection cutoff for these four analytes was 5 ng/mL.

Immunoassays can typically detect both parent drug and major metabolites. Based on cross-reactivity profiles published for the DRI® (Microgenics), EMIT® II Plus (Beckman Coulter), and CEDIA® (PerkinElmer) benzodiazepine immunoassays, we derived a formula to predict the total apparent concentration of alprazolam and clonazepam that each immunoassay would detect, which takes into account the cross-reactivity factor for each analyte and metabolite. We compared this calculated apparent level to the cut-off level (200 ng/mL) to estimate detection rates of each immunoassay for urine samples confirmed positive. The percent of positive samples above 200 ng/mL was defined as the sensitivity of an immunoassay to each drug, and the percent of samples positive by LC-MS/MS, but negative (below 200 ng/mL) by the immunoassay was defined as the false-negative rate. For the CEDIA assay, cross-reactivity was provided with and without hydrolysis by beta-glucuronidase.

The statistical analyses were carried out using SAS 9.3 (SAS Institute, Cary, NC).

Results

Of the three assays evaluated, EMIT II has the highest sensitivity for alprazolam and metabolites, at 84%. False negative rates are predicted to vary from approximately 15-50% with the assays evaluated. None of the assays have adequate sensitivity for clonazepam, with false negative rates estimated to exceed 98%. Sensitivity is improved by pre-analytical hydrolysis, as evidenced by the CEDIA + glucuronidase results. This step requires added complexity and time, and is not feasible for most laboratories performing benzodiazepine screening. The sensitivity of each

immunoassay that was included in our study (considering a cutoff of 200 ng/mL for the apparent concentration) is shown below:

For Alprazolam:

CEDIA sensitivity: 4157/5926 = 70.15%
CEDIA+ glucuronidase sensitivity: 4670/5926 = 78.81%

EMIT II sensitivity: 4989/5926 = 84.19%
DRI sensitivity: 2934/5926 = 49.51%

For Clonazepam:

CEDIA sensitivity: 53/4032 = 1.31%
CEDIA+ glucuronidase sensitivity: 1609/4032 = 39.91%

EMIT II sensitivity: 18/4032 = 0.55%
DRI sensitivity: 20/4032 = 0.50%

Limitations of this study include our use of a formula to predict the total apparent concentration of alprazolam and clonazepam that each immunoassay would detect. The formula takes into account the cross-reactivity factor for each analyte and metabolite, and the concentrations of each analyte determined previously by LC-MS/MS. Manufacturers were contacted to provide the most up-to date information on all tested metabolites, but cross-reactivities were not available for all metabolites. The unlisted metabolites may or may not react with each screening assay, which could increase the sensitivity above the calculated level.

Conclusions

The immunoassays evaluated here are inappropriate for assessing patient compliance with clonazepam, and may be inappropriate for assessing compliance with alprazolam. If there is clinical reason to expect clonazepam or alprazolam in a urine drug test, we recommend a definitive testing method such as LC-MS/MS.

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Value of CYP Genetic Testing for Opioid Therapy: An Exploratory Combined Cross-sectional and Longitudinal Study in a Chronic Pain Cohort

Naissan Hussainzada[1,2], Ruth Landau[3], Matthew Ruehle[1,2], Kathy Egan-City[1,2], Carol Meares[1,2], Steven Passik[1,2], Kenneth Kirsh[1]
[1]Millennium Laboratories, San Diego, CA, USA, [2]Millennium Research Institute, San Diego, CA, USA, [3]University of Washington, Seattle, WA, USA

Purpose

Multiple factors influence patient response to chronic opioid therapy and genetics represents an innovative target for personalizing treatment to optimize analgesia. The liver enzyme CYP2D6 represents a clinically relevant pathway for processing commonly used opioids such as hydrocodone, oxycodone, tramadol and codeine. While the emerging body of clinical evidence and consensus guidelines is important for highlighting the value of opioid pharmacogenetic in patient management, there remain some gaps in the literature. In this poster presentation, we describe the results of a cross-sectional analysis from the first phase of a longitudinal examination of the impact of CYP2D6 genotype and phenotype information on clinical outcomes in a cohort of patients with chronic pain receiving opioid therapy.

Method

A total of 130 adult patients (>18 years old) with a diagnosis of chronic pain receiving stable opioid monotherapy with hydrocodone, oxycodone, or tramadol were enrolled at several sites around the country. Demographics and a variety of pain variables were collected at baseline. Patient DNA was extracted from saliva samples and sent for CYP2D6 genotyping. Patients were then assessed at three follow-up visits that were spaced one month apart.

Results

A total of 130 patients were evaluated in the cross-sectional phase of the study. Subjects with reduced CYP2D6 metabolism (i.e. poor or intermediate metabolizers) were significantly more likely to have difficulty achieving functional goals compared to extensive or ultra-rapid metabolizers. Furthermore, CYP2D6 genotype results impacted clinical decision-making during management for a significant number of patients, particularly those with variant (non-normal) CYP2D6 genotype results. In general, patients were more likely to experience medication changes if they were variant metabolizers for CYP2D6. Management changes included dose increases, changes to dose schedules, or an opioid medication switch.

Conclusions

These results corroborate a number of previous studies that demonstrate elevated risk of side effects in patients with abnormal CYP2D6 metabolism receiving oxycodone, hydrocodone, or tramadol. The results also suggest that genotype information can impact patient care and that clinicians are likely to use such information for a significant portion of their patients that receive pharmacogenetic evaluation.

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Fixed-Dose Subcutaneous Methylnaltrexone in Patients With Advanced Illness and Opioid-Induced Constipation: Results of a Randomized, Placebo-Controlled Study and Open-Label Extension

Janet Bull[1], Charles Wellman[2], Robert Israel[3], Andrew Barrett[4], Craig Paterson[4], William Forbes[4]
[1]Four Seasons, Flat Rock, Arkansas, USA, [2]Hospice of the Western Reserve, Cleveland, Ohio, USA, [3]Progenics Pharmaceuticals, Inc., Tarrytown, New York, USA, [4]Salix Pharmaceuticals, Inc., Raleigh, North Carolina, USA

Purpose

Subcutaneous methylnaltrexone, dosed based on body weight, is efficacious and well tolerated for opioid-induced constipation (OIC) in patients with advanced illness; however, fixed-dose methylnaltrexone may improve ease of administration.

Method

A phase 4, double-blind, randomized, placebo-controlled trial (RCT; ClinicalTrials.gov identifier: NCT00672477) included adults with advanced illness and OIC (<3 bowel movements in the past week and no bowel movement in 24 hours, or no bowel movement in 48 hours) who were receiving stable doses of opioids. Patients were randomly assigned to receive methylnaltrexone (8 mg or 12 mg by body weight [38 to <62 kg or ≥62 kg, respectively]) or placebo every other day for 2 weeks. Patients completing the RCT could enroll in an open-label extension (OLE) study (ClinicalTrials.gov identifier: NCT00672139) with methylnaltrexone administered as needed. The primary endpoint was percentage of patients with rescue-free bowel movement (RFBM) within 4 hours after ≥2 of the first 4 doses in the first week. Secondary endpoints included patients with first RFBM ≤4 hours after the first dose; RFBM ≤4 hours after ≥4 of the maximum 7 doses; mean number of RFBM or bowel movements (BM) ≤24 hours after dosing; and the percentage of patients using rescue laxatives in the RCT. This study was approved by institutional review boards and ethics committees.

Results

In the RCT, of 237 patients randomized, 230 received ≥1 study dose (116 and 114 patients received methylnaltrexone and placebo, respectively). Of 156 patients entering the OLE study, 149 received ≥1 dose of methylnaltrexone. In the overall RCT population (n=230), the most common underlying advanced illness was cancer (66.1%), the median daily morphine equivalent dose was 176.8 mg/d, and the mean OIC duration was 76.6 weeks. The percentage of patients achieving the primary endpoint was 62.9% and 9.6% for methylnaltrexone and placebo groups, respectively ($P<0.0001$). The time to RFBM after the first dose was rapid in the methylnaltrexone group, with median time of 0.8 hour versus 23.6 hours in the placebo group ($P<0.0001$). Significant differences favoring methylnaltrexone were observed for all RCT secondary efficacy endpoints measured. The percentage of patients receiving methylnaltrexone or placebo with first RFBM ≤4 hours after the first dose was 69.8% and 17.5%, respectively ($P<0.0001$). The percentage of patients receiving methylnaltrexone or placebo with RFBM ≤4 hours after ≥4 of the maximum 7 doses was 62.2% and 4.9%, respectively ($P<0.0001$). The mean number of BM ≤24 hours after dosing was 4.9 and 3.0 at week 1 for patients receiving methylnaltrexone or placebo, respectively ($P<0.0001$), and 3.2 and 2.2 ($P=0.0083$) at week 2. The mean number of RFBM ≤24 hours after dosing was 4.9 and 2.7 at week 1 for patients receiving methylnaltrexone or placebo, respectively ($P<0.0001$), and 3.2 and 2.0, respectively ($P=0.0024$), at week 2. Rescue laxatives were used in the RCT by 27.2% and 39.6% of patients receiving methylnaltrexone or placebo, respectively ($P=0.0020$). Efficacy results during the 10-week OLE were consistent with results for the 2-week RCT. In the RCT, the most common adverse events (methylnaltrexone vs placebo, respectively) were abdominal pain (33.6% vs 16.7%), nausea (11.2% vs 15.8%), and disease progression (8.6% vs 14.9%).

Conclusions

Fixed-dose methylnaltrexone demonstrated robust and durable efficacy, and it was well tolerated in treating OIC in patients with advanced illness.

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Effect of workplace- versus home-based physical exercise on musculoskeletal pain in healthcare workers: Cluster randomized controlled trial

Markus Due Jakobsen[1,2], Emil Sundstrup[1,2], Mikkel Brandt[1], Kenneth Jay[1,3], Per Aagaard[2], Lars Andersen[1]
[1]National Research Centre for the Working Environment, Copenhagen, Denmark, [2]Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark, [3]Electronics and Computer Science, Faculty of Physical and Applied Sciences, University of Southampton, Southampton, UK

Purpose

Regular physical exercise is important for preventing and reducing musculoskeletal pain, but the optimal setting to achieve high adherence and effectiveness remains unknown. This study investigated the effect of workplace versus home-based physical exercise on musculoskeletal pain among healthcare workers.

Method

200 female healthcare workers (Age: 42.0, BMI: 24.1, Pain intensity: 3.1 on a scale of 0-10) from 18 departments at three hospitals participated. Participants were randomly allocated at the cluster level to 10 weeks of: 1) workplace physical exercise (WORK) performed during working hours for 5x10 minutes per week and up to 5 group-based coaching sessions on motivation for regular physical exercise, or 2) home-based physical exercise (HOME) performed during leisure time for 5x10 minutes per week. Both groups received ergonomic counseling on patient handling and use of lifting aides. Average pain intensity (0-10 scale) in the low back and neck/shoulder was primary outcome.

Results

2.2 (SD: 1.1) and 1.0 (SD: 1.2) training sessions were performed per week in WORK and HOME, respectively. Pain intensity, back muscle strength and use of analgesics improved more following WORK than HOME ($p<0.05$). Between-group differences at follow-up (WORK vs. HOME) was -0.7 points for pain intensity [95% CI -1.0 to -0.3] 5.5 Nm for back muscle strength [95% CI 2.0 to 9.0] and -0.4 days per week for use of analgesics [95% CI -0.7 to -0.2].

Conclusions

Workplace physical exercise is more effective than home-based exercise in reducing musculoskeletal pain, increasing muscle strength and reducing the use of analgesics in healthcare workers.

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Non-Systemic Transdermal (NST) Pain Therapy Reduces Oral Pain Medication in a Population of 65 Years Old or Older Patients

Dean Juge[1,2], Rob Gussenhoven[1,3], Tino Unlap[1,4]
[1]University of Alabama @ Birmingham, Birmingham, AL, USA, [2]DeTOURE, LLC, Rome, GA, USA, [3]DermaTran Health Solutions, Rome, GA, USA, [4]Patient Outcomes Analytics, Birmingham, AL, USA

Purpose

In 2008, the U.S. Census Bureau estimated 38.9 million or 12.8% of the total population was 65 years old or older, a number that is growing rapidly. A majority of elderly persons have significant chronic pain problems but are poorly treated. Because of age-induced alterations, including alterations in CNS, hepatic and renal functions, drug ADMEs are altered and make treating chronic pain in elderly patients with oral pain medication a less attractive option. We conducted an outcomes survey that showed that Non-Systemic Transdermal (NST) pain creams reduced pain, improved quality of life and reduced the use of oral pain medications by 38% in a population of 65 years old and older patients suffering with a variety of chronic pain conditions. Therefore, NST pain therapy is an excellent alternative to treat chronic pain in 65 years old and older patients. Because NST pain therapy was effective in reducing oral pain medication use in 65 years old and older chronic pain patients, this study was conducted in order to determine the specific classes of oral pain medications whose uses were reduced in patients undergoing NST pain therapy.

Method

A group of patients 65 years old and older (n=925) were asked to indicate whether their use of oral pain medication had decreased, increased or stayed the same while undergoing NST pain therapy. If decreased, they were asked to indicate the class and the specific drugs whose uses were decreased during the NST pain therapy.

Results

Our results showed that 38% of the patients, 65 years and older, decreased in their use of oral pain medication and consists of: Anti-inflammatory (55%), Narcotics (38%), and Nutritional supplements (28%). Of the Narcotics, Hydrocodone was reduced by 45%, Tramadol was reduced by 35% and Oxycodone was reduced by 18%.

Conclusions

This study shows that NST pain therapy is an excellent substitute for oral pain medication for the treatment of chronic pain in 65 years old and older patients. It is effective in reducing pain, improves quality of life and reduces and replaces the use of oral pain medications.

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Comparison of the Risk of Opioid Overdose among Patients Prescribed Extended-release Opioids versus Immediate-release Opioid Analgesics

Aditi Kadakia, Coplan, Angela DeVeaugh-Geiss
Purdue Pharma L.P., Stamford, CT, USA

Purpose

There is debate about the relative contribution of immediate release (IR) versus extended- release (ER) opioids to opioid overdose particularly among patients. FDA has mandated class labeling changes for all ER and long-acting opioid products such that full prescribing information must state "because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve {product name} for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain". However there is very little research that has compared the risk of overdose among patients prescribed IR versus ER opioid analgesics in a systematic way. Surveillance systems like DAWN measure overdose outcomes on a population level and it is unclear as to how many occur in patients versus non-patients and identification of opioid formulation (including differentiation between IR and ER formulations) depends on accurate classification of formulation from emergency department records. Thus this study was done to compare the risk of opioid overdose among patients prescribed ER versus IR opioid analgesics, adjusting for differences between patients prescribed ER and IR opioids that are related to overdose risk, such as substance use disorders, sedative hypnotic (SH) use, psychiatric comorbidity and daily opioid dose.

Method

We conducted a retrospective cohort study using members from the MarketScan commercial insurance database from January 2008–March 2012. All adults with a new opioid prescription were included in the cohort. All patients were followed from the first (index) prescription until the first of: 1) end of insurance enrollment, 2) end of data for administrative reasons, or 3) first episode of opioid overdose. Opioid overdose/poisoning was defined using ICD9CM codes 965.00, 965.02, 965.09. Daily opioid dose was calculated as the number of pills dispensed per day (number of pills dispensed in prescriptions divided by number of days that prescription was dispensed) multiplied by tablet strength. The daily dose for each prescription was then converted to a morphine-equivalent dose (MED) by multiplying it with a standard conversion factor for each opioid. A total opioid dose from all opioids (IR and/or ER opioids) taken on a particular day was obtained by summing across all prescriptions. The MED was divided into 50 mg/day categories and person time in each category was calculated. Overdose cases were categorized based on the average dose on days used in the 30 day window preceding the overdose (day of overdose and 29 days prior). Incidence rates per 100 person years of opioid use were calculated for IR opioids alone, ER opioids alone and both IR and ER opioids together, and were expressed as % of patients per year of use. Rate ratios for determining effect of opioid type on overdose adjusting for other covariates were calculated using Poisson regression.

Results

There were 95 million members enrolled in MarketScan during the study period, of which 9.6 million received new opioid dispensings. There were 585,483 person-years of opioid use, of which 92.7% of person time was spent on IR opioids alone, 3.9% on ER opioids alone and 3.4% on both IR and ER opioids. 3,224 patients were diagnosed with opioid overdose/poisoning, of which 89% were identified from a hospitalization or emergency room visit indicating clinical severity. 44.3% had no opioid dispensed within 30 days prior to overdose. Many more patients diagnosed with an overdose were dispensed IR opioids (1,413) than ER opioids alone (70), and 313 were dispensed both. The

unadjusted rate of overdose per year of use for all opioids combined was similar for IR and ER opioids (0.26% vs. 0.31%), but was higher for ER+IR opioids together (1.57%). The final model included SH use, age, daily opioid dose, and baseline substance abuse disorder and psychiatric diagnoses. The adjusted risks of overdose were similar for ER versus IR opioids (rate ratio {RR} = 0.84, 95% CI: 0.66 - 1.08, p=0.1740), but the risk of overdose was considerably higher for ER+IR opioids together than ER opioids alone (RR=4.09, 95% CI: 3.13-5.33) or IR opioids alone (RR=3.44, 95% CI: 2.91 -4.07). For patients dispensed IR and ER oxycodone, the risk of overdose was not different for IR oxycodone use alone versus ER oxycodone alone (RR =1.03, 95% CI: 0.66-1.59), but was higher for ER oxycodone +any IR opioids together versus ER oxycodone alone (RR=2.25, 95% CI: 1.40- 3.64). For patients dispensed IR and ER morphine, the risk of overdose was higher for IR morphine use alone versus ER morphine alone (RR =3.46, 95%CI: 1.23-9.73), and was higher for ER morphine +any IR opioids together versus ER morphine alone (RR=5.48, 95%CI: 2.61-11.52).

Conclusions

The risk of opioid overdose did not differ among patients prescribed ER opioids alone versus IR opioids alone. However, the risk of overdose was considerably higher among patients dispensed ER plus IR opioids concomitantly versus ER opioids alone or IR opioids alone. These data indicate that the risk of opioid overdose does not differ between ER and IR opioids when they are used as single opioids. However, the two combined are associated with considerably increased risk. Guidelines for opioid prescribing may need to consider the use of IR and ER opioids together as polypharmacy with increased risk of opioid overdose.

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Intranasal Abuse Potential Study of a Once-Daily, Single-Entity, Extended-Release Hydrocodone Tablet (Hysingla™ ER) in Recreational Opioid Users

Stephen Harris[1], Salvatore Colucci[1], Ram Kapil[1], Allesandra Cipriano[1], Pierre Geoffroy[2], Talar Hopyan[2], Naama Levy-Cooperman[2]
[1]Purdue Pharma L.P., Stamford, CT, USA, [2]INC Research Toronto, Toronto, ONT, Canada

Purpose

A once-daily, single-entity, extended-release hydrocodone bitartrate tablet (HYD; Hysingla™ ER) has been formulated using a proprietary extended-release technology that provides physicochemical attributes intended to impart abuse deterrent properties. The intranasal abuse potential of fine-milled and coarse-milled HYD (using an industrial mill and razor blade, respectively) were compared to hydrocodone powder and placebo.

Method

Study design, conduct, analysis and interpretation followed FDA's Jan-2013 draft guidance, *Abuse-Deterrent Opioids - Evaluation and Labelling*. Healthy subjects with a history of recreational opioid use who were not physically dependent on opioids were enrolled. An intranasal hydrocodone powder dose of 60 mg was selected in an initial placebo-controlled dose-selection study phase. Then additional eligible subjects successfully completed a blinded qualification evaluation confirming that they could tolerate a 60 mg IR hydrocodone dose and could adequately differentiate the effects of hydrocodone from placebo. Subjects (N=32) then received the 4 treatments in a randomized, double-blinded fashion (7-day washout between treatments): fine-milled HYD 60 mg tablet, coarse-milled HYD 60 mg tablet, 60 mg hydrocodone powder, and placebo. Abuse potential was evaluated using subjective pharmacodynamic (PD) assessments including: visual-analog scales (VAS) for 'At the Moment' Drug Liking, 'High', 'Overall Drug Liking', 'Take Drug Again', 'Good Effects', and 'Bad Effects', as well as Subjective Drug Value and Pupillometry (objective measure of opioid effects). Plasma samples were collected to characterize hydrocodone and metabolite pharmacokinetics (PK), and safety was assessed.

Results

Primary PD findings for hydrocodone powder vs. placebo confirmed study validity. Mean Emax values for positive PD measures were greatest for 60 mg hydrocodone powder, followed by the two tampered 60 mg HYD treatments and placebo. Statistical analysis of PD measures indicated that intranasal administration of tampered HYD treatments had lower abuse potential than hydrocodone powder. Study treatments were well-tolerated.

Conclusions

Overall, the study results support the conclusion that HYD has meaningful abuse-deterrent physicochemical properties.

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In Vitro Evaluation of Morphine ARER Potential for Abuse via Injection

Eric R. Kinzler[1], Ray DiFalco[2], Carmela Pantaleon[1], Stefan Aigner[1]
[1]Inspirion Delivery Technologies LLC, Valley Cottage, New York, USA, [2]Cerovene, Valley Cottage, New York, USA

Purpose

The misuse, abuse, and diversion of prescription opioids are major public health concerns. The CDC has defined prescription drug abuse as an epidemic in the US and has encouraged the development of abuse-deterrent formulations. Although extended-release (ER) opioids remain an important cornerstone in the medical management of chronic severe pain, the high potency of ER opioid formulations combined with abusers' intentional manipulation (crushing) of ER products to induce "dose dumping" can lead to serious consequences including respiratory depression and death. Regulatory approval of novel abuse-deterrent opioids is based, in part, on a combination of in vitro and in vivo studies that rigorously test each abuse-deterrent formulation for abuse potential via routes of administration commonly employed by recreational drug abusers for intentional misuse. Epidemiologic data suggest that ER morphine formulations are commonly manipulated and misused via the oral, intranasal, and intravenous routes of administration. An abuse-deterrent formulation of ER morphine, Morphine abuse-resistant extended release (Morphine ARER), is under development and designed to be resistant to physical manipulation, maintain its intended ER characteristics even when manipulated, and form a non-syringeable viscous material in liquid environments to prevent passage through a needle. Laboratory tests have shown that Morphine ARER tablets are physically difficult to manipulate and maintain their ER characteristics in a variety of solvents despite aggressive physical manipulation. To assess whether these physiochemical properties may reduce the potential for abuse of Morphine ARER via injection, a series of syringeability, injectability, and small-volume extractability laboratory tests were performed.

Method

Syringeability, injectability, and extractability of 100-mg tablets of Morphine ARER (Inspirion Delivery Technologies LLC) were compared with a commercially available controlled-release morphine sulfate (CR-morphine) tablet using water as the vehicle. Morphine ARER tablets (n = 5) were either left intact, cut with a knife, or ground in a coffee grinder for 60 seconds and placed in glass vials containing 1 mL or 5 mL of water for 1, 5, 10, or 30 minutes with and without agitation (100 RPM). At each time point, attempts were immediately made to draw the mixture (syringeability) into a 10 cc syringe fitted with a 27-, 24-, or 18-gauge needle. Difficulty was assessed by the laboratory technician on a scale of 1 (very easy to syringe/inject) to 10 (impossible to syringe/inject). To test injectability, mixtures were placed into the open barrel of a 10 cc syringe and then attempts were made to force the mixture through the needle with the plunger. Difficulty was assessed using the syringeability scale described previously. All tests were completed in an iterative fashion whereby the smallest needles were tested first; if passage through the needle was successful, the larger needles were not tested. Finally, if liquid was syringeable or injectable under any condition, the volume was recorded and analytically tested for morphine concentration.

Results

Crushed CR-morphine passed easily through the smallest needle and released approximately half of its morphine within 1 minute and nearly all within 5 minutes. In contrast, manipulated Morphine ARER tablets immediately formed a non-syringeable viscous material under each condition. It was impossible to pass any volume of crushed or cut Morphine ARER tablets through a needle in 1 mL or 5 mL water even when using very large 18-guage needles. As expected, intact Morphine ARER tablets released slightly larger amounts of morphine with larger volumes, longer times, and agitation but intact Morphine ARER tablets did not "dose dump" under any condition.

Conclusions

The inherent physiochemical properties within Morphine ARER prevented its syringeability, injectability, and extraction when tablets were manipulated in an attempt to defeat their ER characteristics and prepare them for injection. Furthermore, intact Morphine ARER tablets did not release high amounts of morphine despite being subjected to rigorous laboratory conditions that are likely unattainable by typical drug abusers. When combined with laboratory data showing that manipulated tablets maintain their ER characteristics in household and laboratory solvents, these data further suggest that Morphine ARER has abuse-deterrent properties that may aid in reducing abuse via the injection route of administration.

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Methods to estimate the prevalence and healthcare costs of undiagnosed opioid abuse among commercially-insured individuals

Amie Shei[1], Brad Rice[1], Noam Kirson[1], Caroline Enloe[1], Katharine Bodnar[1], Howard Birnbaum[1], Pamela Holly[2], Rami Ben-Joseph[2]
[1]Analysis Group, Inc., Boston, MA, USA, [2]Purdue Pharma L.P., Stamford, CT, USA

Purpose

The health and economic burden of prescription opioid abuse and dependence ("opioid abuse") is substantial. The rate of diagnosed opioid abuse among commercially-insured individuals was estimated to be over 18.6 per 10,000 in 2011. Estimates of the excess annual healthcare costs of diagnosed opioid abuse exceed $10,000 per patient among commercially-insured individuals. Much of opioid abuse remains undiagnosed, however, and the true prevalence, costs, and overall burden of undiagnosed opioid abuse are unknown. Stigma associated with opioid abuse and its treatment may hinder the diagnosis and treatment of opioid abuse. In addition, opioid abuse is likely to be underreported in administrative claims databases due to potential factors such as lack of recognition of the condition, reluctance to put a potentially damaging diagnosis in the patient's record, and reimbursement considerations. Previous estimates of the prevalence of undiagnosed abuse relied on assumptions and the best-available data at the time but did not account for differences between types of payers. In addition, prior research on the healthcare costs of undiagnosed opioid abuse relied on expert opinion. To date, there have been no published studies that empirically estimate the healthcare costs of undiagnosed abuse. Therefore, this study explored several methodological approaches for estimating the prevalence and healthcare costs of undiagnosed opioid abuse among commercially-insured individuals.

Method

This study focused on commercially-insured individuals. Survey data from a nationally-representative sample of commercially-insured individuals and administrative claims from a large commercial claims database were combined in order to estimate the rate of undiagnosed opioid abuse. The rate of past-year pain-reliever abuse among commercially-insured individuals ages 12 and above reported by the National Survey on Drug Use and Health (NSDUH) was considered to reflect the total (diagnosed and undiagnosed) rate of opioid abuse in the commercially-insured population in the U.S. in 2011. De-identified OptumHealth Reporting and Insights ("OptumHealth") commercial claims data were used to estimate the rate of diagnosed opioid abuse among commercially-insured beneficiaries ages 12-64 in 2011. The rate of undiagnosed opioid abuse in 2011 was calculated as the difference between the NSDUH and OptumHealth estimates.

The OptumHealth database was also used to estimate the healthcare costs of undiagnosed opioid abusers. Diagnosed opioid abusers were identified using ICD-9-CM diagnosis codes for opioid abuse/dependence, and they were required to be ages 12-64 and to have continuous non-HMO coverage throughout a 24-month study period centered on the date of the first opioid abuse/dependence diagnosis. It was assumed that their pre-diagnosis costs were a proxy for undiagnosed opioid abuse costs, and three different definitions of the pre-diagnosis period and post-diagnosis period (defined below) were examined. The per-patient ratio of healthcare costs between the pre-diagnosis costs and the post-diagnosis costs of diagnosed abusers was then calculated for each of these approaches.

Results

The total rate of opioid abuse estimated using the NSDUH was 0.57% among commercially-insured individuals in 2011. The rate of diagnosed opioid abuse using the OptumHealth commercial claims database was 0.19% in 2011. The difference between these two rates was 0.38%, representing the rate of undiagnosed opioid abuse among commercially-insured individuals in 2011.

For the analysis of healthcare costs of undiagnosed opioid abusers, the sample selection criteria resulted in the identification of 3,928 diagnosed opioid abusers. As mentioned above, we examined three different approaches to estimating the healthcare costs of undiagnosed opioid abuse, as alternative definitions of pre-diagnosis period costs and post-diagnosis period costs may result in different estimates. One approach used the annualized 6-month pre-diagnosis period costs as a proxy for undiagnosed opioid abuse, and the ratio between the annualized 6-month pre-diagnosis period costs and the 12-month period centered on the diagnosis date was 69.2%. Another approach used the 6-month pre-diagnosis period as a proxy for undiagnosed opioid abuse, and the ratio between the 6-month pre-diagnosis period costs and the 6-month post-diagnosis period costs was 52.9%. A third approach used the 12-month pre-diagnosis period costs as a proxy for undiagnosed opioid abuse, and the ratio between the 12-month pre-diagnosis period costs and the 12-month post-diagnosis period costs was 52.8%.

Conclusions

Assuming that the pre-diagnosis period can be used as proxy for the costs of undiagnosed abuse, the per-patient costs of undiagnosed opioid abuse were 52.8%-69.2% of the per-patient costs of diagnosed opioid abuse, depending on the methodological approach used. While the per-patient healthcare costs of undiagnosed opioid abusers are lower than those of diagnosed opioid abusers, the higher prevalence of undiagnosed opioid abuse implies that undiagnosed opioid abuse represents a substantial burden to commercial payers.

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Effect of Crushing on Oxycodone DETERx® compared with OxyContin®: A Clinical Evaluation

Ernest Kopecky[1], Patrick Noonan[2], Melinda O'Connor[1], Ravi Varanasi[1], William Poirier[1], Alison Fleming[1]
[1]Collegium Pharmaceutical, Inc, Canton, MA, USA, [2]PK Noonan Pharmaceutical Consulting, LLC, Williamsburg, VA, USA

Purpose

Extended-release(ER) opioid formulations offer several clinical advantages including the convenience of less frequent dosing, decreased fluctuations in plasma levels, more consistent analgesia over the dosing period, and less night-time awakening due to pain. However, the non-medical use and abuse of prescription opioids has become a significant public health problem of epidemic proportion. To reduce misuse and abuse, abuse-deterrent (AD) formulations have been developed; novel formulations are in clinical development.

The currently marketed oxycodone ER formulation (OxyContin® reformulated AD formulation [ADF]) is a monolithic tablet formulation with crush resistant features. While crush resistance is one of the methods to achieve abuse-deterrence, published data indicate that chewing and crushing can defeat the ER properties of OxyContin ADF[1], resulting in a PK profile similar to immediate-release (IR) oxycodone.

Oxycodone DETERx® (DETERx) is an ER, AD, microsphere-in-capsule formulation designed to retain its ER properties following common tampering methods such as crushing, chewing, and preparation for intravenous (IV) injection. The small particle size of Oxycodone DETERx microspheres also allows for administration via enteral tube or by sprinkling onto soft food, thereby enabling a continuum of care for patients who initially can swallow, but develop swallowing difficulty with disease progression or due to iatrogenic etiology.

The primary objective of this study was to assess the safety and pharmacokinetics of intact and crushed Oxycodone DETERx relative to OxyContin® ADF.

Method

Ethics approval was obtained prior to start of study. In an open-label, 5-treatment, 5-period, active-controlled, naltrexone-blocked, cross-over comparison study, subjects were randomly assigned to receive each of the following 5 treatments with a standardized meal:

- Oxycodone DETERx 40 mg (capsule intact)
- Oxycodone DETERx 40 mg (capsule contents crushed)
- OxyContin 40 mg (tablet intact)
- OxyContin 40 mg (tablet crushed)
- Oxycodone IR 40 mg (2 x 20 mg tablets crushed)

Blood samples were collected pre-dose and for a duration of 36hr post-dose in the DETERx and OxyContin treatment groups. For the Treatment Period with crushed IR oxycodone, blood sampling continued for a duration of 24hr after dosing. There were at least 5 days between each treatment to provide sufficient washout time between treatments. Plasma samples were analyzed by HPLC for oxycodone. Standard PK parameters were calculated including: C_{max} (the maximum observed plasma concentration), T_{max} (the time to reach maximum plasma concentration), AUC_{INF} (the area under the plasma concentration versus time curve from time zero to infinity), partial AUC, and abuse quotient (AQ) (C_{max}/T_{max}). Safety and tolerability were assessed through treatment-emergent adverse events (TEAEs), vital sign measurements, oxygen saturation, and hematologic, biochemical, and urinalysis laboratory parameters.

Results

Thirty-eight (38) subjects completed the study. Both crushed and intact DETERx treatments resulted in lower peak plasma concentrations than crushed IR oxycodone; C_{max} values were 62.9ng/mL, 67.5ng/mL, and 79.4ng/mL, respectively. Crushed DETERx was bioequivalent to intact DETERx. Median T_{max} for crushed DETERx was not significantly longer ($p=0.1849$) than intact DETERx. Cumulative PAUC(0-1.75hr) values for crushed and intact DETERx treatments (23.4hr.ng/mL, 12.9hr.ng/mL, respectively) were much lower than that of crushed IR oxycodone (87.1hr.ng/mL). AQ values for DETERx crushed (16.5ng/mL/h) and intact (20.9ng/mL/h) treatments were substantially lower than for crushed IR oxycodone (62.3ng/mL/h). In contrast, crushed OxyContin was bioequivalent to crushed IR oxycodone, but not to intact OxyContin due to a substantially higher C_{max} compared with intact OxyContin; C_{max} values were 78.4ng/mL, 79.4ng/mL, and 64.9ng/mL, respectively. The median T_{max} for crushed OxyContin was the same as for crushed IR oxycodone (1.75hr), and was 3.25hr shorter than intact OxyContin ($p<0.0001$). Cumulative PAUC(0-1.75hr) value for crushed OxyContin (81.4hr.ng/mL) was similar to crushed IR oxycodone (87.1hr.ng/mL), but substantially different than intact OxyContin (14.5hr.ng/mL). As expected based on increased C_{max} and decreased T_{max} observed for crushed OxyContin relative to the intact OxyContin tablets, the AQ for crushed OxyContin (58.1ng/mL/h) was similar to crushed IR oxycodone (62.3ng/mL/h), and much higher than for intact OxyContin (14.0ng/mL/h). All AEs were mild or moderate in intensity. No serious adverse events were reported. There were no clinically significant findings or trends noted from vital signs, oxygen saturation levels, or physical examination findings.

Conclusions

These data demonstrate that upon physical manipulation (crushing), the ER formulation of OxyContin AD is broken down resulting in "dose dumping" as evidenced by the similar pharmacokinetic profile when compared with crushed IR oxycodone, while crushed DETERx retains its ER profile. These results suggest that Oxycodone DETERx may be less favored by abusers following crushing compared with reformulated OxyContin ADF.

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Human Abuse Potential of Intranasally Administered Oxycodone DETERx®: An Abuse-Deterrent, Extended-Release Formulation

Ernest Kopecky, Melinda O'Connor, Ravi Varanasi, Alison Fleming
Collegium Pharmaceutical, Inc., Canton, MA, USA

Purpose

Prescription opioid analgesics are potent and effective in the management of chronic pain. Extended-release(ER) opioid formulations provide an analgesic effect over a prolonged dosing interval. Abusers frequently tamper with these formulations due to the relatively high drug load and attempt to subvert the ER mechanism to access the entire drug load at once. Many conventional ER formulations are susceptible to tampering techniques such as breaking, crushing, or chewing. Crushed ER formulations can then be used intranasally (IN) to achieve high plasma concentrations and maximize the euphoric effects. To mitigate these risks of abuse, abuse-deterrent (AD) formulations are in clinical development. In order to evaluate the potential for these formulations to reduce abuse risk, the FDA issued a draft guidance recommending data from each of 3 categories of premarketing studies for evaluation of AD formulations. The purpose of Category 3, human abuse potential studies, is to evaluate the probability of the attractiveness or likability of a formulation to abusers.

Oxycodone DETERx® (DETERx) is an ER, AD, microsphere-in-capsule formulation, designed to retain its ER properties following common tampering methods such as crushing, chewing, and preparation for IV injection. Category 1 (laboratory-based in vitro manipulation and extraction studies) and Category 2 (pharmacokinetic [PK] studies) for Oxycodone DETERx were conducted as per the FDA guidance and reported previously[1].

The objective of this study was to evaluate the human abuse potential of crushed Oxycodone DETERx 40 mg following IN administration, intact Oxycodone DETERx 40 mg following oral(PO) administration, and crushed immediate-release(IR) oxycodone 40 mg following IN administration.

Method

Ethics approval was obtained prior to start of the study. Male and female subjects, who were non-dependent, non-tolerant to opioids with a history of recreational insufflation of opioids, following successful screening, entered the Drug Discrimination Phase, which comprised of a Naloxone Challenge Test and a Drug Discrimination Test. Subjects who were eligible to continue to the Double-blind Treatment Phase were randomized in a 1:1:1:1 ratio to receive 1 of 4 sequences of 4 single-dose treatments in a double-blind, double-dummy design: crushed DETERx 40 mg dosed IN, intact DETERx 40 mg dosed PO, crushed IR oxycodone 40 mg dosed IN, and placebo. The primary endpoint was Drug Liking, measured at pre-defined time points up to 24 hours post-dose using a bipolar visual analogue scale (VAS). Additional endpoints evaluated were: Drug Effects Questionnaire(DEQ), Overall (Global) Drug Liking(ODL), Addiction Research Center Inventory-Morphine Benzedrine Group(ARCI-MBG), Take Drug Again(TDA), Price Value Assessment Questionnaire(PVAQ), Pupillometry, and Ease of Snorting. During each Treatment Period, blood samples for PK evaluation were collected at pre-dose and at pre-defined intervals post-dose. Plasma samples were analyzed by HPLC for oxycodone to determine standard PK parameters. Safety was monitored through adverse events (AEs), vital signs, oxygen saturation, and clinical labs (chemistry, hematology, urinalysis). Nasal safety was evaluated by subjective evaluation of IN irritation, burning, runny nose/nasal discharge, facial pain/pressure, and nasal congestion per FDA Guidance for Industry: Abuse Deterrent Opioids - Evaluation and Labeling (January 2013).

Results

Thirty-six (36) subjects completed the study. For the primary endpoint (Drug Liking E_{max}), crushed DETERx IN had a significantly lower LS Mean(LSM) E_{max} (61.88) in comparison with IR oxycodone IN (LSM E_{max}: 82.57) for Drug Liking ($p<0.0001$). LSM TE_{max} for DETERx IN was 3.40hr compared with 1.01hr for IR oxycodone IN ($p = 0.0019$). LSM E_{max} for Drug Liking was significantly lower for crushed DETERx IN than for DETERx PO (61.88 vs 67.87, $p < 0.0001$). For positive effects such as Any Drug Effects, Good Drug Effects, and High, the differences in LSM E_{max} between IR oxycodone IN and DETERx IN and the differences between IR oxycodone IN and DETERx PO were statistically significant for each of the effects-higher for IR oxycodone IN. LSM E_{max} for Bad Drug Effects was numerically highest for DETERx IN, although it was not statistically different between IR oxycodone IN and DETERx IN or between IR oxycodone IN and DETERx PO. For nausea, sleepiness, and dizziness, IR oxycodone IN produced statistically higher LSM E_{max} than either DETERx treatment. Overall Drug Liking, Take Drug Again, ARCI/MBG, PVAQ, and pupillometry also showed statistically higher E_{max} values for IR oxycodone IN than for DETERx administered IN or PO. No substantial difference was observed between placebo and DETERx IN for ODL and TDA. PK results supported the abuse potential results with crushed DETERx IN resulting in a lower mean peak plasma concentration than both intact DETERx PO and crushed IR oxycodone IN. Point estimates for C_{max} for crushed DETERx IN were 73.02% of DETERx PO and 48.72% of crushed IR oxycodone IN. For nasal effects assessment, subjects reported the highest levels of irritation, burning, and facial pain with DETERx IN at earlier time points. Other than AEs associated with DETERx IN, the safety profile was consistent with an opioid.

Conclusions

A human abuse potential study was conducted using Oxycodone DETERx capsules, consistent with the FDA AD guidance, indicating that likeability of Oxycodone DETERx IN was significantly lower than that of IR oxycodone IN or Oxycodone DETERx PO. The data suggest that the IN route of abuse for Oxycodone DETERx will not be attractive to abusers; low oxycodone plasma levels, poor euphoric effects, and unpleasant nasal effects collectively resulted in poor likeability of Oxycodone DETERx IN by recreational opioid abusers.

References

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Bilateral Parsonage Turner Syndrome Masquerading as Cervical Radiculopathy

Ranga Krishna[1,2], Eric Hirsch[1], Daniel Afonin[1]
[1]New York Methodist Hospital, Brooklyn, New York, USA, [2]Brooklyn Hospital, Brooklyn, New York, USA

Purpose

Parsonage Turner Syndrome (PTS) refers to a rare, idiopathic inflammation of the brachial plexus first described in 1943 (McNamara et al. 2012). The syndrome is marked by acute shoulder pain, often beginning at the top of the shoulder blade and progressing to the upper arm, which lasts from a few days to several weeks and is followed by weakness, paresthesia, and loss of function in the shoulder and upper arm. (Squintani et al. 2009) Diagnosis can be aided by nerve conduction and imaging studies. (Tjoumakari 2012) Symptoms usually resolve themselves in 18-24 months, but atrophy of the muscle may occur and can be treated with physical therapy. Although its etiology is unclear, PTS is known to be associated with post-pregnancy, post-surgery, post-vaccination, post-trauma, and autoimmune disease. (Kumar et al. 2013), (Monteiro et al. 2013) PTS has an incidence of 1.64 /100, 000 person-years, occurring more often in males (2:1) and on the right side. (Kumar et al. 2013). Bilateral presentation occurs in only 26% of cases. (Squintani et al. 2009) In patients with a history of PTS, particularly those with a bilateral presentation, degenerative changes in the cervical spine are possible.

Method

The patient is a 39 year old female with a history of bilateral parsonage turner syndrome. There was no obvious predisposing factor for her condition, and her symptoms of bilateral pain and weakness in the shoulder and upper arm were initially diagnosed as cervical radiculopathy. A diagnosis of bilateral parsonage turner syndrome was eventually made, and her symptoms were treated with physical therapy with complete resolution. Two years after the onset of her PTS symptoms she was in a motor vehicle accident and suffered severe neck pain and numbness in the right arm. An MRI of the cervical spine was ordered to assess the cervical spine.

Results

MRI of the cervical spine revealed a 1.2 cm segment of abnormal signal intensity in the T2 weighted images of the cervical cord from mid C5 to the mid C6 level consistent with wallerian degeneration. These degenerative changes are likely a remote effect of the inflammation associated with bilateral PTS.

Conclusions

Parsonage Turner Syndrome can mimic rotated cuff injuries, but it presents a set of unique clinical indications. For patients with a history of PTS, remote effects in the cervical spine are possible, as demonstrated in this case presentation. Our recommendation is that patients who have parsonage turner syndrome should be given a cervical MRI at 12 and 24 months after diagnosis to investigate possible degenerative changes and establish a clear clinical correlation with PTS.

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The Effect of Myofascial Release on Dyspnea: A Case Report

Vishal Varshney[1], Greg Siren[2], Brenda Lau[1,2]
[1]Department of Anesthesiology, Pharmacology and Therapeutics, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada, [2]CHANGEpain Clinic, Vancouver, British Columbia, Canada

Purpose

Dyspnea, defined as "an uncomfortable sensation of breathing", is a common symptom of cardiopulmonary disease, including asthma and chronic obstructive pulmonary disorder [1]. A well-elucidated mechanism of dyspnea suggests that afferent information from joints, tendons, fascia and muscles of the chest wall influences the sensation of dyspnea [2].

Myofascial release is a hands-on technique that facilitates a stretch into restricted, contracted fascia and muscle [3]. Through histologic changes, muscle becomes softer and more pliable. As lung muscle elasticity is a function of lung capacity, it can be hypothesized that reducing chest wall rigidity through reducing myofascial tension would have a beneficial effect on lung capacity.

Dry needling is a form of myofascial release, defined as the penetration of a needle through skin without the introduction of any drug [4,5]. This technique is used widely to treat acute and chronic pain, however the mechanism remains unclear. It is suggested that the analgesic and anti-inflammatory effect of dry needling is multifactorial and related to the nervous, immune and endocrine systems [5-8].

The purpose of this case report is to demonstrate the role of myofascial release on the treatment of dyspnea in adult asthma, its influence on baseline pulmonary function testing, and some possible mechanisms how this occurs.

Method

The subject is a 57 year-old female legal assistant with left arm complex regional pain syndrome (CRPS) diagnosed in 2009. She has a 34 year history of asthma requiring multiple emergency room presentations for exacerbations triggered by seasonal allergens despite being on daily corticosteroid and beta-agonist inhalers.

In November 2012, dyspnea symptoms were acutely worsened by an anaphylactic reaction to a wasp sting. This was treated in hospital with EpiPen and Ventolin nebulizers. One week after this episode she presented for regularly-scheduled treatment of her CRPS pain and was noted to have significant shortness of breath, wheeze, and was unable to speak in full sentences. Vital signs showed blood pressure 130/61, heart rate 91, oxygen saturation 92% on room air, and respiratory rate 18. She was offered chest myofascial release through dry needling. With the patient sitting upright, a single 30G ½ inch needle was inserted approximately 50 times at 1mm skin depth along the patient's anterior chest fascia bilaterally from T1 to T3, and T5.

Results

The patient immediately stopped wheezing and she expressed feeling better, more relaxed and able to lie flat and speak in full sentences. Oxygen saturation increased immediately from 92% on room air to 97% on room air.

Symptomatic improvement was corroborated by a change in pulmonary function test (PFT) performance, particularly with a 104% sustained increase in her forced vital capacity (FVC) and a 112% sustained increase in her forced

expiratory volume after 1 second (FEV1), as seen in PFTs performed at one month and six months after myofascial release.

Conclusions

The impact of myofascial release on the patient's dyspnea was qualitatively shown by a resolution in symptoms, and quantitatively shown by improvement in PFTs. We propose three mechanisms by which dry needling affects dyspnea and inflammatory responses in asthma. A biomechanical theory suggests that mechanical stimulation through dry needling suppresses skeletal muscle electrical activity and improves length and tension of taut muscle fibers. A somatic-sympathetic convergence theory suggests that stimulation of skin and fascia directly activate same-level post-ganglionic sympathetic fibers. A neuroimmunomodulation theory suggests nociceptive fibers are activated during inflammatory states and release immune-acting mediators to modulate innate immune responses.

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Injection and Smoking Resistance of EG-001, an Abuse-Deterrent ER Morphine in Clinical Development

Karsten Lindhardt[1], Torben Elhauge[1], Nikolaj Skak[1], Edward J. Cone[1]
[1]Egalet Corporation, Wayne, PA, USA, [2]PinneyAssociates, Bethesda, MD, USA

Purpose

Morphine is on the World Health Organization (WHO) Model List of Essential Medicines. The WHO list tabulates the most efficacious, safe, and cost-effective medicines for the treatment of priority conditions in a basic healthcare system. In addition, extended-release morphine is the most commonly prescribed long-acting opioid in the United States. Notwithstanding its importance as an analgesic, morphine has a high abuse potential, and pharmaceutical morphine is highly sought by drug abusers. There is currently no abuse-deterrent (AD) morphine available on the market. Although many factors influence the route of administration of opioids for abuse, morphine abusers prefer the injection route because of the rapid onset of effects. Abusers sometimes also attempt the administration of opioids by the smoking route because of a similar rapid onset of effects. Egalet Corporation (Wayne, PA) has developed an extended-release, oral morphine formulation, EG-001, based on its proprietary AD drug delivery system (Guardian™ technology), which has physical and chemical barriers intended to deter common methods of abuse. This formulation transforms into a gel (viscous solution) that resists injection when hydrated with small amounts of aqueous media. The polymer matrix also presents a barrier to attempts at vaporization that prevent abuse via the smoking route. The purpose of this study was to perform a comprehensive laboratory assessment of syringeability and vaporization (simulated smoking) experiments with EG-001. The study was designed based on Category 1 procedures presented in the United States Food and Drug Administration's 2013 Draft Guidance for Industry Abuse-Deterrent Opioids - Evaluation and Labeling.

Method

Syringeability and simulated smoking studies were conducted by a third-party laboratory (DrugScan, Horsham, PA). Syringeability studies were conducted with EG-001 tablets (intact tablets and powder) under a variety of conditions (solvents, volume, temperature, time, agitation) frequently used in tampering methods for the preparation of injectable solutions. EG-001 tablets were tested against MS Contin® (Purdue Pharma, Stamford, CT) with and without various heat pretreatments (eg, "crispin," which involves heating the formulation in an oven/microwave before attempting to dissolve the active ingredients for injection). Syringe barrels were fitted with various gauge needles prior to filling. Solutions that were successfully loaded into the syringe were analyzed for morphine content.

Simulated smoking studies were conducted to simulate "chasing the dragon" procedures used for the inhalation of opioids. Typical smoking attempts involve abusers placing the drug on foil with application of intense heat to the underside. The heat melts and chars the powder and some drug may be vaporized. Abusers inhale the vapor above the foil with a hollow instrument (eg, a soda straw). Initial studies with EG-001 were conducted to define optimal heating conditions (heating temperature and duration of heating) for vaporization of morphine salt and free base. Following optimization of conditions (temperature, heating time), ground EG-001 was tested against pure morphine sulfate (the active drug in EG-001) in the simulated smoking apparatus. The smoking device was designed to capture vaporized morphine, which could then be analyzed. Residual drug was also measured. Different heat sources (including, for example, a Sterno burner) were also tested.

Results

Both untreated and heat pretreated EG-001 tablets and powders were highly resistant to solution preparation for injection. Treatment with various solvents produced a viscous mass that was intractable and could not be loaded into

a syringe for injection. Typically, only small volumes of liquid could be drawn into a syringe fitted with different needle gauges. The assayed morphine content in syringes generally was less than 10% of the starting dose (100 mg), whereas 30%-60% of the MS Contin dose was easily prepared into small volumes suitable for injection. Use of different solvents, volumes for injection (up to 10 mL), temperatures, and extraction times did not alter the extraction of EG-001. The high viscosity of the resulting solutions prevented preparation for injection, and dilution of the viscous solutions with high solvent volumes made them impractical for injection.

Simulated smoking studies were initially conducted with reference standards of morphine sulfate and morphine base for the optimization of temperature and time of heating. At lower temperatures, morphine remained in the residue and was not vaporized; at extremely high temperatures, there was evidence of substantial thermal degradation and loss of morphine. Simulated smoking studies with powdered EG-001 tablets under optimized conditions demonstrated that the product produced only minor traces of vaporized morphine. Use of an intense heat source for heating EG-001 was also explored but was equally unsuccessful. It was clear from these studies that the presence of excipients substantially interfered with the vaporization of morphine from the product.

Conclusions

EG-001 tablets displayed extreme gelling when treated with various solvents, implying this formulation will not be injectable; in contrast, the comparator product was easily dissolved and loaded into a syringe in solvent volumes suitable for injection. Simulated smoking studies under optimized conditions for vaporization of morphine were highly unsuccessful, indicating that the formulation is unlikely to be abused by this route. Considering the hardness of the formulation, coupled with its gelling properties and the characteristics of its excipients, EG-001 is expected to be an AD morphine product that will present significant barriers to abuse via the injection and smoking routes.

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Legislative and Media Impact on Provider Knowledge and Attitudes toward a Recently Approved Opioid Analgesic

Sara Lindsay, Chris Herndon
Southern Illinois University Edwardsville School of Pharmacy, Edwardsville, IL, USA

Purpose

The purpose of this research is to assess the impact of media reporting on the opioid analgesic, hydrocodone bitartrate extended-release capsules (Zohydro ER). The recently approved medication is an extended release single entity hydrocodone product. The approval of this medication has been the source of controversy since an FDA advisory board recommended 11 to 2 against approval. The manufacturer, Zogenix, has met with resistance from state governments over concerns about the abuse potential of this chronic pain medication. The nuances, which make this medication different from currently available extended release opioids, are minimal; however, a key difference is hydrocodone bitartrate extended-release (HBER)'s lack of special characteristics which decrease ease of abuse by snorting or injecting. Despite the controversy, the drug was made available earlier this year without an abuse deterrent formulation. This study used a nationally distributed questionnaire to assess the impact of the negative media coverage and regulatory litigation on providers' knowledge of and attitudes towards the FDA approved medication, HBER.

Method

The primary investigator of this research is an SIUE School of Pharmacy Doctor of Pharmacy Candidate completing requirements for a senior research experience. The knowledge and attitudes questionnaire has been approved through the Southern Illinois University Edwardsville Institutional Review Board. The questionnaire was developed to assess the clinical utility of HBER. Subjects were invited to participate via email using a contact database for those health professionals that have previously attended the medical conference, PAINWeek. The survey collected demographic data as well as knowledge and attitudes about HBER. The survey consisted of thirteen questions assessing knowledge of available extended release and long acting opioids, eleven questions assessing attitudes about abuse deterrent formulations and prescribing HBER and twelve questions assessing the participants' level of agreement with factors influencing their clinical judgment to prescribe certain extended release opioids and the extent of acceptance towards others.

Results

Participants will have the opportunity to complete the questionnaire until August 31, 2014. Preliminary data will be collected between August 1 and August 15, 2014 and reported at the PAINWeek Annual Conference.

Conclusions

Numerous media sources have reported data that have impacted the clinical use of the extended release opioid, Zohydro ER. When comparing equianalgesic doses, HBER is comparable to other available extended release opioids. Increasing health care provider knowledge about HBER is necessary to expand the clinical utility of available opioid analgesics to for the treatment of chronic pain. This study has the potential to provide important information about the level of knowledge and shared attitudes of health care providers nationwide.

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A Hybrid Pain Independent Study within a School of Pharmacy

Sara Lindsay, Tabetha Todd, Chris Herndon
Southern Illinois University Edwardsville School of Pharmacy, Edwardsville, IL, USA

Purpose

Epidemiologic data suggest that pain affects more people than diabetes, heart disease, and cancer combined, yet pain management education is covered to a limited extent within healthcare professional degree programs. Not surprisingly, opioid analgesics are among the most commonly prescribed medication classes in the United States. Unfortunately, curricular devotion to pain and its treatment is disproportionately under-represented given these statistics. Students in the Doctor of Pharmacy program at Southern Illinois University Edwardsville (SIUE) School of Pharmacy receive approximately ten hours of pain-related lecture during the three years of didactic curriculum within required core courses. Although an elective, Pain and Palliative Care Pharmacotherapy (PHEL 764) is a two credit hour course offering available during the 3rd professional year. This course is well- received among students and consistently has 100% enrollment. This course provides students with a comprehensive overview of pain management, hospice, and palliative care practice in health system models. In response to student interest in this area, a hybrid pain independent study was developed. The purpose of this class is to provide advance practice skills focused on pain management utilizing pre-existing educational resources and clinical cases selected by the course facilitator.

Method

The independent study is available to pharmacy students in their third professional year who have successfully completed PHEL 764. Students enrolled in the two credit hour independent study have the opportunity to augment the knowledge gained in the pain-focused elective and advance their abilities to manage acute and chronic pain syndromes. Students learn through completing the American Society of Health-System Pharmacists Foundation Pain Traineeship Levels I & II modules, composing patient care plans, developing innovative practice models and participating in web- based didactic seminars delivered by nationally recognized providers. The ASHP Foundation modules supplement principles covered in PHEL 764 to expand upon topics such as the pathogenesis, assessment, and management of pain, opioid and non-opioid therapy, equianalgesic dosing, alternative delivery methods, as well as characteristics and treatment of a variety of pain syndromes. Detailed patient care plans were reviewed and discussed as a teaching tool to reinforce the concepts learned throughout the course. These plans required students to use evidence-based medicine to recommend drug therapy, identify outcome goals, monitoring parameters, and analyze adverse drug reactions / interactions. Additionally, students are expected to complete a project, with the first cohort of students developing a complete business plan for specialized clinical pharmacy services for pain management.

Results

The hybrid pain focused independent study implemented at SIUE School of Pharmacy provides students with knowledge and experiences that cannot be obtained through other courses available in the Doctor of Pharmacy curriculum. Students are encouraged to ask questions and use critical thinking skills to make informed decisions in all aspects of the course. The course encourages students to network with other professionals in the field who have similar specialties and interests to further the education process. Additional curriculum focused on the pathogenesis and pharmacotherapy of various pain conditions provides students in the Doctor of Pharmacy program at SIUE School of Pharmacy unparalleled opportunities to succeed as a proficient pharmacist. Pharmacists with an advanced understanding of the management of pain can play an integral role on a multidisciplinary team.

Conclusions

Education on the management of pain is an essential component to the core curriculum provided to all health care providers. In order to provide exceptional patient care, adequate course offerings concordant with the prevalence of health problems experienced are essential. Novel learning opportunities provide health profession students enhanced opportunities to either specialize or further solidify their basic knowledge base.

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Practicing Pharmacists' Knowledge, Skills, and Attitudes of Pain Management

Kashelle Lockman[1], Deborah Helmink[2], Christopher Herndon[2], Mary Lynn McPherson[1]
[1]University of Maryland School of Pharmacy, Baltimore, MD, USA, [2]Southern Illinois University Edwardsville School of Pharmacy, Edwardsville, IL, USA

Purpose

Analgesics routinely top lists ranking the most prescribed medications in the United States. Pharmacists may have responsibilities to evaluate prescriptions but are also often consulted to recommend medication regimens. In addition, they are often consulted to evaluate and manage adverse effects of medications. The Accreditation Council for Pharmacy Education (ACPE) provides standards of general competencies graduating pharmacy students must attain but does not outline subject matter for pharmacy curricula. Therefore, the amount of education in pain pharmacotherapy a pharmacist may receive varies widely. The Strategic Planning Summit for Pain and Palliative Care Pharmacy Practice recently stated that pharmacists providing patient care in all practice settings require a core understanding of pain and palliative care. Pharmacy is a field that has drastically changed over the past two decades, both with the change to a doctorate of pharmacy as the entry-level degree, and increasing postgraduate training as pharmacotherapy specialists providing direct patient care. Pharmacists may obtain knowledge and skills in this practice area through pre-graduate curricula, postgraduate clinical training, and/or continuing education. The purpose of this study is to identify areas of weakness or strength in knowledge, skills, and attitudes of pain management among practicing pharmacists.

Method

An online survey assessing knowledge, skills, and attitudes of pain management was developed and distributed by email to members of 4 professional pharmacy associations in Maryland and Illinois. The survey was used to collect demographic information and assessed knowledge, skills, and attitudes in six domains of pain management, including: pain assessment, pharmacologic approach for different pain etiologies, pain medication dosing, adverse event management, nonpharmacologic approaches to pain management, and abuse/misuse/diversion. The survey included 1 self-assessment and 1 attitude question per domain. In addition, 2 questions were included to assess actual knowledge and skills for each domain. The survey also included educational needs assessment questions to determine respondent preferences for timing and delivery of continuing education in pain management. Survey responses were collected and analyzed from September to October 2012. Data were analyzed using general descriptive statistics, chi square, and analysis of variance as appropriate (SPSS 20.0, IBM; Armonk, NY).

Results

One-hundred and thirty-five pharmacists began the survey and 104 completed the survey. Over 60% of participants worked in inpatient pharmacy and more than 45% have been practicing for 20 years or more. Most pharmacists felt that pain management was important and they also felt somewhat skillful in tasks in each pain knowledge domain included in this survey. Knowledge-based questions relating to medication dosing (68.3%) and adverse event management (63.9%) were answered correctly by more pharmacists than questions relating to the other domains. Questions related to nonpharmacologic approaches to pain management were answered correctly by 46.2% of pharmacists. Pharmacists who were practicing for 3-5 years had a statistically significant higher score on the knowledge-based questions compared to pharmacists with over 20 years of experience. There was no difference in average scores in the knowledge-based questions between pharmacists with differing levels of pain management continuing education in the past 5 years. More respondents (74.9%) were likely or very likely to participate in online training versus a 1-day workshop (55%). Fewer respondents also said they were not likely or would not participate in

online training (8.1%) versus live training sessions as a stand-alone workshop (16.3%). Of distance educational methods, respondents preferred self-paced online modules, followed by webinars, to podcasts and videoteleconference. They were least likely to participate in education delivered by twitter or other social networking sites.

Conclusions

While respondents to this survey believed pharmacists have an important role in pain management, survey results indicate potential for improvement in pharmacists' knowledge and skills in pain management through educational initiatives. Pharmacists were decidedly unsure about their knowledge level with most feeling "somewhat" well trained, and this self-perception was consistent with a relatively poor overall score on the knowledge based questions. Future educational initiatives should address identified knowledge deficits in pharmacy school curricula and in post-graduate education. Flexible online educational initiatives are likely to increase participation of pharmacists in pain-related continuing education.

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Development of the Pain Practice Behaviors Scale

Kimberlee Trudeau, Cristina Los, Kevin Zacharoff
Inflexxion, Inc., Newton, MA, USA

Purpose

A self-report scale was created to assess the behaviors of practitioners who have prescribed opioid medications to chronic non-cancer pain patients in the last 90 days. It was developed for use in a field trial to measure practitioner prescribing behaviors before and after exposure to an educational intervention on opioid management practices.

This 31-item scale is separated into three subscales which measure practice behaviors 1) before opioids are prescribed (17 items), 2) during follow up visits with patients who are currently using opioids (7 items), and 3) in response to suspected aberrant drug-related behavior (7 items). Practitioners are asked to rate how often they or a member of their treatment team employ the following practice behaviors on a 5-point Likert scale: 1 = Never, 2 = Rarely, 3 = Sometimes, 4 = Often, 5 = Always.

Method

Development of this measure included multiple iterations over the course of three years, including item development and expert review then participant testing: a) pilot testing, b) cognitive pre-testing, and c) field testing including a test-retest reliability subsample.

Items were developed based on practices associated with universal precautions for prescribing opioids. These items were reviewed for face validity by several experts.

Pilot Testing. We recruited participants who have prescribed opioid medications in the last 90 days through announcements placed in the PainEDU weekly newsletter in February 2013 to complete a short anonymous survey.

Cognitive Pre-testing. We recruited participants through announcements placed in the PainEDU weekly newsletter in August 2013. A structured one hour phone interview was conducted after each participant completed an online version of the revised survey. Responses to the specific items, interpretation of item wording, and overall impressions of the scale were discussed.

Reliability Testing Sub-study of the Efficacy RCT. Participants were recruited for the efficacy RCT from August 28, 2013 until October 28, 2013 through: 1) the PainEDU website and newsletter; 2) flyers, emails and face to face meetings at hospitals; and 3) flyers, emails and conference books at pain conferences. A small sample of participants from the RCT were randomly selected to complete the new scale at baseline and again three days post baseline.

Results

Pilot Testing. We recruited 88 opioid prescribers to complete the survey about their practice behaviors in the past 90 days. Sixty-seven percent reported that they had started any patients on an opioid regimen. Ninety-three percent reported that they had conducted a follow up visit. Seventy-six percent reported that they had managed patients who may have displayed signs of drug misuse. Two percent reported "no" to all three of these stem questions and therefore did not receive any of the practice behavior items. The items showed good variability and good internal reliability (Cronbach's alphas ranged between .62 and .84). Several changes were made to the scale after reviewing

the results with a consultant, specifically, 1) stem items were revised to account for a team approach (e.g., Did you or a member of your team....?), 2) one item was added to subscales 1 and 2, and 3) a new stem item with related item set was created for subscale 3.

Cognitive Pre-testing. The individual questions were interpreted as intended and were generally positively endorsed (i.e., "Always" or "Often") by the five participants. A few participants reported that they learned a lot from the survey items and plan to change their practice (e.g., they plan to expend more effort to involve families in treatment).

Reliability Testing. Cronbach's alphas for the baseline scores for the RCT sample (N = 238) were 0.92 for subscale 1 (started a patient on an opioid regimen), 0.81 for subscale 2 (follow up procedures), and 0.81 for subscale 3 (suspected aberrant drug-related behavior). Results from the test-retest subsample (n=54) indicated that this new scale has good test-retest reliability: intra-class correlations were 0.93 for subscale 1, 0.76 for subscale 2, 0.85 for subscale 3, and 0.86 for the total mean score.

Conclusions

The new Pain Practice Behaviors scale was developed through a multiple step process including pilot testing, cognitive pre-testing, and reliability testing. It has item variability, internal reliability, and test-retest reliability and is recommended for further investigation.

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Long-term Safety and Effectiveness of Once-daily, Single-entity Hydrocodone, Formulated with Abuse Deterrent Properties (Hysingla™ ER) in Chronic Nonmalignant and Nonneuropathic Pain: Results of an Open-label Study

Warren Wen[1], Louise Taber[2], Shau Yu Lynch[1], Catherine Munera[1], Steven Ripa[1]
[1]Purdue Pharma L.P., Stamford, CT, USA, [2]Arizona Research Center, Phoenix, AZ, USA

Purpose

The purpose of this uncontrolled study was to evaluate the long-term safety and effectiveness of a single-entity, once-daily, hydrocodone (20, 40, 60, 80, 120 mg/day) tablet formulated with abuse deterrent properties (HYD; Hysingla™ ER) for the treatment of controlled or uncontrolled, moderate to severe, chronic pain in opioid-naïve and opioid-experienced patients.

Method

The treatment period of this open-label study consisted of a core study (which included a dose-titration period of up to 45 days and a 12-month maintenance period) and an optional 24-week extension period. At the beginning of the dose-titration period, eligible patients had their pre-study pain regimen converted to HYD. Throughout the dose-titration period, patients' HYD doses were adjusted until adequate analgesia was achieved at a tolerated dose (ie, until a stable HYD dose was achieved). Patients who achieved a stable HYD dose at the end of the dose-titration period continued HYD treatment in the maintenance period. A cohort of patients who completed the maintenance period was eligible to enter the optional extension period. Throughout the maintenance and extension periods, dose adjustments were permitted at the discretion of the investigators.

The safety of HYD was analyzed and summarized based on adverse events, aberrant drug behavior assessments, audiologic assessments, clinical laboratory assessments, ECG assessments, and vital sign assessments. The treatment effectiveness of HYD was evaluated based on pain relief, sleep, and overall function. The long-term effectiveness of HYD was also evaluated based on the need for HYD dose adjustments and the use of concomitant short-acting opioid and non-opioid analgesics throughout the maintenance and extension periods.

Results

Nine hundred twenty-two patients were treated with HYD during the dose-titration period; of these, 728 (79%) patients entered the maintenance period. Of the 728 patients, 410 (56%) patients completed the maintenance period, 106 (15%) patients discontinued treatment due to adverse events (AEs), and 32 (4%) discontinued treatment due to lack of therapeutic effect (LOTE). Of the patients who completed the maintenance period, 106 patients entered the extension period; of these, 83 (78%) patients completed the extension period, 7 (7%) patients discontinued treatment due to AEs, and no patient discontinued treatment due to LOTE.

During the core study, the most frequently reported treatment-emergent AEs (TEAEs; by ≥5% of patients) included nausea, constipation, vomiting, fatigue, dizziness, somnolence, headache, which were typical side effects of systemic mu-opioid agonist analgesics. During the extension period, incidence of TEAEs was lower and no TEAEs occurred in ≥5% of patients. The incidences of study drug abuse (< 0.5% of patients) and diversion (2% of patients) were low during the core study; no study drug abuse or diversion was reported during the extension period. Evaluation of safety assessments related to audiology, clinical laboratory, ECG, and vital signs did not reveal safety concerns.

The evaluation of the treatment effectiveness of HYD showed significant improvements from baseline in pain relief as patients reached a stable HYD dose and this improvement was maintained throughout the maintenance and extension

periods. Improvements in sleep, overall function, and QoL outcomes were also observed. The majority of patients did not require HYD dose adjustments during the maintenance and extension periods. Additionally, supplemental opioid analgesic use was reduced from baseline during the core study and extension period. Supplemental nonopioid analgesic use during the core study was similar to that at baseline; however, during the extension period, nonopioid analgesic use was reduced.

Conclusions

This uncontrolled study demonstrated that long-term use of HYD was safe in the treatment of patients with moderate to severe chronic pain. Effectiveness, measured as favorable changes from baseline, was also observed; analgesia and improvements in functions were obtained early, with the full extent of effectiveness generally established when a stable HYD dose was achieved. Overall, the improvements in analgesia and functions were maintained during the long-term treatment without continued requirement for dose increase.

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Collaborative Health Outcomes Information Registry (CHOIR): Open source cloud based platform to generate and support learning healthcare systems

Sean Mackey[1], Ming-Chih Kao[1], Karon Cook[2], Garrick Olson[1], Teresa Pacht[1], Darnall Beth[1], Susan Weber[1]
[1]Stanford University, Palo Alto, CA, USA, [2]Northwestern University, Chicago, IL, USA

Purpose

The Institute of Medicine (IOM) in Relieving Pain in America report (2011) called for the development of national patient registries to support the development of learning healthcare systems. In particular for the management of patients with chronic pain, the IOM has called for national patient outcome registries that can support point-of-care decision making and large-scale assessment of safety and effectiveness of therapies.

Method

In answer to the call from the IOM, we developed the Stanford-NIH Pain Registry, an open-source web application to assess patients and to support clinic staff with integrating the pain registry into the clinic workflow. Patient assessment features are designed for use on mobile devices with touch interfaces (smart phones and tablets), while also supporting desktop web browsers. Key technologies used include Java, Oracle database, Google Web Toolkit, and jQuery Mobile.

Results

Since roll-out in August 2012 and the subsequent slow ramp-up, over 4,400 unique patients have completed surveys, with over 49,000 NIH PROMIS assessments. Surveys were completed at home via email link, or at the Pain Clinic, using computers, iPads, Android tablets, and Chrome notebooks.

Conclusions

In conclusion, we have created an open source, extensible platform CHOIR (Collaborative Health Outcomes Information Registry) that enables rapid definition and deployment of data capture tools. This represents a successful par0tnership between the NIH and Stanford with funding from most of the NIH Institute Directors. Future works include the expansion of survey items, into additional disease areas, dissemination of code, as well as networked registry build-out.

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Pain Improvement Initiative in a Nursing Facility: One-on-one nursing education to improve pain documentation

Kasey Malotte, Christine O'Neil
Duquesne University, Pittsburgh, PA, USA

Purpose

Pain is a particular problem in nursing homes, where it is frequently under assessed, underreported, and undertreated. Adequate and consistent pain assessment can be challenging due to a variety of barriers including lack of standardized pain assessment tool and documentation, inadequate documentation and lack of organization commitment. Without adequate assessment of pain and consistent documentation it is difficult for anyone to initiate or maintain a treatment regimen with confidence. Therefore, the purpose of this study is to provide and evaluate effectiveness of nursing education regarding adequate pain documentation during as needed medication administration.

Method

Education was given by a pharmacist to nursing staff on a one-on-one basis. The in-service included an explanation on three elements needed for adequate documentation. These elements included (1) location and (2) severity of the pain before the medication was given and (3) severity of the pain ~1 hour after the medication was given. Compliance with documentation guidelines was assessed by reviewing electronic medication administration records over a (insert time period for review). A score from 0-3 was given based on level of compliance to these 3 elements. These scores were averaged for each nurse to determine their compliance with pain documentation before and after the education.

Results

A total of 39 nurses were eligible for the in-service education, of which 24 nurses received the education (61.5%). These were selected using convenience sampling. Preliminary data analysis shows before the education was given there was no significance found between those who did and did not receive education ($p=0.112$). There was a significant difference found before and after for pain compliance documentation for all nurses ($p<0.001$), nurses who received the education ($p<0.001$) and nurses who did not receive the education ($p=0.017$).

Conclusions

From these preliminary results, it seems as though the education improved pain documentation for the 3 critical elements. Both groups of nurses improved their level of pain documentation compliance. This is likely due to close working environment and passive staff development efforts. This project will hopefully contribute to better pain control and pain care due to increased documentation evidence of the residents' pain level, efficacy of current regimen as well as serve as evidence to improve nursing education practice.

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Assessment of Opioid Rescue Medication Use in Patients with Postbunionectomy Pain Treated with Diclofenac Potassium Liquid-Filled Capsules

Delia Mancoci[1], Joyce, S. Willens[2], Neel Mehta[3], Bobbie Sue Brown[1]
[1]Depomed, Inc., Newark, CA, USA, [2]Villanova University, Villanova, PA, USA, [3]Weill Cornell Medical College of Cornell University, New York, NY, USA

Purpose

Although opioids are associated with risks for abuse, addiction, and diversion that resulted in tighter legal regulations regarding their prescription and distribution, their use in treatment of acute pain continues to increase. No analgesics approach is without risk, but a well balanced approach using the most effective interventions while minimizing harm will improve the safety and recovery profiles for patients with acute pain. Therefore, better management of acute pain exploiting non-opioid agents with distinct mechanisms of action, efficacy, and safety profile is needed. Nonsteroidal, anti-inflammatory drugs (NSAIDs), which are very effective on somatic and breakthrough pain, are one of the most common non-opioid analgesics used for the management of pain.

Diclofenac is one of the most widely used NSAIDs for treatment of acute pain. Diclofenac potassium liquid-filled capsule (DPLFC; Zipsor®, Depomed, Inc., Newark, CA), which is approved for the treatment of mild-to-moderate acute pain in adults, is a low-dose formulation of diclofenac that uses patented dispersion technology to facilitate more rapid and consistent gastrointestinal absorption. In two clinical studies in patients with post-bunionectomy pain, DPLFC provided a significantly greater reduction in pain intensity compared with placebo, regardless of patients' baseline pain level. The current analysis was designed to more comprehensively characterize the use of opioid rescue medication (RM) in patients with post-bunionectomy pain treated with DPLFC vs. placebo, and to describe the relationship between pain intensity and opioid RM use.

Method

Data from two randomized, placebo-controlled studies of DPLFC to treat pain after first-metatarsal bunionectomy (with osteotomy and internal fixation) were integrated and analyzed. Following surgery, patients reporting a score of ≥4 on the 11-point Numeric Pain Rating Scale (NPRS, where 0=no pain, 10=worst pain imaginable) received placebo or 25 mg DPLFC (n=188 patients/group) every 6 hours during the 48-hour inpatient period through the end of outpatient dosing on Day 4. Opioid RM (hydrocodone/acetaminophen tablets, 5 mg/500 mg) was available as needed, but ≥1 hour post-study medication. Opioid RM use, mean pain intensity on the NPRS over time, and adverse events (AEs) for ±RM groups were assessed. Regression analyses were performed to characterize predictors of opioid RM use. Statistical significance was set at $p \leq 0.05$.

Results

Fewer patients in the DPLFC arm compared with the placebo arm requested opioid RM during the inpatient (4.8–44.7% vs. 25.0–90.4%) and outpatient (3.7–16.0% vs. 13.1–46.4%) periods. Also, during the inpatient period, patients receiving DPLFC requested opioid RM less often and took smaller amounts compared with patients receiving placebo.

For patients with moderate pain at baseline, DPLFC alone seemed sufficient to provide adequate pain relief. In general, patients who requested opioid RM experienced significantly higher mean pain intensity at baseline than those who did not request opioid RM (Placebo: 7.4 vs. 6.3, $p=0.0207$; DPLFC: 7.9 vs 6.5, $p<0.0001$). Consistent with this, pain intensity after surgery ($p<0.0001$) or at second dose ($p<0.0001$) were predictive of opioid RM use.

Although not statistically significant, there was a trend towards greater change in pain intensity over time for patients treated with both DPLFC and opioid RM compared with patients in the placebo group who received only opioid RM. From Dose 1 to Dose 10 (at the end of the 48-h inpatient period), patients in the placebo group using opioid RM (n=173) reported the mean reduction in pain intensity of –4.75. In comparison, DPLFC patients who used opioid RM (n=92) reported the mean reduction in pain intensity of –6.10.

Compared with patients taking opioid RM, patients in either group who did not take opioid RM reported less AEs (Placebo: 55.7% vs. 29.4%; DPLFC: 40.6% vs. 26.0%). The most common AEs in the opioid RM group were nausea, vomiting, headache, dizziness, and constipation.

Conclusions

In summary, patients treated with DPLFC requested opioid RM less frequently than patients receiving placebo, and pain intensity was a significant risk factor for the use of opioid RM. When used with the opioid RM, DPLFC provided slightly greater, although not statistically significant, reduction in pain intensity over time when compared with the opioid RM alone. Finally, reduced use of opioid RM by patients treated with DPLFC was associated with reduction in AEs. These results suggest that DPLFC has an opioid-sparing effect and may be beneficial alone or when combined with opioids in the management of acute pain.

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Efficacy of Lubiprostone in Constipation Caused by Non-Diphenylheptane Opioid Use in Patients with Chronic Non-cancer Pain: Pooled Analysis of 3 Randomized Controlled Trials

Shadreck Mareya[1], Douglas Drossman[2], Taryn Losch-Beridon[1], Gayle Dolecek[1]
[1]Sucampo Pharma Americas, LLC, Bethesda, MD, USA, [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Purpose

Oral lubiprostone is approved at a dose of 24 mcg twice daily (BID) to treat opioid-induced constipation (OIC) in adults with chronic non-cancer pain. However, its effectiveness has not been established in patients taking methadone or other diphenylheptane opioids. Two well-controlled studies of lubiprostone in OIC found a dose-dependent decrease in its efficacy in those patients using diphenylheptane opioids; patients taking diphenylheptanes were excluded from a third, similarly designed, well-controlled study. This analysis pools efficacy and safety data from the non-diphenylheptane populations of the 3 individual trials.

Method

We pooled data from 3 multicenter, 12-week, double-blind, randomized, placebo-controlled trials in patients with OIC. Study subjects were ≥18 years old and using opioids to treat chronic non-cancer pain. Patients were randomized to self-administer either lubiprostone 24 mcg (n=572) or placebo (n=568) BID. Efficacy endpoints analyzed included change from baseline (CFB) in weekly spontaneous bowel movement (SBM) frequency at week 8, week 12, and overall. Other endpoints were median time to first SBM and overall CFB in specific OIC symptoms: constipation severity, straining, stool consistency, abdominal bloating, and abdominal discomfort.

Results

Study populations were demographically similar across the 3 trials. Analysis of the pooled data revealed that mean CFB in SBM frequency at week 8 was significantly greater in the lubiprostone group compared to the placebo group (increase of 3.1 vs 2.5 SBMs/week, respectively; $P=0.006$). Similar results were seen at week 12 (CFB of 3.2 vs 2.7 SBMs/week for lubiprostone vs placebo, respectively; $P=0.040$) and overall (CFB of 3.0 vs 2.3 SBMs/week, respectively; $P<0.001$). Lubiprostone therapy also resulted in a significantly shorter median time to first SBM compared to placebo (28.5 h vs 40.0 h, respectively; $P<0.001$). Lubiprostone therapy also resulted in statistically significant improvements over placebo in constipation severity, straining, stool consistency, abdominal bloating, and abdominal discomfort ($P\leq0.015$). Lubiprostone was generally well tolerated, with no clinically meaningful safety differences from placebo observed.

Conclusions

Statistically significant improvements in SBM frequency, time to first SBM, and OIC-related symptoms confirmed the overall benefits of lubiprostone therapy in patients with OIC resulting from chronic treatment with non-diphenylheptane opioids, in this pooled analysis of phase 3 trials. This research was funded by Sucampo Pharma Americas, LLC, Bethesda, MD, and Takeda Pharmaceuticals International, Inc., Deerfield, IL.

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Internet discussion by recreational abusers of prescription drugs: A post-marketing evaluation of the abuse potential of tapentadol.

Emily McNaughton[1], Ryan Black[1], Sarah Weber[1], Theresa Cassidy[1], Stephen Butler[1]
[1]Inflexxion, Inc., Newton, MA, USA, [2]Janssen Scientific Affairs, LLC, Titusville, NJ, USA

Purpose

Abuse of prescription opioid pain relievers continues to be a serious public health concern. Tapentadol, a prescription analgesic, is thought to have mechanisms of pharmacologic action: μ-opioid receptor agonism and norepinephrine reuptake inhibition. Tapentadol immediate release (IR) is indicated for the management of moderate to severe acute pain in adults; while tapentadol extended release (ER) is indicated for pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate and for neuropathic pain associated with diabetic peripheral neuropathy in adults. Tapentadol is Schedule II under the Controlled Substance Act in the US. Lower μ-opioid receptor affinity compared to other CIIs along with noradrenaline reuptake inhibition, which tends to not be significantly rewarding, may be associated with lower abuse potential. Research on individuals in substance abuse treatment suggests that tapentadol abuse potential may be lower than other Schedule II opioids. Actual abuse rates, however, may be the result of factors other than a medication's appeal to individuals who would abuse medications, such as limited prescribed availability. Internet discussion of drug abuse is considered a "leading edge" indicator of abuse potential of pharmaceuticals. This study explored the extent to which online discussion of tapentadol by recreational abusers reflects interest in and desire to obtain and abuse tapentadol and comparator analgesics. Toward this end, we applied methods developed over the past seven years as part of the NAVIPPRO® Web Informed Services (WIS®) program to the question of the abuse potential of tapentadol and comparator analgesics.

Method

Online messages posted on seven drug-abuse web forums between January 2011 and September 2012 were evaluated. Proportions of posts and unique authors discussing tapentadol were compared with eight comparator compounds (oxycodone, oxymorphone, hydromorphone, hydrocodone, morphine, buprenorphine, tramadol, and fentanyl). Post content was coded by trained reviewers to compare endorsement for abuse of tapentadol with two comparators, one drug with high desirability for abuse, oxymorphone, and one with an established low abuse profile to anchor the low end of endorsement for abuse spectrum, tramadol. Using the coded data, an Endorsement Ratio (ERo), that quantifies the degree to which online messages endorse a pharmaceutical product for abuse, was calculated. The ERo is a ratio of the probability of endorsing compound A divided by probability of discouraging compound A.

Results

The study of Internet posts examined a corpus of 1,940,121 messages posted during the study period from the selected web forums. The proportion of all posts discussing tapentadol (pr = 0.0003) was significantly lower than any of the comparator compounds (range OR from 16.6 for fentanyl to 104.3 for oxycodone; all ps < .001). Similarly, the proportion of unique authors discussing tapentadol (pr = 0.004) was significantly lower than any of the comparator compounds (range OR from 12.7 for oxymorphone to 59.4 for oxycodone; all ps < .001). A total of 2,117 posts were coded and included in the analysis for endorsement: 309 for tapentadol and 904 each for the comparators. Analyses yielded an ERo of 2.14 for tapentadol which was significantly lower than the other Schedule II compound, oxymorphone (ERo = 5.08; p = .0011). Endorsement of abuse of tapentadol, which may still be establishing a stable abuse profile within the online community monitored, could not be differentiated from tramadol (ERo = 1.66; p =

.33). Tramadol has a long-established profile of low abuse and a low-level of desirability for abuse among the compounds as measured by the ERo. Thus, the present ERo data analysis suggests that individuals in this population, who have a high interest in recreational abuse of prescription medications, tend to discuss tapentadol in terms that reflect the lowest levels of desirability of the prescription opioids we have examined in this and other studies.

Conclusions

We examined a sample of posts written on recreational drug abuse web forums to evaluate the interest in abusing tapentadol as compared with other opioid analgesics. Findings suggest less interest in abusing tapentadol than other analgesics based on the amount of discussion. The level of endorsing the product for abuse was also low. Relatively low discussion levels and low endorsement for abuse are presumed to reflect lower interest in the product and a relatively low desire to obtain the medication for abuse purposes. These findings are consistent with the hypothesis that tapentadol may be have a reduced abuse liability.

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Tapentadol abuse potential: A post-marketing evaluation using a sample of individuals evaluated for substance abuse treatment

Stephen Butler[1], Emily McNaughton[1], Ryan Black[1], Theresa Cassidy[1]
[1]Inflexxion, Inc., Newton, MA, USA, [2]Janssen Scientific Affairs, Titusville, NJ, USA

Purpose

Abuse of prescription opioid pain relievers continues to be a serious public health concern. Tapentadol, a prescription analgesic, is thought to have two mechanisms of pharmacologic action: μ-opioid receptor agonism and norepinephrine reuptake inhibition. Tapentadol immediate release (IR) is indicated for the management of moderate to severe acute pain in adults; while tapentadol extended release (ER) is indicated for pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate and for neuropathic pain associated with diabetic peripheral neuropathy in adults. Tapentadol is Schedule II under the Controlled Substance Act in the US. Lower μ-opioid receptor affinity compared to other CIIs along with noradrenaline reuptake inhibition, which tends to not be significantly rewarding, may be associated with lower abuse potential. Thus, there is reason to believe that tapentadol abuse potential as manifested in postmarketing studies may be lower than other Schedule II opioid analgesics. This work reflects an initial examination of prevalence of abuse for tapentadol and specified comparator prescription analgesics at the compound and formulation-specific level using data from a large, nationally-based sample of individuals assessed for substance use problems.

Method

We examined a sentinel sample of adults assessed between January 2011 and September 2012 within the NAVIPPRO® substance abuse treatment surveillance system employing the Addiction Severity Index-Multimedia Version (ASI-MV®). The ASI-MV is a computer-administered, clinical interview that collects self-reported past 30-day drug abuse including specific prescription products. Patients differentiate abuse of prescription products using screen images. This observational, cross-sectional study examined the relative prevalence of self-reported past 30-day abuse of tapentadol and eight specific comparator compounds (oxymorphone, hydromorphone, hydrocodone, morphine, fentanyl, oxycodone, tramadol, and buprenorphine) and immediate-release (IR) and extended-release (ER) versions or long-acting (LA) products. Prevalence of abuse was measured as the probability of past 30-day abuse among the total study sample and as the probability of abuse adjusted for prescription volume during the study period for compound and IR and ER/LA products separately.

Results

From January 2011 through September 2012, 113,914 assessments were obtained from 624 facilities in 38 states. Tapentadol abuse was reported significantly less often ($p < .001$) than comparator compounds. Relative risk estimates unadjusted for prescription volume showed prevalence of tapentadol abuse to be significantly lower than all other compounds (range: oxycodone, RR = 162.39 to fentanyl, RR = 12.62). Prevalence of tapentadol IR abuse was lower than all IR comparator products (range: hydrocodone, RR= 171.57 to oxymorphone IR, RR = 5.03), with the exception of fentanyl IR ($p = .06$) and tapentadol ER abuse was lower than all other ER/LA comparators (range: oxycodone ER, RR = 315.45 to tramadol ER, RR = 7.65) except hydromorphone ER ($p = .79$). A significant portion of a given product's abuse prevalence appears to be explained by that product's prescribed availability. In the present study, about 60% of unadjusted abuse prevalence was explained by the number of prescriptions dispensed per quarter. To account for prescribed availability, prescription-adjusted regression results (i.e., risk per 10,000 prescriptions) were computed for the compounds, IR products, and ER/LA products separately. Prescription-adjusted abuse risk of tapentadol was significantly lower than all other compounds except hydrocodone ($p = 0.325$) and

tramadol, for which the prescription-adjusted relative risk was significantly less than that of tapentadol (p = <.001). Similarly, prescription-adjusted abuse risk of tapentadol IR was significantly lower than all other IR comparators except hydrocodone IR (p = 0.287) and tramadol IR, for which the prescription-adjusted relative risk was significantly less than that of tapentadol (p = <.001). Prescription-adjusted abuse risk for tapentadol ER was significantly lower than all other ER/LA comparators, except for hydromorphone ER (p = 0.06).

Conclusions

We examined a high-risk sample of individuals evaluated for substance abuse treatment. Within this substance abuse treatment population, tapentadol abuse was seen infrequently and, on a prescription basis, was less likely to be abused than most of the examined analgesics. These findings are consistent with the hypothesis that by having two mechanisms of action, μ-opioid receptor agonism and norepinephrine reuptake inhibition, and low affinity for the μ-opioid receptor, tapentadol may be associated with a reduced abuse liability. The early nature of these findings and other limitations suggest that further monitoring and analysis of tapentadol's abuse risk is warranted.

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Knowledge, Skills and Attitudes in Caring for Older Adults with Advanced Illness Among Staff Members of Long-Term Care and Assisted Living Facilities: An Educational Needs Assessment

Nina Cimino[1], Kashelle Lockman[1], Marian Grant[2], Mary Lynn McPherson[1]
[1]University of Maryland School of Pharmacy, Baltimore, MD, USA, [2]University of Maryland School of Nursing, Baltimore, MD, USA

Purpose

In long-term care and assisted living facilities, many groups of healthcare professionals contribute to the work of the healthcare team. More than doctors, nurses, and pharmacists, the healthcare team is also composed of nursing aides, social workers, and physical therapists, among others. These staff members perform essential, direct patient care activities and are an integral part of the healthcare team.

Method

An educational needs assessment was conducted to determine the learning needs and preferences of staff members of long-term care and assisted living facilities related to providing care for patients with life-limiting illnesses. The educational needs assessment consisted of an anonymous, internet-based survey in which respondents rated their perceived importance, skills, and interest in learning more about four topics related to providing palliative or end-of-life care. The four topics were: principles of palliative care, pain assessment, pain management, and management of non-pain symptoms. Survey respondents were also asked to provide information regarding their learning preferences as well as demographic information.

Results

Responses were received from 99 staff members, the majority of whom (n= 92) worked in long-term care facilities. Respondents included nurses (n= 29), social workers (n= 27), nurse practitioners (n= 6), activities director/coordinator (n= 5), speech therapists (n=4), physical therapists (n= 4), occupational therapists (n= 2), one physician, and one nursing aide. Staff members placed importance on understanding topics such as principles of palliative care, pain assessment, pain management, and non-pain symptom management. The majority of survey respondents were also somewhat interested or very interested in learning more about these topics. The majority of respondents (n= 77) were very interested in learning more about caring for patients with serious illness or at the end of life through an online course on the computer at their own convenience.

Conclusions

We believe staff members at long-term care and assisted living facilities in Maryland would benefit from a course tailored to these identified educational needs which is designed to overcome previously identified educational barriers.

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Medication Management at the End of Life for Clinical Supportive Hospice and Palliative Care Practitioners

Mary Lynn McPherson
University of Maryland School of Pharmacy, Baltimore, Maryland, USA

Purpose

Hospice is a patient and family-centric model of care for individuals with a life-limiting illness likely to result in patient death within six months. Hospice care provides expert medical care, pain and symptom management and psychosocial and emotional support for the patient and family. Slightly less than half of the patients who died in the United States during 2011 received hospice care; over one million US citizens who died in 2011 were under the care of hospice at the time of their death.

While a family member generally serves at the patient's primary caregiver, an entire team of hospice health care professionals provide the care necessary to achieve the aforementioned goals. This includes physicians, pharmacists, nurses, spiritual counselors, social workers, bereavement specialists, home health aides, therapists, volunteers and others. The care provided to hospice patients by nurses and physicians accounts for about 30% of the hospice labor force. The majority of the care is provided by the "non-nurse, non-physician" practitioners described above.

Evidence presented by variety research demonstrates that hospice supportive professionals feel poorly qualified to support effective medication management in end of life care. Based on these findings, an educational needs assessment was conducted, an online training course on medication management was developed and launched and changes in knowledge, skills and attitudes of hospice practitioners in medication management was measured.

Method

An educational needs assessment was conducted including expert interviews, a focus group interview, an online survey and a literature search. One hundred eleven hospice supportive practitioners employed by Seasons Hospice & Palliative Care participated in the online survey. Respondents were asked if they felt they had an important role in assisting patients and families optimize medication management, their confidence in performing this role, and their level of interest in an online educational training program aimed at increasing skills in assisting patients, families and caregivers in effective medication management.

Based on an extremely response to the educational needs assessment and survey, an online training program was developed and deployed addressing six domains of knowledge: principles of palliative care, medication management, assessment of pain, pathogenesis of pain, pain management and management of nonpain symptoms. These six domains were partitioned into four discrete modules. Each module contained a self-assessment activity (formative feedback provided), narrated PowerPoint presentations, and a post-assessment activity. Before beginning the course, and again at the end of the course, participants completed a survey of attitudes, self-perceived skills and knowledge in all six domains. Changes in matched responses were compared and analyzed using Chi Square or Fisher's Exact Test.

Results

Results of the educational needs assessment showed that 100% of respondents felt medication management was an important goal in hospice care. The majority of respondents felt "somewhat confident" in their ability to participate in medication management, and overwhelmingly supported the idea of online training in this area.

Seventeen providers completed all elements of the course. Four RNs, 8 social workers, 2 music therapists, one volunteer coordinator and two chaplains. Ninety percent of respondents felt a working knowledge of medication management in all six domains was very important at the beginning of the course, and 92% felt similarly at the end of the course (/=0.81). However self-perceived skills in all six domains improved, with an overall improvement from 48% feeling "very confident" before the course, to 86% achieving this outcome by the end of the course (p=0.0001). Knowledge improved in all domains with an overall improvement from 70% of questions answered correctly at the beginning of the curse to 82% questions answered correctly by the end of the course (p=0.004).

Conclusions

Participants felt that medication management was an important skill to possess (attitudes were very strong both before and after completing the course). Self-perceived skill and knowledge improved in all six domains of medication management which will hopefully result in improved patient outcomes.

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Study on the Role of Gender in Pain Perception Differences amongst Chronic Pain Patients.

Brian Meshkin, Tobore Onojighofia, Dan Schwarz, Bilikis Akindele, Derrick Holman, John Hubbard, Lisa Davila
Proove Biosciences, Irvine, CA, USA

Purpose

Pain sensitivity is believed to be influenced by sociocultural, psychological, and biological factors. Though the basis for gender difference in pain perception is unknown, a number of studies on pain sensitivity suggests that pain tolerance is generally higher in males when compared to female subjects. The purpose of this study is to determine gender differences in pain perception amongst chronic pain patients.

Method

2,701 chronic pain subjects (1,598 (59.2%) women and 1,103(40.8%) men) from 48 Clinic sites across the United States were enrolled in this IRB-approved cross-sectional study. All 2701 patients completed a Pain VAS rating their perception of pain on a scale from 0 to 10. Subjects with a Pain VAS score of 0 were excluded from the study. Low pain perception was defined as a score of 1, 2 or 3 (n=249, 9.2%). Moderate pain perception was defined as a score of 4, 5, or 6 (n=1248, 46.2%). High pain perception was defined as a score of 7, 8, 9 or 10 (n=1,204, 44.6%).

Results

Cross tab analysis using IBM SPSS Version 21 showed an association between gender and pain perception. Further analysis using a multinomial logistic regression found females to be more associated with High Pain perception (poor pain tolerance) and males to be associated with low pain perception (Good pain tolerance). (P=0.036, OR 1.345.)

Conclusions

This study suggests that there exist a difference in pain perception due to gender. Women are more associated with poor pain tolerance (High Pain Perception) compared to males in this study and this is in line with findings from many other studies. Findings in this study validates prevailing evidence and knowledge that gender plays a role in pain perception.

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Perception of Analgesia in Narcotic Users with Chronic Pain: A Multi-Center Cross-Sectional Study Comparing Genotype to Pain VAS (P.A.I.N. Study)

Brian Meshkin, Tobore Onojighofia, Dan Schwarz, Bilikis Akindele, Derrick Holman, John Hubbard, Lisa Davila
Proove Biosciences, Irvine, CA, USA

Purpose

Various studies have explored modalities for objectively evaluating pain perception, including functional MRI and genotype. In this study, researchers from Proove Biosciences evaluated its proprietary practice-based evidence (PBE) database to conduct a cross-sectional analysis of genotype with Pain VAS. The purpose of the study is to evaluate whether genotype can help objectively stratify patient perception of pain among chronic pain patients taking narcotics.

Method

2,721 subjects diagnosed with chronic pain currently taking prescription opioid pain medications (1,584 women and 1,137 men) from 48 Clinic sites across the United States were enrolled in this IRB-approved cross-sectional study. All 2721 patients completed a Pain VAS rating their perception of pain on a scale from 0 to 10. Subjects diagnosed were genotyped using a RealTime PCR TaqMan assay from Proove Medical Laboratories (Irvine, CA). The following single nucleotide polymorphisms (SNPs) were evaluated: COMT (Val158Met), DRD2 (A2/A1, A1/A1), DRD1 (-48A/G), and OPRK1 (36G>T). Subjects with no pain (Pain VAS) were excluded from the study. Low pain perception was defined as a score of 1, 2 or 3 (n=249, 9.2%). Moderate pain perception was defined as a score of 4, 5, or 6 (n=1259, 46.2%). High pain perception (High Pain Sensitivity) was defined as a score of 7, 8, 9 or 10 (n=1,213, 44.6%). A multinomial logistic regression analysis was performed using IBM SPSS Version 21.

Results

Statistical significance was found among all four variants to help objectively stratify pain perception. The DRD1 variant was found to be more prevalent in the low pain perception population compared to high pain perception population [$p<0.043$, OR 1.334 (95% CI 1.009 - 1.764), PPV 84.44% (95% CI 81.97% - 86.70%)]. Among subjects with a moderate pain perception, the COMT and OPRK variants were more prevalent compared to those with high pain perception [COMT: $p<0.007$, OR 1.25 PPV: 52.41%, OPRK: $p<0.032$, OR 1.19 PPV 51.09%. Among subjects with a high pain perception, the DRD2 variant was more prevalent compared to subjects with moderate pain perception ($p<0.041$, OR 1.25, PPV 52.61%).

Conclusions

This retrospective analysis provides a potential genotypic analysis to stratify pain perception, and a more objective method to define subjective Pain VAS perceptions.

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INVESTIGATION OF GENETIC VARIATIONS IN THE MESOLIMBIC DOPAMINE SYSTEM AND ELEVATED RISK OF OPIOID ABUSE IN CHRONIC PAIN PATIENTS

Brian Meshkin, Tobore Onojighofia, Dan Schwarz, Bilikis Akindele, Derrick Holman, John Hubbard, Lisa Davila
Proove Biosciences, Irvine, CA, USA

Purpose

The objective of this study is to evaluate the prevalence of mesolimbic genotypes linked to neurochemical deficiency among chronic pain patients taking narcotic pain medications

Method

5130 subjects diagnosed with chronic pain and taking prescription narcotics were genotyped with TaqMan SNP genotyping assays (Life Technologies, Carlsbad, CA) using the proprietary Narcotic Risk analysis from Proove Biosciences. The following single nucleotide polymorphisms (SNPs) in the mesolimbic dopamine reward system were used in the evaluation: DRD1 -48A>G, DRD2 A1 allele, DRD4 -521C/T, DAT1, COMT Val158Met, OPRK1 36G >T, OPRM1 A118G, DBH -1021 C/T, 5-HT2A -1438G/A, 5-HTTLPR, GABA 1519T>C, and MTHFR C677T.

Results

Statistically significance was found in all 12 SNPs, DRD2 (15% v. 5% p<0.001), DRD4 -521C/T (34% v. 3% p<0.001), OPRK1 36G > T (28% v. 8% p=0.024), OPRM(5% v. 1% p=0.035), DRD1 (11% v. 27% p<0.001), Dopamine Beta Hydroxylase (DBH -1021 (10% v. 5% p=0.003), Methylene Tetrahydrofolate Reductase (MTFHR C677T 13% v 7% p=0.004), Gamma-Aminobutyric Acid (GABA) (1519T>C GABA(A)gamma 2 (21% v. 63% p<0.001), Serotonin 2a Receptor (5-HT2a 1438 G/A) (7% v. 10% p=0.01), Serotonin Transporter (SLC6A4) (2% v. 15% p<0.001), and Catechol-O-Methyltransferase (COMT Val108/158Met (25.5% v. 25% p=0.024).

Conclusions

There is a higher prevalence of genetic predisposition in the mesolimbic dopamine system among chronic pain patients taking prescription narcotic pain medications. The higher prevalence of these variants may provide information to medical personnel to help improve therapeutic decisions.

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Use of Prescription Claims Data to Identify Claimants at a Higher Risk of Fraud, Waste, and Abuse

Brooke Mueller[1,2], Matthew Foster[1]
[1]Helios, Tampa, FL, USA, [2]University of Florida, Gainesville, FL, USA

Purpose

The use of opioid medications to treat pain associated with workplace injuries is prevalent. There has been an increased national awareness of opioid use over the past several years due to the fraud, abuse, addiction, and cost associated with these medications. A need exists for a service that identifies high risk claimants, facilitates the urine drug testing process, and provides interpretation and recommendations for action to clients based on the results.

The Helios Drug Testing and Monitoring (DTM) service deters diversion and drug abuse while promoting appropriate use of opioid medications by facilitating urine drug testing at the prescriber level. This service ensures that an on-going monitoring program is in place for injured workers at risk for fraud, waste, and abuse. The DTM service utilizes a proprietary application to identify injured workers in need of additional monitoring for their chronic opioid therapy and engages a Helios clinical pharmacist to work in conjunction with the urine drug testing laboratory and the injured worker's prescriber.

A comprehensive study was performed to assess the proprietary criteria used to identify potentially high risk Injured Workers who may benefit from the additional clinical oversight of the Helios Drug Testing and Monitoring service.

Method

The algorithm for identifying potentially high-risk injured workers as candidates for urine drug testing examines a workers' compensation payor's population of injured workers with a date of injury greater than 90 days. Risk factors are identified based on the injured worker's workers' compensation prescription profile over the previous 90 days and results of other Helios clinical programs. Each risk factor is assigned a risk score and those injured workers with a total risk score equivalent to or exceeding a predetermined risk score threshold are identified as potentially high-risk injured workers who may benefit from the Helios DTM service.

Results of urine drug tests performed on those patients identified as potentially high-risk by Helios between March and December 2013 were analyzed for consistency with the injured worker's current medication regimen as reported by the ordering prescriber to the laboratory at the time of specimen submission. The effectiveness of injured worker identification of urine drug testing candidates was measured by determining the percentage of claimants identified, who had an inconsistent urine drug test once testing was performed. Inconsistent tests were defined as those where the reported prescribed medications were not found in the urine, non-prescribed medications were detected, and/or an illicit substance was found.

Results

Approximately 75% of the 1,784 identified injured workers that had a urine drug test performed during the study period had an initial test result (during the study period) that was deemed inconsistent by the laboratory. In comparison, two-thirds (66.7%) of tests performed during the same time frame on payor-referred patients and slightly over half (51.3%) of prescriber-initiated patients had initial urine drug tests that were classified as inconsistent.

While the use of multiple prescribers and multiple pharmacies are considered by many to be risk factors for misuse and abuse, an analysis of Helios criteria for identifying potentially high risk patients revealed a higher percentage of patients filling their prescriptions at multiple pharmacies and/or having prescriptions for opioids written by multiple prescribers had a urine drug test result consistent with their current medication regimen. However, a higher percentage of patients who received a prescription for a stimulant and/or those that were receiving therapy of a long-acting opioid pain reliever in the absence of any short-acting analgesic returned a test result that was inconsistent with their current medication regimen. The overutilization of a short-acting opioid-acetaminophen combination medication and the long-term utilization of carisoprodol (Soma) were the least predictive regarding the outcomes of a patient's urine drug test result.

Conclusions

A combination of risk factors derived from prescription claim information can be used to accurately identify patients at a higher risk for fraud, waste, and abuse. Early monitoring for compliance of these patients may lead to a reduction in risk or identification of issues requiring a change in therapy. Helios' proprietary identification program successfully identified patients noncompliant with therapy, as suggested by inconsistent urine drug test results at a higher rate than those identified by the payor or the prescriber. Further studies should be performed to analyze the identification criteria to determine which criteria are predictive of inconsistent test results.

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Treatment of Postherpetic Neuralgia with Gastroretentive Gabapentin: Pain Intensity, Pain Interference, and Safety

Srinivas Nalamachu[1], Naum Shaparin[2], Daniel Kantor[3], Sunil, J. Panchal[4], Richard Rauck[5]
[1]International Clinical Research Institute, Overland Park, KS, USA, [2]Montefiore Pain Center, Bronx, NY, USA, [3]University of Florida, Jacksonville, FL, USA, [4]National Institute of Pain, Tampa, FL, USA, [5]Carolinas Pain Institute, Winston-Salem, NC, USA

Purpose

Postherpetic neuralgia (PHN), a neuropathic pain syndrome that occurs in response to nerve damage, is the most common complication of herpes zoster (shingles). Pain associated with PHN frequently interferes with patients' physical function and their quality of life. Thus, improvement in various aspects of quality of life, in addition to control of neuropathic pain, may provide quality patient care and improve patients' overall well-being.

The effective management of PHN remains an ongoing challenge, all current treatments are symptomatic, and patients may be left undertreated. Gabapentin was the first oral medication approved by the Food and Drug Administration (FDA). A novel formulation of gabapentin utilizing gastroretentive technology (gastroretentive gabapentin, G-GR; Gralise®, Depomed, Inc., Newark, CA) resulted in more efficient drug absorption, improved bioavailability, and reduced dosing frequency from thrice daily to once daily. The efficacy and safety of G-GR was established in two randomized, placebo-controlled Phase 3 studies, and confirmed in an open-label, Phase 4 study.

To gain further insight into the effectiveness of G-GR in reducing pain intensity and improving patients' quality of life, as well as into the safety profile of G-GR in treatment of PHN, we integrated and analyzed data from clinical trials of G-GR. Also, to better understand how key patient-reported outcome measures relate to patients' overall well-being, we examined relationships among various efficacy, safety, and patient demographic variables. Such characterizations can better guide treatment decisions and assessment of treatment of neuropathic pain.

Method

Data from two double-blind, randomized, placebo-controlled, Phase 3 studies and one open-label, single-arm, Phase 4 study of patients with PHN who received G-GR were integrated. Patients were titrated to 1800 mg/day G-GR over 2 weeks, followed by 8 (Phase 3) or 6 (Phase 4) weeks of stable dosing with G-GR 1800 mg taken once daily with the evening meal. The Visual Analog Scale (VAS) for the assessment of pain intensity and the Brief Pain Inventory (BPI) for the assessment of pain qualities and pain interference were completed at baseline and end of study (Week 10 for Phase 3 and Week 8 for Phase 4). Patients' Global Impression of Change (PGIC) for the assessment of overall improvement was completed at end of study. Safety assessments included the incidence of adverse events (AEs). Multivariable logistic regression analyses were performed to examine correlations among efficacy and safety measures. Statistical significance was set at $p \leq 0.01$.

Results

The integrated dataset included 546 patients in the efficacy population and 556 in the safety population. The mean change from baseline in pain intensity measured on the VAS was statistically significant ($p<0.0001$). Likewise, mean changes from baseline in pain quality and pain interference scores measured on the BPI were statistically significant (all $p<0.0001$). According to the PGIC, 45.2% felt "Much" or "Very much" improved at the end of G-GR treatment.

Among all baseline characteristics and efficacy variables tested, VAS score at baseline and at Week 2 (early pain relief; both $p<0.0001$), and BPI average pain at baseline ($p=0.0099$) were significant predictors of changes in pain

intensity on the VAS. The VAS score at baseline (p=0.0045) and at Week 2 (p=0.0007), and the BPI current pain at Week 2 (p=0.0102) were predictors of feeling "Much" or "Very Much" improved on the PGIC. Not pain intensity scores but the BPI sleep interference score at baseline (p=0.0140) was predictive of the improvement in the average of 7 BPI interference scores.

G-GR was generally well tolerated. In total, 53.2% of patients reported ≥1 AE, and 12.9% discontinued treatment due to AEs. The incidence of AEs decreased rapidly from 21% to 8% after 3 weeks of G-GR treatment, and reached steady low levels of 3–4% after 5 weeks of treatment. Female gender was the only predictive factor (p=0.0006) for reporting any AEs at any time during G-GR treatment. Not patient demographics but moderate or severe AEs were predictors of discontinuations due to AEs (p=≤0.0001 and p=0.0006, respectively).

Conclusions

The efficacy results demonstrated statistically significant reductions in all measures of pain intensity and pain interference with patients' lives at the end of G-GR treatment. The analysis of predictive factors suggested the key role of pain relief and sleep improvement in the management of PHN. Finally, because the tolerability of G-GR did not appear to be affected by patients' age, and given that PHN is a disease for which the risk and duration of PHN increases with age, G-GR seems to be particularly well-suited for the management of PHN.

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Medical and Illegal Marijuana Use among Persons Who Inject Drugs

Scott Novak, Mark Edlund, Alex Kral
RTI International, RTP, NC, USA

Purpose

Pain patients often argue that marijuana is an efficacious treatment for numerous types of chronic and acute pain, and less addicting than opioid-based pain medications. Marijuana is currently classified as an illegal substance by the federal government, specifically because it is viewed as having no medically accepted therapeutic value. However, 38 states including California have some form of medical marijuana legislation. In medically approved states, the licensed medical provider just issues a letter of recommendation for an ID card, which allows a patient to purchase medical marijuana. There is no prescription for a specific medication and dose. The federal view holds that medical marijuana represents an avenue for illegal users to secure a legal supply. The current study seeks to examine this possibility by characterizing the demographic and clinical characteristics of the highest-risk marijuana users, namely persons who inject drugs (PWIDs). We specifically compare those currently receiving medical marijuana treatments from illegal marijuana users. This study is an attempt to discern whether any differences in the two populations would indicate differential selection, either by patients self-selecting into legal prescriptions or prescribers screening out meritless diagnoses. Such differences between the illegal and legal medical users could offer evidence that medical marijuana use represents a distinct clinical population from illegal use. This finding would fail to support the legal access argument and offer additional evidence for the legitimacy of medical marijuana treatment.

Method

We screened and recruited PWIDs in San Francisco (n=705) at baseline, with collection occurring between October, 2011 and April 2014.Targeted sampling methods were used to identify and recruit persons who inject drugs from locations known to have a high prevalence of PWIDs, including syringe exchange programs, homeless encampments, free food distribution locations, outside drug use markets. The eligibility criteria for the study were; 18 years old or older, current or recent injection of illicit drugs (past 30 days) as verified by checking for signs of venipuncture ("tracks"), and ability to provide informed consent. Surveys were administered via computer aided survey interviewing software (CAPI) with a trained interviewer administering the questions. Items captured lifetime and current consumption patterns for marijuana and illicit drugs, the influence of biological, psychological and social-contextual characteristics on marijuana consumption, and the sources of and access to marijuana. Survey items were classified into the following domains: (1) Demographics (2) physical health status (3) mental health status (4) substance use (5) perceptions toward drugs (6) experience with overdose (7) health care utilization (8) injection practices (9) sexual behavior and (10) experience with substance abuse treatment. Each survey lasted approximately 30 minutes in length. Participants were compensated $20 for their time spent participating in the baseline interview. All procedures were approved by RTI's Institutional Review Board.

Results

At baseline, there were 705 participants, most of whom were male (80%). The racial composition was 54% white, 25% black, 7% Hispanic, and 13% other race. In terms of age, 11% were ages 18-29, 36% were 18-44y, 32% were 45-54y, and 22% were aged 55 or older. 62% were homeless, and 72% had a high graduate degree/GED equivalent. In terms of substance use, approximately 90% reported lifetime use of marijuana, and 60% reported use in the past month. Of those, only 20% reported receiving a legitimate prescription for medical marijuana. We compared the demographic and psychosocial characteristics between illegitimate marijuana users and those reporting legal prescriptions. Those who had legal prescriptions were statistically more likely to be employed (20% versus 5%),

have higher incomes (10k versus 2k per year), and have some form of insurance (80% versus 5%). In terms of mental and physical health, those with a legitimate prescription for medical marijuana were more likely to have HIV (14% versus 2%), and less likely to have a mood disorder (30% versus 65%). Illegal marijuana users had higher levels of illicit drug use, in terms of the number of drugs used, the number of total days used, and overdose history. We also ascertained physical health status using several standard pain scales, and those with medical marijuana treatment reported lower rates of impairment than those using illegally. Medical marijuana users were more likely to report neurological disorders and lower back pain, whereas illegal users reported more foot and leg injuries. Taken together, medical marijuana users appear to have higher levels of psycho-social functioning than illegal users.

Conclusions

There are concerns that persons with extensive drug use careers may seek medical marijuana treatment as an opportunity to gain legal access. Findings from this study suggest otherwise. This study cannot comment on why there were differences in the populations of medical versus illegal marijuana users in terms of channeling/selection effects. Nonetheless, there is a need for future research to disentangle the factors that influence demand for medical marijuana and the role of physician-gatekeepers in prescribing to different types of patient populations.

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Perspectives on Intravenous Oxycodone for Control of Postoperative Pain

Joseph V. Pergolizzi, Jr.[1,2], Gianpietro Zampogna[4], Robert Taylor, Jr.[4], Robert B. Raffa[5]
[1]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]Department of Pharmacology, Temple University School of Medicine, Philadelphia, PA, USA, [3]Department of Anesthesiology, Georgetown University School of Medicine, Washington, DC, USA, [4]NEMA Research Inc., Bonita Springs, FL, USA, [5]Department of Pharmaceutical Sciences, Temple University School of Pharmacy, Philadelphia, PA, USA

Purpose

Inadequate control of postoperative pain may have serious clinical and financial implications: under-treated postoperative pain can delay ambulation, hamper rehabilitation, increase length of hospital stay, require re-admission, diminish quality of life, decrease patient satisfaction, set the stage for chronic postsurgical pain syndromes, and cause suffering and distress to patients and their families. Intravenous (IV) analgesia provides particular advantages in the immediate postoperative period, but there is insufficient evidence in the literature to support the use of one opioid analgesic over another. The purpose of this literature review was to summarize the safety, efficacy, and particular advantages of the use of IV oxycodone versus other IV opioids for the control of postoperative pain.

Method

The PubMed database was searched for the keywords "intravenous" and/or "oxycodone" and/or "IV" for clinical trial and review articles published since database inception. A total of five clinical studies were identified that described the use of IV oxycodone for postoperative pain. Studies were reviewed in order to determine IV oxycodone's safety and efficacy. Additional articles were evaluated for relevancy in relation to IV oxycodone's pharmacology, potency compared to other opioids, and use in special populations such as older adults or pediatrics.

Results

IV analgesia has particular advantages in the immediate postoperative period. IV morphine is widely used, but there is a trend toward the use of oxycodone. Oxycodone has greater bioavailability than morphine and its analgesic effect resides mainly in the parent drug. Metabolized via the CYP2D6 (minor) and CYP3A4 (major) pathways, polymorphisms in these enzymes ("slow" or "fast" metabolizers) seem to have only minor clinical impact. Unlike morphine and many other agents, oxycodone is able to readily cross the blood-brain barrier (BBB). Published studies of laparoscopic hysterectomy patients, laparoscopic cholecystectomy patients, major surgery patients (breast reconstruction or major spinal surgery), and abdominal surgery patients comparing IV oxycodone to other IV opioids report that oxycodone is an effective analgesic and may offer specific advantages. Some studies show that IV oxycodone may be associated with greater pain control, fewer or less severe adverse events, and faster onset of action, but these results are not consistent across all studies. Oxycodone has been reported to be safe in the geriatric and other special populations when adequate clinical adjustments are made.

Conclusions

Although oxycodone is an "old drug", dating back to 1917, a complete understanding of its pharmacology and clinical benefits is still evolving. With a similar to better analgesic effect than IV morphine, IV oxycodone may offer specific advantages for intravenous or PCA use for postoperative pain. In addition, Oxycodone produces opioid-related side effects, as does morphine, but some studies have found fewer or less severe adverse events with oxycodone at equianalgesic doses. Thus IV oxycodone appears to be a potentially important "new" drug for postoperative pain control.

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Can Public Policy Reduce Prescription Opioid Abuse Rates? Interim Results from Florida

Joseph V. Pergolizzi, Jr.[1,2], Jo Ann LeQuang[4], Gianpietro Zampogna[4], Robert Taylor, Jr.[4], Robert B. Raffa[5], Hani Michael Annabi[1]
[1]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]Department of Pharmacology, Temple University School of Medicine, Philadelphia, PA, USA, [3]Department of Anesthesiology, Georgetown University School of Medicine, Washington, DC, USA, [4]NEMA Research Inc., Bonita Springs, FL, USA, [5]Department of Pharmaceutical Sciences, Temple University School of Pharmacy, Philadelphia, PA, USA

Purpose

Patterns of opioid prescribing vary within the United States. The 10 states that prescribe the most opioid painkillers are located in the South.[1]Many factors may contribute to these prescribing patterns, such as efforts to compensate for the under treatment of pain, lack of specialized training on prescription opioids among prescribers, and limited patient education. Unfortunately, along with the wider appropriate use of prescription opioids, there were in 2009 in Florida, 732 so-called "pill mills" –– pain clinics that inappropriately prescribed and often dispensed large quantities of opioid analgesics.[4]Of the 100 physicians who dispensed the largest quantity of oxycodone in the United States, 98 practiced in Florida.[2]From 2003 to 2009, overdose deaths in Florida increased by 61%,[2]while overdose deaths specifically related to prescription drugs increased 84.2% (from 7.3 to 13.4 per 100,000 population), with oxycodone leading the increase (up 264.6%).[3]When opioid-related deaths were correlated in an adjusted analysis to opioids dispensed, there was a 6% increase in the rate of oxycodone-related overdose deaths for every one pill prescribed per person.[4]In 2009, four times as many people died from prescription drug overdoses in Florida as from illicit drug overdoses.[3]However, prescription drug prescribing and overdose deaths decreased abruptly from 2010 to 2012. This swift and decisive reversal raises important questions. What did Florida do and why was it so effective so quickly? The purpose of our study was to explore possible determinants for the sudden and significant decrease in opioid consumption, abuse, and associated overdose deaths in Florida.

Method

We evaluated the literature and press to determine what steps were taken in Florida to explore possible determinants of this decrease.

Results

In 2010-2011, Florida undertook decisive steps to reduce the large opioid abuse, misuse and diversion problem:[2]

- Legislative interventions were implemented to regulate pain clinics [5]
    - Pain clinics had to register with the state; many "pill mills" were raided, had assets seized, and some were closed.
    - The Florida Surgeon General limited dispensing of Schedule II or III substances to legitimate offices and clinics.
- A prescription-drug monitoring program (PDMP) was put into place.[5]
    - A mandatory dispenser reporting program became associated with the new PDMP

Implementation of these requirements resulted in a number of positive outcomes: 250 "pill mills" were closed, and high-volume oxycodone-dispensing clinics decreased from 98 to zero from 2010 to 2013, respectively.[2]This major change removed a large source used by drug dealers[6] (drug-abusing patients rely more on dealers to get drugs).[7]

In the prior years (2003 to 2010), drug overdose deaths increased 58.9%, even though there were 24 district medical examiners in place who were required to report to the Florida Medical Examiners Commission (FMEC) on all drug-related deaths (for any decedent with any of 50 monitored drugs) and whether or not drug(s) played a causal role in death.[2] Increased regulation resulted in:

- Drug overdose deaths decreased by 16.7% from 3,201 in 2010 to 2,666 in 2012[2]

- Peak prescription drug overdose deaths decreased from 2,722 in 2010 to 2,116 in 2012[2]

In this time period, there were significant decreases in oxycodone, methadone, and morphine diversion and there was a small but significant decrease in hydrocodone diversion.[5]Reductions (or increases) in prescriptions for a specific drug were mirrored by reductions (or increases) in overdose rates.[2]

Oxycodone overdose deaths decreased across all demographic groups, but the greatest decreases occurred among men (57%) and non-Hispanic whites (52.6%). Decreases were also greater among younger versus older individuals.

Conclusions

Florida had long been known for lax regulation of opioids, a proliferation of pill mills, and high rates of opioid-related morbidity and mortality, but the state was able to rapidly and dramatically reverse this trend with decisive legislative action, including governmental regulations and implementation of a PDMP. This suggests that policy-level interventions by state governments may be an important element in reducing prescription opioid abuse. The temporal association between legislative actions and drug overdose rates suggest that the initiatives in Florida contributed to the significant decrease in oxycodone-overdose death rates.

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Healthcare Providers' Knowledge, Attitudes, and Practices of Abuse-deterrent Formulations of Opioids

Joseph V. Pergolizzi Jr[1,2], Robert Taylor Jr[4], Robert B. Raffa[5], Eric R. Kinzler[6]
[1]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]Department of Anesthesiology, Georgetown University School of Medicine, Washington, DC, USA, [3]Department of Pharmacology, Temple University School of Medicine, Philadelphia, PA, USA, [4]NEMA Research Inc., Bonita Springs, FL, USA, [5]Department of Pharmaceutical Sciences, Temple University School of Pharmacy, Philadelphia, PA, USA, [6]Inspirion Delivery Technologies LLC, Valley Cottage, NY, USA

Purpose

Practitioners play an important role in identification and mitigation of prescription opioid abuse. Inadequate knowledge regarding the topic can lead to under-vigilance (impeding deterrence) or over-vigilance (impeding legitimate pain relief). Understanding practitioners' knowledge, attitudes, and practices (KAP) regarding opioids and abuse-deterrent formulations (ADFs) may help identify gaps and guide development of improved multidisciplinary pain-management strategies. Therefore, we conducted a survey to investigate KAP of healthcare providers attending a conference on pain.

Method

Using a convenience sampling approach, healthcare providers attending a CME pain management conference held in Las Vegas (PAINWeek 2013) were asked to complete a survey that consisted of 16 questions addressing topics such as patient risk, diversion, opioid misuse, routes of abuse, abuse-deterrent technologies, and legal ramifications of prescribing opioids and ADFs. Healthcare providers were given the option to take part in a paper- or electronic-based version of the survey, and were entered into a raffle for a small prize if they completed the survey.

Results

A total of 123 healthcare providers from across the United States completed the survey. Practitioner specialties were diverse and included areas such as acute care, anesthesiology, chronic pain management, emergency medicine, and family medicine. The mean duration of practice experience was 16.3 years. The majority was aware of diversion practices of abusers and has considered prescribing ADFs in patients who have moderate to high risk for abuse; however, not all practitioners were knowledgeable of how diversion occurs. Less than half (45%) of those surveyed recognized that most abusers (~70%) get their drugs from friends or relatives and just 54% believed that more than half of recreational abuse is sourced through diversion of a legitimate prescription. Practitioners (45%) identified crush-resistance as the best abuse-deterrent technology whereas just 9% preferred sequestered antagonists. Surprisingly, many practitioners were unaware of the impact of ADF technology: 80% did not know that diversion rates of extended-release oxycodone decreased approximately 60% after the introduction of an ADF oxycodone. A majority (65%) of practitioners surveyed were concerned about legal liability if non-ADFs were prescribed despite the availability of ADFs. Finally, practitioners believe that the best methods for disseminating information about prescription drug abuse in light of FDA recommendations are live lectures (31.7%) and mandatory training for licensure (26.8%).

Conclusions

Practitioners were largely unaware that approximately 70% of abused opioids are sourced through a friend or family member and more than 80% of those drugs are prescribed by a single healthcare professional. This is concerning considering only 22% of practitioners would consider prescribing ADFs for all patients. Providers should think beyond

the patient and consider incorporating an assessment for risk of diversion of their prescription as part of their risk management plan. Increasing practitioners' knowledge about opioid abuse may help optimize risk management plans, encourage judicious prescribing, and, in turn, reduce opioid abuse, misuse, and diversion.

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Characterization of the Human Skin Percutaneous Absorption of Lorazepam using the Franz Finite Dose *in vitro* Permeation Test Model

Daniel Banov, Gus Bassani, Bryan Prescott, Maria Carvalho
PCCA, Houston, Texas, USA

Purpose

The human skin percutaneous absorption of transdermal compounded formulations containing lorazepam incorporated in the proprietary bases Lipoderm and Lipoderm ActiveMax, was evaluated using the Franz Finite Dose *in vitro* Permeation Test Model (IVPT). Lorazepam is an anxiolytic, sedative, hypnotic and antipsychotic drug commonly prescribed by physicians to relief anxiety and restlessness. When the oral route of administration is compromised (e.g. hospice care), topical lorazepam represents a viable alternative provided that the drug is absorbed transdermally. The Franz Finite Dose IVPT Model has proven to be a valuable tool for the study of percutaneous absorption and determination of the pharmacokinetics of topically applied drugs. It has also proven to accurately predict *in vivo* percutaneous absorption kinetics since this model uses *ex vivo* human torso skin mounted in specially designed diffusion chambers allowing the skin to be maintained at a temperature and humidity that match normal *in vivo* conditions. Therefore, the Franz Finite Dose IVPT Model was selected to characterize the percutaneous absorption of lorazepam into and through the skin by evaluating the total absorption, rate of absorption and the skin content of lorazepam applied to the outer surface of the skin.

Method

The percutaneous absorption of lorazepam was measured using *ex vivo* human torso skin samples, without obvious signs of disease, from two male and one female donors (Hispanic and Caucasian races). The skin samples were dermatomed, cryopreserved, sealed in a water-impermeable bag and stored at approximately -20°C prior to use. The skin samples were then rinsed in water and cut into small sections to fit on nominal 2.0 cm^2 diffusion cells. The dermal (receptor) chamber was filled to capacity with a receptor solution. The integrity of each skin section was evaluated by testing its permeability to titrated water prior to the experiment. Lorazepam 5 mg/g was incorporated in Lipoderm and also in Lipoderm ActiveMax and each compounded formulation was then applied to the skin sections (5 mg/cm^2) of the three *ex vivo* human torso skin donors (3 replicates per donor). A receptor solution was placed bathing the inner surface of the skin sections in order to measure the rate of appearance of lorazepam. The percutaneous absorption of the drug was evaluated over a period of 48 hours. During the exposure period, samples of the receptor solutions were removed at pre-selected times (0, 2, 4, 8, 12, 24, 32 and 48 hours) and were analyzed for lorazepam content using the HPLC/UV analytical method. After the last sample of the receptor solutions (collected at 48 hours), the skin sections were washed, tape stripped (to remove the stratum corneum) and separated into the epidermis and dermis to evaluate the skin content of the drug.

Results

The total absorption, rate of absorption and the skin content (distribution) of lorazepam was determined for a total of two test formulations containing lorazepam 5 mg/g and propylene glycol 10% (w/w) in Lipoderm and Lipoderm ActiveMax, respectively. The absorption results indicate the percutaneous absorption of lorazepam through the skin whereas the distribution results indicate the percutaneous absorption into the skin. The total absorption and the skin content were determined after 48 hours from a single application of the transdermal compounded formulations in the skin sections. The total absorption corresponded to the total recovered in the receptor solutions and the skin content corresponded to the mass recovered of lorazepam in the stratum corneum, dermis and epidermis ($\mu g/cm^2$). The rate of percutaneous absorption, on the other hand, is a time-averaged value and it was determined as the mean flux of

lorazepam, collected at the receptor solution under the skin (μg/cm^2/h), over the 48-hour period. The absorption and distribution profiles of lorazepam were similar for both Lipoderm and Lipoderm ActiveMax test formulations. The rate of percutaneous absorption of lorazepam was also similar for both test formulations, though differing in magnitude. The rate of percutaneous absorption showed a slow rise to a peak flux of lorazepam occurring approximately 30 hours after dose application, followed by a slow decline in flux thereafter. Mass accountabilities corresponded to 99% and 104% for the Lipoderm and Lipoderm ActiveMax test formulations, respectively.

Conclusions

Lorazepam - an anxiolytic, sedative, hypnotic and antipsychotic drug - penetrates into and through *ex vivo* human torso skin, following *in vitro* topical application of transdermal compounded formulations. It is concluded that the transdermal bases Lipoderm and Lipoderm ActiveMax may be used in pharmaceutical compounding for the preparation of transdermal compounded formulations.

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Risk of Androgen Deficiency Among Men Using Commonly Prescribed Opioids

Andrea Rubinstein[1], Diane Carpenter[1]
[1]Kaiser Permanente Medical Group, Santa Rosa, CA, USA, [2]Kaiser Permanente Division of Research, Oakland, CA, USA

Purpose

Opioids suppress testosterone in men who use them daily for chronic pain, and men on long-acting opioids have rates of androgen deficiency of 54-87%. Previous studies have reported a dose-response relationship, but none have shown definitively that low testosterone is related to opioid dose. We have shown in previous studies that duration of action plays a role in androgen deficiency, with long-acting opioids more likely to be associated with low testosterone than equipotent doses of short-acting opioids. More recently, we also found that higher dose was associated with elevated odds of androgen deficiency, but this risk was higher in subjects on short-acting opioids than on long-acting opioids. For the current study our goal was to assess the individual effects of a diverse group of commonly prescribed opioids on androgen levels in men while controlling for dose, age, and other comorbidities that may suppress the production of testosterone.

Method

We conducted a retrospective cohort study using Kaiser Permanente Northern California (KPNC) administrative databases to identify men on stable doses of a single opioid. Subjects with diagnoses of cancer or endocrine disorders other than stable, treated primary hypothyroidism were excluded. All subjects had a total testosterone level measured before 10 am while they were on their regular opioid regimen. All subjects were taking exactly one of the following opioids in the 100 days before the testosterone test: fentanyl (in transdermal form), hydrocodone, morphine, methadone, or oxycodone. All subjects had purchased at least 90 days' supply of one of the aforementioned opioids in the 100 days before their testosterone blood tests, thereby meeting our criteria for chronic daily opioid use. All opioids were long acting except hydrocodone, which is exclusively short acting, and oxycodone, which was used in either a long-acting (oxycodone SR) or a short-acting (oxycodone IR or oxycodone-acetaminophen preparations) formulation, or as the combination of the long-acting form plus the short-acting form for breakthrough pain. Logistic regression was employed to assess the association between individual opioids and androgen deficiency, controlling for dose, obesity, age, hypertension, and hyperlipidemia. Hydrocodone was used as the referent for the regression analysis because in preliminary analyses it was associated with the lowest incidence of androgen deficiency among the opioids examined.

Results

This study included 1121 men. Men on fentanyl were more likely to be androgen deficient than men on hydrocodone (odds ratio [OR] 26.40, 95% CI 2.88-241.87). Men on methadone (OR 7.39, 95% CI 3.31-16.49) and men on oxycodone (OR 3.17, 95% CI 1.87-5.36) were also more likely to be androgen deficient than men on hydrocodone. Morphine was not significantly more associated with androgen deficiency than hydrocodone (OR 2.42, 95% CI 0.93-6.38), but the sample included only 48 men taking morphine alone.

We found significant interaction between drug and dose: dose was associated with different odds of androgen deficiency depending on the opioid. Risk associated with dose was reported for each 10-mg increase in dose, holding the drug constant. Dose was associated with an increased risk in androgen deficiency in men on hydrocodone (OR 1.18, 95% CI 1.09-1.27) and in men on oxycodone (OR 1.01, 95% CI 1.00-1.02). Higher dose was not associated with an increased risk of androgen deficiency among men on fentanyl, methadone, or morphine.

Age, diabetes, hypertension, and hyperlipidemia were highly correlated with each other; we therefore created a summary variable for these characteristics. Each subject was given a count of the conditions diabetes, hypertension, and hyperlipidemia; this value was combined with age categorized as <50 or ≥50 years.

Men who were ≥50 years and who had 2 or 3 of the conditions diabetes, hypertension, and hyperlipidemia were more likely to be androgen deficient than men who were <50 years of age and who did not have diabetes, hypertension, or hyperlipidemia (2 conditions and age ≥50 years: OR 1.98, 95% CI 1.29-3.03; 3 conditions and age ≥50 years: OR 3.06, 95% 1.75-5.33).

Men who were obese were also more likely to be androgen deficient than those who were not (OR 2.24, 95% CI 1.71-2.93).

Conclusions

Men taking fentanyl, methadone, and oxycodone were significantly more likely to be androgen deficient than men taking hydrocodone; these odds ratios were large. The odds were not significantly higher for men taking morphine, but the small sample might have hampered our ability to see a significant difference.

Dose was associated with increased odds of androgen deficiency, but only for the two opioids that were available in short-acting forms.

Testosterone levels should be checked regularly in men who are prescribed opioids.

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Factors predicting the prescribing of opioid analgesics: Results of a national survey on primary care physician attitudes and treatment patterns for patients with chronic pain

Gregory Salinas, Holder Nevins, Terry Glauser
CE Outcomes, LLC, Birmingham, AL, USA

Purpose

A major public health problem in the United States, chronic pain has been estimated to affect up to a third of Americans. Depending on the type of pain, patients may benefit from a variety of both pharmacologic and nonpharmacologic treatments. There are specific guidelines for managing pain in different anatomical locations (eg, knee or back) as well as guidelines from a number of different authoritative sources for the chronic use of opioid analgesics. However, many physicians do not prescribe opioids for patients with chronic pain, even when risks are low. The purpose of this study was to use data from a national survey on physician practice patterns and attitudes regarding chronic pain management to identify the factors involved in prescribing opioids.

Method

After a thorough literature review and a series of focus groups conducted to ascertain the perception of physicians regarding barriers to prescribing opioid therapies, an online survey was designed and nationally distributed to primary care physicians (PCPs) in February 2014. Data collected from 250 PCPs were compiled for descriptive analysis and analyzed to determine differences among various demographic groups. Logistic regression was used to determine the main predictors of physician prescription of opioid analgesics for patients with chronic pain.

Results

Two hundred and nineteen survey respondents rated themselves as "prescribers" of opioid analgesics for chronic moderate-to-severe noncancer pain and 31 said that they did not prescribe opioid analgesics ("non-prescribers"). Most prescribers and non-prescribers were only somewhat confident in prescribing long-acting/extended-release opioid analgesics, educating patients about potential misuse of opioid analgesics, their ability to provide patients with relief from moderate-to-severe pain, and treating patients with moderate-to-severe pain. Patient-related factors about which more than half of both prescribers and non-prescribers were very concerned included patient development of addiction, the potential for misuse of opioid analgesics, and the potential for patient abuse of opioid analgesics. Major physician-related factors that inhibit prescription of opioid analgesics are lack of availability of abuse-deterrent medications, regulatory oversight, and REMS. Almost half of respondents (40% prescribers, 48% non-prescribers) were not familiar with REMS for long-acting/extended-release opioids. The primary predictors for physician prescription of opioids include physician confidence in chronic pain management, reduction of patient barriers, and reduction of physician barriers. Familiarity with REMS and chronic pain patient load has no effect on prescribing.

Conclusions

Appropriate use of opioids are a critical component of chronic pain management. The regression analysis implied that increasing physician confidence and decreasing physician and patient barriers are key to increasing opioid analgesic prescription. Future educational efforts should continue to focus on how PCPs can protect themselves from legal issues, such as how to assess risk, document risk assessment, and use state prescription monitoring programs. These educational activities should range from basic (awareness of tools for risk screening) to more advanced (how to use opioid risk agreements and talk to patients about the risks and benefits of these medications).

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Balancing Pain Relief and Opioid-Induced Gastrointestinal Side Effects: Insights from a Structured Review of Social Media Platforms

Cynthia B. Whitman[1], Corey Arnold[2], Haridarshan Patel[3], Justin L. Scopel[4], Mark Reid[1,5], Brennan M.R. Spiegel[1,5]
[1]Cedars-Sinai Center for Outcomes Research and Education, Los Angeles, CA, USA, [2]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA, [3]Global Outcomes and Epidemiology Research, Takeda Pharmaceuticals, Inc., Deerfield, IL, USA, [4]US Medical Affairs, Takeda Pharmaceuticals International, Inc., Deerfield, IL, USA, [5]VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA

Purpose

Opioids are commonly prescribed for both chronic and acute pain patients. However, they cause gastrointestinal (GI) side effects, such as nausea, bloating, and (in >40%) constipation, that may diminish quality of life and medication adherence. We hypothesize that patients struggle to balance pain relief against opioid-induced GI side effects. To better understand the patient illness experience, we analyzed data from several social media platforms using manual qualitative analysis as well as quantitative analysis using statistical topic models. Our goal was to understand the patient illness experience from free-range social media posts regarding pain management, opioid-induced GI side effects, and associated patient-doctor communication. Our secondary aim was to compare the results of manually-driven qualitative and computer-driven quantitative analyses, with the goal of identifying common themes elicited using the two different approaches.

Method

Using a Java-based computer program, we collected tweets from Twitter during a three-week period from March 25-April 6, 2014, and e-forum posts from health-related social networking sites regardless of timestamp. To locate relevant content in the data set, keywords related to opioids, gastrointestinal side effects, and opioid-induced constipation (OIC) were defined by domain experts. We integrated these keywords and associated logic (e.g., a post may be relevant if it contains one keyword, but not another keyword) in a Java program to identify relevant Twitter and e-forum posts. For our qualitative analysis, content identified as relevant was then manually coded with ATLAS.ti software to categorize and report representative quotes.

To explore the collected data for relevant content not captured by our keyword sets, we fitted Latent Dirichlet Allocation (LDA) models to the data and relaxed our keyword rules. LDA provided an automatic and probabilistic method for semantic theme discovery by learning sets of contextually co-occurring words, called topics, which are then used to model content (i.e., content is modeled as different percentages of topics). Topics provide a method for dimensionality reduction, allowing for the expedited review of content and its retrieval from large data sets. We created two distinct 50-topic models: one relating to constipation using the keyword "constipation" and all of its derivatives, and one filtered to find patient-doctor communication using the keywords "doctor," and "doc." Topics discovered by these models were then used to further characterize our data collection.

Results

Of 264,040 tweets and 217,199 e-forum posts extracted by our data collection algorithms, 10,645 (4%) tweets and 4,416 (2%) posts were relevant to OIC as identified by our keyword-based rules; these sets formed the basis for our qualitative evaluation. In our qualitative analysis, we identified 40 patients questioning their opioids because of the severity of their GI side effects, namely nausea, vomiting, and constipation. One patient explains, "My knee's on fire but the pain pills make me constipated!" Forty-eight patients mentioned modifying or discontinuing opioids due to side effects, or that their doctor changed their drug regimen for that reason. Thirty-two patients mentioned needing or

having communication with their doctors about opioid-induced GI side effects. Among these, 11 distrusted, disagreed with, or were not informed by their doctors regarding opioid-induced GI side effects and treatments. Another 12 reported modifying opioids after communicating with their doctors. Only eight patients believed their doctors listened or provided them with relevant side-effect information.

After fitting the LDA models to our sets of data using automated coding algorithms, we only examined quotes with a weighting of 0.1 or greater onto a given topic and determined them to be relevant. Quotes with a weighting of less than 0.1 were found to be of limited relevance to a given topic. Seven of fifty topics fitted for constipation contained a higher than average proportion of relevant social media tweets and posts (range: 6-72%), examples include (1) natural remedies for constipation, (2) pain relief from opioids, (3) chronic pain and medication, (4) quality of life and constipation, (5) pain relief versus GI side effects. Similarly, 13 of 50 topics related to patient-doctor communication contained higher than average percentages of relevant quotes (range: 8-32%), examples include (1) discussing opioid dosage, (2) patients questioning doctors' knowledge, (3) patients following doctors' orders.

Conclusions

The data from social media platforms highlight patients' struggle to balance pain management and opioid-induced GI side effects. Qualitative analysis revealed that patients modify opioid regimens without medical advice, are unprepared to treat opioid-induced GI side effects, and feel unable to communicate with their doctors about them. Quantitative analysis identified similar themes reflecting the relationships between GI side effects, pain, and opioids; however, these models achieve only a limited understanding of patients' experience. Overall, these data reveal a need for doctors to increase communication with patients with opioid-induced GI side effects, and to explore effective treatment alternatives.

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An evaluation of the FDA Adverse Event Reporting System database for a signal of disproportionate reporting of cardiac arrhythmia associated with the buprenorphine transdermal system.

Nelson Sessler, Ekaterina Walker, Jerod Downing, Paul Coplan
Purdue Pharma, Stamford, CT, USA

Purpose

Buprenorphine, a partial mu-opioid receptor agonist, is approved in the US for use parenterally as intra operative anesthetic for acute pain [Buprenex® approved 1981], orally to treat opioid addiction [Subutex® and Suboxone® tablets/film approved 2002/2010] and transdermally to treat chronic pain [Butrans® approved 2010]. In the US, Butrans is only approved for dosages up to 20 mcg/hr with Prescribing Information (USPI) stating: "a Butrans dose of 40 mcg/hour (given as two 20 mcg/hour Butrans Transdermal Systems) prolonged mean QTc by a maximum of 9.2 (90% CI: 5.2-13.3) msec across 13 study assessment time points." The USPIs for buprenorphine tablets/film/injectable do not have similar potential QT prolongation warnings. Importantly, the recommended target dose of Suboxone on the USPI is 16 mg/day which corresponds to approximately 2.2 mg buprenorphine absorbed systemically per day. This level of buprenorphine absorption is approximately 4 times greater than the 0.48 mg/day buprenorphine absorbed by a patient using a single Butrans 20 mg patch. In Europe, higher dose buprenorphine patches (TransTec® 35, 52.5 and 70 mcg/hr) have been available for nearly a decade. The objective of this study is to evaluate the FDA Adverse Event Reporting System (FAERS) database for a signal of disproportionate reporting of events consistent with medical concept of QTc prolongation or Torsade de Pointes (TdP) associated with buprenorphine products relative to methadone. Methadone is an opioid with documented QTc interval prolongation and clinically-documented association with TdP, and therefore can act as "positive control" of disproportionality signal in FAERS.

Method

Data from the FDA AERS from 1969 to 1Q2013 was extracted using Oracle Health Sciences quantitative signal detection program, Empirica Signal™ (Version 7.3). All reports with buprenorphine, fentanyl (transdermal formulation), or methadone (oral formulation) categorized as primary suspect, secondary suspect, interacting or concomitant medication were identified. Cases involving buprenorphine were subgrouped by formulation. The Standardized MedDRA Query for Torsade de Pointes and/or QT prolongation (SMQ/TdP) was used to identify cases of interest. The SMQ/TdP consists of 6 "narrow" preferred terms (electrocardiogram QT interval abnormal, electrocardiogram QT prolonged, long QT syndrome, long QT syndrome congenital, Torsade de Pointes, and ventricular tachycardia), and 14 "broad" preferred terms (cardiac arrest, cardiac death, cardiac fibrillation, cardio-respiratory arrest, electrocardiogram repolarization abnormality, electrocardiogram U-wave abnormality, loss of consciousness, sudden cardiac death, sudden death, syncope, ventricular arrhythmia, ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia). Frequencies for age, sex, outcome, and drug role in the adverse event were calculated along with yearly reporting rates. The Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm which implements empiric Bayesian models to screen for associations between the drug and previously unidentified adverse drug reactions was used to calculate Empirical Bayes Geometric Mean (EBGM) values, which are the ratios of the observed to the expected number of drug-event pairs (reporting ratios). Empirical Signal system was used to perform the analysis, and the Reporting ratios (EBGM values) were estimated with their 95% CI (EB05, EB95) using the Empirical Signal system.

Results

A total of 46,188 FDA AERS cases involving an opioid of interest were available from 1969 to 1Q2013 consisting of 6,309 that involved oral methadone, 29,974 transdermal fentanyl, 592 Butrans, 4,936 Suboxone, 2,184 Subutex,

756 Buprenex, and 2,405 buprenorphine NOS. Oral methadone was associated with a disproportionality signal of increased risk of TdP (EBGM 4.92, 95% CI: 4.699-5.149). The buprenorphine product subgroups were all associated with a reported ratio for Torsade de Pointes and/or QT prolongation [SMQ/TdP broad] under the threshold of 2.0 used for signal detection, including buprenorphine transdermal (EBGM 1.763, 95% CI: 1.283-2.376), buprenorphine/naloxone sublingual tablets/film (EBGM 1.651, 95% CI: 1.488-1.827), buprenorphine sublingual tablets/film (EBGM 0.781, 95% CI: 0.623-0.969), buprenorphine injectable (EBGM 1.47, 95% CI: 1.042-2.026), and buprenorphine NOS (EBGM 1.56, 95% CI: 1.353-1.791). Fentanyl patch also has a disproportionality ratio less than 2.0 (EBGM 0.976 (95% CI 0.925-1.03). Similar trends were observed when data was limited to the SMQ/TdP narrow terms, timeframe 2002-2013, and in sensitivity analysis by gender and age≥ 65 years.

Conclusions

Cases of cardiovascular events associated with proarrhythmic potential that mention buprenorphine use, including Butrans, have been reported to the FDA MedWatch system. Oral methadone did have a positive signal of a large number of clinical outcomes associated with cardiac arrhythmia relative to all adverse event reports, but Butrans did not. Furthermore, the ratio of clinical outcomes associated with cardiac arrhythmia to all adverse events was similar for buprenorphine and fentanyl patches and for sublingual formulations of buprenorphine that deliver approximately 4 times the amount of absorbed buprenorphine as the buprenorphine patch.

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Abuse potential study of ALO-02 (extended-release oxycodone surrounding sequestered naltrexone) compared with immediate-release oxycodone and placebo when crushed and administered intranasally to non-dependent, recreational opioid users.

Beatrice Setnik[1], Candace Bramson[2], Kenneth W. Sommerville[1,3], Kyle Matschke[4], Naama Levy-Cooperman[5], Pierre Geoffroy[5]
[1]Pfizer Inc, Durham, NC, USA, [2]Pfizer Inc, Groton, CT, USA, [3]Duke University Medical Center, Durham, NC, USA, [4]Pfizer Inc, Collegeville, PA, USA, [5]INC Research, Toronto, ON, Canada

Purpose

Extended-release opioids can be an effective treatment for chronic pain, but widespread misuse, abuse, and diversion limit their safe use. Novel extended-release opioid formulations using pharmacologic and/or physical barriers to deter abuse are in development. ALO-02 is one such formulation and comprises capsules filled with pellets of extended-release oxycodone hydrochloride (an opioid agonist) surrounding sequestered naltrexone hydrochloride (an opioid antagonist). Since intranasal administration is a common route of abuse of prescription opioids, the present abuse potential study was conducted using intranasal administration of crushed ALO-02. The objective of the study was to compare the relative pharmacodynamic effects, including drug liking and high, of crushed ALO-02 with crushed oxycodone hydrochloride immediate-release (IR) and placebo administered intranasally to healthy, non-dependent, recreational opioid users.

Method

This was a randomized, double-blind, placebo- and active-controlled, 4-way crossover study (ClinicalTrials.gov: NCT 01775189) conducted in compliance with local and international ethical principles. The study included a naloxone challenge, drug discrimination, and treatment phase. During each of the four treatment periods (separated by ≥5 days), participants received a crushed single dose of either one or two placebos (weight-matched to AL0-02 or oxycodone IR), 30 mg ALO-02 (containing 3.6 mg naltrexone), or 30 mg oxycodone IR. The primary endpoints were drug liking and high on 0-100 point bipolar and unipolar visual analog scales, respectively. The principal parameters of interest were mean peak effect (E_{max}) and effect occurring over 2 h post-dosing (AUE_{0-2h}).

Results

Thirty-two participants (84% male, 91% white, mean age 35 years) were randomized into the treatment phase with 28 completing all treatments. Study validity was confirmed by the significantly higher ratings on measures of drug liking and high associated with 30 mg oxycodone IR compared with placebo ($p<0.0001$). Intranasal administration of 30 mg ALO-02 resulted in significantly lower ratings relative to 30 mg oxycodone IR on drug liking (E_{max}: 60.5 vs. 92.8; AUE_{0-2h}: 105.4 vs. 160.0) and high (E_{max}: 25.2 vs. 86.9; AUE_{0-2h}: 27.1 vs. 136.4) ($p<0.0001$) (primary endpoints). Adverse events (AEs) occurred most frequently with oxycodone IR (N=32, 100% of participants), followed by ALO-02 (N=18, 60%) and fewest with placebo (≤33% in both groups). The most common (>10% of participants) AEs for ALO-02 were euphoric mood, dysgeusia, fatigue, and somnolence.

Conclusions

When crushed and administered intranasally to nondependent, recreational opioid users, ALO-02 showed significantly lower abuse potential, as indicated by significantly decreased scores of drug liking and high, as well as other positive subjective effects, compared with crushed oxycodone IR.

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Efficacy and safety of ALO-02 (extended-release oxycodone surrounding sequestered naltrexone) capsules in the treatment of moderate-to-severe chronic low back pain

Richard Rauck[1], Martin Hale[2], Almasa Bass[3], Candace Bramson[4], Glenn Pixton[3], Beatrice Setnik[3], Paul Meisner[3], Kenneth Sommerville[3,5]
[1]Center for Clinical Research, Carolinas Pain Institute, Winston Salem, North Carolina, USA, [2]Gold Coast Research, LLC, Plantation, Florida, USA, [3]Pfizer Inc, Durham, North Carolina, USA, [4]Pfizer Inc, Groton, Connecticut, USA, [5]Duke University Medical Center, Durham, NC, USA

Purpose

Long-acting opioids are an effective part of chronic pain management, but there is accumulating evidence that they are increasingly misused or abused. To reduce risks associated with opioid treatment, abuse-deterrent formulations of opioids are being developed. ALO-02 is one such formulation comprising capsules containing pellets of extended-release oxycodone hydrochloride (HCl) surrounding sequestered naltrexone HCl. The objective of this study was to evaluate the efficacy and safety of ALO-02 compared with placebo in the treatment of moderate-to-severe chronic low back pain (CLBP).

Method

This was a multicenter, 12-week, double-blind, placebo-controlled, enriched enrollment randomized withdrawal study in patients with moderate-to-severe CLBP requiring around-the-clock analgesia. After an initial screening period (≤2 weeks), an open-label conversion and titration period (4-6 weeks) was conducted where all subjects received ALO-02 (oxycodone HCl/naltrexone HCl) from 10 mg/1.2 mg up to 80 mg/9.6 mg administered twice daily approximately 12 hours apart. Treatment responders were then randomized to either a fixed dose of ALO-02 or placebo in the treatment period (12 weeks) followed by a 2-week post-treatment study drug taper. Daily average low back pain rating over the last 24 h was recorded in an eDiary using an 11 point Numeric Rating Scale (NRS)-Pain (0 = no pain; 10 = worst possible pain). The primary endpoint was the change in mean NRS-Pain score from randomization to the final 2 weeks of the treatment period. Key secondary endpoints were the change in the Roland Morris Disability Questionnaire (RMDQ) and Patient's Global Assessment (PGA) of Low Back Pain from randomization to the end of the treatment period. Additional secondary endpoints included the percentage of patients who reported being "satisfied" or "very satisfied" on the Satisfaction with Treatment questionnaire, the amount of acetaminophen used as a rescue medication, and the proportion of patients reporting improvement in weekly average diary NRS-Pain scores. Safety of ALO-02 in the treatment of CLBP was determined by assessing adverse events (AEs) and opiate withdrawal using the Clinical Opiate Withdrawal Scale (COWS).

Results

Of the 663 patients screened, 410 received ALO-02 during the open-label conversion and titration period. 281 patients were randomized to the treatment period (n=134, placebo; n=147, ALO-02). In the intent-to-treat population, 57.5% of patients were opioid-naïve prior to this study. Change in mean NRS-Pain score between ALO-02 and placebo from baseline to end of the DB treatment period was significantly different favoring ALO-02 (difference=-0.62; p=0.0114). For RMDQ Total scores and PGA, changes from randomization to the end of the treatment period were not statistically significant. In response to the Satisfaction with Treatment assessment, 79.7% of patients receiving ALO-02 and 59.2% of patients receiving placebo reported being 'satisfied' or 'very satisfied' with treatment (p=0.0004). Eighty-four (57.5%) patients treated with ALO-02 and 59 (44.0%) patients in the placebo group reported ≥30% improvement in weekly average NRS-Pain scores from screening to final 2 weeks of the treatment period (p=0.0248). During the treatment period, 167.7 mg/day and 252.1 mg/day of acetaminophen on

average was used as a rescue medicine by patients in the ALO-02 group and placebo group, respectively. In the treatment period, 56.8% of patients in the ALO-02 group and 56.0% of patients in the placebo group experienced a treatment-emergent AE (TEAE). The most common treatment-related TEAEs for ALO-02 compared with placebo during the treatment period were nausea, vomiting, and constipation. Five patients experienced an AE of withdrawal syndrome during the treatment period; 1 with placebo and 4 with ALO-02. 97.6% of patients receiving placebo and 95.0% of patients receiving ALO-02 during the treatment period had maximum COWS scores <5, indicating no opiate withdrawal. 1.6% of patients treated with placebo and 5.0% of patients treated with ALO-02 had mild withdrawal. One patient (0.8%) in the placebo group had moderate withdrawal. There were no deaths during the course of this study.

Conclusions

ALO-02 is effective in significantly reducing NRS-Pain scores in patients with CLBP. ALO-02 is safe and well-tolerated in these patients, with AEs consistent with opioid therapy.

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Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of the Safety and Analgesic Efficacy of MNK-155, Extended-Release Hydrocodone Bitartrate/Acetaminophen Tablets, in an Acute Pain Model

Neil Singla[1], Rachel Margulis[2], Kenneth Kostenbader[2], Yanping Zheng[2], Thomas Barrett[2], Dave Melikian[2]
[1]Lotus Clinical Research LLC, Pasadena, CA, USA, [2]Mallinckrodt Pharmaceuticals, Hazelwood, MO, USA

Purpose

To evaluate the efficacy and safety of MNK-155 (Mallinckrodt Pharmaceuticals, Hazelwood, MO), a fixed-dose combination (FDC) extended-release (ER) hydrocodone bitartrate (HB)/acetaminophen (APAP) analgesic, compared with placebo in patients with acute moderate to moderately severe pain over the first 48 hours following unilateral bunionectomy. ER HB/APAP (7.5/325 mg) tablets have a biphasic, ER and immediate-release formulation and are being developed for the management of acute pain that cannot be managed adequately with nonopioid analgesics.

Method

On the first postoperative day following standard perioperative care, patients randomized to active treatment received a single 3-tablet loading dose of ER HB/APAP (22.5/975 mg total dose) at hour 0, followed by 2 tablets of ER HB/APAP (15/650 mg total dose) every 12 hours (q12h) thereafter; patients randomized to placebo treatment received a single 3-tablet dose of placebo at hour 0 followed by 2 placebo tablets q12h thereafter. Active and placebo treatment continued until no longer needed for pain relief up to the end of the 48-hour study period or until early discontinuation.

Results

ER HB/APAP demonstrated efficacy greater than placebo across several validated pain measures. Pain reduction, as measured by the primary endpoint of summed pain intensity difference at 48 hours ($SPID_{48}$), was significantly greater in patients receiving ER HB/APAP vs placebo ($P<0.001$). Time to onset of pain relief was statistically significantly shorter in patients receiving ER HB/APAP vs placebo ($P<0.001$). $SPID_{48}$ showed that ER HB/APAP provided superior pain relief throughout the 48-hour double-blind dosing period, and SPID dosing interval analyses demonstrated consistent, superior pain relief for each dosing interval. Mean total pain relief (TOTPAR) scores indicated greater pain relief with ER HB/APAP vs placebo over the 48-hour double-blind dosing period and within each interval. Mean pain intensity difference (PID) was statistically significantly greater in patients receiving ER HB/APAP vs placebo beginning 30 minutes after the first dose ($P<0.05$); differences were maintained across the dosing interval. The safety profile of ER HB/APAP was consistent with that of other fixed-dose combination (FDC) opioid analgesics.

Conclusions

Over the 48-hour postoperative study period, ER HB/APAP provided rapid, significant, and consistent analgesic efficacy superior to placebo over a 12-hour dosing interval and exhibited tolerability similar to other FDC opioid analgesics in patients with acute pain that cannot be managed adequately with nonopioid analgesics.

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Design and Implementation of a Comprehensive Safe-Use Initiative for Zohydro® ER

Edward Smith III[1], Stephen Farr[1], Herbert Neumann[2], Arthur Morelli[3], Jeffrey Gudin[4]
[1]Zogenix, Inc., Emeryville, CA, USA, [2]R3xperts LLC, Redwood City, CA, USA, [3]Arthur F. Morelli and Associates, San Diego, CA, USA, [4]Pain Management Center, Englewood Hospital and Medical Center, Englewood, NJ, USA

Purpose

The therapeutic benefits of opioid analgesics are widely recognized. However, the misuse, abuse, and diversion of prescription opioid analgesics are a significant public health concern, as they may result in addiction, unintentional overdose, and death. Zogenix®, Inc. has implemented comprehensive, voluntary initiatives to support the appropriate use of their prescription medications. For Zohydro® ER (hydrocodone bitartrate extended-release [ER] capsules), the program goals are to proactively minimize the potential for abuse, misuse, addiction, overdose, and diversion of hydrocodone bitartrate ER capsules. Zohydro ER is an opioid agonist and a US Drug Enforcement Agency (DEA) Schedule II controlled substance 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. Zogenix provides educational resources and training to prescribers, pharmacists, and patients; utilizes a rigorous surveillance system to detect and identify potential safety issues associated with the use of Zohydro ER; and proactively implements corrective actions as needed. Zogenix has developed a coordinated approach that utilizes both internal resources and external consultants to oversee the benefits/risks of Zohydro ER.

Method

The internal Zogenix Advisory and Action Committee (ZAAC) and an expert External Safe-Use Board (ESUB) have been established to analyze and interpret signal identification from multiple data streams, including drug safety databases, past 30-day abuser and non-abuser surveillance data (e.g., general population exposures), prescriber information, pharmacy distribution data, and non–third-party payment information. The goals of these groups have been to provide feedback and recommendations to the company to ensure the safe use of Zohydro ER and to minimize the risk associated with this opioid analgesic. The ZAAC was developed with a multidisciplinary composition from within the company to review educational and training initiatives and surveillance data. The Zogenix president and chief executive officer (CEO) regularly attend these ZAAC meetings. The ESUB members were selected based on their specific knowledge and experience with the safe use of opioid analgesics, and the chairperson ensured representation from various complementary disciplines (i.e., pain medicine, addiction medicine, drug surveillance, pharmacovigilance, epidemiology/risk management, pharmacy policy, law enforcement, and patient advocacy). The ESUB has been designed to operate independently, with direct and open access to the Zogenix CEO and board of directors, and may directly report any findings to the US Food and Drug Administration (FDA) and/or the DEA. The long-term effectiveness of ZAAC activities and ESUB recommendations will be determined using a set of metrics or quality measures under development. Regular ESUB reviews will focus on the data used to evaluate abuse, misuse, and diversion of Zohydro ER.

Results

The ESUB was established in early 2014 and comprises 7 members currently serving 2-year terms. At least 8 databases and safe-use resources are being regularly evaluated by the ZAAC and ESUB to identify potential safety risks. Data analyses by the 12-member ZAAC occur twice monthly. In addition, the ESUB has full ongoing access to the data; the ESUB evaluates and provides recommendations for specific interventions, based on a quarterly review of the data. Multiple surveillance data streams provide broad coverage for potential safety indicators with Zohydro ER, which are being analyzed and interpreted to identify potential safety signals that may result in immediate action

by the ZAAC. Examples of surveillance data streams being assessed include prescription patterns; pharmacovigilance data; medical information data; retail pharmacy distribution and product flow data; distribution information on SaferLock™ (locking pill bottle caps) and LOCKMED™ (combination lock pill boxes); the Drug Diversion Program, which receives input from 300 drug diversion investigators and regulatory agencies; sentinel system reports of abuse through the Addiction Severity Index-Multimedia Version (ASI-MV®), which measures past 30-day abuse in addiction treatment centers; and unintentional and intentional exposures reported by poison control centers through the RADARS® System. Analysis of these surveillance data streams to date has demonstrated that during the first 3 full months after launch, approximately 30% to 35% of new patients prescribed Zohydro ER utilized patient educational kits, and approximately 10% of patients requested SaferLock caps and LOCKMED boxes, suggestive of an unmet need for easy access to patient tools that help minimize product access and diversion by non-patients. Zogenix intends to provide updates on these surveillance data and educational tools to the FDA, DEA, and other stakeholders, and to publish data on the effectiveness of its risk mitigation initiatives for Zohydro ER.

Conclusions

Zogenix has implemented multimodal and complementary initiatives designed to monitor the safe and appropriate use of Zohydro ER with further plans to design and apply outcome metrics and quality measures. Zogenix is committed to working with FDA, DEA, and other stakeholders to implement best practices within the industry to support the safe and appropriate use of prescription opioid analgesics, focused on mitigating risks associated with use of Zohydro ER, as well as future products. To our knowledge, this the first public description of an external safety review board with this level of corporate access, independent authority, and regular, ongoing activities.

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Relative bioavailability of a new tamper resistant extended-release oxycodone/naloxone combination product

Hans-Juergen Stahlberg, Martin Brett, Sebastian Schwier, Anika-Anina Philipp
Grünenthal GmbH, Aachen, Germany

Purpose

- to evaluate the relative bioavailability of a GRT TRF-ER OxyNal formulation (Test) in comparison to the marketed reference product Targin®
- to assess further pharmacokinetic (PK) parameters and the safety and tolerability of both formulations

Method

STUDY

- open, randomized, 4 treatment periods with 2 consecutive 2-way crossover phases
- single dose (SD) administrations
- wash-out period between the administrations: at least 5 and no more than 14 days
- fasted and fed conditions

Sixteen healthy white male subjects aged 18 years to 55 years

PHARMACOKINETIC / STATISTICAL EVALUATION

- non-compartmental analysis for oxycodone and nal-3-gluc
- parametric (ANOVA) point estimates and 90% confidence intervals (CI) calculated for the ratios T/R of C_{max}, AUC_{0-t} and AUC
- T could be considered bioequivalent to R if the 90% CIs for the key PK parameters fell within the acceptance range of 80.00%-125.00%.

Results

Under both fasted and fed conditions, the 90% CIs for the ratios T/R of AUC0-t and Cmax for oxycodone and AUC0-t for naloxone-3-glucuronide were within the range 0.80 to 1.25. The CI for Cmax of naloxone-3-glucuronide was outside this range.

Single oral dose administration of 40 mg/20 mg oxycodone hydrochloride/naloxone hydrochloride as test formulation and reference formulation was safe and well tolerated under fasted and fed conditions. The most frequently observed treatment emergent adverse events (TEAEs) are in line with the published data in the SmPC of the reference formulation Targin®.

Conclusions

The data demonstrate that the TRF combination has comparable in-vivo performance to the reference.

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Extended-release hydrocodone bitartrate in chronic pain: reduction in pain intensity is associated with functional improvement

Charles Argoff[1], Paul Arnstein[2], Steve Stanos[3], Cynthia Y. Robinson[4], Bradley S. Galer[4], Errol Gould[4], Arnold Gammaitoni[4]
[1]Albany Medical College, Albany, NY, USA, [2]Massachusetts General Hospital, Boston, MA, USA, [3]Rehabilitation Institute of Chicago Center for Pain Management, Chicago, IL, USA, [4]Zogenix, Inc., Emeryville, CA, USA

Purpose

In clinical trials, pain relief which is typically reported as mean change in pain score, is challenging to translate into individual patient response. An effective predictor of improvement in an individual patient may be the achievement of a moderate (30%-<50%) or substantial (≥50%) reduction in pain score. If this level of reduction in pain results in improved functional outcomes and quality of life, it may serve as a simple predictor of functional benefit in individual patients in a busy clinical practice. The purpose of this posthoc analysis was to evaluate the various levels of pain relief observed in a placebo-controlled study of hydrocodone-ER (HC-ER) in subjects with chronic low back pain and the association of these levels of pain reduction with secondary functional outcomes.

Method

This Phase 3 multicenter, enriched enrollment, randomized withdrawal study began with an open-label, conversion/titration (C/T) period (≤6 weeks) where subjects with moderate-to-severe chronic low back pain were converted from their current opioid to individualized doses (20-100 mg) of HC-ER dosed every 12 hours (q12h). The starting total daily dose of HC-ER was about 20%-30% less than the dose determined from the Opioid Conversion Table. Every 3-7 days during the C/T period, the dose could be increased by 20 mg/day (ie, 10 mg q12h) to a maximum of 200 mg daily or until a stabilized dose was attained. After the C/T period, subjects were randomized in a double-blind fashion to HC-ER or placebo for a 12-week treatment phase. Hospital Anxiety and Depression Scale (HADS), Oswestry Disability Inventory (ODI), Quebec Back Pain Disability Scale, and Subject Global Assessment of Medication (SGAM) scores were taken at screening, the end of the C/T period, and at the end of the study. Average pain over the previous 24 hours was similarly assessed using an 11-point numeric rating scale (NRS; 0=no pain, 10=worst pain imaginable) during study visits. The 5 categories describing pain relief (≥50%, 30%-<50%, 15%-<30%, 0%-<15%, and no change or worse) were based on the change in average pain NRS score from screening to the end of the study. Results from the HC-ER and placebo groups were pooled for this analysis.

Results

A total of 510 subjects enrolled in the study, 302 subjects entered the treatment phase, and 288 subjects in either the HC-ER or placebo group had data at screening and the end of the study or early termination and were included in this analysis. At screening, mean±SD ODI total score was 62.2±13.1, Quebec Back Pain Disability Scale total score was 48.9±18.9, and HADS anxiety and depression total scores were 5.7±3.2 and 4.8±3.4, respectively. Moderate or substantial reductions in pain from screening to end of study or early termination was demonstrated by 27.4% and 47.9% of subjects, respectively. At the end of the study or at early termination, subjects with moderate or substantial decreases in pain scores demonstrated a 4.4±12.0 (P=0.002) and a 10.8±16.6 (P<0.001) point decrease in ODI total score, respectively. Similarly, subjects in these 2 pain categories demonstrated decreases in the Quebec Back Pain Disability Scale of 7.1±19.9 (P=0.003) and 12.6±21.8 (P<0.001) points, respectively. No statistically significant change in HADS anxiety or depression scale was observed in any category of pain response at the end of this 12-week study. SGAM was significantly improved only in the subjects who had substantial improvement in pain scores (P<0.001).

Conclusions

Moderate and substantial levels of pain relief were associated with the greatest improvements in ODI and Quebec Back Pain Disability Scale scores, with greater improvements seen in subjects reporting substantial pain relief. These results suggest that a simple assessment of change in pain scores in individual patients can be used to predict functional improvement and therefore the ultimate success of treatment, particularly in the busy clinical setting. Approximately 75% of the subjects in this study having chronic low back pain experienced these levels of pain improvement.

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Effectiveness of Tapentadol Prolonged Release (PR) Versus Oxycodone/Naloxone PR for Severe Chronic Low Back Pain With a Neuropathic Pain Component

Ralf Baron[1], Andreas Schwittay[2], Andreas Binder[1], Claudia Schumann[2], Dietmar Falke[3], Ilona Steigerwald[3]
[1]Division of Neurological Pain Research and Therapy, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Germany, [2]Practice for General Medicine, Special Pain Therapy & Palliative Medicine, Böhlen, Germany, [3]Medical Affairs Europe & Australia, Grünenthal GmbH, Aachen, Germany

Purpose

Tapentadol is a centrally acting analgesic with 2 mechanisms of action, μ-opioid receptor agonism and noradrenaline reuptake inhibition. Tapentadol prolonged release (PR) has been shown to be effective and well tolerated for managing moderate to severe chronic osteoarthritis knee pain, low back pain, pain related to diabetic peripheral neuropathy, and cancer pain, as well as for severe chronic low back pain with or without a neuropathic component. A fixed-dose combination of oxycodone/naloxone PR has also been shown to be effective and well tolerated for the management of moderate to severe chronic low back pain. An equianalgesic ratio of approximately 5:1 has been established for tapentadol PR versus oxycodone PR in earlier randomized, controlled trials. The purpose of this randomized, controlled, open-label, phase IIIb/IV study was to evaluate the effectiveness of tapentadol PR versus oxycodone/naloxone PR, including effects on neuropathic pain as secondary outcomes, for the management of severe chronic low back pain with a neuropathic pain component in opioid-naive patients. Results for the primary effectiveness endpoint, one of 2 co-primary endpoints for this study, and secondary effectiveness endpoints related to neuropathic pain symptoms are presented here; results for the other primary endpoint, quality of life and function measures, and safety and tolerability outcomes are presented in separate abstracts.

Method

Eligible patients with severe pain (average baseline pain intensity ≥6 on an 11-point numerical rating scale-3 [NRS-3; average 3-day pain intensity] and a baseline painDETECT rating of "positive" or "unclear") were randomized to twice-daily tapentadol PR 50 mg or oxycodone/naloxone PR 10 mg/5 mg. After a 21-day titration period (maximum twice-daily doses: tapentadol PR 250 mg or oxycodone/naloxone PR 40 mg/20 mg plus oxycodone PR 10 mg), target doses were continued for 9 weeks. The primary effectiveness endpoint (one of 2 co-primary endpoints) was the change in NRS-3 from baseline (randomization) to final evaluation. Secondary endpoints were related to analyses of painDETECT and Neuropathic Pain Symptom Inventory (NPSI) questionnaires, used to evaluate the effects of treatment on neuropathic pain-related symptoms. An analysis of covariance model, including treatment and pooled center as factors and baseline value as a covariate, was used to evaluate the primary effectiveness endpoint (per protocol set) and painDETECT and NPSI outcomes (full analysis set). The last observation carried forward was used for imputing missing assessments for all effectiveness endpoints. Because the trial design was planned with 2 interim analyses, an inverse normal method was used for the primary analyses to correct for multiplicity. For the primary effectiveness endpoint, non-inferiority of tapentadol PR versus oxycodone/naloxone PR was established if the upper limit of the 2-sided 97.5% repeated confidence interval (RCI) of tapentadol PR minus oxycodone/naloxone PR was <1.3 (non-inferiority margin). This RCI was also used to provide evidence of superiority (if it did not include zero).

Results

For the primary effectiveness endpoint, mean (SD) pain intensity decreased in the tapentadol PR group (n = 117) from 7.6 (1.01) at baseline to 3.9 (2.62) at final evaluation (least-squares [LS] mean [standard error of the mean (SEM)] change from baseline to final evaluation, -3.7 [0.25]; $P < 0.001$); in the oxycodone/naloxone PR group (n = 112), mean (SD) pain intensity decreased from 7.6 (0.96) at baseline to 4.8 (2.48) at final evaluation (-2.7 [0.26]; *P*

<0.001). The LS mean difference between treatment groups in the change in pain intensity was −1.0 (*P* <0.001 for non-inferiority). The non-inferiority of tapentadol PR compared with oxycodone/naloxone PR was demonstrated by the exact RCI of tapentadol PR minus oxycodone/naloxone PR (97.5% RCI: [-1.820, -0.184]). Furthermore, the RCI yields significant and confirmatory evidence of superiority for tapentadol PR versus oxycodone/naloxone PR. In the tapentadol PR and oxycodone/naloxone PR groups, respectively, mean (SD) total painDETECT scores were 22.3 (5.25) and 22.5 (4.79) at baseline and 11.9 (7.76) and 14.6 (7.37) at final evaluation. The respective LS mean (SEM) changes from baseline to final evaluation were -10.8 (0.67; *P* <0.001) with tapentadol PR and -7.9 (0.69; *P* <0.001) with oxycodone/naloxone PR, showing a significantly greater improvement with tapentadol PR versus oxycodone/naloxone PR (LS mean difference [95% confidence interval] between groups, -2.9 [-4.7, -1.0]; *P* = 0.002). The NPSI overall feeling score and all subscores improved significantly from baseline to final evaluation in both treatment groups (*P* <0.001), and significantly greater improvements were observed in all NPSI subscores with tapentadol PR versus oxycodone/naloxone PR, as follows: burning pain (-0.38 vs -0.28), pressing pain (-0.33 vs -0.23), paroxysmal pain (-0.39 vs -0.28), evoked pain (-0.33 vs -0.23), and paresthesia/dysesthesia (-0.36 vs -0.25; all *P* ≤0.005 for tapentadol PR vs oxycodone/naloxone PR).

Conclusions

Results for the primary effectiveness endpoint of this study were positive, demonstrating non-inferiority and, additionally, confirmatory evidence of superiority for the effectiveness (reduction in pain intensity [NRS-3] from baseline to final evaluation) of tapentadol PR compared with oxycodone/naloxone PR in opioid-naive patients with severe chronic low back pain with a neuropathic pain component. Furthermore, significantly greater improvements in neuropathic pain-related symptoms, based on painDETECT and NPSI results, were demonstrated with tapentadol PR versus oxycodone/naloxone PR. Based on these trial results, tapentadol PR can be considered a first line option for managing severe chronic low back pain with a neuropathic component.

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Safety and Tolerability of Tapentadol Prolonged Release (PR) Versus Oxycodone/Naloxone PR for Severe Chronic Low Back Pain With a Neuropathic Pain Component

Andreas Binder[1], Ralf Baron[1], Andreas Schwittay[2], Claudia Schumann[2], Dietmar Falke[3], Ilona Steigerwald[3]
[1]Division of Neurological Pain Research and Therapy, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Germany, [2]Practice for General Medicine, Special Pain Therapy & Palliative Medicine, Böhlen, Germany, [3]Medical Affairs Europe & Australia, Grünenthal GmbH, Aachen, Germany

Purpose

Tapentadol prolonged release (PR) has been shown to be effective for managing moderate to severe chronic nociceptive and neuropathic (diabetic peripheral neuropathy-related) pain, with improved tolerability (particularly gastrointestinal tolerability) compared with oxycodone controlled release (CR) and morphine CR. The better gastrointestinal tolerability profile for tapentadol PR is likely related to its 2 mechanisms of action, μ-opioid receptor agonism and noradrenaline reuptake inhibition. A fixed-dose combination of oxycodone PR (a pure μ-opioid agonist) and naloxone (an opioid antagonist proposed to act on opioid receptors in the gut and to reduce opioid-induced constipation) has also demonstrated efficacy for the management of moderate to severe chronic pain, with proposed improvements in opioid-induced constipation compared with oxycodone PR alone. An equianalgesic ratio of approximately 5:1 has been established for tapentadol PR versus oxycodone PR in earlier randomized, controlled trials. This study evaluated the safety and tolerability of tapentadol PR versus oxycodone/naloxone PR for the management of severe chronic low back pain with a neuropathic pain component in opioid-naive patients. Results for one of the 2 co-primary endpoints for this study, along with safety and tolerability outcomes, are presented here; results for the other primary endpoint (the primary effectiveness endpoint), secondary effectiveness endpoints, and quality of life and function measures are presented in separate abstracts.

Method

In this randomized, controlled, open-label, phase IIIb/IV study, eligible patients with severe pain (average pain intensity ≥6 on an 11-point numerical rating scale-3 [NRS-3; average 3-day pain intensity] at baseline and a rating of "positive" or "unclear" on the painDETECT questionnaire at baseline) were randomized to twice-daily tapentadol PR 50 mg or oxycodone/naloxone PR 10 mg/5 mg. After a 21-day titration period (maximum twice-daily doses: tapentadol PR 250 mg or oxycodone/naloxone PR 40 mg/20 mg plus oxycodone PR 10 mg), target doses were continued for 9 weeks. Change in bowel function (evaluated using the Patient Assessment of Constipation Symptoms [PAC-SYM] total score) from baseline (randomization) to final evaluation was evaluated as one of 2 co-primary endpoints. An analysis of covariance (ANCOVA) model, including treatment and pooled center as factors and baseline value as a covariate, was used to evaluate PAC-SYM outcomes in the per protocol set. Because the trial design was planned with 2 interim analyses, an inverse normal method was used for the primary analyses to correct for multiplicity. Non-inferiority of tapentadol PR compared with oxycodone/naloxone PR was established if the upper limit of the 2-sided 97.5% exact repeated confidence interval (RCI) on the treatment difference (tapentadol PR minus oxycodone/naloxone PR) was less than the non-inferiority margin of 0.7. Treatment-emergent adverse events (TEAEs) were recorded throughout the study and evaluated for the safety set. Incidences of TEAEs were compared between treatment groups (Fisher's exact test; descriptive analyses).

Results

For the primary endpoint, mean (standard deviation) PAC-SYM scores with tapentadol PR (n = 117) and oxycodone/naloxone PR (n = 112), respectively, were 0.56 (0.643) and 0.61 (0.667) at baseline and 0.70 (0.689) and 0.72 (0.680) at final evaluation (least squares mean [standard error] changes from baseline to final evaluation:

0.07 [0.06] and 0.14 [0.062], respectively). The PAC-SYM score did not change significantly from baseline with tapentadol PR ($P = 0.235$), but increased significantly (indicating worsening bowel function symptoms) with oxycodone/naloxone PR ($P = 0.022$). Respective changes in both groups were below the published minimal clinically important difference for PAC-SYM. The 97.5% exact RCI for the PAC-SYM total score was [-0.259 to 0.121], showing non-inferiority for tapentadol PR versus oxycodone/naloxone PR. The incidence of gastrointestinal TEAEs overall was lower with tapentadol PR (n = 130) versus oxycodone/naloxone PR (n = 128) during the titration (40.8% vs 50.0%) and whole treatment (44.6% vs 51.6%) periods. For tapentadol PR versus oxycodone/naloxone PR, significantly lower incidences of the following TEAEs were observed: constipation during the titration (12.3% vs 25.8%; $P = 0.007$) and whole treatment (15.4% vs 25.8%; $P = 0.045$) periods; vomiting during the titration (6.9% vs 16.4%; $P = 0.02$) and whole treatment (7.7% vs 16.4%; $P = 0.036$) periods; and mild, moderate, or severe nausea, vomiting, and/or constipation during titration (32.3% vs 46.1%; $P = 0.03$). Other TEAEs (≥10% in either group; tapentadol PR vs oxycodone/naloxone PR) during the whole treatment period were fatigue (30.0% vs 24.2%), nausea (22.3% vs 18.0%), and dizziness (18.5% vs 17.2%). For these and all other individual TEAEs ≥5%, no significant between-group differences were observed. With tapentadol PR and oxycodone/naloxone PR, respectively, 33.8% and 62.5% of patients discontinued treatment during the whole treatment period, most commonly due to adverse events (20.0% vs 40.6%).

Conclusions

Results for this co-primary endpoint were positive, demonstrating non-inferiority for the change in the PAC-SYM score from baseline to final evaluation for tapentadol PR versus oxycodone/naloxone PR. Tapentadol PR was associated with significantly lower incidences of constipation and vomiting and with a lower rate of discontinuations due to adverse events than oxycodone/naloxone PR. The better tolerability profile for tapentadol PR versus oxycodone/naloxone PR suggests that tapentadol PR is a favorable strong analgesic option in opioid-naive patients with severe chronic low back pain with a neuropathic pain component.

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Effects of Tapentadol Prolonged Release (PR) Versus Oxycodone/Naloxone PR on Quality of Life and Function Measures in Patients With Severe Chronic Low Back Pain With a Neuropathic Pain Component

Andreas Schwittay[1], Ralf Baron[2], Andreas Binder[2], Claudia Schumann[1], Dietmar Falke[3], Ilona Steigerwald[3]
[1]Practice for General Medicine, Special Pain Therapy & Palliative Medicine, Böhlen, Germany, [2]Division of Neurological Pain Research and Therapy, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Germany, [3]Medical Affairs Europe & Australia, Grünenthal GmbH, Aachen, Germany

Purpose

Severe chronic pain, particularly that associated with a neuropathic pain component, can have a significant negative impact on health-related quality of life. Tapentadol prolonged release (PR), a centrally acting analgesic with μ-opioid receptor agonist and noradrenaline reuptake inhibitor activities, has been shown to be effective and well tolerated for managing severe chronic low back pain with or without a neuropathic component, and has been associated with significant improvements in health-related quality of life in these patients. A fixed-dose combination of oxycodone/naloxone PR has also been shown to be effective for managing moderate to severe chronic low back pain and improving quality of life. An equianalgesic ratio of approximately 5:1 has been established for tapentadol PR versus oxycodone PR in earlier randomized, controlled trials. This study evaluated the impact of tapentadol prolonged release (PR) and oxycodone/naloxone PR on quality of life and function measures as secondary outcomes in patients with severe chronic low back pain with a neuropathic pain component. Results for the quality of life and function measures are presented here; results for the 2 co-primary endpoints, secondary effectiveness endpoints, and safety and tolerability outcomes are presented in separate abstracts.

Method

In this randomized, controlled, open-label, phase IIIb/IV study, eligible patients with severe pain (average pain intensity ≥6 on an 11-point numerical rating scale-3 [NRS-3; average 3-day pain intensity] at baseline and a rating of "positive" or "unclear" on the painDETECT questionnaire at baseline) were randomized to twice-daily tapentadol PR 50 mg or oxycodone/naloxone PR 10 mg/5 mg. After a 21-day titration period (maximum twice-daily doses: tapentadol PR 250 mg or oxycodone/naloxone PR 40 mg/20 mg plus oxycodone PR 10 mg), target doses were continued for 9 weeks. Quality of life and function were evaluated using the Short Form-12 (SF-12) and EuroQol-5 Dimension (EQ-5D) questionnaires. Patients and investigators reported their impression of the overall change in a patients' condition since starting treatment on the patient global impression of change (PGIC) and clinician global impression of change (CGIC), respectively. An analysis of covariance (ANCOVA) model, including treatment and pooled center as factors and baseline value as a covariate, was used to evaluate the SF-12 and EQ-5D in the full analysis set. The last observation carried forward (LOCF) was used for imputing missing assessments.

Results

With tapentadol PR (n = 130), significant improvements from baseline to final evaluation were observed in both SF-12 summary scores (least-squares [LS] mean [standard error of the mean (SEM)] change from baseline to final evaluation: physical component summary, 9.74 [0.795]; mental component summary, 3.08 [0.846]) and all domain scores (physical functioning, 8.36 [0.826]; role-physical, 7.26 [0.712]; bodily pain, 10.99 [0.946]; general health, 8.45 [0.870]; vitality, 4.94 [0.806]; social functioning, 5.25 [0.887]; role-emotional, 4.76 [0.947]; and mental health, 5.16 [0.839]; all $P < 0.001$). With oxycodone/naloxone PR (n = 126), significant improvements were observed in the SF-12 physical component summary score (LS mean [SEM] change from baseline to final evaluation, 6.20 [0.806]) and physical functioning (5.07 [0.836]), role-physical (4.67 [0.722]), bodily pain (7.46 [0.957]), general health (4.31 [0.882]), social functioning (2.29 [0.900]), role-emotional (2.59 [0.981]), and mental health (2.97 [0.858]) domain

scores (all $P \leq 0.012$). Improvements in the SF-12 physical component summary score and physical functioning, role-physical, bodily pain, general health, vitality, and social functioning domain scores were significantly greater with tapentadol PR than with oxycodone/naloxone PR ($P \leq 0.017$). With tapentadol PR and oxycodone/naloxone PR, respectively, mean (standard deviation) EQ-5D health status index scores were 0.32 (0.295) and 0.34 (0.311) at baseline and 0.67 (0.317) and 0.57 (0.314) at final evaluation. EQ-5D scores improved significantly from baseline to final evaluation in both treatment groups (LS mean [SEM] change from baseline to final evaluation: tapentadol PR, 0.34 [0.028]; oxycodone/naloxone PR, 0.24 [0.028]; both $P < 0.001$), with significantly greater improvement with tapentadol PR versus oxycodone/naloxone PR ($P = 0.010$). With tapentadol PR and oxycodone/naloxone PR, respectively, ratings of "very much improved" or "much improved" were reported by 53.8% (70/130) and 29.4% (37/126) of patients on the PGIC and by 58.5% (76/130) and 34.1% (43/126) of investigators on the CGIC at final evaluation.

Conclusions

Tapentadol PR was associated with greater improvements in quality of life and function measures than oxycodone/naloxone PR in opioid-naive patients with severe chronic low back pain with a neuropathic pain component. The favorable effects of tapentadol PR versus oxycodone/naloxone PR on quality of life were consistently shown across different validated measures and coincided with improvements in effectiveness and tolerability outcomes (as described separately). In conclusion, tapentadol PR can be proposed as a preferred option for treating severe chronic pain with a neuropathic pain component.

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Improved Accuracy of Medication Compliance Determination and Significant Reduction in Turn-Around Time using a Qualitative Time-of-Flight Mass Spectrometry and Immunoassay-based Screening Approach.

Kelly Doyle[1], Chantry Clark[2], Frederick Strathmann[1,3]
[1]University of Utah, Salt Lake City, USA, [2]ARUP Laboratories, Salt Lake City, USA, [3]ARUP Institute for Clinical and Experimental Pathology, Salt Lake City, USA

Purpose

Conventional approaches to pain management compliance testing utilize antibody-based screens and point of collection (POC) cups for rapid and initial assessment. Disadvantages of POC cups and immunoassay-based screens include low specificity, false positivity/negativity, narrow detection profiles within drug classes, and limited ability to accurately determine compliance with the results. Positive results typically require confirmation by mass spectrometry while negative results often go uninvestigated resulting in inefficient and potentially incorrect compliance determination.

Method

In this study, compliance determination from urine specimens using a comprehensive hybrid assay that combines heterogenous immunoassays with acceptable performance and time-of-flight (TOF) mass spectrometry was compared to a conventional immunoassay screen with reflex to mass spectrometry confirmation workflow. Our objectives were to (1) compare the in-lab turn-around time (TAT) and total TAT between assays; (2) determine if false negative/positive results from the immunoassay screen are resolved by the hybrid assay; and (3) demonstrate the utility of the hybrid assay in providing qualitative evidence of specific compounds within a drug class and overall compliance assessment.

Results

ANOVA and posthoc analysis of three months of patient results indicated a statistically significant reduction in the mean analysis time for the hybrid assay compared to screen with reflex for both in-lab (32.2 hrs) and total time (76.5 hrs) and for confirmation alone (19.2 hrs in-lab time; 32.2 hrs total time). Accuracy of compliance interpretation was conducted on 42 residual urine specimens with known prescription histories and a positive immunoassay screen result. A subset of samples was also analyzed using the NexScreen POC cups with performance nearly equivalent for the NexScreen POC and conventional immunoassay with the exception of three additional positive benzodiazepine results identified by the POC device. The hybrid assay was superior in confirming compliance per patient (33/42 vs. 27/42) and per prescription (48/57 vs. 40/57), as well as in identifying evidence of non-prescription substance abuse (12 vs. 8).

Conclusions

These data demonstrate the utility of a combined mass spectrometry and immunoassay approach in providing clinicians a method to determine medication compliance and substance abuse.

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An Alternative Strategy for Pain Management Compliance Testing using a Combination of Immunoassay and Time-of-Flight Mass Spectrometry.

Gwendolyn McMillin[1,2], Stephanie Marin[1], Kamisha Johnson-Davis[1,2], Bryan Lawlor[3], Frederick Strathmann[1,2]
[1]ARUP Institute for Clinical and Experimental Pathology, Salt Lake City, USA, [2]Department of Pathology, University of Utah, Salt Lake City, USA, [3]ARUP Laboratories, Salt Lake City, USA

Purpose

An alternative strategy for the evaluation of pain management compliance testing is presented. Our objectives were to (1) provide a unique laboratory workflow designed to provide results quicker than a conventional screen with reflex to confirmation approach; (2) reduce the need for follow-up testing associated with high false positive immunoassays, and (3) combine the use of time-of-flight mass spectrometry with selected immunoassays to obtain desired specificity while being mindful of cost and reimbursement challenges.

Method

The mass spectrometry portion of the assay was conducted using an Agilent 6230 Time-of-Flight mass spectrometer. The immunoassays were homogeneous enzyme immunoassays conducted on a Beckman Coulter AU400 analyzer with Syva® Emit® II Plus reagents (Siemens) and DRI® reagents (Microgenics). Opioids (19), benzodiazepines (10), zolpidem, amphetamine-like stimulants (6), and methylphenidate metabolite were detected by TOF to maximize specificity and sensitivity of these thirty-seven drug analytes. Barbiturates, cannabinoid metabolites, carisoprodol, cocaine metabolites, ethyl glucuronide, methadone, phencyclidine, propoxyphene, and tramadol were detected by HEIAs with false positive rates determined to be < 5% for all drug classes (range of 0% to 5%). Turnaround time was measured for overall turnaround time and analytical "in-lab" turnaround time.

Results

The most commonly detected drug classes were opiates/opioids, cannabinoids, benzodiazepines and amphetamines. For the traditional screen with reflex approach, greater than 90% of the immunoassay results confirmed positive except for PCP (0%), amphetamines (50%) and propoxyphene (50%). In the combined approach using immunoassay and TOF mass spectrometry, historic performance provided an expected positive confirmation of 95% of immunoassay results with no requirement for follow-up testing for results generated by TOF mass spectrometry. Time to result was significantly reduced as compared to the traditional approach.

Conclusions

The combination of immunoassay and time-of-flight mass spectrometry for pain management compliance testing provides a simplified and sufficiently specific testing process as an alternative to the conventional screen with reflex to confirmation approach. Benefits include a reduction in the overall turn-around-time, potential for reduced need for follow-up testing, decreased cost and a suitable combination of methods for appropriate reimbursement under currently available strategies.

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Prediction of plasma oxycodone concentration ranges in patients at steady state from quantitated oral fluid levels

Richard Stripp[1], Neel Mehta[2,3], Frank Kunkel[4], Naum Shaparin[5], Cynthia Whiteman[1], Elizabeth Fey[1]
[1]Sterling Healthcare Services, Huntington, New York, USA, [2]Weill-Cornell Pain Medicine Center, New York, New York, USA, [3]New York Presbyterian Hospital, New York, New York, USA, [4]Accessible Recovery Services, Pittsburgh, Pennsylvania, USA, [5]Montefiore Medical Center, Bronx, New York, USA

Purpose

Urine as a drug testing matrix provides limited interpretive information, as it primarily determines the presence or absence of a drug. Blood is currently the preferred matrix for analysis of biologically active drug levels in individuals enrolled in opioid pain management programs. However, due to invasive and costly blood collection techniques, improved systems and methods to interpret total body drug concentration are desirable. Oral fluid is a direct filtrate of the blood and therefore, theoretically, the best alternative matrix for plasma drug concentration correlation. Thus, the use of oral fluid as a means to predict plasma oxycodone concentration was assessed. Utilization of a pharmacokinetic mathematical model in conjunction with established pharmacokinetic variables allowed for the calculation of an oral fluid derived plasma equivalent concentration. This enabled the assessment of the oral fluid derived oxycodone concentration within a determined expected steady state concentration range in plasma, based on a provided dosing regimen, without the necessity of drawing blood.

Method

Simultaneous oral fluid and plasma samples (n=94) were collected from steady state pain management patients prescribed oxycodone for chronic pain. Salivary pH was determined and patient demographic and medical information obtained at time of sample collection for use in algorithm. The paired oral fluid and plasma samples were successfully analyzed by LC/MS-MS, alongside a series of standards of known concentration, such that a calibration curve was generated and quantitative oxycodone concentration reported for both matrices. An oral fluid derived plasma equivalent concentration was calculated through a mathematical model utilizing the quantitated oral fluid drug concentration, salivary pH, and established pharmacokinetic drug parameters. This derived plasma oxycodone concentration was then compared to the steady state therapeutic oxycodone concentration range, calculated based on patient dosing regimen and referenced pharmacokinetic variables, allowing an assessment of the interpretive value of oral fluid to assess plasma oxycodone levels.

Results

Applying the pharmacokinetic model allowed for conversion of the quantitated oral fluid concentration to an equivalent plasma concentration. The quantitated plasma concentrations for each donor served as the known controls for compliance assessment. The relationship of these two values was assessed for correlation either both above, within or below the previously determined expected steady state therapeutic range of each donor. The correlation coefficient between the quantitated and derived equivalent plasma concentrations was 0.78. Evaluating agreement between the derived plasma value and quantitated plasma values showed an 89.4% concordance. 79.8% of the agreeing concentration pairs both fell within therapeutic range, while 5.3% and 4.3% demonstrated agreement for both above range and below range respectively. 10.6% of the sample pairs did not show agreement. Disagreement observed between the two values can be explained by a variety of factors including; non-compliance, lack of steady state, oral fluid contamination, unreported medications taken for breakthrough pain, inaccurate medication history provided, individual pharmacogenomics, and health status.

Conclusions

Oral fluid is a convenient and advantageous alternative specimen for drug monitoring, as compared to blood. Correlation of oxycodone concentration in the two matrices established oral fluid as an acceptable matrix for oxycodone prescription monitoring. This study provides a novel application of basic pharmacokinetic knowledge to the pain management industry simplifying and improving oxycodone dose regimen monitoring through the use of oral fluid drug testing. This method has potential further application to interpret predicted plasma drug concentrations derived from oral fluid based on determined steady state plasma drug concentration ranges for expanded opioids and other drug classes.

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Effect of two contrasting interventions on upper limb chronic pain, disability, work ability and physical capacity: Randomized controlled trial

Emil Sundstrup[1,2], Markus Due Jakobsen[1,2], Kenneth Jay[1,2], Roger Persson[3], Per Aagaard[2], Lars Andersen[1]
[1]National Research Centre for the Working Environment, Copenhagen, Denmark, [2]Institute for Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark, [3]Department of Psychology, Lund University, Lund, Sweden

Purpose

Chronic pain and disability of the arm, shoulder and hand severely affect labor market participation. Ergonomic training and education is the default workplace strategy to reduce physical exposure and thereby prevent aggravation of pain. An alternative strategy could be to increase physical capacity of the worker by physical conditioning. The aim of the study was to investigate the effect of two contrasting interventions, conventional ergonomic training (usual care) versus resistance training, on pain, disability, work ability and physical capacity in individuals with upper limb chronic pain exposed to highly repetitive and forceful manual work.

Method

This two-armed parallel-group, examiner-blinded, randomized controlled trial with allocation concealment was conducted among slaughterhouse workers in Denmark, Europe. Sixty-six adults with chronic pain in the shoulder, arm, or hand and work disability were randomly allocated to 10 weeks of specific resistance training for the shoulder, arm and hand muscles for 3 x 10 minutes per week, or ergonomic training and education (usual care control group). The primary outcome measure was the change from baseline to 10-week follow-up in pain intensity (average of shoulder, arm and hand, scale 0-10), and secondary outcomes included disability (Work module of DASH questionnaire), work ability (Work Ability Index) as well as isometric shoulder and wrist muscle strength. Blinding of participants is not possible in behavioral interventions. However, at baseline outcome expectations to the two interventions were similar. The trial was registered in ClinicalTrials.gov (NCT01671267) prior to enrolment of participants.

Results

Pain intensity, disability, work ability and muscle strength improved more following resistance training than usual care ($p<0.001$, <0.05, <0.05, <0.0001, respectively). Pain intensity decreased by 1.5 points (95% confidence interval -2.0 to -0.9) following resistance training compared with usual care, corresponding to an effect size of 0.91 (Cohen's d). Additionally, half of the participants performing resistance training demonstrated much improvement in chronic pain symptoms (i.e. at least 50% pain reduction) and a quarter experienced some improvement (i.e. between 25-50% pain reduction).

Conclusions

Resistance training at the workplace results in a clinical relevant reduction in pain along with improved disability, work ability and muscle strength in adults with upper limb chronic pain exposed to highly repetitive and forceful manual work. Thus, the observed reduction in chronic pain following resistance training was paralleled by functional improvements of the shoulder, arm and hand during daily work as well as increased physical capacity.

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Development of an Opioid Monitoring Clinic for high risk patients on chronic opioid therapy at Las Vegas Southern Nevada Healthcare System

Richard Talusan[1], Jennifer Kawi[2], Lori Candela[2]
[1]Las Vegas Southern Nevada Healthcare System, Las Vegas, USA, [2]University of Nevada Las Vegas, School of Nursing, Las Vegas, USA

Purpose

The prevalence of opioid abuse and misuse among veterans with nonmalignant chronic pain has been reported at around 30% (Von Korff et al., 2011), with nearly 7-fold occurrence compared to the general population (Baser et al., 2013). Due the pervasiveness of opioid abuse and misuse in veterans, a quality improvement project was initiated to develop and implement an Opioid Monitoring Clinic (OMC) as a clinical referral system within the primary care service of a Veterans Affairs (VA) facility. Based on published literature, the OMC is one of the first known Advanced Practice Registered Nurse (APRN)-led clinic that was developed and implemented in the United States. The OMC was developed in the Las Vegas Southern Nevada Healthcare System's Primary Care service and implemented in July 2013 to provide assistance to primary care providers (PCP) in intensively monitoring and managing opioid use for their high-risk patients on chronic opioid therapy. Patients considered at high risk for opioid abuse and misuse included those on morphine equivalent dose of at least 100mg/day, history of illicit substance abuse, current aberrant behaviors such as frequent request for early refills, constant request for opioid dose increases without medical indication, and/or recurrent loss of opioid medications.

Method

This quality improvement project utilized a descriptive approach to evaluate the APRN-led OMC through a retrospective chart review among veteran participants. IRB approval was received. Risks and benefits were discussed and informed written consents were completed for all participants.

The OMC was implemented with support from administration in a VA facility serving approximately 60,000 veterans. Consultation with the Chief of Primary Care and collaboration with Pharmacy Service, Laboratory Service, Nursing Service, and Health Administration Service were ensured. Patients were referred to the OMC for intensive monitoring and/or adjustment of their opioid therapy consistent with the current Department of Veterans Affairs/Department of Defense clinical practice guideline for the management of opioid therapy for chronic pain (Department of VA/DoD, 2010). The OMC staff screened patients for eligibility and were offered an appointment for evaluation. Urine drug screens (UDS) with confirmation testing of their prescribed opioids were conducted on all patients referred to the OMC. They were screened for potential "doctor shopping" through the state's Prescription Drug Monitoring Program where they reside. All patients were asked to complete the Brief Pain Inventory questionnaire by Cleeland and were assessed for risk for opioid abuse and misuse with the use of the Pain Screening Tool by Atluri and Sudarshan. Further, patients were asked to sign an Opioid Pain Agreement.

Results

A total of 287 (277 males and 10 females) patients were seen in the OMC. The most common source of pain was chronic low back pain. 27% of patients referred to the OMC were on concurrent use of other controlled substances such as benzodiazepines and/or amphetamines. 38% of patients were found to have unexpected UDS findings (negative opioid confirmation testing despite reported current use of opioids, active illicit drug use) and 19% were found to be "doctor shopping." Patients found to be abusing and/or misusing their prescription opioids and/or found to be using an illicit substance were discontinued on opioid therapy and were referred for appropriate treatment as

indicated (i.e., Alcohol and Drug Treatment Program for addiction or abuse of illicit substance). Patients found to be "doctor shopping" were informed of their illegal activity, strongly advised of the need to use only one source of prescriber for their opioid therapy, otherwise will be discharged from the OMC for non-adherence and referred back to the primary care provider.

Patients primarily on short acting opiates were tried on long-acting opiates. Lastly, patients at very high dose opiates (>200mg morphine equivalents per day) were slowly tapered down to less than 200mg per day. The combination of intensive monitoring with the use of frequent UDS, frequent office visits, PDMP database inquiry to identify abuse and misuse of opioids, appropriate switch from short acting to long acting opioids, and reduction of daily opioid dose for those at very high doses resulted in a drastic reduction of average morphine equivalence dose (MED) among patients seen in the OMC. The baseline MED of patients referred to the OMC was 100.4mg per day and this was effectively reduced to 47.7mg per day or a 52% reduction in opioid dose among patients seen in the OMC.

Conclusions

The OMC reduced the morphine equivalent dose of patients referred to the clinic by more than 50%. The drastic reduction in the opioid dose of patients referred to the OMC resulted from evidence-based strategies utilized to help identify abuse of prescription opioids, use of illicit substances that can cause opioid-related complications, discovery of "doctor shopping," and appropriate reduction of overall opioid dose per patient due to the change from short acting to long acting opioids. The OMC can be an effective program to help identify abuse and misuse of prescription opioids among high-risk patients.

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Needs-Based implementation of an opioid monitoring clinic for high risk patients on chronic opioid therapy in the Department of Veterans Affairs Las Vegas Southern Nevada Healthcare System

Richard Talusan, Jacqueline Smith, Melvin Diggs
Department of Veterans Affairs Las Vegas Southern Nevada Healthcare System, Las Vegas, NV, USA

Purpose

A recent Needs Assessment online survey on primary care providers (PCPs) employed by the VA Las Vegas Southern Nevada Healthcare System indicated overwhelming support for the creation of an Opioid Monitoring Clinic (OMC). The OMC would assist PCPs in the management of high risk patients on opioid therapy for chronic nonmalignant pain. According to studies, patients at high risk for prescription abuse and misuse may include patients who display aberrant behaviors that include frequent requests for escalating opioid dosage and/or early refills due to reported loss of their prescription opioids or running out early. The OMC can assist PCPs in managing high risk patients with the goal of improving the overall quality of pain management by treating patients according to current evidence-based Department of Veterans Affairs/Department of Defense (VA/DoD) clinical practice guideline. The OMC is managed by a team consisting of an advanced practice registered nurse (ARPN), registered nurse (RN), a licensed practical nurse (LPN), and a medical support assistant member (MSA). The OMC staff ensures that patients referred and admitted into the OMC program are seen within 30 days, their prescription opioids are refilled as indicated when due, and their pain symptoms are addressed using a multidisciplinary approach for pain management.

Method

All PCPs received an online survey in January 2013 to assess PCPs' interest for an opioid monitoring clinic in the management of patients at high risk for prescription abuse and misuse. The survey solicited PCPs compliance with current VA/DoD clinical practice guideline recommendations on the management of chronic opioid therapy patients. A component included in the guideline is the use of state Prescription Drug Monitoring Program (PDMP) database to discover possible "doctor shopping", urinary drug screens (UDS) to identify active illicit substance use and/or to confirm active use of prescribed opioids. Subsequently, a follow up survey was accomplished the following year to identify changes in PCPs practice regarding the clinical practice guideline and satisfaction with OMC.

In addition to the surveys, the OMC staff also developed four continuing education sessions targeted for the clinical staff including physicians, APRNs, and nurses. Two sessions were delivered to the medical staff (physicians and APRNs) as a Grand Rounds medical continuing education. One session was delivered to the primary care nursing staff during their all staff meeting. Lastly, one session was delivered to all APRNs during their quarterly meeting. All sessions were an hour long and the content included statistics on opioid abuse and misuse and recommendations from evidence-based clinical practice guidelines on the management of chronic nonmalignant pain on chronic opioid therapy.

Results

100% of PCPs (n=32) reported strong interest in the creation of the OMC to assist them in managing high risk patients. 88% of PCPs reported monitoring their patients on chronic opioid therapy using UDS. In the follow-up survey, 100% of PCPs (n=31) reported regularly monitoring their patients on chronic opioid therapy using UDS. This finding is supported by the 30% increase in the number of UDS ordered in the facility from the time of OMC implementation in July 2013 through December 2013. Additionally, 69% of PCPs reported using PDMP to monitor their patients. 92% of PCPs reported overall satisfaction with the OMC and the same percentage of PCPs felt that the OMC program resulted in a positive impact to primary care service. This finding is supported by the nearly 300 high risk patients already referred by their PCPs to be seen, evaluated, and managed in the OMC. The majority of PCPs

also reported decreases in the number of walk-ins and telephone calls from patients on chronic opioid therapy as well, facilitating enhanced accessibility for other patients. Although not a primary goal of the OMC, a significant cost savings in opioid prescription has been recognized in the VA Las Vegas due to discontinuation of opioid therapy on patients found to be abusing and misusing their prescription opioids and patient founds to be doctor shopping. The cost saving also comes from the drastic reduction in opioid dose of veterans seen in the OMC due to implementation of a multidisciplinary approach for chronic pain management and dose reduction.

Conclusions

The team-managed OMC program recently implemented in the VA Las Vegas Southern Nevada Healthcare System has been very well received by PCPs and patients alike. PCPs reported improved satisfaction due to decreased walk-ins and telephone calls from high risk patients on chronic opioid therapy as these patients were now managed by the OMC. Patients also benefited from the OMC program as OMC staff ensured timely refill and ease of access to the OMC. Additionally, patients who were found to be abusing or misusing their prescription opioids were discontinued on opioid therapy and were referred for appropriate intervention and treatment.

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Use of a Shared Medical Appointment in the Opioid Monitoring Clinic

Lynn Ansher, Richard L. Talusan
VA Southern Nevada Healthcare System, Las Vegas, NV, USA

Purpose

The Shared Medical Appointment (SMA), or group visit, has been shown to be an effective strategy for improving access by reducing wait times for appointments through increased patient capacity per slot; reducing organizational cost through improved provider productivity and improved patient appointment efficiency, and improving overall patient satisfaction and healthcare outcomes. 100 million Americans suffer from chronic pain and approximately 12 million Americans abuse and misuse prescription opioids. Approximately 6000 patients in the VA Southern Nevada Healthcare System are on opioid therapy for chronic non-cancer pain, with nearly 300 having been referred by their primary care provider (PCP) to the Opioid Monitoring Clinic (OMC) to assist PCPs in managing their care and monitoring for opioid abuse and misuse. A Shared Medical Appointment (SMA) was developed for patients enrolled in the OMC, with the goals of improving overall quality of chronic pain management through provision of a patient-centered supportive environment, and enhanced patient education on self-management skills and on risks of opioid misuse/abuse. Additional goals included improving patient access to follow-up appointments and promoting timely medication renewals. The SMA can offer the same content of a one-to-one visit with added benefits of a cohesive group process stemming from the interdisciplinary focus on holistic care, self-management, and group learning. The purpose of this project was to offer an alternative to the traditional one-to-one visit to ascertain patient satisfaction and benefit as compared to a traditional visit, as well as assess effectiveness with regard to clinical outcomes.

Method

Participants for the SMA were selected from those patients currently being followed in the OMC, following initial evaluation and at least one follow up visit with the prescribing Nurse Practitioner (second author). A chart review was conducted by the first author to determine appropriateness for the SMA. Exclusion criteria included the following: active suicidal ideation; history of hostile or inappropriate behavior directed toward staff related to opioid medications, or previous evaluation by this author and a determination that the patient was not appropriate due to the likelihood of inappropriate behaviors (monopolizing group, inability to redirect, poor interpersonal skills). The structure of the SMA was based upon recommendations from the existing literature. Sessions were scheduled once every four weeks to coincide with patients' opioid medication renewal schedule. At each visit, queries were run for each patient in the Prescription Drug Monitoring Program database to determine if opioids had been obtained anywhere other than through this clinic, and a UDS with opioid confirmation was ordered. Vital signs were taken by nursing staff at check-in, then each patient completed the Brief Pain Inventory. The authors then provided an educational component (chronic care model, best practices, self-management skills), followed by an open discussion of the topic, and participants' questions and concerns. Participants were pulled out of the group to meet with the prescriber individually for evaluation and reassessment of the ongoing plan of care, then returned to the group interaction. Participants completed a session evaluation at the end of each 90 minute SMA.

Results

Two cohorts totaling twelve patients participated in the SMA, with Cohort 1 attending 3 SMAs and Cohort 2 attending 2; the aggregate increase in clinic access was 86.7%. Participants completed an evaluation following each session, yielding a total of 18 evaluations. Participants utilized a 5-point Likert scale with responses ranging from "strongly disagree" (1) to "strongly agree" (5), to evaluate the SMA on several dimensions. Participants rated the effectiveness of/satisfaction with the SMA as compared to a 1:1 visit on the following dimensions (average rating in

parenthesis): quality of care (4.2); how well individual concerns were addressed (4.4); maintenance of confidentiality/privacy (4.5). Participants also rated the value of the presence of a multidisciplinary staff (4.6), shared discussion with patients with similar health care concerns (4.7), and if the SMA improved the efficiency of renewal of opioid medications (4.4). Participants rated the SMA favorably on all dimensions, indicating that their healthcare needs were met as well by the SMA as by a 1:1 visit, as well as offering additional benefits not present in a 1:1 visit. Mean clinical outcomes from admission to the OMC to most recent evaluation reflect a 24% decrease in daily morphine equivalent dose; 22% decrease in BPI pain intensity scores, and a 12% reduction in scores measuring interference with functional status. Of the ten patients referred for aberrant behaviors (illicit substance use, obtaining opioids from more than one source, UDS negative for opioids despite reported regular use), 70% demonstrated improvement/compliance through appropriate behavioral changes with regard to their reason for referral: UDS negative for illicit substances (or positive only for cannabinoids provided patient has a Nevada State Medical Marijuana license) (4 of 6); PDMP negative for obtaining opioids outside of this clinic (1 of 1); UDS positive for opioids (2 of 3).

Conclusions

Evaluation of patients participating in an SMA for the OMC indicates that the SMA provides comparable quality of care as a 1:1 visit, as well as offers benefits not available in a 1:1 visit (improved clinic access, opportunities for group support and learning, multidisciplinary providers at the same visit). There was moderate improvement in pain intensity and functionality as measured by the Brief Pain Inventory. The SMA also resulted in improved adherence to overall treatment guidelines, including a reduction in daily opioid dose, abstention from use of illicit substances, and abstention from obtaining opioids from other sources.

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Hormone Abnormalities In Uncontrolled Chronic Pain Patients

Forest Tennant
Veract Intractable Pain Clinic, West Covina, CA, USA

Purpose

There is a group of chronic pain patients who do not respond to standard treatments including non-pharmacologic measures, and antidepressants, anti-inflammatories, neuropathic agents, and opioids. Due to a lack of adequate treatment some become dysfunctional, immobilized, bed or house bound, and suicidal. Uncontrolled pain is known to have profound effects on endocrine function, and normalization of key hormones may be necessary for pain control. This study was done to identify some hormone abnormalities generated by uncontrolled pain, and to use a hormone profile to help develop an adequate treatment plan for chronic pain patients who have not been able to find relief with standard measures.

Method

Sixty-one (61) chronic pain patients were referred for evaluation and treatment because they had not responded to standard regimens of opioids, antidepressants, neuropathic agents, and anti-inflammatories. This serum hormone profile was done prior to any change in therapy: (1) corticotropin (ACTH), (2) cortisol, (3) pregnenolone, (4) progesterone, (5) dehydroepiandrosterone (DHEA), and (6) testosterone. An abnormality was considered to be any serum level above or below the normal, serum range used by the testing laboratory. Specific therapy approaches were directly targeted at correcting hormone abnormalities so that within 60 days patients had enough pain control to carry on activities of daily living. High hormone levels presumed the need for increased analgesia and low levels presumed a need for hormone replacement as well as enhanced analgesia.

Results

The great majority (49; 80.3%) had at least one hormone abnormality. Every hormone showed a significant percentage of abnormalities: (1) ACTH (27.3%); (2) cortisol (32.8%); (3) pregnenolone (20.8%); (4) progesterone (20.8%); (5) DHEA (37.2%), and (6) testosterone 37.2%). Seven patients (7; 11.5%) showed significant pituitary-adrenal-gonadal suppression as indicated by low ACTH plus two or more low levels of adrenal-gonadal hormones. Three patients had severe adrenal insufficiency with cortisol levels less than 1.0 ug/dl and three had severe gonadal insufficiency with testosterone levels less than 3.0 ng/dl. Treatment strategies targeted at the correction of specific hormone elevations or deficiencies helped control pain to the point that all patients, within 60 days, could function and carry out activities of daily living.

Conclusions

Chronic pain patients who do not respond to standard pharmacologic treatments may demonstrate profound hormone abnormalities. Treatment strategies may have to include correction of hormone abnormalities to attain effective pain control.

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Poor Oral Opioid Response and Malabsorption

Forest Tennant
Veract Intractable Pain Clinic, West Covina, CA, USA

Purpose

Some chronic pain patients complain that the majority of medical agents, including opioids, which they take, are ineffective when taken by the oral route. To date there are no reported, systematic attempts to identify malabsorption as a significant clinical condition that must be routinely addressed. Opioid malabsorption appears to be an increasing problem due to bariatric surgery, diabetic gastroenteropathy, autoimmune disorders, and genetic conditions. This study was done to develop a protocol to diagnose opioid malabsorption in chronic pain patients who do not respond to oral opioids.

Method

Ten chronic pain patients who did not respond to multiple oral opioids including oral hydromorphone, were evaluated with this protocol: (1) history of gastrointestinal surgery, autoimmune disorder, genetic disease, and diabetes; (2) serum opioid levels; (3) cytochrome P450 enzymatic testing, and (4) challenge with sub-cutaneous hydromorphone, 2.0 to 20 mg given over a two-hour period. Assessed during the hydromorphone challenge were blood pressure, pulse rate, pupil size, and pain relief. Hydromorphone was chosen as the challenge agent, because it is rapid acting and doesn't require cytochrome P450 metabolism. Once malabsorption was identified, a non-oral opioid treatment regimen was administered.

Results

Patients all showed low or non-existent opioid serum levels. Every patient responded to the hydromorphone challenge which documents at least some degree of gastrointestinal malabsorption. Six of the 10 patients had multiple cytochrome P450 enzyme defects. The other patients had histories of gastrointestinal surgery, autoimmune disease, or diabetes. All patients responded to non-oral, opioid administration by the sublingual, transdermal, suppository, or injection routes.

Conclusions

Gastrointestinal absorption of opioids is dependent upon a normal cytochrome P450 enzyme system, and the majority of patients studied here had multiple cytochrome P450 defects. Other causes of malabsorption include gastrointestinal surgery, autoimmune disease, and diabetic enteropathy. Patients with a history of poor response to oral opioids and other medications should be evaluated for gastrointestinal malabsorption.

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Business plan development for clinical pharmacy services in pain as part of a novel independent study course offering

Tabetha Todd, Sara Lindsay, Chris Herndon
Southern Illinois University of Edwardsville School of Pharmacy, Edwardsville, IL, USA

Purpose

Each year, 40 million U.S. patients suffer from inadequate pain control after surgery. In addition to the negative impact on quality of life, hospitals are now being penalized via third party payers and the Centers for Medicare and Medicaid Services (CMS) for low patient satisfaction scores of which pain is a component. Workforce data from the American Society of Health-System Pharmacists suggests that an overwhelming majority of hospitals in the US desire specialized pharmacy services in pain management. Healthcare institutions are operating in a customer service oriented, cost conscious environment. They are seeking ways to stand out in the market and maximize revenues. There is an opportunity for new business models to address this emerging need in a fiscally sound manner that both reduces costs and improves patient outcomes. One such business model is a contract clinical pharmacy services company that specializes in pain management offering pre and post-operative consultations for elective surgeries.

Method

The business model is based on providing clinical pharmacy services focused on pain management. These services would be provided to institutions on a weekly basis for an annual retainer. The business would provide pain management consultant services to institutions without the need for recruiting or employing a clinical pharmacy specialist. The business model focuses on improving several outcomes such as unplanned readmissions, opioid related adverse events, formulary review and patient satisfaction scores. In the proposed business model, pharmacists provide patients pre-operative counseling on pain medication use, education on realistic pain expectations and pre-discharge consultation to optimize pain control while minimizing misuse and abuse of medications. Pharmacists would also make recommendations to the medical staff about patient specific pain management plans in opioid tolerant or complex cases. The model utilizes pharmacists to facilitate cost avoidance by decreasing the number of medications errors and adverse events associated with the management of postoperative pain. Due to the Affordable Care Act, health systems are being evaluated by payers and accrediting organizations based partly on patient satisfaction through Value Based Purchasing metrics. As a result, the goals of this proposed service are to increase patient satisfaction scores of the contracted institutions via pre-operative planning and education as well as support services in the creation and management of policies, procedures, and formulary considerations.

Results

Market analysis of the greater St. Louis metropolitan area showed sixty-three institutions within the target market. Due to first to market status with anticipated high demand, it is conservatively estimated that 13% of the market will be captured initially. Strength Weakness Opportunity Threat (SWOT) analysis highlights include: limited availability of pain experts within clinical pharmacy and the ability to provide these services economically to institutions as strengths; resistance to collaboration by institutional staff as a potential weakness; novel business plan that meets a market need as an opportunity and the ability of larger health systems to provide similar services within their network of hospitals as a potential threat. The operational planning shows that it is possible to provide these services with little initial overhead by first starting with two pharmacists specially trained in pain management who provide services for elective surgeries, develop interdisciplinary pain protocols, and make recommendations to pharmacy and therapeutics committees. Ultimately the model expands to include additional part time pharmacists providing the proposed contract services. The model also provides tracking and analysis of opioid-related adverse events to be used for institutional quality improvement. Financial analysis for this business model is positive. Conservative estimated annual profits are

$21,000-58,000 for the first fiscal year and $73,000-162,000 for the second depending on percent of market share obtained. Break even analysis shows profitability with a minimum of four contracts annually. By the end of fiscal year two, the contribution margin is projected to be $44. There are also significant incentives for institutions to utilize this service. Optimal pain management can lead to a decreased overall healthcare costs, decreased readmissions, increased cost savings, improved patient care and improved hospital total performance scores. This will result in increased incentive payments from CMS through the Value Based Purchasing defined by the Affordable Care Act.

Conclusions

There is an opportunity for new business models using pain-focused clinical pharmacy services to meet institutional needs in an interdisciplinary, fiscally sound manner that both reduces costs and improves patient outcomes. One such model is a contract clinical pharmacy service company that specializes in pain management offering pre and post-operative consultations for elective surgeries and ad hoc support of administrative considerations. In this model, patients benefit by improved quality of life via optimized pain management, institutions benefit by providing enhanced patient care resulting in increased reimbursements and the business benefits by providing superior pain management care while maintaining sustainability.

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Inadvertent Intra-Discal Injection with TFESI Utilizing Kambin's Retrodiscal Approach in the Treatment of Acute Lumbar Radiculopathy

Kevin Trinh[1], Christopher Gharibo[2], Steve Aydin[1]
[1]Hofstra North Shore, LIJ School of Medicine, Long Island, NY, USA, [2]NYU Langone - Hospital for Joint Diseases, NY, NY, USA

Purpose

Kambin introduced an endoscopic intervertebral discectomy by a posterolateral approach that he defined as Kambin's approach.[7] Kambin's approach is a right triangle over the dorsolateral disc, where the hypotenuse is the exiting nerve root, the base is the superior border of the caudal vertebra, and the height is the dura/traversing nerve root (Figure 1.1 and 1.2). In a study performed by Ji woong Park et al, they noted Kambin's retrodiscal approach is as efficacious as the subpedicular, "safe triangle" approach.[8] According to recent literature, there have also been intravascular injection during retrodiscal placement as well.[9] We would like to report a previously unreported complication, where a Kambin's retrodiscal approach for TFESI resulted in an inadvertent intradiscal injection and discuss the undesirable complications that may result from such a needle placement.

Method

- History and Physical were completed for the patient, with review of recent MRI images
- Patient was in prone position with supporting pillows under abdomen to reduce lumbar lordosis
- Sterile preparation with betadine
- Area was draped, and skin anesthetized with 1% lidocaine
- Using fluoroscopic guidance a 3.5-inch 22 Gauge spinal needle was inserted toward Kambin's retrodiscal approach via the oblique view
- Both anterior-posterior and lateral views were obtained to confirm precise location of needle placement
- Lateral radiography was used to place the needle tip at the posterior and inferior aspect of the intervertebral foramen
- When the needle reached the final location, an aspiration test was conducted to check for blood detection
- An injection of contrast medium was administered under live real-time fluoroscopy which resulted in a discogram. (Figure 3.1 and 3.2)
- In the absence of aberrant flow, corticosteroid was then injected*

Results

For many decades, the subpedicular approach has been and continues to be the method of choice for transforaminal epidural steroid injections (TFESI), particularly for the treatment of acute lumbar radiculopathy due to disc herniation. As noted previously, the radicular, radiculomedullary and artery of Adamkiewicz may traverse through any part of the intervertebral foramen and there have been case reports of spinal cord infarction due to presumable vascular injury.[10]. There have been variety of mechanisms proposed for this vascular injury ranging from mechanovascular injury to vasospasm, ascending arterial dissection, compressive hypoperfusion as well as air or particulate steroid embolism.[11] In response to these complications, a subset of practitioners have adopted Kambin's retrodiscal approach for TFESI although there are no controlled studies comparing one approach to another.

Discogram studies have shown spinal infection incidence such as discitis is 1 in 800 to 1 in 1000.[12] As for the risk of vascular injury and nerve damage, an analysis by Rathmell et al. identified 31 reported cases of spinal cord injuries and 8 cases of strokes from cervical injections administered between 2005 and 2008.[13] Considering that an average

of 8 million epidural injections are performed each year, the occurrence of a spinal infection is greater than 200 times more than either nerve or vascular injury.

As contamination remains the most common cause of infection in spinal injections, strict adherence to proper sterile technique is emphasized. As for mechanical nerve injury, Kambin's retrodiscal approach may also increase the risk of directly damaging the nerve at the lower 1/3 of the foramen. Therefore, while Kambin's retrodiscal approach may or may not decrease the risk of vascular injury, it certainly facilitates the risk of infectious injury to the disc and mechanical injury to the nerve root.

Conclusions

Kambin's retrodiscal approach has been postulated as a safe means to the transforaminal approach although it may also contain the same vasculature. However, due to Kambin's posterior-inferior approach, there may be a higher incidence of needle placement into the disc and mechanical nerve injury. We believe that this case is the first reported case of its kind to show inadvertent intradiscal injection using Kambin's approach. This infectious and mechanical risk is a potential complication of Kambin's approach and needs to be kept in mind as we aim to improve overall lumbar transforaminal epidural steroid injection safety.

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Quantitation of 52 Compounds in Urine by HPLC-MS/MS for Forensic Toxicology

Kristine Van Natta, Marta Kozak
Thermo Fisher Scientific, San Jose, CA, USA

Purpose

Forensic toxicologists face an ever-expanding list of compounds for analysis. The need to reliably quantitate large-panel assays with ion ratio confirmation is continually increasing. Large panel assays are required in order to speed sample analysis time, lower analytical costs and obtain results quicker. Here we developed and preliminarily analytically evaluated an HPLC-MS/MS method for the quantitation of 52 compounds in human urine for forensic toxicology.

Method

Samples were processed by enzymatic hydrolysis followed by urine dilution. Briefly, an aliquot of urine was spiked with internal standard and incubated with ß-glucuronidase enzyme. The resulting mixture was centrifuged and further diluted before an aliquot was analyzed by gradient HPLC and triple quadrupole mass spectrometry. Two SRM transitions were monitored for each compound to obtain ion ratio confirmation. Total run time is seven minutes. Calibrators and controls were prepared by spiking compounds into blank synthetic urine in the range of 1 to 1000 ng/mL. Intra- and inter-assay accuracy and precisions were determined by processing and analyzing a calibration curve along with quintuplicate controls at four different concentrations on three different days.

Results

Limits of quantitation were defined as the lowest concentration which had back-calculated values within 20%, ion ratios within defined tolerance (tolerance dependent upon actual ratio), and quality controls meeting the above two requirements. Limits of detection were defined as the lowest calibrator with a detectable chromatographic peak with a lower limit of 1 ng/mL. Using these criteria, cut-offs were met, and in many cases exceeded, for all of the compounds tested in this study with the exceptions of ibuprofen and THC-carboxylic acid metabolite. Ibuprofen was limited by quality control precision, and THC metabolite was limited by ion ratio confirmation. Intra-assay precisions for quality control replicates were within 20% by definition for passing criteria, and most were within 10%.

Conclusions

The analytical method presented can quantitate 52 forensic compounds in synthetic human urine with sufficient accuracy and precision to meet cut-off values.

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Fast analysis of 7 benzodiazepines in urine by LDTD-MS

Kristine Van Natta, Marta Kozak
Thermo Fisher Scientific, San Jose, CA, USA

Purpose

Rapid screening is critical for many forensic toxicology laboratories. Laser diode thermal desorption coupled with high-resolution, accurate-mass mass spectrometry was evaluated to support this application. Sample analysis with LDTD is on the order of seconds as opposed minutes for LC/MS, allowing for rapid generation of results. Since chromatographic separation is eliminated by using LDTD, HRAM adds the selectivity required to analyze compounds all simultaneously introduced in to the MS by the LDTD source.
The question investigated in this study was whether LDTD can offer limits of detection comparable to a traditional LC/MS approach and compatible with the required cutoffs for urine screening.

Method

Samples were prepared by enzymatic hydrolysis followed by liquid-liquid extraction. Calibration standards in the range of 1 to 1000 ng/mL and controls at 10, 25, 50 and 100 ng/mL were prepared in negative urine. A 96-well LazWell plate was prepared by depositing 5 µL of an EDTA solution onto the plate and drying. Then 5 µL of the organic supernatant was aliquoted onto the same plate and again dried. Samples were introduced in the quadrupole-orbitrap mass spectrometer by thermal desorption from the plate using a LDTD source. The method was evaluated by analyzing calibration curves and replicate quality control samples. Additionally, donor samples were analyzed and the results were compared to data generated using a conventional HPLC approach.

Results

Required quantitation limits were achieved or surpassed for all compounds tested and ranged from 1 to 10 ng/mL. Controls show acceptable accuracy and precision within 30% for this screening method. Matrix effects were limited. Comparison of results of donor samples with traditional LC-MS method gave $R2>0.9$ indicating good agreement.

Conclusions

Limits of quantitation obtained with LDTD are sufficient for a quantitative screening method. LDTD is environmentally friendly since it uses no LC solvents and thus generates no LC waste. The APCI ionization mode of LDTD limits matrix effect in samples. LDTD offers a fast, accurate, and reproducible way of screening drugs of abuse in urine for forensic toxicology.

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Radiofrequency Ablation of the medial nerves: Does the pre-operative use of Gabapentin reduce postoperative nerve pain? Susan L. Varner, DNP, APRN-BC, FNP-BC and Cynthia A. Leaver, PhD, APRN-BC, FNP-BC

Susan Varner, Cynthia Leaver
Brandman University, Irvine, CA, USA

Purpose

80% of all Americans will suffer from some type of neck or back pain sometime in their lives. The pathology associated with back and neck pain is variable. The pain originating from the facets is treated by Radiofrequency Ablation (RFA) of the medial nerves. Although RFA can provide 6-24 months of improved pain relief, 30% of RFA patients will suffer from postoperative neuritis. The purpose of the study is to determine if Gabapentin used prior to RFA could reduce the incident of postoperative neuritis. Gabapentin is commonly used to treat neuropathic pain. Gabapentin is a pharmaceutical drug which specifically mimics the cell structure of a neurotransmitter Gamma-Amino Butyric Acid (GABA) which acts in an inhibitory manner to reduce nerve excitability. This study asks the following research questions: Did the RFA procedure reduce postoperative pain?; Is there a relationship between preoperative Gabapentin use and postoperative neuritis?; What is there an association between preoperative Gabapentin use and postoperative neuritis?; Is the association between preoperative gabapentin and postoperative neuritis a dose dependent association?; and, Did gender or age influence the onset of postoperative neuritis after RFA?

Method

This study implements is a pre-treatment and post-treatment retrospective chart review of clinical outcomes in patient who have had RFA of the medial nerves of either cervical or lumbar spine, at regional clinic for over a six month period of time. The following variables were identified: the underlying diagnosis of facet pathology; if preoperative Gabapentin use and dose; and postoperative results with subjective description of pain (burning, tingling pain) and any postoperative symptoms described by the patient. All patients' records were reviewed one month post procedure for symptoms associated with post-operative neuritis.

Results

Two Hundred charts were reviewed (N=200), three patients were lost to follow-up. A total of n=97 charts were reviewed. Females n=119 (64%), Males n=79 (39.6%), Median Age=52 with a Standard Deviation of (SD) 11yrs. Using an analogy pain scale from 1-10, the number 10 being the worse was used to compare Pre and Post pain after RFA. A two 2-tailed Wilcoxon was used to relate the findings. The pain before RFA was 7 and after the procedure 4. 48 patients reported having zero pain after RFA. Using a Standard X2 Analysis with Yates Corrected, 49 patients who were not on gabapentin did not develop neuritis; whereas, 127 patients on gabapentin did not develop neuritis. The findings showed a statistically significant relationship (P=0.0001) between the use of gabapentin and onset of postoperative neuritis. A Linear regression reflected a negative directional relationship, meaning as the dosage of Gabapentin increased, the incident of neuritis decreased. A Fisher's exact t-test was used to calculate if there was an association between the different pre-RFA gabapentin doses and post-operative pain. Those patients not on gabapentin, 53.19% developed neuritis verses 31.82 % those patients on at least 900mg of Gabapentin per day developed neuritis. This was a 22.38% decreases in postoperative neuritis. A multiple linear regression analysis showed no relationship with age or gender with the incident of postoperative neuritis; however, there was a near statistical significances with age with a P=0.0654.

Conclusions

Patients reported lower pain levels after RFA procedures compared before RFA procedures. The statistic found a significant association was identified between the preoperative use of gabapentin and postoperative neuritis. This would suggest Gabapentin plays role in reducing postoperative neuritis after RFA. A reduction of postoperative neuritis can have an additive effect of improved patient outcomes with a faster recovery and return to work, and a reduction in additional medical expenses associate with postoperative complications.

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Efficacy and Safety of Methylnaltrexone for Opioid-Induced Constipation in Patients With Chronic Noncancer Pain: A Placebo Crossover Analysis

Eugene Viscusi[1], Andrew Barrett[2], Craig Paterson[2], William Forbes[2]
[1]Thomas Jefferson University, Philadelphia, Pennsylvania, USA, [2]Salix Pharmaceuticals, Inc., Raleigh, North Carolina, USA

Purpose

In patients with chronic noncancer pain, efficacy of subcutaneous methylnaltrexone for treatment of opioid-induced constipation (OIC) was examined in a 4-week, randomized, controlled trial (RCT; ClinicalTrials.gov identifier: NCT00529087), followed by an 8-week open-label extension (OLE) phase. The current analysis evaluated the reproducibility of findings from the RCT by examining data from patients treated with placebo who crossed over to methylnaltrexone in the OLE.

Method

Adults who were taking ≥50 mg oral morphine equivalent/day who had OIC were randomized to receive methylnaltrexone 12 mg or placebo for 4 weeks followed by open-label methylnaltrexone (as needed) for 8 weeks. OIC was defined as an average of <3 rescue-free bowel movements (RFBMs; bowel movement[s] occurring without any laxative during the previous 24 hours) per week, associated with ≥1 of the following: hard or lumpy stools, straining during bowel movements, or a sensation of incomplete evacuation after a bowel movement. Patients were evaluated during both the RCT and OLE phases according to: 1) RFBMs within 4 hours of the first dose; 2) percentage of injections resulting in any RFBM within 4 hours; and 3) percentage of patients experiencing ≥3 RFBMs/week and 1 RFBM increase from baseline in weekly rate. This study was approved by institutional review boards and ethics committees.

Results

Of the 162 patients who had received placebo in the RCT, 134 patients (median morphine equivalent dose, 150 mg/day) were enrolled in the OLE and crossed over to methylnaltrexone treatment. The predominant primary pain condition was back pain, and patients reported a mean of 1.1 RFBM/week at baseline. During placebo treatment in the RCT, 9.7% of patients experienced an RFBM within 4 hours of first dose, and 9.0% of all placebo injections resulted in any RFBM within 4 hours. By contrast, during methylnaltrexone treatment in the OLE, 45.9% of patients experienced an RFBM within 4 hours of the first dose, and 34.5% of all methylnaltrexone injections resulted in any RFBM within 4 hours. When expressed according to percentage of patients experiencing ≥3 RFBMs/week and ≥1 RFBM increase over baseline, weekly values ranged from 35% to 41% during placebo treatment in the RCT, suggesting there was an absence of patients developing tolerance to OIC over time while on placebo (ie, no active treatment for OIC). However, with methylnaltrexone treatment, this percentage increased to >70% within the first week of the OLE and remained relatively stable throughout the OLE. The most common adverse events during methylnaltrexone treatment in OLE versus during placebo treatment in RCT, respectively, were abdominal pain (9.7% vs 1.5%), nausea (5.2% vs 6.7%), and urinary tract infection (5.2% vs 1.5%).

Conclusions

Findings during placebo treatment further establish the profile of OIC and support that little or no gastrointestinal tolerance develops over time with continued use of opioids. Findings under open-label conditions establish the reproducibility and durability of methylnaltrexone for the treatment of OIC.

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Pregabalin in fibromyalgia patients taking antidepressant medication for comorbid depression: A comprehensive overview of a randomized, two-way crossover, double-blind, placebo-controlled study

Richard Vissing[1], Jaren Landen[2], Pritha Bhadra Brown[3], Joseph Scavone[2], Andrew Clair[3], Lynne Pauer[2]
[1]Pfizer Inc, Louisville, KY, USA, [2]Pfizer Inc, Groton, CT, USA, [3]Pfizer Inc, New York, NY, USA

Purpose

Fibromyalgia (FM) is characterized by widespread pain and tenderness, often accompanied by other symptoms including disrupted sleep and fatigue. Depression is a frequent comorbidity in patients with FM, and many of these patients take antidepressant medication for their depression. How to manage FM pain in these patients is an important clinical question. Pregabalin is an approved treatment option for FM. Previous trials of pregabalin required patients to discontinue antidepressant medication prior to enrolment. Therefore the efficacy and safety of pregabalin has not been evaluated in FM patients taking antidepressants for comorbid depression in a controlled clinical environment. Here, we provide a comprehensive overview of results from a Phase 3b, randomized, two-way crossover, double-blind, placebo-controlled study of pregabalin in FM patients taking a selective serotonin reuptake inhibitor (SSRI) or a serotonin/norepinephrine reuptake inhibitor (SNRI) for comorbid depression.

Method

Men and women with FM were aged ≥18 years and at randomization had a mean pain score ≥4 on an 11-point numeric rating scale (NRS), based on the mean of the last 7 days. Treatment was for two 6-week periods separated by a 2-week, single-blind taper/washout phase. Patients were randomized 1:1 to pregabalin/placebo or placebo/pregabalin. Pregabalin (twice-daily allocation) starting dose was 150mg/d, optimized to 300 or 450mg/d during the first 3 weeks of each treatment period and then maintained at this level for the remaining 3 weeks. Patients had a documented diagnosis of major depressive disorder (MDD), dysthymia or depression not otherwise specified (NOS). Patients were taking either a single SSRI or SNRI for ≥3 months and at a stable dose for ≥2 months prior to randomization. Antidepressant medication was continued throughout the study. The primary efficacy endpoint was mean pain score. Secondary endpoints included: number of 30% and 50% pain responders; Hospital Anxiety and Depression Scale-Anxiety and -Depression (HADS-A and HADS-D) scores (range 0-21, higher scores indicating more severe anxiety/depression); Fibromyalgia Impact Questionnaire (FIQ) total score (range 0-100, higher scores indicating greater impairment) and subscale scores; and Subjective Sleep Questionnaire (SSQ), including sleep quality based on an 11-point NRS (higher scores indicating better sleep quality). A post-hoc analysis of the proportion of Patient Global Impression of Change (PGIC) responders (very much or much improved) at endpoint was also performed. Adverse events (AEs) were reported throughout the duration of the study.

Results

197 patients were randomized; 181 received ≥1 dose of pregabalin and 177 placebo. 93.3% were women and the mean (SD) age was 50.1 (10.0) years. At baseline, 84 (43.5%) patients had MDD, 101 (52.3%) depression NOS and 8 (4.2%) dysthymia; 101 (52.3%) patients were taking an SSRI and 92 (47.7%) an SNRI. Mean (SD) HADS-A and HADS-D scores were 8.3 (3.9) and 8.0 (3.6), indicating mild anxiety and depression, respectively, and mean (SD) pain score was 6.7 (1.2), indicating moderate pain. At endpoint, mean pain scores were significantly ($P<0.05$) lower with pregabalin compared with placebo (treatment difference –0.61; 95% confidence interval [CI] –0.91, –0.31). Pregabalin also significantly lowered mean pain scores in those taking an SSRI (difference –0.48; 95% CI –0.89, –0.07) or an SNRI (difference –0.76; 95% CI –1.21, –0.31). Significantly more pregabalin- than placebo-treated patients were 30% (45.3% vs. 27.7%) and 50% (26.0% vs. 15.8%) pain responders. Compared with placebo, pregabalin also significantly improved HADS-A score (difference –0.95; 95% CI –1.40, –0.50), HADS-D score

(difference –0.88; 95% CI –1.37, –0.39), FIQ total score (difference –6.60; 95% CI –9.33, –3.87) and all subscale scores, and sleep quality (difference 0.57; 95% CI 0.31, 0.84). Significantly more patients were PGIC responders with pregabalin (49.1%) than placebo (32.2%). Discontinuation rates owing to AEs were 6.1% and 3.4% with pregabalin and placebo, respectively. 4 serious AEs were reported, 3 (1.7%) with pregabalin and 1 (0.6%) with placebo, but none were considered related to treatment. The most frequently reported AEs with pregabalin compared with placebo were dizziness (28.2% vs 6.8%), somnolence (19.9% vs 4.5%), and constipation (10.5% vs 2.3%).

Conclusions

Pregabalin significantly reduced pain severity compared with placebo in patients with FM taking either a single SSRI or SNRI for comorbid depression. In addition, pregabalin reduced pain severity irrespective of the type of antidepressant taken. Pregabalin also significantly improved anxiety and depressive symptoms, patient function and global status, and sleep quality. The safety profile of pregabalin was consistent with previous studies and current product labelling. Pregabalin may be a treatment option for FM patients currently taking antidepressant medication for comorbid depression.

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Epidemiology of Conditions Associated with Pain and the Use of Analgesic and Non-Analgesic Treatments in Pediatrics

Laura Wallace, Stacy Baldridge, Rayna Matsuno
Purdue Pharma LP, Stamford, CT, USA

Purpose

The published medical literature does not contain many estimates of the prevalence of conditions associated with pain in pediatric patients nor does it have much data on the use of outpatient analgesic and non-analgesic treatments for pediatric pain based on large, real-world, generalizable samples. Previous work has characterized pediatric opioid use, but has not evaluated the overall pediatric pain landscape or characterized non-opioid treatments of pain in children. A better understanding of the pattern of conditions associated with pain in children, the characteristics of these patients, and the ways in which such pain is being managed can help to inform provider education, treatment guidelines, and the design of pediatric pain studies.

The objectives of this study were:

1. To estimate the prevalence of conditions associated with acute and chronic pain in pediatric patients.
2. To describe the demographic and clinical characteristics of pediatric patients with medical conditions associated with pain.
3. To characterize the use of various pharmacological treatments, including both analgesics (NSAIDs, COX-2 inhibitors, and opioids) and non-analgesics (anticonvulsants, muscle relaxants, antidepressants, and topical treatments), for conditions associated with pain.
4. To provide a contrast of the prevalence and treatment of conditions associated with pain in pediatric patients with Commercial vs. Medicaid insurance.

Method

This study was a descriptive retrospective cohort study using data from the MarketScan Commercial and Medicaid databases for 2009-2012. These databases contain demographic, prescription, diagnosis, and procedure data on over 25 million pediatric patients. A list of conditions associated with pain was developed in consultation with experts on pediatric pain; it included a wide variety of conditions known to be associated with acute or chronic pain. These conditions were grouped into categories including: orthopedic conditions, malignancies, surgeries, trauma, genetic conditions, and other painful conditions, such as arthritis and migraine.
Descriptive statistics were used to assess: the prevalence of each of the conditions over one year, patient medical and demographic characteristics, the proportion of patients receiving various drugs used to treat pain (including NSAIDS, COX-2 inhibitors, immediate-release or extended-release opioids, and non-analgesics, such as anticonvulsants and muscle relaxers),and the treatment duration for each of the treatments. All analyses were stratified by insurance type, underlying medical condition, and demographics (eg, age group 0-5, 6-11 or 12-16).

Results

This study included data on 25.5 million pediatric patients from throughout the United States. Of these children, 1% had orthopedic conditions, 1.8% malignancies, 0.3% surgeries, 3.5% trauma, and 0.7% genetic conditions associated with pain; 8.7% of patients had a specific diagnosis of pain. These diagnoses varied by age, with most showing higher prevalence in older children. Treatment varied substantially by condition, and many (>50% in for most of the

conditions evaluated) children did not receive any prescription pain treatments. Overall, IR opioids were used in 17.7% of pediatric patients with conditions associated with pain, compared to ER opioids in 0.1%, NSAIDS in 7.5%, antidepressants in 4.0%, anticonvulsants in 2.0%, topical treatments in 1.4% and glucocorticoids in 4.9%. For both Commercially-insured and Medicaid patients using prescription opioids, IR opioids were the most commonly used analgesic treatment for pain, with use more common in the Medicaid population: in Commercially-insured patients, IR opioid use ranged from 14.8% among surgery patients to 27.3% among patients with orthopedic conditions, while in Medicaid patients it ranged from 25.8% among surgery patients to 45.3% among patients with orthopedic conditions; ER opioids were very seldom used in pediatric patients, regardless of diagnosis. The types of analgesic and non-analgesic treatments used in pediatric patients with pain-associated conditions varied substantially by condition and the age of the patient, with the highest prevalence of pharmacological treatment use in older children. The duration of prescriptions also varied by drug and condition. The majority of analgesics were prescribed for <30 days, while non-analgesics had longer durations of use. For example, in Commercially-insured patients, IR opioids were used for <30 days in 97.7%, compared to 48.3% for non-analgesics.

Conclusions

Conditions associated with pain in children are relatively common, but children do not always receive pharmacologic treatment for these conditions. Outpatient analgesic treatments for pain are prescribed in less than half of patients; this proportion varies substantially by condition, insurance type, and the age of the patient. Outpatient non-analgesic treatments were used slightly more frequently than opioid analgesics; the extent of their use varied by condition and insurance type. Duration of use for non-analgesic treatments was generally less than 60 days.

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Analysis of Pre-Screening Data from Pediatric Pain Trials

Laura Wallace, Eduardo Rodenas, Rayna Matsuno, Aditi Kadakia
Purdue Pharma LP, Stamford, CT, USA

Purpose

It is customary to present descriptive characteristics of subjects in clinical trials. For trials in rare or difficult to access populations, such as pediatric patients with pain severe enough to require treatment with opioids, it can also be informative to describe the characteristics of patients who were ineligible for a study or did not consent to participate. This information can help investigators and clinicians to better understand the study's context and generalizability to the underlying patient population, as well as to inform future studies within the same population.
The population of interest for this study was pediatric pain patients age 6-16.

The primary objectives of this study were to:

1. Describe the demographic and clinical characteristics and pre-study treatments of pediatric pain patients who did and did not enroll in an opioid clinical trial.
2. Describe reasons for ineligibility or non-consent among patients who did not enroll.

Method

The clinical trial included centers in 14 countries including Belgium, Estonia, Finland, Germany, Greece, Guatemala, Hungary, Israel, New Zealand, Poland, Romania, Spain, the United Kingdom, and the United States. Data were collected on patients who underwent pre-screening assessments to determine whether or not they were eligible to enroll in the study. Based on these pre-screening data, we used descriptive statistics to evaluate the demographics (age and sex), prior treatments (including drug, dose, and duration of use), patient characteristics (including opioid tolerance and ability to swallow tablets) and medical conditions of patients pre-screened for inclusion in the trial. Pain conditions of interest included: acute pain, chronic pain, burn, surgery, trauma, genetic condition, malignancy, orthopedic condition, other pain, and not specified. All analyses were stratified by whether or not patients went on to enroll in the study.

Results

A total of 1811 pediatric pain patients were pre-screened; 123 were enrolled into the trial and 1688 were ineligible or did not consent. Enrolled and non-enrolled patients differed with respect to age, sex, pain condition, and opioid use. Subjects who enrolled were older (mean age 13.7, SD=2.3) than patients who did not enroll (mean age 12.7, SD=3.8). There were slight differences between those who enrolled and those who did not by sex; the majority of enrolled subjects were female (55.5%), while the majority of patients who did not enroll were male (52.5%). The top three pain-related conditions among enrolled subjects were malignancy (25.2%), orthopedic conditions (15.5%), and surgery (14.6%); for those who did not enroll they were malignancy (15.4%), surgery (13.9%), and trauma (9.4%). Oxycodone was the most commonly used opioid (61.7% in enrolled, 66.0% in non-enrolled), followed by morphine (8.5% and 13.4%, respectively) and hydrocodone. The duration of opioid therapy differed between patients who enrolled and those who did not; 24.5% of those who enrolled used opioids for < 7 days and 64.9% for ≥ 28 days; for non-enrolled the percentages were 54.9 and 37.3%, respectively. Non-enrolled patients were more commonly on lower doses than those who enrolled.

The most common reason for not participating in the trial were the failure to meet inclusion criteria specifying opioid needs (including requirements for dose and expected duration of use), which was cited for 44.6% of those who were pre-screened but did not enroll. Other common reasons for not participating were the age requirement of 6 to 16 years , opioid tolerance requirements, inability to swallow tablets, and use of epidural opioids prior to dosing with study drug.

Conclusions

A very large population of patients needed to be pre-screened to find sufficient patients to enroll in a pediatric opioid trial. Only about 7% of those screened were eligible and willing to be included in the trial. The high numbers of required pre-screens to reach enrollment goals reinforce the difficulty of doing pediatric research in pain. Patients who enrolled in the study were older, more commonly female, had different pain conditions and greater pain treatment requirements compared to those who did not.

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The Risk of Cardiovascular Events in Opioid Agonist/Antagonist Combination Products Compared to Other ER Opioids

Laura Wallace[1], Chuck Wentworth[2], Nelson Sessler[1], Paul Coplan[1]
[1]Purdue Pharma LP, Stamford, CT, USA, [2]Analytic Consulting Solutions, Wakefield, RI, USA

Purpose

There have been theoretical concerns among regulatory agencies that peripheral mu opioid antagonists might increase the risk of cardiovascular events. These concerns are based on potential effects of opioid withdrawal on the autonomic nervous system, including changes in hemodynamic parameters, that could increase the risk of cardiovascular events in susceptible patients.

In addition to single-entity opioid antagonists, such as naloxone and naltrexone, antagonists are also used in combination with opioid agonists. For example, an extended-release (ER) combination of oxycodone and naloxone is currently approved in the United Kingdom (UK). Because of the concerns about single-entity opioid antagonist effects on cardiovascular events, it is also of interest whether agonist/antagonist combination products might precipitate opioid withdrawal and thus increase the risk of cardiovascular (CV) events. However, there is little literature to support or refute this. This study was conducted to estimate the risk of CV events in patients prescribed ER oxycodone/naloxone (OXN) compared to those prescribed single entity ER oxycodone (OXY) or ER morphine (MOR) using healthcare utilization data from the UK THIN database.

The objectives of this study were:

1. To characterize the incidence rate of ischemic cardiovascular events among patients prescribed ER opioid agonist and agonist/antagonist products in the UK.
2. To compare CV event rates between different types of ER opioids: ER oxycodone/naloxone (OXN), ER oxycodone (OXY), or ER morphine (MOR), stratified by and adjusted for age, sex, duration of use, and select medical comorbidities

Method

This was a retrospective cohort study of patients prescribed select ER opioid analgesics who were treated in general practices participating in THIN, an anonymized patient record database containing data from over 450 medical practices covering more than 7.5 million patients in the UK, between January 2005 and August 2012. These patients needed to be free of a history of major cardiovascular events (stroke or MI) during the time period prior to their index date (defined as the first prescription for one of the three study drugs- ER oxycodone/naloxone, ER morphine, or ER oxycodone). THIN data include demographics, medical diagnoses, and prescriptions.

Incidence rates of CV events (including major events and all ischemic events) per 100 patient-years of treatment were calculated for patients prescribed OXN, MOR or OXY. Ischemic cardiovascular events were grouped into two categories. Major adverse cardiovascular events (including stroke, myocardial infarction, and cardiovascular death) and all ischemic cardiovascular events (including both those in the 'major events' category and others, such as transient ischemic attack, coronary artery bypass, and angina). : Incidence was stratified by age and sex. Multivariate Cox proportional hazard modeling was performed to compare CV event rates in patients prescribed OXN compared to MOR and OXY, adjusted for age, sex, duration of opioid use, and select medical comorbidities (such as history of hypertension , hyperlipidemia, obesity, and diabetes).

Results

The study included 46,883 patients without a history of major CV events: 2,343 were prescribed OXN, 32,031 were prescribed MOR, and 12,509 were prescribed OXY. The median duration of use was 41 days for OXN and 62 days for both MOR and OXY. There were 14, 280, and 98 major CV events in the OXN, MOR and OXY groups, respectively. All ischemic CV event numbers were: 38, 715, and 285 for the OXN, MOR and OXY groups, respectively. Older patients were well represented in the sample, with 43.9%, 51.8% and 43.9% over age 65 for OXN, MOR and OXY respectively. Risk factors for CV events, such as hypertension, diabetes, and hyperlipidemia, were common in all three treatment groups.
The incidence of major events was low and similar across all treatment groups, at 1.26 per 100 patient-years for OXN, 1.38 for MOR, and 1.14 for OXY. Rates varied by age, sex, and duration of use. Hazard ratios (HR) were adjusted for age, sex, comorbidities, concomitant medications, and duration of use. The adjusted HR comparing OXN with MOR was 0.97 (95% CI: 0.7-1.4) for any CV events and 0.86 (95% CI: 0.5-1.5) for major events. The adjusted HR comparing OXN with OXY was 0.99 (95% CI: 0.7-1.4) for any CV events and 1.34 (95% CI: 0.8-2.4) for major events. Similar patterns were seen for OXN compared to the other drugs for the 'all ischemic cardiovascular events' category.

Conclusions

No significant differences in CV risk were observed among patients prescribed the opioid agonist/antagonist combination product (oxycodone/naloxone) vs. those prescribed ER morphine or ER oxycodone in a relatively large sample of patients without pre-existing history of major cardiovascular events who were prescribed OXN, MOR, or OXY in the United Kingdom.

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Assessment of Hospice Healthcare Professionals' Preferences Regarding a Drug Reference Guide for Parenteral Medication Administration

Hsiao-Ting Wang[1], Lynn McPherson[1]
[1]University of Maryland Medical Center, Baltimore, MD, USA, [2]University of Maryland School of Pharmacy, Baltimore, MD, USA

Purpose

Parenteral routes of administration such as intravenous (IV), subcutaneous (SC), intramuscular (IM) remain an important way to deliver medications in the hospice patient population. The selection of a proper route of administrations is important due to the nature of terminal illness and the frailty of this patient population. Existing drug reference textbooks or online databases are available to provide information on how to handle parenteral medications bu each with a different focus. IF a medication is not formulated or not FDA-approved in a route of administration desired by healthcare providers, other strategies such as primary literature research or anecdotal user experience will then be considered. The search process can be time-consuming and the result from anecdotal experience can be lack of scientific evidence. Currently, there is no literature describing the needs of a drug reference guide for parenteral medication administration in hospice care. Our study aims to assess the preferences of hospice healthcare professionals regarding the development of such drug reference guide, and also what are the most clinically relevant pieces of information to be included.

Method

A single-center, voluntary and anonymous electronic survey was conducted through an online survey system. Physicians and nurses who work at the inpatient hospice units operated by a national hospice program, were contacted as a group by emails, inviting them to participate in this voluntary and anonymous survey. People who are not working at the inpatient hospice units operated solely by this national hospice program regardless of their profession were not invited to participate; therefore were excluded. A total of twelve questions were included in the survey. Response rate was calculated based on the number of respondents and the number of people that the survey was sent to on the list. Descriptive statistics was used to summarize the characteristics of participants, and the characteristics of these in- patient hospice units at which they work. In order to assess baseline user behaviors, participants were asked to provide information on current search strategy regarding finding alternative routes of parenteral medication administration. Participants were also asked to provide preferences on the format, and any clinically relevant pieces of information that they deem necessary to be included in a potential drug reference guide that is better tailored to hospice care. The study was approved by the University of Maryland Institutional Review Board.

Results

Forty-eight hospice healthcare professionals responded to the survey. The majority respondents were nurses, followed by physicians and nurse practitioners. Eighty percent of respondents worked in an in-patient hospice unit with 11 to 20 beds, and over seventy percent of respondents reported that at least 75% of beds in their inpatient hospice units were general inpatient level of care. Nearly half of hospice patients at the surveyed institution required parenteral medications 50% of the time during their stay, and hospice healthcare providers were often required to search for information on parenteral drug administration at least on a weekly basis. Compatibility was the most common information searched, which was consistent with prior literature, but information on dosage, dosage forms, dosing intervals, and adverse reactions associated with parenteral drug therapy were also among the top five drug information questions. When such questions arose, hospice healthcare providers often consulted with other healthcare

professionals, most frequently, pharmacists, or resorted to readily-available drug reference guides, either from an electronic database or a nursing textbook. "Drugs.com" was the most commonly used electronic resource, followed by "Medscape", and then "Micromedex." Only one respondent listed "PubMed", a primary literature search engine, as the most common way to look for drug information. For textbook references, nursing drug reference was the most commonly used.

Of the twenty pieces of pre-determined drug information relating to parenteral administration listed for respondents to rank from extremely important or relevant to not at all important or relevant., most respondents selected "recommended dose of medication" as extremely important or relevant, as well as "recommended administration rate, dosing intervals, FDA-approved routes of administrations and compatibility with other medications." Finally, both in-print and electronic with searchable features were the two most desirable formats of a potential drug reference guide.

Conclusions

The need for a hospice-specific drug reference guide on parenteral medication administration is evident. The clinically relevant pieces of information desired to be included in such drug reference guide match with the drug information questions that hospice healthcare providers often need to search for. The preferred format also reflects current user behaviors- electronic or paper based. Understanding the preferences of end users, we can now utilize the results of the survey to construct the proposed drug reference guide. We expect this hospice-specific drug reference guide on parenteral medication administration will help clinicians in providing safe and effective therapeutic management.

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Identification and Resolution of Actual and Potential Drug Related Problems in a Hospice Population

Hsiao-Ting Wang[1,2], Lynn McPherson[2], Joy Chou[2,3], Erin McCartin[2]
[1]University of Maryland Medical Center, Baltimore, MD, USA, [2]University of Maryland School of Pharmacy, Baltimore, MD, USA, [3]Martinburg VA Medical Center, Martinsburg, WV, USA

Purpose

Medicare and other payers have set regulations for hospice programs to ensure proper care of patients at the end of life, referred to as the "Hospice Conditions of Participation (CoP's)." One requirement in this regulation requires a comprehensive medication review for every patient admitted to hospice, including a detailed review of all prescription and non-prescription medications and herbal remedies. The CoP's stipulate that the review needs to be done by an individual who is educated and trained in drug therapy management. Since 2008 when this regulation was enacted, there has been little published on the type of drug-related problems identified on these requisite medication regimen reviews, or the outcome of the recommendations made. At the Hospice of Chesapeake, a local hospice system in the state of Maryland, a clinical pharmacist reviewed the medication regimen for all patients admitted to the hospice program, and generated clinical pharmacy note identifying actual or potential drug related problems, and suggested recommendations. This note was then entered into the patient's electronic medical record and accessible to the nurse case manager, who was responsible for reacting to the note and documenting outcomes as appropriate. Our study aimed to characterize the types of these drug-related problems identified, and examine the actions taken in response to the recommendations, including the percentage of nursing notes acknowledging the recommendations and the percentage of recommendations implemented.

Method

A preliminary, retrospective chart review was conducted. Patients admitted during the first full weeks of January, April, July and October 2011, who were discharged by death, were included. Drug-related problems as reported by the clinical pharmacist were tabulated and categorized into 11 pre-determined categories: drug use without indication, need for additional drug therapy, inappropriate drug selection, overdosage, underdosage, adverse drug effect, drug interaction, failure to receive or take drug therapy, drug allergy implications, formulary issues, and laboratory monitoring. Recommendations were also noted either be consultative (e.g., a potential drug related problem) or specific (e.g., an actual drug related problem). Demographic information collected included patient age, gender, admitting diagnosis and number of comorbid medical conditions.

A secondary analysis was conducted on the first patient assigned to each nurse employed by the hospice in each of the quarters. Only patients who lived at least five days after admission and were discharged by death prior to data collection were included. For each drug-related problem identified by the pharmacist, an analysis of subsequent action steps was conducted. This included any documentation in the nurses notes regarding the recommendations, and eventual changes to the medication regimen consistent with the recommendations. The study was approved by the University of Maryland Investigational Review Board.

Results

150 clinical pharmacy notes were written during the four study week periods. Of this cohort, 62% of the patients were female, and the average age of all patients was 76.5 years. Cancer was the primary admitting diagnosis. A total of 386 drug-related problems were identified; 340 (88%) were consultative and 46 (12%) were specific. Overdose was the most common problem identified (44%), followed by drug without indication (41%), formulary

issues (8%), inappropriate drug selection (3%), drug allergy implications (2%), underdose (1%), drug interaction (1%), and need for additional therapy (<1%).

Secondary analysis included 45 patients with demographics consistent with the larger cohort. A total of 183 drug-related problems were identified; 165 (90%) consultative and 18 (10%) specific. A total of 111 (61%) of drug related problem recommendations were accepted, and changes were made to the drug regimen. However, only 40% of drug-related problems were documented in nurses notes.

Conclusions

The patient population studied was representative of the hospice population served by this program. The potential drug-related problem of medication overdose was the most frequently identified problem (e.g., antihypertensive and antidiabetic medications). Over 60% of the recommendations to reduce or stop these medications were implemented. Drug use without indications (e.g., supplements) was also a large category of the identified drug-related problems. Over half of these recommendations were accepted. One area of improvement is nursing documentation in acknowledgement of the drug-related problems identified and resolution of such problems. This will require education on documentation and IT system change as deemed necessary.

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Intranasal Human Abuse Potential of a Novel Abuse-deterrent Extended-release Formulation of Morphine

Lynn Webster[1], Carmela Pantaleon[2], Manish S Shah[3], Ray DiFalco[3], Matthew Iverson[2], Michael D Smith[1], Eric R Kinzler[2], Stefan Aigner[2]
[1]PRA Health Sciences, Salt Lake City, Utah, USA, [2]Inspirion Delivery Technologies LLC, Valley Cottage, New York, USA, [3]Cerovene, Valley Cottage, New York, USA

Purpose

The misuse and abuse of opioid medications such as morphine continues to rise despite concerted efforts to increase public awareness and reduce drug diversion of prescriptions for nonmedical use. A variety of methodologies have been employed to decrease the overall abuse potential of prescription opioids. These include incorporating opioid antagonists or aversive agents that are exposed only upon intentional manipulation, pro-drugs that are only activated via the intended route of administration, and incorporation of physiochemical barriers to increase the hurdles in preparing the formulation for misuse and abuse. Although each approach has unique benefits and drawbacks, many simply incorporate physical barriers to minimize legitimate patients' exposure to nontherapeutic agents. Because higher C_{max} and shorter T_{max} are associated with more liking and euphoria, abusers commonly manipulate (crush) extended-release (ER) opioid formulations to alter the sustained-release properties to increase bioavailability of the opioid. Following manipulation, the intranasal route of administration is widely used by opioid abusers because of its rapid delivery and lack of first-pass metabolism for some opioids (eg, morphine). A novel formulation of an ER morphine sulfate tablet using an abuse-resistant (ARER) technology has been developed to resist physical manipulation, retain its ER characteristics even if manipulated, and form a non-syringeable gelatinous mass in aqueous environments to provide barriers to the routes of administration that are common for abuse of morphine. To assess whether these physiochemical barriers have the potential to reduce drug liking in human subjects, an intranasal drug liking study was performed in recreational opioid abusers.

Method

A randomized, double-blind, double-dummy, placebo-controlled, 4-way crossover study evaluated the abuse potential and safety of equivalent doses of crushed intranasal and intact oral Morphine ARER (Inspirion Delivery Technologies, LLC, Valley Cottage, NY) compared with a commercially available controlled-release morphine sulfate (CR-morphine) formulation in nondependent, recreational opioid users. The study consisted of a naloxone challenge test, a drug discrimination test to ensure participants could tolerate the dosage and accurately discriminate the drug, a treatment period, and a follow-up period. The treatment period consisted of a single dose of 4 treatments. Treatments included 60 mg of crushed intranasal Morphine ARER, intact oral Morphine ARER, crushed intranasal CR-morphine, and intranasal/oral placebo. The primary variable of interest was to determine the abuse potential of crushed intranasal Morphine ARER relative to crushed intranasal CR-morphine. Drug liking was measured on a 100-mm bipolar visual analog scale where 0 represents maximum disliking, 50 represents a neutral response of neither liking nor disliking, and 100 represents maximum liking. Secondary evaluations were also measured (eg, good effects of the drug, drug high, and take drug again). Safety assessments included adverse events (AEs), clinical laboratory assessments, 12-lead electrocardiograms, and physical examination findings.

Results

Forty-eight subjects entered and passed the naloxone challenge; of these, 27 passed the drug discrimination test, and 25 completed the treatment phase. There was a 45% reduction in maximum mean drug liking (E_{max}) for crushed intranasal Morphine ARER compared with crushed intranasal CR-morphine ($P < .0001$). There were 64% and 59% reductions in early drug liking (the area under the drug liking curve from 0 to 1 hour [AUE_{0-1}] and 0 to 2 hours [AUE_{0-}

$_2$]) when comparing crushed intranasal Morphine ARER with crushed intranasal CR-morphine (P = .0005 and P = .0199, respectively). There was no significant difference in E_{max}, AUE_{0-1}, or AUE_{0-2} when comparing crushed intranasal Morphine ARER with intact oral Morphine ARER. Most subjects (68%) experienced at least a 10% reduction in drug liking for crushed intranasal Morphine ARER compared with crushed intranasal CR-morphine. This trend continued with 56% of subjects experiencing at least a 30% reduction and nearly half of subjects (48%) experiencing at least a 50% reduction in drug liking. When comparing crushed intranasal Morphine ARER vs CR-morphine, subjects reported significantly lower desire to use Morphine ARER again compared with CR-morphine (P = .0341). Additionally, subjects reported significantly lower mean scores for crushed intranasal Morphine ARER for good effects of the drug (P = .0004), drug high (P = .0001) and overall drug liking (P = .007) compared with crushed intranasal CR-morphine. The most common AEs included nasal congestion, rhinorrhea, and epistaxis, all of which are associated with intranasal administration of a drug. Classic opioid-related AEs were observed including nausea, vomiting, and generalized pruritus.

Conclusions

In this well-controlled human abuse potential study, crushed intranasal Morphine ARER has significantly reduced maximum drug liking, early drug liking, and willingness to take drug again compared with crushed intranasal CR-morphine. These data suggest that Morphine ARER has a lower abuse potential via the intranasal route of administration. Drug liking for crushed intranasal Morphine ARER was not significantly different from intact Morphine ARER taken orally, suggesting similar abuse potentials between crushed intranasal and intact oral treatments. Other than AEs associated with intranasal administration, the safety profile of Morphine ARER was consistent with an opioid-containing drug.

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Efficacy and Safety of Once-daily Hydrocodone (Hysingla™ ER) in CLBP

Warren Wen[1], Steve Sitar[2], Shau Yu Lynch[1], Ellie He[1], Steven Ripa[1]
[1]Purdue Pharma L.P., Stamford, CT, USA, [2]Orange County Research Institute, Anaheim, CA, USA

Purpose

Immediate-release hydrocodone combination analgesics are frequently prescribed for the treatment of chronic pain. Because of the risks associated with nonopioid components of some of the combination products (eg, liver toxicity associated with acetaminophen), there is a medical need for a single-entity hydrocodone product. In the context of chronic opioid treatment, it was thought to be desirable to develop a formulation that also offers less frequent dosing than the IR analgesics. The objective of this study was to evaluate the analgesic efficacy and safety of single-entity, once-daily hydrocodone 20 mg to 120 mg tablets (HYD; Hysingla™ ER) in opioid-naïve and -experienced patients with uncontrolled moderate to severe CLBP. This product was formulated with abuse-deterrent properties.

Method

This multicenter, double-blind, placebo-controlled study employed an enriched enrollment, randomized withdrawal design. Out of 905 patients who were treated with HYD during the open-label titration period, 588 (65%) were randomized into the double-blind period to continue to receive HYD (N=296, 20-120 mg taken once daily, average daily dose 57 mg) or a matching placebo (N=292). Patients randomized to placebo were tapered off in a blinded taper with HYD according to a pre-specified tapering schedule, 3 days on each step-down dose (reduced by 25-50% from the previous dose). Patients were allowed to use rescue medication (immediate-release oxycodone 5 mg tablet) up to 6 doses (6 tablets) per day depending on their randomized dose level.

Results

The mean average daily pain scores (SE) (0-10 Numeric Rating Scale) in randomized patients were 7.4 (0.07) at screening and 2.8 (0.07) at pre-randomization (the beginning of the double-blind period) for both the HYD and placebo groups. During the double-blind period, 77% HYD-treated patients completed the 12-week treatment and 72% patients completed on placebo; 5% discontinued due to lack of therapeutic effect and 6% due to adverse events in the HYD group, and 15% discontinued due to lack of therapeutic effect and 3% due to adverse events in the placebo group. In the primary efficacy analysis, HYD demonstrated superior pain reduction over placebo at week 12 of the double-blind period ($P = .0016$); this result was supported by sensitivity analyses using different approaches to handling missing data. Proportions of patients achieving ≥ 30% and ≥ 50% improvement in pain from screening baseline also favored HYD over placebo ($P = .0033$ and .0025, respectively). HYD was generally well tolerated, with no new safety concerns.

Conclusions

HYD was shown to be an efficacious treatment for CLBP in this study. HYD was generally well tolerated. There were no new or unexpected safety concerns detected during the study.

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Evaluation of Once-daily Hydrocodone (Hysingla™ ER) in Patient Subgroups

Warren Wen, Shau Yu Lynch, Ellie He, Steven Ripa
Purdue Pharma L.P., Stamford, CT, USA

Purpose

Patients with chronic pain are a heterogeneous population with diverse demographic characteristics and medical conditions. It is important to understand how each of clinically relevant patient subgroups responds to and tolerates pain treatment with opioids. The objective of this study is to evaluate the treatment effectiveness and tolerability of single-entity, once-daily hydrocodone 20 mg to 120 mg tablets (HYD; Hysingla™ ER) in patient subgroups with moderate to severe chronic pain. This product was formulated with abuse-deterrent properties.

Method

This multicenter, open-label, long-term study enrolled patients with nonmalignant and nonneuropathic chronic pain which was either controlled or uncontrolled. Out of 922 patients who were treated with HYD during the dose titration period, 728 (79%) achieved a stable HYD dose and entered a 12-month maintenance treatment period (average HYD dose 65 mg). The study was designed to reflect pain practice in the community setting; short-acting opioid and nonopioid analgesics were allowed during the study. The patient population was categorized into clinically relevant subgroups based on their gender, age (<65 vs ≥65 years), baseline pain intensity (moderate pain <7 vs severe pain ≥7, 0-10 Numerical Rating Scale [NRS]), prior opioid experience (naïve vs experienced), psychiatric conditions (depression or anxiety vs not), HYD dose level at the end of titration (< 60 mg vs ≥ 60 mg), and baseline pain management (controlled or uncontrolled pain). The analgesic effect and effects on function and tolerability profile (opioid-related AEs) were evaluated for each subgroup.

Results

Across all investigated patient subgroups, clinically significant pain reduction from baseline was achieved with HYD treatment (at least 2 point on the NRS), with opioid-naïve patients, patients with severe pain (baseline average pain 7.9), or uncontrolled pain (baseline average pain 7.0) having even greater pain reduction, as expected; the only exception was in patients with controlled pain at baseline (baseline average pain 3.9) in whom 1 point reduction in pain was still observed. Similarly, there were significant improvements in patient's physical function and activities of daily living as measured by Brief Pain Inventory, SF-36, and MOS Sleep -R. These treatment effects were maintained throughout the 12-month treatment period. The tolerability profiles for all subgroups were as expected with no new or unexpected safety concerns.

Conclusions

HYD was shown to be an effective treatment in improving pain scores, physical function, and activities of daily living in clinically relevant patient subgroups. Each of the patient subgroups tolerated HYD well.

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Evaluation of once-daily hydrocodone (Hysingla™ ER) in users of immediate-release hydrocodone combination products

Warren Wen, Shau Yu Lynch, Ellie He, Steven Ripa
Purdue Pharma L.P., Stamford, CT, USA

Purpose

Immediate-release hydrocodone combination products have been frequently used to treat patients with chronic pain. These products present concerns to clinicians and at-risk patients because of the toxicities of their nonopioid components, primarily liver toxicity associated with acetaminophen. These concerns effectively impose a ceiling on the total daily dosage of such products. Furthermore, these products require dosing 4-6 times a day. Patients currently treated for their chronic pain conditions with hydrocodone combination products may benefit from switching to a single-entity (acetaminophen-sparing), extended-release hydrocodone analgesic. The purpose of this analysis was to evaluate the analgesic effectiveness and safety of single-entity, once-daily hydrocodone 20 mg to 120 mg tablets formulated with abuse-deterrent properties (HYD; Hysingla™ ER) in patients with moderate to severe chronic pain who transitioned from hydrocodone combination products.

Method

Data used in this post-hoc analysis were from two phase 3 studies: a 12-week, placebo-controlled, double-blind study, and an open-label, long-term study with a 12-month maintenance treatment period. The placebo-controlled, double-blind study evaluated the efficacy of HYD in patients who were treated with a hydrocodone combination product for their chronic pain prior to study participation; the analgesic efficacy variable was the patient's average pain in the last 24 hours score. The long-term study further examined the persistence of the analgesic effect of HYD in patients previously treated with a hydrocodone combination product. Safety of HYD in these patients was evaluated for both the placebo-controlled study and the long-term study. Treatment satisfaction with HYD treatment was examined.

Results

Among patients in the placebo-controlled study who had previously used hydrocodone combination products (N=129), HYD (N=62) demonstrated clinically meaningful and statistically significant pain relief at week 12 compared to placebo (N=67) in both primary and sensitivity analyses (Δ's=0.64 to 0.98; *P's* = .0078 to .0357). Among patients in the long-term study who had previously used hydrocodone combination products, clinically significant improvements from baseline in pain relief (eg, 30% reduction in pain) were achieved with HYD treatment, and these treatment effects were maintained throughout 12-month treatment period. The HYD doses during the 12-month maintenance treatment were stable and few patients required more than one dose level increase. The majority of patients (98%) found the once-daily HYD regimen more convenient relative to their incoming hydrocodone combination product regimen. The safety profiles, both when compared with placebo and in long-term treatment, were as expected and representative of that of full-mu opioid analgesics. No new or unexpected safety concerns were identified.

Conclusions

HYD was demonstrated to be a convenient and effective analgesic treatment in improving pain relief patients who had previously taken hydrocodone combination products. These patients tolerated HYD well and found the once-daily regimen with HYD more convenient.

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No Hearing Impairment from Once-daily, Single-entity Hydrocodone Treatment (Hysingla™ ER): Results of 2 Phase-3 Studies

J. Walter Kutz, Jr[1], Kathleen Campbell[2], Angela Shoup[1], Warren Wen[3], Shau Yu Lynch[3], Ellie He[3], Steven Ripa[3]
[1]University of Texas Southwestern Medical Center, Dallas, TX, USA, [2]Southern Illinois University, Glenarm, IL, USA, [3]Purdue Pharma L.P., Stamford, CT, USA

Purpose

Cases of sensorineural hearing impairment have been reported with the chronic use/overdose of hydrocodone/acetaminophen combination products. The specific agent (ie, either hydrocodone or acetaminophen) responsible for hearing impairment is unclear. Evidence from mouse model studies and prospective human studies has suggested acetaminophen as the primary ototoxic agent. Whether exposure to hydrocodone alone in humans results in sensorineural hearing impairment has not been established. This analysis evaluates the potential effect of a single-entity, once-daily, hydrocodone (20, 40, 60, 80, 120 mg/day) tablet (HYD; Hysingla™ ER) on hearing function during treatment of moderate-to-severe chronic pain in both opioid-naïve and opioid-experienced patients.

Method

Results from patients in a double-blind placebo-controlled study (consisted of a dose titration period and a 12-week double-blind period) and an open-label long-term safety study (consisted of dose titration period and a 12-month maintenance period) were integrated. Baseline hearing status of patients was established using a comprehensive audiologic assessment which consisted of air-conduction pure-tone audiometry, bone-conduction pure-tone audiometry, speech reception threshold, word recognition, and tympanometry assessments. Air-conduction pure-tone audiometry assessments were performed during HYD treatment and a comprehensive audiologic assessment was performed at the end of HYD treatment. All audiologic assessments were performed by licensed audiologists. The primary analysis of hearing function consisted of results from air-conduction pure-tone audiometry assessments in the conventional frequency range (500 Hz to 8,000 Hz). In this analysis, patients with worsening in hearing sensitivity is defined as those with air-conduction pure-tone audiometry thresholds meeting the American Speech-Language-Hearing Association (ASHA) criteria (ie, a threshold shift of ≥ 20 dB from baseline at one frequency and/or, a threshold shift of ≥ 10 dB from baseline at 2 adjacent frequencies, and/or loss of response in 3 or more adjacent frequencies where responses were present at baseline). To best understand the inherent variability of air-conduction pure-tone audiometry tests, improvement in hearing sensitivity was also analyzed, which is defined as those changes in air-conduction pure-tone audiometry thresholds meeting the ASHA criteria in the reverse direction.

Results

A total of 1207 HYD-treated patients were included in this integrated analysis. The study population was primarily white (74%) and < 65 years of age (88%); 58% of the study population were female and 53% were opioid experienced. A total of 431 patients had ≥ 3 months of exposure, 187 patients had ≥ 6 months of exposure, and 144 patients had ≥ 12 months of exposure. The mean (SD) cumulative number of days on HYD was 95 (120). The mean (SD) average daily HYD dose was 49 (27) mg. During the double-blind period of the placebo-controlled study, 292 patients and 296 patients were exposed to placebo and HYD, respectively. Race, age, gender, and prior opioid experience status were balanced between placebo- or HYD-treated patients in the double-blind period of the placebo-controlled study.

The mean changes from baseline air-conduction pure-tone audiometry results in the conventional frequency range at the end of HYD treatment were generally small (< 1.0 dB), bidirectional, and not clinically notable. No significant

treatment group difference was observed for placebo- or HYD-treated patients in the double-blind period of the placebo-controlled study.

During HYD exposure, a slightly larger proportion of patients had improvement in hearing sensitivity (11%) than the proportion of patients who had worsening in hearing sensitivity (8%). Similar results were observed for placebo- or HYD-treated patients in the double-blind period of the placebo-controlled study. Among those with worsening in hearing sensitivity, no patients had progressive hearing loss. The pattern of these results suggests lack of drug-induced ototoxicity.

Conclusions

The results from audiologic assessments showed inherent variability of hearing test modalities. The results do not suggest any signal of drug-induced ototoxicity with HYD treatment.

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Diversion and Illicit Sale of Extended Release Tapentadol in the United States

Nancy West[1], Marie-Claire Le Lait[1], Steven Kurtz[2], John Burke[3], Nabarun Dasgupta[4], Vikhyat Bebarta[5], Richard Dart[1,6]
[1]Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority, Denver, CO, USA, [2]Center for Applied Research on Substance Use and Health Disparities, Nova Southeastern University, Ft. Lauderdale, FFL, USA, [3]National Association of Drug Diversion Investigators, Lutherville, MD, USA, [4]Epidemico, Inc., Boston, MA, USA, [5]Department of Emergency Medicine, Antonio Military Medical Center, San Antonio, TX, USA, [6]Department of Emergency Medicine, University of Colorado School of Medicine, Aurora, CO, USA

Purpose

Prescription opioid analgesics are commonly prescribed for patients with moderate to severe pain. Tapentadol is a recently approved centrally acting analgesic with two synergistic mechanisms of action: μ-opioid receptor agonism and inhibition of norepinephrine re-uptake. The immediate release (IR) form of tapentadol (Nucynta®, Janssen Pharmaceuticals, Inc.) was introduced in 2009. The extended release (ER) formulation was approved in 2011 and is available as Nucynta ER® (Janssen Pharmaceuticals, Inc.) In the United States, the ER product utilizes a proprietary crush-resistant formulation. We compared rates of diversion events and related cost of obtaining tapentadol IR and tapentadol ER as well as other Schedule II opioid medications in street transactions in the United States.

Method

The centrally acting opioid analgesics included in this analysis were tapentadol IR, tapentadol ER, and a group of other Schedule II opioids comprised of oxycodone IR and ER, hydromorphone IR and ER, oxymorphone IR and ER, morphine IR and ER tablets, and methadone tablets. This study is based on data from the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System Drug Diversion Program and the StreetRx™ crowd-sourcing website. Drug diversion officers from 260 participating agencies in 49 U.S. states submitted data quarterly on the number of documented drug diversion cases within their jurisdiction for the specific drugs of interest between July 1, 2011 and June 30, 2013. Diversion rates were determined by dividing the number of diversion cases in a jurisdiction by the population of the same jurisdiction and, separately, dividing by drug availability as represented by the number of people filling a prescription in the jurisdiction. Poisson regression with a Bonferroni multiple comparisons adjustment was used to compare the average rates over the study period.

StreetRx is an anonymous public website that uses crowd-sourcing to enable real-time data collection of the price paid, the formulation, and dose strength for diverted pharmaceutical products. The median street price per milligram from StreetRx reports for opioid analgesics submitted between October 1, 2011 and December 3, 2013 for tapentadol ER, tapentadol IR, and other Schedule II opioid products combined were calculated and compared using the Wilcoxon rank-sum test.

Results

The average quarterly diversion rates were 0.003 for tapentadol IR, 0.0004 for tapentadol ER, and 1.54 for other Schedule II opioid tablets per 100,000 population. The tapentadol ER rate was significantly lower than the comparison Schedule II opioid tablets ($p<0.0001$) and tapentadol IR ($p=0.0015$). Rates based on drug availability were 0.043 for tapentadol IR, 0.018 for tapentadol ER, and 0.285 for Schedule II opioid tablets per 1,000 prescriptions dispensed. The tapentadol ER prescriptions dispensed rate was significantly less than the other Schedule II opioid prescriptions dispensed rate (adjusted $p=0.0003$) but similar to tapentadol IR (adjusted $p=0.41$). The median street price per milligram was $0.16 (tapentadol IR), $0.10 (tapentadol ER), and $1.00 (other Schedule II opioid

tablets). The median street price for tapentadol ER was significantly less than that of other Schedule II opioid tablets (adjusted $p<0.0001$) but not significantly different than tapentadol IR (adjusted $p=1.000$)

Conclusions

Our results indicate that tapentadol ER is rarely sold illicitly in the United States. In the two years since its introduction, diversion rates for tapentadol ER have remained low. In contrast, illicit distribution of other Schedule II opioids is significantly higher. Further, the black market prices of tapentadol IR and tapentadol ER are significantly lower, particularly in comparison to prices for other Schedule II opioids.

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Discordance between Patient and Healthcare Provider Reports of the Burden of Opioid-Induced Constipation During Chronic Pain Management

Catherine Datto[1], Robert LoCasale[1], Hilary Wilson[2], Karin Coyne[2]
[1]AstraZeneca Pharmaceuticals, Wilmington, DE, USA, [2]Evidera, Bethesda, MD, USA

Purpose

Opioid analgesics are increasingly being used for the treatment of chronic noncancer pain. Constipation is a common symptom of opioid-induced bowel dysfunction, and has been reported with prevalence ranging from 40%-80% in patients with chronic noncancer pain. There are limited data regarding the burden of opioid-induced constipation (OIC), laxative utilization patterns, and the effectiveness and safety/tolerability of laxatives in treating patients with chronic pain and OIC. The goal of this study was to better understand real world issues related to treating OIC and to describe the discordance in perception of OIC held by patients versus their healthcare providers (HCPs), as the presence of OIC can impact clinical outcomes, quality of life, and work productivity.

Method

Patients on daily opioids for ≥4 weeks for chronic noncancer pain with OIC were recruited into a 24-week prospective longitudinal study of OIC burden. Patients were invited to participate either by phone or during their usual care visits. Patients were recruited from a variety of care settings in 4 countries (the United States, Canada, the United Kingdom, and Germany), and were managed by primary care physicians, chronic pain specialists, neurologists, orthopedists and orthopedic surgeons, back pain specialists, and rheumatologists. Patient questionnaires included the Benefit, Satisfaction, and Willingness to Continue questionnaire (BSW; designed to capture the patient's perception of the effect of his/her OIC treatment in terms of benefits, satisfaction, and willingness to continue treatment) and the Work Productivity and Activity Impairment Questionnaire, Specific Health Problem (WPAI-SHP; a self-reported quantitative assessment of the effect of constipation on work productivity, daily activities, and classroom impairment). HCPs were surveyed about the experience of individual patients related to the perceived burden of illness of OIC, symptoms, OIC treatment patterns, laxative use, and OIC treatment satisfaction. The patient questionnaires were completed at baseline and week 24. The HCP survey was to be completed at baseline and week 24 for all patients who completed the baseline survey. The week 24 HCP survey involved detailed questions regarding patient visits during the follow-up period, so if patients did not return for a follow-up visit, this data could not be collected. Statistical analyses were descriptive.

Results

Chart reviews were completed for 486 of 489 (99.4%) eligible patients at baseline and 477 (97.5%) at week 24. The HCP baseline survey was completed for 464 (94.9%) patients; at week 24, 457 (93.5%) surveys were completed, of which 125 (27.4%) involved patients with visits during the follow-up period. Most eligible patients were female (62.2%) and white (84.9%). Agreement between patient and HCP reports of constipation presence at baseline was 61.1%. HCPs reported not knowing the laxative treatment status of 24.6% of their patients at baseline, with 54.9% concordance for patient- and HCP endorsement of laxative use. At baseline, patients reported a range of satisfaction with constipation treatment on the BSW questionnaire ("Very dissatisfied," 22.7%; "A little dissatisfied," 28.4%; "A little satisfied," 25.8%; "Very satisfied," 23.2%), while the majority of HCPs reported that their patients had "moderate satisfaction" (53.1%) or "very little satisfaction" (28.9%) in responding to a similar treatment satisfaction question. At week 24, patients more commonly reported dissatisfaction ("Very dissatisfied," 16.0%; "A little dissatisfied," 44.0%; "A little satisfied," 29.3%; "Very satisfied," 10.7%), while HCPs most commonly reported "Moderate satisfaction" (69.3%) or "Very little satisfaction" (26.7%). Patient reports of the overall benefit of constipation treatment on the BSW at

baseline were divided ("No benefit," 33.8%; "Little benefit," 36.8%; "Much benefit," 29.4%). By contrast, the majority of HCPs reported treatments were "Slightly adequate" (41.7%) or "Moderately adequate" (34.5%) in responding to a similar question about treatment adequacy in relieving OIC. At week 24, patients more commonly reported "Little benefit" (54.9%) of OIC treatment, while HCP reports remained divided ("Slightly adequate," 43.1%; "Moderately adequate," 51.0%). Among patients who reported "moderate interference" or "complete interference" with the ability of their opioid medication to control pain at baseline, HCPs most commonly perceived these patients' pain as "mostly managed" at baseline and week 24.

Conclusions

There is a disconnect between the patients' experiences related to OIC versus HCPs' perception of patients' OIC symptoms, the strategies they use to attempt to manage them, and how their symptoms impact the ability of opioid medication to control pain. The disparate perceptions between patients and their HCPs regarding the importance and severity of OIC complicate pain management and demonstrate a need for greater communication. Clinical education and coordination of care by HCPs, including nursing professionals, may help to address the need to better appreciate and proactively manage the burden of OIC in patients with chronic, noncancer pain.

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The Impact of Opioid-Induced Constipation (OIC) on Pain Management

Catherine Datto[1], Robert LoCasale[1], Hilary Wilson[2], Karin Coyne[2]
[1]*AstraZeneca Pharmaceuticals, Wilmington, DE, USA,* [2]*Evidera, Bethesda, MD, USA*

Purpose

Opioid analgesics are commonly used to treat moderate-to-severe pain. Patients with chronic noncancer pain who are treated with opioids have a reported prevalence of opioid-induced constipation ranging from 40%-80%. In these patients there are limited data on laxative utilization patterns and the effectiveness and safety/tolerability of laxatives in treating OIC in patients with chronic noncancer pain. The goal of this study was to generate real world evidence data prospectively in patients who develop OIC, and to better understand treatment approaches and patient outcomes with commonly used laxative medications, as well as how OIC affects pain management.

Method

Patients aged 18-85 years receiving daily opioids for ≥4 weeks for chronic noncancer pain who reported OIC were recruited into a 24-week prospective longitudinal study of OIC burden. Patients were recruited from a variety of healthcare settings in the United States, Canada, the United Kingdom, and Germany, and included patients managed by primary care physicians, chronic pain specialists, neurologists, orthopedists and orthopedic surgeons, back pain specialists, and rheumatologists. Patients completed the Benefit, Satisfaction, and Willingness to Continue questionnaire (BSW; designed to capture the patient's perception of the effect of his/her OIC treatment in terms of perceived benefit, satisfaction, and willingness to continue treatment) at baseline to week 24. Laxative inadequate response (LIR) was defined over the last 2 weeks prior to survey completion as having sufficient laxative use (use of ≥1 laxative ≥4 times) and inadequate response (<3 bowel movements [BMs] or ≥1 of the following BM-defined symptoms from the Patient Assessment of Constipation Symptoms measure scored moderate, severe or very severe: BMs too hard, BMs too small, straining to have a BM, and feeling like you had to pass a BM but could not. Patients who described LIR were further categorized into 1xLIR (as defined above) and 2xLIR subgroups. 2xLIR was defined over the past 2 weeks prior to the baseline or HCP visits as sufficient use of ≥2 laxative agents from at least 2 different classes ≥4 times each and inadequate response (<3 BMs or ≥1 BM-defined symptom).

Results

Chart reviews were completed for 486 of 489 (99.4%) eligible patients at baseline and 477 (97.5%) at week 24. 62.2% of eligible patients were female and 85% were white. The most common chronic pain diagnosis was back pain (65.4%). The most common opioids prescribed at baseline were oxycodone (40.7%), morphine (16.3%), hydrocodone/dihydrocodeinone (16.3%), and tramadol (15.6%). 65.1% of patients reported constipation within 1 month after starting opioid pain medication (4.4% the first day, 34.7% within the first week, 26.0% within 2-4 weeks). About half (48.9%) of patients reported that constipation moderately or completely interfered with the ability of their opioid medication to control pain. At baseline, 7.6% of patients (n=37) reported having changed how they used their opioid pain medications in the past 7 days in order to have BMs. This proportion changed during the course of follow-up visits (8.9%, week 8; 3.5%, week 20, 3.5%, week 24). The majority of these patients either reduced the amount of pain medication used (43.2%), or temporarily interrupted use (48.6%). Satisfaction with the resulting relief in their constipation symptoms from changing their opioid medication ranged from 59.4% at week 8 to 29.2% at week 12. Most patients who changed their opioid medication reported that their resultant pain was a little worse or much worse at baseline and throughout the follow-up period. Most patients were dissatisfied (55.6%) with their constipation treatment at baseline. At baseline, the most commonly utilized treatments for OIC over the past 2 weeks were natural/behavioral therapies (probiotics, natural dietary changes, increased fluids, increased exercise, fiber

supplements; 83.4%) and over-the-counter (OTC) laxatives (69.7%). Over time, the proportion of patients using natural/behavioral therapies or OTC laxatives, and those with 1xLIR and 2xLIR fluctuated, demonstrating that patients changed their laxative use over time while their symptom burden remained relatively unchanged.

Conclusions

Data from this longitudinal study show the burden of OIC over time. The prevalence of these bothersome OIC symptoms suggests that patients may be inadequately treating their OIC and/or that their current therapies may be lacking in efficacy and tolerability. A significant unmet need remains in the chronic, noncancer pain population suffering from OIC.

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Heroin Use Among Pain Patients Prescribed Opioids

Patricia Woster, Michael DeGeorge, Mancia Ko, Daniel Garcia
Ameritox, Baltimore, MD, USA

Purpose

In 2012 about 669,000 Americans reported using heroin in the past year,[1] according to the National Survey on Drug Use and Health (NSDUH). This number has been on the rise since 2007. Current research suggests that abuse of prescription opioid medications may lead some individuals to use heroin. Nearly half of young people who inject heroin surveyed in three recent studies reported abusing prescription opioids before starting to use heroin. With the decrease in availability of prescription opioids due in part to state legislative changes and closing of "pill mills", some individuals reported switching to heroin because it is cheaper and easier to obtain than prescription opioids.[2-4]

This trend appears to be driven largely by young adults aged 18-25, among whom there have been the greatest increases. The number of people using heroin for the first time is high, with 156,000 people starting heroin use in 2012, which is nearly double the number of people in 2006 (90,000). In contrast, heroin use has been declining among teens aged 12-17.

With this review we sought to explore the use of heroin in patients being treated for pain with prescribed opioids. We also explored whether the use of heroin was associated with the use of other illicit drugs or misuse of prescription medications in this demographic.

Method

A retrospective review was conducted utilizing a database of 171,061 urine samples received from patients prescribed opioids for pain and other prescription medications, and tested for the heroin metabolite, 6-monoacetylmorphine (6-MAM), between January 3, 2012 and January 29, 2014. Samples were classified as heroin positive (a positive liquid chromatography/tandem mass spectrometry result {LC/MS/MS} for 6-MAM) or heroin negative (6-MAM immunoassay (IA) was negative and MS wasn't performed or 6-MAM MS was performed and negative). Samples from patients prescribed morphine, methadone, or buprenorphine were excluded from the analysis.

In addition to heroin, samples were evaluated for the presence of other illicit drugs (cocaine, MDMA, PCP, THC, synthetic cathinones, and synthetic cannabinoids), for the presence of their prescribed medication (opiates, stimulants, synthetic opioids, sedative/hypnotics), and the presence of non-prescribed medications (opiates, stimulants, synthetic opioids, sedative/hypnotics). Logistic regression analyses were used to calculate odds ratios and 95% CIs.

Results

Heroin was positive in 1.3% of urine samples tested. Demographic factors associated with a positive heroin test included: males (OR 2.2; 95%CI, 2.0 - 2.3), age (age 40 - 59 vs age 19 - 39: OR 0.55; 95% CI, 0.50 - 0.60; age 60+ vs age 19 - 39: OR 0.43; 95% CI, 0.37 - 0.50), and insurance status (compared to Commercial Insurance: Medicaid OR 2.3; 95% CI, 2.0 - 2.6). Heroin positive individuals had 12.8 times the odds of a urine drug screen (UDS) positive for cocaine (95% CI, 11.4 - 14.3); 6.8 times the odds to be found with a non-prescribed synthetic opioid (95% CI, 6.1 - 7.5); 2.7 times the odds to test positive for non-prescribed stimulants (95% CI, 2.2 - 3.2), 2.2 times the odds to be positive for THC (95% CI, 1.9 - 2.5) and 1.4 times the odds to test positive for sedative hypnotics (95% CI, 1.3 - 1.6). In addition, individuals testing positive for heroin had 2.8 times the odds to test negative

for prescribed opiates (95% CI, 2.6 - 3.1) or prescribed sedative hypnotics (95% CI, 2.5 - 3.1) and had approximately 1.5 times the odds of testing negative for prescribed stimulants and prescribed synthetic opioids (OR 1.4; 95% CI, 0.9 - 2.2; OR 1.6; 95% CI, 1.3 - 1.9, respectively).

Conclusions

Samples from patients prescribed opioids that tested positive for heroin were more likely to test positive for other illicit drugs such as cocaine and marijuana. In addition, they were more likely to test positive for other non-prescribed medications and negative for medications that were prescribed. Clinicians should consider testing for heroin use when conducting urine drug screens in patients prescribed opioids.

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Low-dose SoluMatrix® Indomethacin: Reduced Opioid Rescue Medication Use in a Phase 3 Study in Patients With Acute Pain Following Bunionectomy

Allan Gibofsky[1], Roy Altman[2], Christopher Gharibo[3], Nabila Babar[4], Daniel Solorio[5], Clarence Young[5]
[1]Hospital for Special Surgery, New York, NY, USA, [2]University of California, David Geffen School of Medicine, Los Angeles, CA, USA, [3]New York University Langone Medical Center, New York, NY, USA, [4]Babar Internal Medicine, LLC, Cincinnati, OH, USA, [5]Iroko Pharmaceuticals, LLC, Philadelphia, PA, USA

Purpose

Indomethacin, a potent non-steroidal anti-inflammatory drug (NSAID) is, like many NSAIDs, associated with dose-related gastrointestinal, cardiovascular, and renal adverse events (AEs). Due to these safety concerns, the US Food and Drug Administration (FDA) issued a Public Health Advisory encouraging physicians prescribing NSAIDs to use "the lowest effective dose for the shortest duration consistent with individual patient treatment goals." SoluMatrix® indomethacin has been developed using SoluMatrix Fine Particle Technology™ to provide efficacy at low doses, and was approved by the FDA for the treatment of mild to moderate acute pain in adults. SoluMatrix indomethacin has demonstrated efficacy in a phase 3 study in patients with moderate to severe acute pain following bunionectomy surgery compared with placebo. Significant reductions in pain intensity, as measured by summed pain intensity difference over 0 to 48h (mean±SE), were reported in the low-dose SoluMatrix indomethacin 40mg TID (509.6±91.9; $P<0.001$), 40mg BID (328.0± 92.9; $P=0.046$), and 20mg TID (380.5±92.9; $P=0.017$) treatment groups, compared with the placebo group (67.8±91.4). Although some analgesia was evident in the celecoxib 200mg BID group (279.4±91.9]; $P=0.103$), the summed pain intensity difference over 0 to 48 h was not statistically significant compared with placebo. Here we report on opioid-containing rescue medication usage in this study.

Method

This phase 3, multicenter, randomized, double-blind, parallel-group, active- and placebo-controlled study enrolled 462 patients, aged 18-68 years, with moderate to severe postsurgical pain (≥40 mm/100 mm by Visual Analog Scale) following bunionectomy. Patients were randomized to receive low-dose SoluMatrix indomethacin capsules (40mg TID or BID or 20mg TID), celecoxib 400mg loading dose followed by 200mg BID, or placebo. Patients were permitted to receive opioid-containing rescue medication (hydrocodone/acetaminophen 10mg/325mg every 4-6h or oxycodone/acetaminophen 7.5mg/325mg every 6h as needed). The prospectively defined secondary efficacy parameters included proportion of patients using rescue medication over 0 to 48h, total rescue medication usage over 0 to 24h and 0 to 48h, and time to first use of rescue medication. *Post hoc* analyses included: the proportion of patients using rescue medication over 0 to 24h and 24 to 48h, and total use of rescue medication over 24 to 48h. Safety was evaluated by the incidence of AEs and changes in vital sign measurements.

Results

Patients were predominantly female (384/462, 83.1%) and white (333/462, 72.1%); mean±SD age was 41.2±12.5 years. The proportion of patients using rescue medication was substantially reduced over 0-24h, 24-48h, and 0-48h in the SoluMatrix indomethacin 40mg TID (0-24h:76/93, 81.7%, $P=0.003$; 24-48h:25/93, 26.9%, $P<0.001$; 0-48h:76/93, 81.7%, $P=0.003$), 40mg BID (0-24h:81/91, 89%, $P=0.051$; 24-48h:27/91, 29.7%, $P<0.001$; 0-48h:82/91, 90.1%, $P=0.078$), and 20mg TID (0-24h:80/91, 87.9%, $P=0.034$; 24-48h:32/91, 35.2%, $P<0.001$; 0-48h:81/91, 89%, $P=0.052$) treatment groups compared with the placebo group (0-24h:91/94, 96.8%; 24-48h:60/94, 63.8%; 0-48h:91/94, 96.8%). Substantially fewer patients used rescue medication during the 24-48h period in the 40mg TID, 40mg BID, and 20mg TID SoluMatrix indomethacin treatment groups (26.9%, 29.7%, and 35.2%, respectively) compared with the placebo group (63.8%). Consistent with this observation, significantly fewer

opioid-containing tablets (mean±SD) were used during this period by patients treated with SoluMatrix indomethacin: 40mg TID (0-24h:2.3±1.7; 24-48h:0.4±0.8); 40mg BID (0-24h:2.2±1.4; 24-48h:0.5±0.9); and 20mg TID (0-24h:2.3±1.7; 24-48h:0.7±1.2; [*P*<0.001 for all]) compared with placebo (0-24h:3.6±1.7; 24-48h:1.4±1.5). Time to first use of rescue medication occurred significantly later in patients treated with SoluMatrix indomethacin 40mg TID (median time 1.5h; HR=0.7, *P*=0.008) compared with placebo (1.29h). Patients treated with SoluMatrix indomethacin 40mg BID (1.6h; HR=0.8, P=0.065) and 20mg TID (1.3h; HR=0.8, P=0.076) used opioid-containing rescue medication at later times compared with those treated with placebo (1.29h), although the differences were not statistically significant. All SoluMatrix indomethacin dosing regimens were generally well tolerated; the most frequent AEs in the combined SoluMatrix indomethacin treatment groups (>5%) included nausea (83/275, 30.2%), postprocedural edema (69/275, 25.1%), headache (36/275, 13.1%), and dizziness (32/275, 11.6%). No serious cardiovascular, gastrointestinal, or renal AEs associated with NSAIDs occurred during this study.

Conclusions

Despite high overall usage of opioid-containing medication, typical for patients with pain following bunionectomy surgery, treatment with SoluMatrix indomethacin was associated with reduced opioid-containing rescue medication usage compared with placebo. The reduced use of opioid-containing rescue medication was most pronounced during the 24-48h period, indicating continued analgesic benefit.

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SoluMatrix® Diclofenac Demonstrates Sustained Opioid-sparing Effects in a Phase 3 Study of Patients With Acute Pain Following Elective Surgery

Charles Argoff[1], Srinivas Nalamachu[2], Lynn Webster[3], Jeff Gudin[4], Clarence Young[5]
[1]Albany Medical College, Albany, NY, USA, [2]Kansas City University of Medicine and Biosciences, Kansas City, MO, USA, [3]CRI-Lifetree, Mount Laurel, NJ, USA, [4]Icahn School of Medicine at Mount Sinai, New York, NY, USA, [5]Iroko Pharmaceuticals, LLC, Philadelphia, PA, USA

Purpose

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for treatment of mild to moderate acute pain and are frequently prescribed as part of multimodal treatment regimens for postoperative pain. NSAID use is associated with serious dose-related gastrointestinal, cardiovascular, and renal side effects. Consequently, the Food and Drug Administration and various medical societies recommend that these agents be used at "the lowest effective dose for the shortest duration consistent with individual patient treatment goals." SoluMatrix® diclofenac has been developed using SoluMatrix Fine Particle Technology™ to deliver effective pain relief at low diclofenac doses and is approved by the FDA for treatment of mild to moderate acute pain in adults. SoluMatrix diclofenac 35-mg capsules produced rapid absorption in a phase 1 pharmacokinetic study with 23% lower systemic exposure compared with diclofenac potassium 50-mg immediate-release tablets while achieving a similar median T_{max} (1.0h). SoluMatrix diclofenac 35-mg (524.0±86.2; $P<0.001$) and 18-mg (393.2±85.5; $P=0.010$) TID and celecoxib (390.2±86.6; $P=0.011$) BID treatment resulted in greater mean (±SD) overall (summed) pain intensity difference compared with placebo (77.1±86.6). Here we present data that evaluated opioid-containing rescue medication usage in the phase 3 study.

Method

This multicenter, randomized, double-blind, parallel-group study enrolled 428 subjects aged 18-65 years who experienced moderate to severe pain (≥40mm/100mm Visual Analog Scale) within 9h after discontinuation of the anesthetic block following bunionectomy surgery. Patients were randomized to receive low-dose SoluMatrix diclofenac 35-mg or 18-mg capsules TID, celecoxib 400-mg loading dose followed by 200-mg capsules BID, or placebo capsules. Patients were permitted to receive opioid-containing rescue medication (hydrocodone/acetaminophen 10mg/325mg every 4-6h or oxycodone/acetaminophen 7.5mg/325mg every 6h) as needed. Prospectively defined secondary endpoints included proportion of patients receiving rescue medication, the amount of rescue medication used during 0-48h following randomization, and time to first use of rescue medication following initial dose of study medication. *Post hoc* analyses included the proportion of patients using rescue medication prior to randomization, from 0-24h, and 24-48h following randomization, and the amount of rescue medication use from 0-24 and 24-48h. Safety was evaluated by adverse events (AEs) and changes in vital signs.

Results

Patients were predominantly female (371/428, 86.7%); white (329/428, 76.9%); and relatively young (mean age ± standard deviation [SD]: 39.7±12.0 years). The proportion of patients using rescue medication prior to randomization was not significantly different among treatment groups ($P\geq0.130$). Fewer SoluMatrix diclofenac 35 mg TID (0-24h:88/107, 82.2%, $P=0.003$; 24-48h: 30/107, 28.0%, $P<0.001$) and 18 mg TID (0-24h:92/109, 84.4%, $P=0.006$; 24-48h:40/109, 36.7%, $P<0.001$) treated patients required rescue medication during 0-24 and 24-48h following administration compared with placebo (0-24h:102/106, 96.2%; 24-48h:64/106, 60.4%). Patients administered SoluMatrix diclofenac 35 mg TID (0-24h:2.0±1.6, $P<0.001$; 24-48h:0.5±1.0, $P<0.001$) or 18 mg TID (0-24h:2.3±1.7, $P<0.001$; 24-48h:0.7±1.2, $P<0.001$) on average (±SD) used fewer rescue medication tablets over 0-

24 and 24-48h following treatment compared with patients receiving placebo (0-24h:3.7±1.6; 0-48h: 1.4±1.4). Patients treated with SoluMatrix 35 mg TID (median 1.6h; Hazard Ratio [HR]=0.6; *P*<0.001) or 18 mg TID (1.6h; HR=0.7; *P*=0.003) also required rescue medication at later time points and at slower rates compared with placebo-treated patients (1.2h). The most frequent nonprocedure-related AEs in the combined SoluMatrix diclofenac treatment groups (>5%) included nausea (59/216, 27.3%); headache (28/216, 13.0%); dizziness (22/216, 10.2%); and vomiting (20/216, 9.3%). No serious AEs occurred in patients receiving SoluMatrix diclofenac.

Conclusions

As expected in patients following bunionectomy surgery, many patients required rescue medication; however, treatment with either SoluMatrix diclofenac 35 or 18 mg TID reduced the need for opioid rescue medication usage throughout the treatment period, including decreases in rescue medication use from 24-48h following the start of treatment. These data suggest that SoluMatrix diclofenac treatment was associated with a persistent reduction in the need for opioid-containing analgesics.

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A Randomized Controlled Trial of Opioid Management Education for Primary Care Physicians Who Treat Chronic Non-cancer Pain

Kevin Zacharoff, Cristina Los, Kimberlee Trudeau, Priyanka Garg
Inflexxion, Inc., Newton, MA, USA

Purpose

Patients with chronic non-cancer pain may sometimes be appropriate candidates for treatment with opioid analgesics over longer periods. In certain patients, the potential for increased functioning and improved quality of life may significantly outweigh the risk of abuse and misuse, even when patients have a history of past or current substance abuse. To routinely deny these patients adequate treatment for pain raises ethical, moral, policy, and practice questions. However, many clinicians may be reluctant to support the use of opioid analgesics for chronic non-cancer pain patients because of concerns about adverse effects, tolerance, and addiction. As part of safe and effective opioid prescribing, it is recommended that healthcare providers incorporate risk assessment into a responsible prescribing framework, along with other monitoring techniques for aberrant drug-related behavior. Therefore, it is important to educate primary care physicians about the safe and effective use of opioid therapy in patients with chronic non-cancer pain to help minimize the risk to patients who may be treated with these medications. This study investigated the effect of opioid management education on the attitudes, knowledge, and behaviors of prescribers of opioid analgesics in the primary care setting.

Method

A randomized controlled trial was conducted to assess the efficacy of a continuing education (CE) pain management program with primary care physicians (N = 238). Participants were recruited through hospitals, professional list serves, and pain conferences. Interested clinicians were randomized to the experimental condition or the control condition. The experimental condition was a new, interactive, online CE program, Managing Addiction and Pain in Primary Care (MAP-PC), which covered topics related to the prescribing of opioid analgesics such as fundamentals of prescribing, comorbidities, safe practices, and effective provider patient interactions. The control condition was exposure to a set of existing text-based, online CE programs that covered the same topics as the MAP-PC program. Over the four month study period participants were asked to complete four hours of the CE courses and were also asked to complete assessments at baseline, one month post baseline and four months post baseline. These online surveys included questions on knowledge, attitudes and behavior around the prescribing of opioid analgesics to chronic-non cancer pain patients from two previously used scales (KNOW Pain 50 and CAOS) and a scale we developed for use in this study (Pain Practice Behaviors Scale). Participants received $300 for completing the surveys.

Results

The participants included physicians (70.6%), nurses/nurse practitioners (22.3%), and physician assistants (7.1%), who specialized in family practice (51.7%), internal medicine (29.0%), and general medicine (4.6%). Over the course of the study, participants in both conditions reported significant improvements in their skills, attitudes, and behaviors related to pain care. However, some differences were found between groups. The experimental condition exhibited significantly greater attitude change over time on the Tamper Resistant Formulation (TRF) and Dosing subscale of the CAOS scale compared to the control condition ($F2, 236 = 3.89$, $p=0.02$). Post-hoc comparisons suggested that participants in the experimental condition were less likely to endorse use of TRFs over time (19.7 baseline to 18.7 at 3 months post-baseline) compared to the control condition (19.3 baseline to 20.0 at 3 months post-baseline). Exploratory analyses were conducted to assess potential moderating effects of physician age and years of experience. A significant three way-interaction with time, condition, and median physician age was found on the aberrant drug-

related behavior subscale of the Pain Practice Behaviors Scale (F1,185= 6.31, p=0.012). Post-hoc comparisons indicated that older physicians (i.e., age 41 +) in the experimental condition exhibited the greatest change in behaviors in response to patients not taking their opioids as prescribed (28.9 baseline to 31.7 at 3 months post-baseline). Specifically, they were more likely to endorse the use of safe-practice behaviors with patients displaying aberrant drug-related behavior after they took the experimental CE program. No differences were found between groups on satisfaction as both groups reported high levels of satisfaction with their online CE experience.

Conclusions

Overall, both education regimens provided to participants were well received, and education was shown to make a positive impact on the attitudes, knowledge, and behaviors of physicians who prescribe opioid analgesics.

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Open-label safety of MNK-155, extended-release hydrocodone bitartrate/acetaminophen tablets, in patients with osteoarthritis or chronic low back pain

Yanping Zheng, Kenneth Kostenbader, Thomas Barrett, Elizabeth Hisaw, Dave Melikia
Mallinckrodt Pharmaceuticals, Hazelwood, MO, USA

Purpose

To assess the safety, tolerability (primary endpoints), and efficacy (secondary endpoints) of MNK-155 (Mallinckrodt Pharmaceuticals, Hazelwood, MO), a fixed-dose combination (FDC) extended-release (ER) hydrocodone bitartrate (HB)/acetaminophen (APAP) analgesic, in patients with chronic noncancer pain (CNCP) caused by osteoarthritis (OA) or chronic low back pain (CLBP). Although ER HB/APAP is being developed for the management of moderate to moderately severe acute pain that cannot be managed adequately with nonopioid analgesics, this model of CNCP was used to assess safety over a longer term than would be possible in a model of acute pain. ER HB/APAP 7.5/325-mg tablets have a biphasic formulation that delivers 25% of the HB and 50% of the APAP by immediate release and the remainder by ER over a 12-hour dosing interval.

Method

This multicenter, phase 3, open-label study included adult patients who had been diagnosed with OA (knee or hip) with moderate to severe pain despite the use of nonopioid or opioid analgesics, or moderate to severe CLBP present for several hours per day for ≥3 months. Patients received a 3-tablet loading dose of ER HB/APAP (22.5/975 mg total dose) on day 1, followed by 2 tablets of ER HB/APAP (15/650 mg total dose) every 12 hours thereafter for up to 35 days. The total daily dose on day 1 was ER HB/APAP 37.5/1625 mg and ER HB/APAP 30/1300 mg each day thereafter. Institutional review board approval and informed consent were obtained before enrollment. Safety was the primary endpoint and was assessed as time to treatment discontinuation; treatment-emergent adverse events (TEAEs); vital signs, pulse, and clinical laboratory tests (chemistry, liver function, and hematology); and compliance. As secondary endpoints, scales of efficacy (modified Brief Pain Inventory-Short Form [mBPI-sf], Western Ontario and McMaster Universities Arthritis index [WOMAC], and Roland-Morris Low Back Pain and Disability Questionnaire [RMQ]) were assessed.

Results

Of the 153 patients enrolled (OA, n=73; CLBP, n=80), 37 (24.2%) discontinued the study early (mean time to discontinuation, 21.3 days). Thirteen patients (8.5%) discontinued because of an AE; the most frequent AEs leading to discontinuation were nausea (n=4), vomiting (n=2), and pruritus (n=2). A total of 88 patients (57.5%) reported ≥1 TEAE, and 65 (42.5%) experienced treatment-related AEs. TEAEs occurring in >10% of patients overall included nausea (16.3%), somnolence (14.4%), and constipation (11.1%). The majority of TEAEs were mild or moderate in severity. Six patients (3.9%) reported 8 severe AEs. One patient (0.7%) reported a serious AE, which was judged by the investigator to be unrelated to study drug; no deaths occurred during the study. Clinically significant changes in laboratory values (as assessed by the investigator and reported as TEAEs) occurred in 13 patients (all with exposure ≥10 days). Most of these individual changes in laboratory values were of mild severity and resolved by end of study. There were no clinically relevant trends in the AEs related to laboratory values, except that half were associated with increased liver enzymes. There were no Hy's Law cases, defined per US Food and Drug Administration guidance as alanine aminotransferase >3 times the upper limit of normal (ULN) or aspartate aminotransferase >3 times ULN, associated with total bilirubin >2 times ULN and alkaline phosphatase >2 times ULN. Changes from baseline to end of study indicated improvements in pain intensity, function, and quality of life in the mBPI-sf, WOMAC, and RMQ scores. The safety profile of ER HB/APAP was consistent with that of other FDC opioid analgesics.

Conclusions

These findings support the safety and tolerability of a 3-tablet loading dose and repeated 2-tablet dosing every 12 hours of ER HB/APAP 7.5/325-mg tablets for long-term use (≤35 days). Although ER HB/APAP is intended for acute pain and not for the treatment of CNCP, efficacy assessments in patients with chronic OA and CLBP showed improvement from baseline to end of study.

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COMPARING THE PREVALENCE AND HEALTHCARE COSTS OF DIAGNOSED OPIOID ABUSE AMONG COMMERCIALLY-INSURED BENEFICIARIES USING TWO DISTINCT COMMERCIAL CLAIMS DATABASES

J. Bradford Rice[1], Noam Y. Kirson[1], Amie Shei[1], Caroline J. Enloe[1], Alice Kate Cummings[1], Katharine Bodnar[1], Howard G. Birnbaum[1], Pamela Holly[2], Rami Ben-Joseph[2]
[1]Analysis Group, Inc., Boston, MA, USA, [2]Purdue Pharma LP, Stanford, CT, USA

Purpose

Prescription opioid abuse has become an important public health concern in the U.S., with an estimated 2.1 million Americans aged 12 or older abusing or dependent on prescription pain relievers in 2012. While prior research has estimated the prevalence and excess healthcare costs of opioid abuse in the U.S., much of this research is based on data that pre-date recent private and public efforts to increase awareness of and reduce prescription opioid abuse.

The purpose of this study was to compare recent estimates of the prevalence of diagnosed opioid abuse and the excess healthcare costs of diagnosed opioid abuse among commercially-insured patients using two different de-identified administrative claims databases. Both analyses employed the same approach, including sample selection, definition of the time period of interest, propensity score matching between opioid abusers and control patients, and calculation of outcome measures, which facilitated comparisons between the two analyses.

Method

Two large commercial claims databases, the OptumHealth Reporting and Insights ("Optum") and the Truven MarketScan Commercial Claims and Encounters ("Truven") databases, were used for these analyses. Data analyzed were from Q1 2006-Q1 2012 for Optum and Q1 2009-Q4 2012 for Truven.

Prevalence rates of diagnosed opioid abuse were estimated annually as the proportion of patients ages 12-64 with ≥1 abuse diagnosis among those with ≥1 month of eligibility during the year. Abuse diagnoses were identified using ICD-9-CM diagnosis codes for opioid abuse or dependence ("abuse"). To estimate excess healthcare costs, patients aged 12-64 with ≥1 abuse diagnosis were observed over a 12-month observation period centered on the date of the first observed abuse diagnosis (i.e., index date). This period was preceded by a 6-month baseline period to assess patient characteristics. Patients were required to have continuous non-HMO coverage throughout the 18-month study period. Potential controls were patients meeting similar inclusion criteria but with no diagnoses for abuse at any point during their observed medical history; their index date was the date of a random medical claim. Abusers were matched 1:1 to controls based on the year of index date, employment status (Optum analysis only), baseline healthcare costs, and propensity score. Per-patient total healthcare costs in the observation period were compared between abusers and matched controls to determine the excess annual healthcare costs of diagnosed abuse. Costs reflected payments made to providers by third-party payers and were measured in 2012 USD.

Results

The prevalence rates calculated in the Truven database were higher than those calculated in the Optum database, though a similar upward trend in the estimated prevalence of diagnosed opioid abuse was found in both analyses (Optum, 11.8 per 10,000 in 2009 vs. 18.6 per 10,000 in 2011; Truven, 15.8 per 10,000 in 2009 vs. 22.5 per 10,000 in 2011).

For the estimates of the excess costs of abuse, 9,291 abusers and 395,901 controls in the Optum database and 38,876 abusers and 903,415 controls in the Truven database met the inclusion criteria. In both analyses, abusers had

significantly higher rates of baseline comorbidities (e.g., congestive heart failure, renal disease, psychotic disorders, and other mental disorders) than did controls. 7,658 (82.4%) of the Optum abusers and 35,857 (92.2%) of the Truven abusers were matched to controls, after which baseline patient characteristics and healthcare resource utilization were well-balanced across cohorts.

During the 12-month observation period, abusers in both analyses had significantly more days in the emergency room (Optum, 2.5 vs. 0.8; Truven, 1.7 vs. 0.6), days hospitalized (Optum, 4.5 vs. 0.9; Truven, 5.5 vs. 0.9), and outpatient visits (Optum, 19.7 vs. 14.4; Truven, 24.1 vs. 16.5) compared to matched controls. This additional healthcare resource utilization led to per-patient excess healthcare costs of $10,627 in the Optum analysis ($20,343 for abusers vs. $9,716 for matched controls) and $11,376 in the Truven analysis ($22,301 for abusers vs. $10,925 for matched controls).

(All of the above comparisons were statistically significant at $p<0.01$.)

Conclusions

Two separate analyses using different commercial claims databases yielded comparable estimates of the prevalence and excess costs of diagnosed opioid abuse despite differences in the databases and analyses. The fact that the results show a consistent increase in the prevalence of diagnosed abuse over time and a similar magnitude of excess healthcare costs of diagnosed abuse validates prior research findings that opioid abuse imposes substantial healthcare costs on commercial payers. In addition, the findings suggest that the results of commercial claims data analyses, at least in the case of opioid abuse, are generalizable to other commercially-insured populations.

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Excessive Pain Medication and Reduced Cognitive Functioning in a Probate Case

Frank Breve[1], Joseph Pergolizzi[2], Lisa Batastini[1]
[1]Mid Atlantic Pharmatech Consultants, LLC, Ventnor, NJ, USA, [2]NEMA Research, Bonita Springs, FL, USA

Purpose

To describe pain clinicians' experience with providing expert witness testimony based on medical record review of a hospitalized patient who received escalating doses of multiple pain medications prior to signing a last will and testament. Documents and records were analyzed to compile evidence which supported the assertion that compromised cognitive functioning deprived subject of testamentary capacity to understand the full nature and extent of a will, which was signed shortly after certain pain medication doses were doubled and tripled to treat excruciating pain from metastatic cancer.

Method

Consultant clinicians were provided complete medical records for a hospitalized patient during a six-week period that suffered from multiple co-morbidities, including severe pain from metastatic cancer. This was a retrospective analysis of an in-patient chart, which included various documentation and assessments by clinical staff, along with pain medication dosing schedules. The data was correlated with physiologic parameters and cognitive function assessments (BIMS) to identify changes during escalating doses of pain medications. Fentanyl patch and OxyContin-SR were the main pain agents used and doses were doubled and tripled respectively, prior to subject signing last will. Other factors noted that were evidentiary of cognitive decline, and associated with CNS side effects, included chemotherapy (rituximab), radiation therapy (cervical spine), other medications used to treat pain (gabapentin and lidocaine patch), and age-related changes in function (mobility, auditory, visual, etc.).

Results

Analysis of subject records indicated that multiple factors likely contributed to reduced cognition, and an evidence-based strategy was utilized. Referenced clinical citations were provided to support each assessment or indication of reduced mental functioning as described in the medical record. Escalating pain doses of a Fentanyl patch (doubling) and sustained-release oxycodone (tripling) that occurred two weeks prior to subject's will signing were highly suspect, and these were correlated with a sixty-seven percent cognitive decline based on BIMS (Brief Interview of Mental Status) score comparisons, which were performed one month before, and five days prior to signing of the will. An additional factor strongly indicative of reduced cognitive functioning was comparison of subject's handwriting (i.e., significant changes in signature) two months prior and at will signing. This was barely recognizable from previously and it was noted the subject expired eleven days after the will signing.

Conclusions

Pain clinicians working in a consultative capacity can provide valuable expertise for attorneys involved with legal cases who seek discovery in probate matters, enabling them to present valid arguments to hypothesize whether or not pain medication may be a probable cause for reduced cognitive functioning. It is crucial to thoroughly analyze medical records to identify if clinical evidence of mental status changes is commensurate with increases in pain medication doses, and how pharmacological properties of these agents impact physiologic functioning, especially with respect to effects on the central nervous system and abnormalities of brain function.

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Safety and efficacy of CL-108 for moderate-to-severe acute pain with reduction of opioid-induced nausea and vomiting

E Hersh[1], B Schachtel[2], S Daniels[3], D Muse[4], K Patrick[5], J Zuniga[6], J Bennett[7], E Schachtel[2], A Papas[8]
[1]University of Pennsylvania, Philadelphia, PA, USA, [2]Charleston Laboratories, Jupiter, FL, USA, [3]Premier Research, Austin, TX, USA, [4]Jean Brown Research, Salt Lake City, UT, USA, [5]Premier Research, Phoenix, AZ, USA, [6]University of Texas-SW, Dallas, TX, USA, [7]University of Indiana, Indianapolis, IN, USA, [8]Tufts University, Boston, MA, USA

Purpose

Opioid-induced nausea and vomiting (OINV) are the most common side effects of opioids used to treat moderate-to-severe acute pain. CL-108 [hydrocodone 7.5 mg/acetaminophen 325 mg (HC/APAP) with fast-absorbed promethazine 12.5 mg] is being developed as a strong analgesic with less OINV.

Method

We designed a randomized, double-blind trial to evaluate the analgesic efficacy of CL-108 compared to placebo (pbo) and OINV compared to HC/APAP. The study was enriched by identifying adults with a propensity for nausea by history (on a Nausea-Prone Questionnaire) and/or direct observation after pharmacologic exposure (on a Hydrocodone Challenge). After surgical removal of at least 2 impacted molar teeth, patients rated pain intensity on a categorical scale (PI-CAT). Patients with moderate or severe pain were randomly allocated to CL-108, HC/APAP, or pbo; over 24 hours (while awake) they used the PI-CAT, a Nausea Intensity Scale and a Vomiting Frequency Scale hourly. They used Opioid Symptom Scales to evaluate other side effects (itchiness, dizziness, drowsiness, constipation, etc). Patients remedicated every 4-6 hours prn and/or took supplementary analgesic or anti-emetic. Primary endpoints were SPID24 (for analgesia) and a composite OINV prevention endpoint (no moderate/severe nausea, vomiting, or antiemetic use over 24 hours).

Results

466 patients were evenly distributed among the treatment groups. Patients who used CL-108 reported significantly greater pain reduction (16.3) compared to pbo (3.2) and the incidence of OINV was significantly greater in patients who used HC/APAP than patients who used CL-108 (OR: 2.7; 95% CI: 1.8-4.1) (both $p < 0.001$). There were no differences between CL-108 and HC/APAP for other opioid-related side effects, no respiratory depression or serious adverse events.

Conclusions

CL-108 is a safe, effective analgesic for moderate-to-severe acute pain with significant reduction of opioid-induced nausea and vomiting.

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"From Catastrophizing to Recovery": Pilot study of a single-session psychobehavioral class to treat pain catastrophizing

Beth Darnall, John Sturgeon, Ming-Chih Kao, Jennifer Hah, Sean Mackey
Stanford University, Palo Alto, CA, USA

Purpose

Pain catastrophizing is a pattern of negative cognitive and emotional responses to actual or anticipated pain. Pain catastrophizing undermines treatment for chronic pain, thus contributing to a cycle of futility in the medical treatment realm.

Standard treatment for pain catastrophizing involves multiple sessions of cognitive behavioral therapy (CBT) thus posing treatment burdens that may stand as barriers to care. To provide efficient treatment, we developed a single-session, 2-hour cognitive-behavioral class to specifically treat pain catastrophizing ("From Catastrophizing to Recovery').

Study Aims:

- To determine feasibility of the single-session class in a mixed-etiology chronic pain clinic sample.
- To determine participant ratings for acceptability, understandability, satisfaction and likelihood to use the information learned.
- To describe preliminary efficacy of the class for reducing pain catastrophizing at 2- and 4-week post-treatment follow-up.

Method

Design: Uncontrolled prospective pilot trial with retrospective chart review.
Setting: Academic chronic pain clinic
Participants: 76 clinic patients attended the free 2-hour class as clinical care. Attendees who completed at least one follow-up PCS were included in the analytic dataset.

THE CATASTROPHIZING INTERVENTION
Didactic Content:
- Mind-body science as it relates to pain and pain catastrophizing.
- How to identify catastrophizing in the moment, and how to self-treat it.

Skills acquisition:
(1) Diaphragmatic breathing and progressive relaxation (to decrease physiologic, cognitive and emotional hyperarousal within the context of pain catastrophizing).
(2) Thought reframing and restructuring to improve cognition and emotion regulation.
(3) Participants develop a customized list of behaviors (to modulate attention and counteract helplessness).

Measures:
Pain Catastrophizing Scale was administered at 3 time points: class baseline, and post-treatment at 2 and 4 weeks via email link. The PCS is a 13-item self-report questionnaire widely used to assess the frequency of catastrophizing thoughts and emotional responses in chronic pain research and clinical settings. The PCS response set is a 0-4 Likert scale (0=Not at all; 4=All the time).

An anonymous survey was administered immediately after the class.
Chart review was conducted to extract diagnoses for major depression and anxiety disorder.

Analyses included repeated measures ANOVA (rANOVA) to account for within subject variability (last observation carried forward imputation was used for missing data). rANOVA compared treatment response by anxiety and depression diagnoses. Post-hoc paired t-tests were used to examine differences in post-treatment and baseline PCS values. Cohen's d was used to determine treatment effect sizes.

Results

High participant ratings were found for acceptability, ease of understanding of class material, satisfaction, and likelihood to use the information and skills learned (>90%).

Ninety-one percent with follow-up data achieved reductions in pain catastrophizing that are considered clinically important.

Large effect sizes were found for PCS baseline to post-treatment Week 2 and 4 (Cohen's $d = 0.85$ and for $d = 1.15$, respectively. Larger studies of longer duration may determine durability of treatment effects.

Treatment response was not impacted by depression or anxiety disorder diagnosis, thus suggesting potential broad applicability of the intervention.

Conclusions

Preliminary findings hold promise that pain catastrophizing may be effectively treated with this efficient, single-session class. If confirmed, the class would greatly expand access to low cost pain care.

Limitations include an uncontrolled study design and relatively brief follow-up period.

Randomized controlled studies with longer duration of follow-up are needed.

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