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Effect size of topical diclofenac with and without DMSO

H. Richard Barthel[1], Morris Gold[2], Robert Axford-Gatley[3], Matthew Wieman[1]
[1]Private Practice, Santa Barbara, CA, USA, [2]Novartis Consumer Health, Inc., Parsippany, NJ, USA, [3]Complete Healthcare Communications, Inc., Chadds Ford, PA, USA, [4]Endo Pharmaceuticals Inc., Chadds Ford, PA, USA

Purpose

Two topical diclofenac formulations approved in the United States for the relief of pain caused by knee osteoarthritis differ in their delivery vehicles. Diclofenac sodium 1% gel (DSG) contains no dimethylsulfoxide (DMSO). Diclofenac sodium 1.5% topical solution (D-DMSO) includes DMSO to improve diclofenac absorption, but human pharmacokinetic data that support this hypothesis are lacking. We hypothesized that if DMSO improves diclofenac absorption, effectiveness would be improved with D-DMSO compared with DSG. The objective of this study was to compare effect size data for DSG and D-DMSO in clinical trials of knee osteoarthritis.

Method

This was a posthoc effect size analysis of 3 published, randomized, controlled, 12-week trials of topical diclofenac for knee osteoarthritis: 2 trials using DSG[1,2] and 1 trial using D-DMSO.[3] Efficacy was assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scales for pain, physical function, and stiffness.

Results

Effect sizes for DSG and D-DMSO were calculated as the mean difference between active treatment and control for each outcome divided by the SD of the outcome. By established criteria, effect sizes of .20-.49 reflect a small treatment effect, 0.5-0.79 a moderate treatment effect, and ≥0.8 a large treatment effect.[4] Our analyses demonstrate that effect sizes for improvement in the WOMAC scales for pain (.26-.29) and physical function (0.23-0.30) were similar for D-DMSO and DSG. DSG had a larger effect size for WOMAC stiffness (0.30-0.50) than did D-DMSO (0.20).

Conclusions

The hypothesized absorption advantage of D-DMSO over DSG is not supported by the observed treatment size effects for WOMAC pain, physical function, or stiffness scales.

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2

Posthoc analysis of pooled safety data from 11 phase 3 clinical trials to identify potential pharmacodynamic drug interactions between tapentadol and SSRIs/SNRIs

Vincent Brett, Christopher Sikes, Jim Xiang, Charles Oh, David Biondi
Janssen Scientific Affairs, LLC, Raritan, NJ, USA

Purpose

Tapentadol is a centrally-acting synthetic analgesic. Preclinical studies have shown tapentadol is a mu-opioid receptor agonist and norepinephrine reuptake inhibitor, and analgesia in animal models is derived from both properties. Tapentadol extended-release (ER) oral tablets prescribing information warns there have been reports of serotonin syndrome with concurrent use of tapentadol and serotonergic drugs. We analyzed pooled safety data from 11 randomized, double-blind, placebo-controlled trials to identify other potential pharmacodynamic drug interactions associated with concomitant use of tapentadol and selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI).

Method

Safety populations were pooled from 7 studies investigating oral immediate-release tapentadol vs placebo over 3-10 days for acute pain and 4 studies of tapentadol ER vs placebo over 15 weeks for chronic pain. All 11 studies permitted SSRIs if dose was stable at baseline and during study, but prohibited SNRIs to avoid confounding analgesic efficacy measurement for tapentadol. Some subjects deviated from protocol and took an SNRI. Across studies, 3269 subjects received tapentadol; 1901 received placebo. Adverse event (AE) incidences were compared for tapentadol vs placebo using safety data from only subjects who took SSRI (n=310), SNRI (n=31), or both (n=4). Thus, all subjects analyzed (N=345) were taking an antidepressant (ie, fluoxetine, paroxetine, fluvoxamine, sertraline, citalopram, escitalopram, venlafaxine, or duloxetine) at baseline. Since SSRIs/SNRIs have an established AE profile, the design of this analysis enabled comparison of AEs reported for Tapentadol+SSRI/SNRI (N=208) vs placebo+SSRI/SNRI (N=137) to assess if adding tapentadol (vs adding placebo) to SSRI or SNRI therapy changed the profile.

Results

Incidences of nausea, vomiting, dry mouth, dizziness, somnolence, pruritis, hyperhidrosis, and hot flush were significantly higher ($P<.05$) for tapentadol+SSRI/SNRI vs placebo+SSRI/SNRI. The incidences of these AEs were similar to those listed in tapentadol labeling. Other AEs occurred at numerically higher rates for tapentadol+SSRI/SNRI vs placebo+SSRI/SNRI, but most were also expected for tapentadol alone. Unexpected AEs with rates >2% for tapentadol+SSRI/SNRI were pharyngolaryngeal pain ($P=.045$), abdominal pain (ns), and myalgia (ns).

Conclusions

This posthoc analysis of pooled clinical trial data did not identify new clinically relevant adverse drug interactions associated with adding tapentadol to SSRI/SNRI therapy.

3

Analysis of illicit substance abuse and medication monitoring by payer type

Lisa Burke, Eric Dawson, Michael DeGeorge, Patricia Woster, Kathryn Bronstein
Ameritox, LTD., Baltimore, MD, USA

Purpose

This study evaluates the association between payer status and illicit substance abuse and prescribed medication monitoring results in a population of patients who underwent urine drug testing in the past 2 years.

Method

A retrospective review was conducted utilizing a database of almost 2 million urine drug samples submitted to Ameritox℠ from July 1, 2010 to June 30, 2012. Data collected included payer type (Commercial Insurance, Medicaid, Medicare, Patient Self-Pay, and Workers' Compensation), State of sample origin, and results of urine drug monitoring. Urine drug monitoring results were analyzed to determine the rates of illicit drugs detected, or a prescribed controlled or pain related medication that was not detected. Analysis of rates of illicit abuse and medication use by State was also conducted. The categorization of results was determined based on a reconciliation of the medication list submitted to Ameritox℠ by the ordering clinician and the urine drug monitoring results. Medications prescribed PRN were eliminated from the analysis.

Results

Overall, 11.9% of the samples were positive for one or more illicit drugs including marijuana, cocaine, heroin, PCP, and/or MDA/MDEA/MDMA. The breakdown of illicit drug present by payer type showed significant differences. Samples received from patients with Medicaid as their primary payer had the highest rate of illicit drugs with 17.1% testing positive. The second highest frequency of samples with illicit drugs, 14.8%, was found in samples that were categorized as Patient Self-Pay. Samples submitted with Commercial Insurance were found to have illicit drugs present in 9.7%. Samples covered by Medicare and Workers' Compensation had the lowest percentages with 8.9% and 8.6% respectively. Thirty-four percent of samples had no evidence of a prescribed controlled or pain related medication. The breakdown of these samples by payer type was more homogeneous. In descending order the frequencies were as follows: Medicare 38%, Medicaid 35.6%, Patient Self-Pay 34.2%, Workers' Compensation 34% and Commercial Insurance 32.4%. In states with greater than 2000 samples available for analysis, Alabama had the lowest rate of illicit drugs (6%) while Massachusetts had the highest (18%). The actual rate of illicit use may actually be higher as some clinicians opt to not test for marijuana. Georgia had the highest rate (39.7%) of samples that were missing the prescribed medication while numerous other states had rates that were slightly lower.

Conclusions

These data suggest that illicit substance use varies by payer type while the absence of clinician prescribed medications in urine samples is a common finding irrespective of a patient's payer status. The finding that 32% or more of samples are missing prescribed medication is consistent with other studies that have looked at medication nonadherence and should lead clinicians to discuss patterns of medication usage with their patients. The results of this very large national study support recent clinical guidelines that emphasize the need to urine drug monitor all patients on chronic opioid therapy.

4

Observations on hydrocodone and its metabolites in oral fluid compared to urine specimens from patients being treated for pain

Jennifer Cao[1], Brookie Best[1,2], Joseph Ma[1,3], Candis Morello[1,4], Rabia Atayee[1,3], Amadeo Pesce[5,6]
[1]University of California, San Diego (UCSD) Skaggs School of Pharmacy and Pharmaceutical Sciences, La Jolla, CA, USA, [2]UCSD Department of Pediatrics, Rady Children's Hospital, San Diego, CA, USA, [3]Doris A. Howell Palliative Care Service, San Diego, CA, USA, [4]Diabetes Intense Medical Management Clinic, Veterans Affairs San Diego Healthcare System, La Jollla, CA, USA, [5]Millennium Research Institute, San Diego, CA, USA, [6]Department of Pathology and Laboratory Medicine, UCSD School of Medicine, La Jolla, CA, USA

Purpose

Hydrocodone is a Schedule II (Schedule III in combination with acetaminophen [APAP]), semisynthetic opioid agonist used to treat moderate to severe pain. Hydrocodone/APAP is currently the number one dispensed prescription drug in the United States. Hydrocodone undergoes extensive first pass metabolism via cytochrome P450 (CYP) 2D6 (O-demethylation) to hydromorphone and via CYP 3A4 (N-demethylation) to norhydrocodone. Hydrocodone, hydromorphone, and norhydrocodone may be excreted in the urine as well as secreted in saliva. Historically, drug monitoring in the pain population has been performed primarily through urine testing, but now oral fluid testing is increasing in use due in part to its low susceptibility to adulteration and ease of collection. Although the use of oral fluid testing is becoming more common in practice, few data exist on concentrations of hydrocodone and its metabolites in oral fluid, or its comparison to urine and plasma concentrations. The primary goal of this retrospective data analysis was to explore the relationship between hydrocodone and its metabolites, and to examine the ranges of oral fluid drug concentrations in specimens from the pain population. The secondary goal was to compare the oral fluid concentrations and metabolic ratios of hydrocodone and its metabolites to the concentrations and metabolic ratios found in urine.

Method

This retrospective data analysis included a cohort of 8677 oral fluid specimens collected from patients between March 2012 and June 2012 that were sent to Millennium Laboratories (San Diego, CA) and analyzed for hydrocodone, hydromorphone and norhydrocodone using liquid chromatography-tandem mass spectrometry (LC-MS/MS). De-identified specimens with reported prescribed hydrocodone and not hydromorphone, and had parent drug and metabolite concentrations above the lower limit of quantification (LLOQ) were included. The LLOQ used for hydrocodone and hydromorphone was 1 ng/mL, and the LLOQ used for norhydrocodone was 2 ng/mL. Specimens that had quantifiable oral fluid concentrations of morphine, codeine or 6-monoacetylmorphine (6-MAM, heroine metabolite) were excluded because these substances may be metabolized to hydrocodone, hydromorphone, and/or norhydrocodone. The same inclusion and exclusion criteria were used for the analysis of over 250,000 de-identified urine specimens tested between March 2012 and June 2012 with creatinine concentrations >20 ng/mL. Statistical analyses and linear regressions were conducted using Microsoft Excel® 2010 and OriginPro v8.6.

Results

A total of 1970 de-identified oral fluid specimens were selected for inclusion in the analysis. 603 (26%) specimens that tested positive for hydrocodone were considered. 58 (2.6%) specimens tested positive for both hydrocodone and hydromorphone, and 332 (15%) tested positive for both hydrocodone and norhydrocodone. For this retrospective analysis, 83,558 de-identified urine specimens with reported prescribed hydrocodone and without reported prescribed hydromorphone were considered. Of those, a total of 77,053 (92%) specimens did not have quantifiable codeine, morphine or 6-MAM. A total of 56,404 (68%) specimens tested positive for hydrocodone. 47,356 (57%)

specimens tested positive for both hydrocodone and hydromorphone, and 55,329 (66%) specimens tested positive for both hydrocodone and norhydrocodone. The concentrations of hydromorphone in oral fluid appeared to be normally distributed, but truncated at the lower end due to the LLOQ of 1 ng/mL. The truncated normal curve may indicate that several specimens would have had measured hydromorphone concentrations below the LLOQ. The mean concentrations (ranges) of hydrocodone were 124 (1.6-6902) ng/mL in oral fluid and 1066 (50-335,164) ng/mL in urine. The mean concentrations (ranges) of norhydrocodone were 9 (2.0-472) ng/mL in oral fluid and 1307 (50-154,802) ng/mL in urine. The metabolic ratio (MR) of norhydrocodone to hydrocodone was 0.07 (0.008-1.3) in oral fluid with a coefficient of variation (CV) of 47%, and 1.2 (0.0002-76) in urine with a CV of 99%. The concentrations of hydrocodone are approximately 9-fold greater in urine than in oral fluid, and the concentrations of norhydrocodone are approximately 145-fold greater in urine than in oral fluid. Additionally, the metabolite to parent ratio is 17-fold greater in urine compared to oral fluid.

Conclusions

More specimens tested positive for norhydrocodone than hydromorphone in oral fluid, similar to prior studies. The positive detection rate of drug and metabolite in oral fluid was much lower than in urine, which suggests that urine is a more accurate matrix to detect hydrocodone using the current method cutoff concentrations. More sensitive LC-MS/MS methods are required to detect lower values in oral fluid. The observed hydrocodone oral fluid concentrations are approximately 10-fold greater than plasma concentrations reported by other studies. Oral fluid testing has advantages for medication monitoring, but further studies are needed to define oral fluid reference ranges.

5

Changes in prescription opioid abuse after introduction of an abuse deterrent opioid formulation

Theresa Cassidy, Emily McNaughton, Stephen Butler, Simon Budman
Inflexxion Inc., Newton, MA, USA

Purpose

Abuse of prescription opioids is a public health problem that has increased steadily over the past 10 years (SAMHSA, 2010). One aspect of the overall strategy to reduce the burden of increasing abuse of prescription opioid medications is the development of the so-called abuse-deterrent formulations (ADFs) or tamper-resistant formulations (TRFs) (ONDCP, 2011). In August 2010, original OxyContin® (oxycodone HCL controlled-release [CR] tablets; Purdue Pharmaceuticals, Stamford, CT) was replaced with reformulated oxycodone CR (ORF), an opioid analgesic formulation with physiochemical barriers to crushing and dissolving intended to reduce abuse by non-oral routes of administration (ROA; eg, injecting, snorting, and smoking). In December 2011, original OPANA® ER (oxymorphone extended release [ER]; Endo Pharmaceuticals Inc., Chadds Ford, PA) was reformulated with similar physicochemical characteristics but was not distributed until early 2012. The period following the introduction of ORF and before the introduction of reformulated oxymorphone ER created a natural experiment at a national scale providing the opportunity to evaluate the impact of introducing a widely-prescribed medication intended to inhibit tampering on the abuse rates of other drugs. The purpose of this study was to examine temporal trends in past 30-day prevalence of abuse of prescription opioids as a class, specific opioid compounds, and other substances of abuse prior to and after the introduction of ORF.

Method

Data were collected from a sample of adults assessed for substance abuse problems and treatment planning at centers in the U.S. using the NAVIPPRO® Addiction Severity Index - Multimedia Version (ASI-MV®) system. The ASI-MV is a standardized clinical interview that collects self-reported data from adults during treatment admission and planning. The ASI-MV collects data on past 30-day abuse of illegal substances as well as product-specific prescription medications. Quarterly estimates of abuse of prescription opioids and other substances were measured as the proportion of abuse reported within the past 30 days among the total study sample. For prescription opioids, abuse was defined as any nonmedical use of a prescription opioid product. Responses to a series of questions regarding use via alternate ROAs, source of the product, and use not as prescribed for pain, establish the individual as having engaged in nonmedical use and was therefore considered to be abuse. Data were reviewed from a total of 122,606 individuals from 347 facilities and 32 states during July 1, 2009, through December 31, 2011.

Results

Among this sample of individuals, quarterly estimates of past 30-day abuse of prescription opioids as a class did not change after introduction of ORF when compared to historical estimates of abuse. An increase was observed in abuse of ER prescription opioids after introduction of ORF (10.21% quarterly average during pre-period vs 12.30% during the post-period, R^2=.5978). After introduction of ORF, increases in quarterly past 30-day abuse were specifically noted at the compound level for single-entity oxycodone immediate-release (IR) (1.79% quarterly average during pre-period vs 2.56% during post-period) and original oxymorphone ER (0.33% quarterly average during pre-period vs 1.01% during post-period). Significant increases in abuse of these 2 opioid compounds were also noted after the introduction of an ADF when rates were evaluated among those who reported abuse of prescription opioids via specific routes of administration. Among individuals who reported abuse via injection, abuse of single-entity oxycodone IR increased in the post-ADF period by 22.4% (x^2=219.97, P<.0001). For original oxymorphone ER, abuse among prescription opioid injectors increased by 11.0% (x^2=107.35, P<.0001). Significant increases in past

30-day abuse of single-entity oxycodone IR (pre-post difference=+18.0%, x^2=213.16, *P*<.0001) and original oxymorphone ER (pre-post difference=+9.4%, x^2=98.39, *P*<.0001) were also noted during the post-ADF period among individuals who report snorting prescription opioids. No discernible changes in quarterly abuse were observed for immediate-release prescription opioids as a group, morphine ER products, or illegal substances such as heroin, cocaine and amphetamine.

Conclusions

Findings indicate an increase in past 30-day abuse of specific prescription opioids, notably original oxymorphone ER and single-entity oxycodone IR, following introduction of ORF compared to historical rates of these medications suggesting a possible shift in abuse towards these products. This finding was particularly evident among those reporting abuse via injection or snorting. In this sample, observed increases were limited to specific prescription opioid products, rather than a generalized increase in analgesics. Abuse of selected street drugs, including heroin, were not observed. Future research is planned to track changes coincident with the recent introduction of reformulated oxymorphone ER.

6

The use of immediate-release opioids as supplemental analgesia during the management of moderate to severe chronic pain with transdermal buprenorphine, a partial mu-opioid receptor agonist

Monica Kwarcinski, Marc Cataldo, Catherine Munera, Bradley Dain
Purdue Pharma, L.P., Stamford, CT, USA

Purpose

To describe the use of immediate-release, full mu-opioid receptor agonists as supplemental analgesia during the management of moderate to severe chronic pain with a partial mu-opioid receptor agonist, Butrans® (buprenorphine) Transdermal System.

Method

Transdermal buprenorphine (Butrans) is approved for the management of moderate to severe chronic pain. Because buprenorphine, has a high affinity for, and slow dissociation from, the mu-opioid receptor and may displace or prevent the binding of competing mu-opioid receptor agonists, there has been confusion whether immediate-release, full mu-opioid receptor agonists could be used concomitantly for supplemental analgesia. A review of current buprenorphine pharmacology literature was performed. Additionally an analysis was performed on the concomitant use of immediate-release opioids during an open-label, long-term clinical trial of transdermal buprenorphine for moderate to severe chronic pain. A search of the published medical literature was also conducted to identify other transdermal buprenorphine clinical trials that reported on the use of immediate-release opioids for supplemental analgesia.

Results

Patients enrolled in the open-label, long-term transdermal buprenorphine clinical trial utilized immediate-release opioids (eg, hydrocodone/APAP, oxycodone/APAP, codeine/APAP) for supplemental analgesia. Additionally, several published clinical studies with higher dose formulations of transdermal buprenorphine (available in Europe) were identified in which the use of immediate-release opioids (eg, oral morphine, tramadol) as supplemental analgesia for pain was allowed.

Conclusions

The use of immediate-release opioids is an acceptable choice for supplemental analgesia during the management of moderate to severe chronic pain with transdermal buprenorphine, a partial mu-opioid receptor agonist. This treatment option is based on the transdermal buprenorphine clinical trial experience, the US Full Prescribing Information for transdermal buprenorphine, and published clinical studies.

7

Risk of opioid shopping behavior: a comparison of 2 opioids in a large nationwide prescription database

M. Soledad Cepeda[1], Daniel Fife[1], Lien Vo[1], Gregory Mastrogiovanni[2], Yingli Yuan[2]
[1]*Janssen Pharmaceutical Research & Development, Titusville, New Jersey, United States Minor Outlying Islands,* [2]*IMS Health, Collegeville, PA, United States Minor Outlying Islands*

Purpose

In recent years, opioid abuse and diversion have been highlighted as public health concerns, and increasing efforts are underway to understand the magnitude and nature of the problem. Obtaining opioid prescriptions from multiple prescribers and pharmacies, known as doctor and pharmacy shopping, are believed to be indicators of opioid abuse and diversion. Tapentadol, a recently approved opioid, has both an opioid and a nonopioid mechanism of action. This could make it less likely to be abused than traditional opioids. The purpose of this study was to compare the risk of shopping behavior between tapentadol immediate release (IR) and oxycodone IR

Method

Retrospective cohort study using the IMS LRx database, which covers 65% of all retail dispensings in the US including cash transactions. Opioid-naïve subjects who filled a prescription for tapentadol or oxycodone from July 2009 to December 2010 were followed for 1 year from the date of the first dispensing (index date). Tapentadol and oxycodone subjects were matched by zip code of the pharmacy dispensing the opioid, specialty of prescriber, age of subject, and index date. The main outcomes were (a) the proportion of subjects who developed shopping behavior, defined as a subject having opioid prescriptions written by >1 prescriber with ≥1 day of overlap and filled at ≥3 pharmacies, and (b) the proportion of subjects who developed heavy shopping behavior, defined by having ≥5 shopping episodes during the 1 year follow-up. Conditional logistic regression models were built to compare the risk of shopping behavior adjusted by gender and prior benzodiazepine use.

Results

A total of 112,821 subjects were exposed to oxycodone, 42,940 to tapentadol. Shopping behavior was seen in 0.8% of the subjects in the oxycodone group and in 0.2% of the subjects in the tapentadol group, for an adjusted odds ratio (OR) of 3.6 (95% CI: 2.9-4.5).

Heavy shopping behavior was also higher in the oxycodone group (0.07%) than in the tapentadol group (0.01%). The adjusted risk of heavy shopping was 6.9 (95% CI: 2.5-16.3).

Among shoppers, the mean number of events (± Standard Deviation) was 2.1±2.6 in the oxycodone group and 1.8±1.9 in the tapentadol group. In the oxycodone group, 28.0% of the shopping events involved exclusively oxycodone, but in the tapentadol group, 0.6% of the shopping events involved exclusively tapentadol. In the oxycodone group, 11.1% of the shopping events did not include oxycodone, but in the tapentadol group, 69.1% of the shopping events did not include tapentadol

Conclusions

The risk of shopping behavior, including heavy shopping, was substantially lower with tapentadol than with oxycodone. Subjects exposed to tapentadol were less likely to shop, developed shopping behavior later, and had fewer shopping episodes than oxycodone subjects. Tapentadol subjects rarely shopped for tapentadol, whereas

oxycodone subjects often shopped for oxycodone. This study is an observational study and its findings should ideally be confirmed with a randomized controlled trial. The lower risk of shopping behavior of tapentadol may be due to its dual mechanism of action and relatively low affinity for the mu receptor.

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Perceived clinical value of data collected by opioid risk assessments

Sadaf Charity, Kevin Zacharoff, Kate Jacquet, Catherine Morlino, Kristen Lawler, Stephen Butler
Inflexxion, Inc., Newton, MA, USA

Purpose

Abuse and misuse of prescription pain medications has become a nationwide epidemic that healthcare providers, pharmaceutical companies, state and federal agencies are all grappling with. At the forefront of this problem are opioid analgesics that are commonly used to manage chronic pain but also pose risks of aberrant drug-related behavior by individuals. Two important tools available to clinicians to help assess risk of prescribing this medication to a patient are validated opioid risk assessment tools such as the Screener and Opioid Assessment for Patients with Pain (SOAPP®) and the Current Opioid Misuse Measure® (COMM). These assessments are self-report tools designed to be completed by the patient, and they generate scores that identify a patient as high, moderate or low risk and also offer risk based monitoring recommendations to the clinicians.

As healthcare settings continue towards adopting Electronic Medical Records (EMRs), it is increasingly important for tools such as the SOAPP® and the COMM® to be available in an electronic format to streamline clinical workflow, simplify adoption, and facilitate integration into EMRs. As these assessments become available in electronic formats, the opportunity to access aggregate/de-identified data from completed assessments becomes possible. Through the interviews conducted in this study we aimed to understand how clinical settings could benefit from data collected by electronic opioid risk assessments. Specifically, what data would be valuable, how would these data be used, and what are the barriers to data collection?

Method

Semi-structured interviews were conducted with 8 participants, 5 clinicians and 3 clinical administrators from various clinical settings across the country. This method was chosen to enable us to gain a deep understanding of the beliefs, attitudes, and behaviors associated with collecting and using aggregate data from electronic versions of the SOAPP® and the COMM® tools, and if access to these data would influence clinical practice in pain care and management. Interviews were conducted over the phone and online conferences. The interview questions covered the following topics: 1) Challenges in treating chronic pain patients with opioids; 2) Current use of or access to aggregate data from patient assessments; 3) How the aggregate patient assessment data would be used, and whether findings would impact clinical processes and decisions; 4) What specific data elements that would be valuable to capture; and 5) Who in the clinic would be responsible for accessing the data and generating reports for clinical use. Finally, interviewees reviewed sample reports generated from aggregate SOAPP and COMM data. Since the process of organizing interview data can be subjective, the KJ-technique was used to analyze interview data. This method allows all stakeholders to contribute to the interpretation of the results and the team to reach consensus. Following these procedures, themes in the interview data were independently grouped by project team members, then discussed. In this way, consensus themes were identified.

Results

All participants reported existing processes for assessing risk in patients that are prescribed opioids. The general consensus was that screeners such as the SOAPP® and the COMM® are an important part of risk assessment, but they should be used in conjunction with other methods such as urine drug screens, medication agreements, medication monitoring practices and clinician assessment. Procedural consistency, high risk patients, the subjective nature of pain, and coordination between multiple providers are all challenges to risk assessment. Most participants (88%) indicated

that they would generate aggregate data reports, themselves, while 50% suggested an administrative staff member would generate the reports. Specific data elements considered important by at least 50% of the participants included: psycho/social situation, quality of life (functioning and activities of daily living), pain level, history and/or current substance abuse, and medication dosage. Most participants (88%) reported that the capacity to track change in data over time would be valuable. Participants indicated that these data would be used for: treatment planning, justification of treatment services, evaluation of clinician performance, and tracking of individual patient progress. In addition, 38% of participants would be interested in being able to compare data from their clinic with other clinics, and 50% saw value in sharing data. Participants provided mixed feedback on the sample report formats (shorter, more graphical report and a longer report that contained more text), 38% preferred the longer reports and 38% preferred the shorter format.

While there were concerns around adopting new technology to complete the electronic versions of the SOAPP® and the COMM®, uncertainty as to how SOAPP/COMM data would influence organizational change and concerns about the reliability of patient data were the biggest barriers. In addition, there were concerns about the challenges in standardizing the use of these tools.

Conclusions

Clinical settings are implementing multi-pronged approaches to assessing opioid risk and then monitoring patients. Standardizing the process for assessing risk in patients continues to be a challenge. Aggregate opioid risk assessment data should track change over time, which could be used to inform important clinical processes including evaluations of clinician performance and treatment justifications. Reports presenting such data must be flexible and allow a high-level view with the ability to drill down further. Although some specific data elements of value were identified, more interviews need to be conducted to confirm these initial findings.

9

Impact of reformulated OxyContin® on abuse through oral and non-oral routes among individuals assessed in substance abuse treatment

Howard Chilcoat[1], Paul Coplan[1], Theresa Cassidy[2], Ryan Black[2], Craig Landau[1], Simon Budman[2], Stephen Butler[2]
[1]Purdue Pharma L.P., Stamford, CT, USA, [2]Inflexxion, Inc., Newton, MA, USA

Purpose

To reduce abuse through non-oral routes of administration that require tampering (eg, injecting and snorting), OxyContin (oxycodone HCl controlled-release) tablets were reformulated with physicochemical barriers to crushing and dissolving. Shipments of original OxyContin (OC) stopped on August 5, 2010, and reformulated OxyContin (ORF) started on August 9, 2010. This study assesses changes in the profile of routes of administration (ROA), rates of abuse through oral and non-oral ROAs, and frequency of abuse in the periods before vs after ORF introduction for OxyContin and comparator opioids (ER oxymorphone and ER morphine) among individuals assessed in substance abuse treatment.

Method

The NAVIPPRO system uses a computer-administered interview (ASI-MV) for adult treatment planning that collects self-reports of past 30 day substance abuse, including prescription opioids. Identification of specific medicines is determined by presenting images along with audio of medication names and street names. Rates of abuse through any route, oral and non-oral routes and frequency of use were measured for OC over 14 months before ORF introduction (June 2009-August 8, 2010, n=69,002 assessments) and compared to ORF in the 20 months following ORF introduction (August 9, 2010-March 2012, n=71,494).

Results

Overall, there was a 41% (95% CI: 37%- 44%) reduction in rates of abuse of ORF vs historical rates for OC, decreasing from 4.06% of assessments for OC in the pre-ORF period vs 2.41% for ORF following its introduction. Reductions in rates were larger for non-oral vs oral ROA. There was a 66% reduction for non-oral ROA (95% CI: 63%-69%) compared to a 17% decline for oral ROA (95% CI: 10%-23%). Average frequency of abuse in the past 30 days declined from 10.75 to 7.48 days in the pre- vs post-ORF periods for OC and ORF, respectively. Rates of abuse for ER oxymorphone increased 246% (95% CI: 199%-301%) and remained steady for ER morphine. Among those respondents reporting abuse of OxyContin, the percent reporting injecting decreased from 35.7% for OC in the before period to 15.9% for ORF after its introduction, snorting decreased from 52.7% to 25.4%, and smoking decreased from 6.4% to 4.2%. No significant change in ROA patterns were observed for the comparator opioids. Abuse of OC persisted in the 20 month after period, but those reports declined over time, likely due to decreasing availability of OC.

Conclusions

These findings indicate that abuse of ORF is lower than historical rates for OC, particularly through non-oral ROA that require tampering, among this sample of individuals assessed in substance treatment. Further research is needed to determine the persistence and generalizability of these findings.

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Comorbidities, pain management, and predictors of therapy initiation in newly diagnosed DPN patients

Chris Kozma[2], Terra Slaton[3], Wing Chow[1], Marcia Rupnow[1]
[1]*Janssen Scientific Affairs, LLC, Raritan, NJ, USA,* [2]*CK Consulting Associates, LLC, St. Helena Island, SC, USA,* [3]*Independent Research Consultant, West Columbia, SC, USA*

Purpose

Of the 25.8 million Americans with diabetes, up to 25% will develop painful diabetic peripheral neuropathy (pDPN). Neuropathic pain associated with DPN can be difficult to treat and guidelines recommend antidepressants and anticonvulsants as first-line treatments in the management of pDPN followed by opioids in patients who have insufficient pain relief. Limited literature reporting examination of treatment patterns within this population have suggested that opioids are the most commonly used class of medications, and that up to 89% of patients receive opioids before or after initiation of pregabalin, gabapentin, duloxetine, or other common nonanalgesic medications for neuropathic pain. Patients with pDPN are generally in poorer health and incur higher healthcare resource utilization and costs than similar patients without pDPN. Moreover, these patients are more likely to have greater numbers of comorbidities, including pain-related conditions, increasing the likelihood that they will be prescribed opioids. Given the clinical and economic burden associated with pDPN, deeper understanding of factors that lead to medication treatment is imperative for optimization of patient outcomes. The purpose of this analysis was to investigate predictors of receiving a new medication (opioid, anticonvulsant or antidepressant) for DPN treatment at the time of diagnosis.

Method

Adult patients with a new DPN diagnosis (ie, defined as no prior DPN diagnosis for at least 1 year) between 1/1/2006 and 6/31/2009 were selected from an employer-based administrative claims database (Thomson MarketScan®). Two groups were identified within the DPN-diagnosed patients: patients having a newly initiated DPN medication vs those having no newly initiated medication. Newly initiated DPN patients were defined by having a prescription claim for an opioid, anticonvulsant, antidepressant or combination of these 3 categories (index medication) within 14 days of the first DPN diagnosis date (index date). Patients were excluded from the newly initiated group if there were any prescription claims for the same generic drug during the 360 days prior to index or if they had a claim with a non-DPN diagnosis between the index date and the date on the index medication that could potentially be related to other indications for the index medication. Patients in the non-newly initiated group were required to have no DPN-related prescription claims that covered the 60 days before index through 14 days after index date (ie, no evidence of ongoing or new therapy). All patients were required to be continuously eligible for 12 months pre- and 6 months post-index. Patients with cancer, pregnancy or receiving long-term care or hospice were excluded. Logistic regression was used to evaluate pre-index factors predicting newly initiated treatment vs no newly initiated treatment and included patient demographics, comorbid conditions, prior medication exposure and resource use variables.

Results

A total of 7,418 DPN patients with newly initiated (NI) medication and 46,335 DPN patients with no newly initiated (NNI) medication were identified. Newly initiated medications included anticonvulsants (48.4%), opioids (27.9%), antidepressants (17.7%) and multiple categories (6%). Mean ages for NI and NNI groups were 61.3 (SD 12.3) and 63.2 (SD 13.2) years with 53.6% and 43.9% females, respectively. The most common healthcare plan was Medicare (NI=36.2%; NNI=43.2%). Cardiovascular comorbidities were high in both groups (NI=69.7%; NNI=67.8%). The percentage of patients diagnosed with neuropathic pain (other than DPN) and musculoskeletal pain conditions prior to

the index DPN diagnosis were greater in the newly initiated group, NI=19% vs NNI=8.9% and NI=61.1% vs NNI=45%, respectively. Other comorbidities included mental disorders (NI=9.4%; NNI=3.7%) and sleep disorders (NI=9.5%; NNI=6.9%). Among NI patients, 53.3% had already been exposed to opioid therapy in the pre-index period (48.9% World Health Organization [WHO] 2 weak opioids, and 15.3% to WHO 3 strong opioids), 27.5% received an antidepressant, and 26.9% received an anticonvulsant. In contrast, among NNI patients 21.6% received opioids (19.9% WHO 2 weak opioids, and 3.9% WHO 3 strong opioids), 3.4% antidepressants, and 3.3% anticonvulsants. The NI group incurred higher costs in the pre-index period (mean $16,699, SD $31,751) compared to the NNI group (mean $11,237, SD $24,098). The logistic model showed prior medication therapy, comorbidities, and inpatient hospitalization to be predictive of receiving a new DPN mediation at index. Patients that had prior exposure to antidepressants and anticonvulsants had odds of a new DPN drug therapy that were approximately 6 times greater than patients with no newly initiated medication at index. Prior exposure to WHO pain ladder medication was also predictive of receiving a new DPN medication.

Conclusions

This study provides insights into comorbidities and medication therapy prior to DPN diagnosis. Presence of musculoskeletal or neuropathic pain comorbidities was high in this sample. In addition, the NI group had higher pain medications use during pre-index and incurred higher healthcare costs. The most significant predictor of receiving a new DPN medication at index was the presence of prior antidepressants or anticonvulsants use. Improved understanding of both nociceptive and neuropathic pain progression and consideration for optimal pain management at various stages are needed in this complex DPN population.

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Prevalence and cost of emergency department visits and inpatient hospitalizations resulting from opioid overdose, abuse or dependence

Chris Kozma[3], Michael Dickson[2], Wing Chow[1], Anisha Patel[1], Marcia Rupnow[1]
[1]Janssen Scientific Affairs, LLC, Raritan, NJ, USA, [2]University of South Carolina, College of Pharmacy, Columbia, SC, USA, [3]CK Consulting Associates, LLC, St. Helena Island, SC, USA

Purpose

The US Centers for Disease Control and Prevention (CDC) reports a parallel increase in the sales of opioid pain medications, opioid-related substance abuse treatment admissions, and opioid-related overdose deaths between 1999 and 2008. Opioid pain medications have been associated with the highest rates of overdose, abuse and dependence relative to other classes of medications. Previous research has explored the costs of opioid-related misuse and abuse in commercial and Medicaid patients using diagnosis codes for abuse, dependence and overdose. Findings point to inpatient cost as a major driver, among all cost components evaluated, of the economic burden associated with opioid-related misuse and abuse. The purpose of this analysis was to examine the prevalence and costs of emergency department visits, with or without inpatient admissions, and hospitalizations for diagnosed opioid-related overdose, abuse, dependence, or other related codes and explore other factors that influence costs using nationally representative hospital data.

Method

Data from the Healthcare Cost and Utilization Project's (HCUP) 2008 and 2009 Nationwide Emergency Department Sample (NEDS) and the Nationwide Inpatient Sample (NIS) were used to obtain national estimates of prevalence and costs for emergency department (ED) visits and hospitalizations. The NEDS and NIS represent a 20% stratified sample of U.S. hospital-based EDs and community hospitals, respectively. The study samples were selected using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for intentional opioid overdose (965.0X or E935.2 in combination with ancillary codes), opioid abuse (305.5X), opioid dependence (304.0X or 304.7X), and any combination of misuse-related diagnoses and the unit of analysis was discharges. Descriptive analyses were performed to estimate the numbers of events per 10,000 discharges, and the average cost per opioid misuse-related diagnoses and for all diagnosis groups (ie, presence of opioid overdose, opioid abuse, or opioid dependence). Costs were estimated using cost-to-charge ratios from the NIS data. Estimated regional cost-to-charge ratios based on the NIS data were used for the NEDS data since this file contains only reported charges. All costs were escalated to December 2011 values based on the medical services component of the Consumer Price Index. Separate analyses were conducted for diagnosis codes appearing in the primary (or first diagnosis) field and any diagnosis field. Overall results and those stratified by age, gender, and ED visit with/without inpatient admission were reported.

Results

Analysis of the NEDS data with approximately 130 million ED discharges in 2009 showed an annual period prevalence (in 10,000s) of 4.4, 1.9, 3.5, and 9.8, respectively for primary diagnosis of opioid overdose, abuse, dependence, or any of these misuse-related diagnoses. Estimated cost per discharge for any of these diagnoses was $894 (95% CI: $816-$973) in 2008 and $992 (95% CI: $929-$1,056) in 2009. Discharges in 2009 with a primary diagnosis of opioid overdose had an average age of 51.7 (SE=.31) and were less likely to be for males (45.6%). Discharges for opioid abuse and dependence occurred in younger patients with an average age of 32.9 years (SE=.39) and 34.9 years (SE=.53), and for a greater percentage of males (66.1% and 64.4%). Similar demographic and prevalence results were observed for 2008 data, and with any opioid misuse-related diagnosis in any diagnosis

field. Stratified costs in 2009 showed small variations except for ED visit. Costs were higher without ($1,162; 95% CI: $1,085-$1,238) than with ($724; 95% CI: $663-$786) inpatient admission to the same hospital and were lower for males ($922; 95% CI: $855-$990) than females ($1,083; 95% CI: $1,022-$1,144). Costs within specific diagnoses groups showed greater variations and ranged from approximately $500-$1,300. Analysis of the 2009 NIS data with approximately 40 million projected hospitalizations, showed an annual period prevalence (in 10,000s) of 15.4, 0.3, 10.5, and 26.2, respectively for primary diagnosis of opioid overdose, abuse, dependence, and any misuse-related diagnosis. Cost/hospitalization with a primary diagnosis of opioid misuse-related diagnosis was $11,094 (95% CI: $10,020-$12,168) in 2008 and $10,687 (95% CI: $9,654-$11,719) in 2009. In 2009, opioid overdose hospitalizations were for older patients (59 years, SE=.33) vs patients with any misuse-related diagnosis (49.9 years, SE=1.07) and had a lower percentage of males, 43% vs 52% for any misuse-related diagnosis.

Conclusions

The cost of an emergency room visit and hospitalization for opioid misuse-related diagnoses was approximately $1,000 and $11,000, respectively. Among the diagnosis groups studied the most common reason for an emergency room visit or hospitalization was opioid overdose. Opioid misuse-related discharges were associated with lower age and occurred in a greater percentage of males. Understanding trends in opioid abuse- or misuse-related emergency room and hospital discharges is necessary for development of prevention strategies and implementation of educational efforts.

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MAP0004 provided consistent migraine pain relief even after repeated administration

Shashidar Kori, Biao Lu, Emilee Connors, Xiaodong Li, Donald Kellerman
MAP Pharmaceuticals, Mountain View, CA, USA

Purpose

Oral tablets are the predominant route of administration for the acute treatment of migraine. Gastric stasis (GS) is commonly associated with migraine, and can significantly alter the rate of intestinal absorption of an oral tablet, leading to inconsistent response to the administered drug. The T_{max} of a triptan administered as a tablet can vary from 25-120 min. MAP0004, an investigational drug that delivers dihydroergotamine (DHE) systemically via the lungs using the TEMPO® inhaler, bypasses the gastrointestinal tract. Consequently, GS is likely to have no effect on the absorption of drug into the bloodstream. MAP0004 administration consistently achieves a DHE T_{max} between 7-12 min. A consistent T_{max}, however, does not necessarily represent a consistent clinical response.

Method

A retrospective analysis was undertaken to determine whether pain relief rates were consistent across the 1st, 5th, 15th, and 25th headache treated with MAP0004.

Results

A total of 153 subjects within the open label, long-term safety study who had at least 25 qualifying migraines were analyzed. Pain relief at 2 hours was seen on an average of 54.1%, and there was no significant difference when comparing subsequent migraines to the first qualifying migraine or comparing the 1st, 5th, 15th and 25th, all together. Similarly, analysis of pain-free values at 2 hours (average=24%), sustained pain relief from 2-24 hours (average=38.4%), and sustained pain free values from 2-24 hours (average=16.7%) were not statistically different from the first qualifying migraine or comparing the 1st, 5th, 15th, and 25th all together.

Conclusions

In this retrospective analysis, MAP0004 provided a consistent and similar response rate in treating an episodic migraine attack, whether it was the 1st, 5th, 15th, or the 25th headache treated.

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Analysis of the development of allodynia: correlation between migraine duration and severity

Biao Lu, Xiaodong Li, Emilee Connors, Shashidar Kori
MAP Pharmaceuticals, Mountain View, CA, USA

Purpose

The purpose of this analysis was evaluate the relationship between allodynia and the duration and severity of migraine to better understand mechanisms related to migraine-induced central sensitization. Allodynia, the perception of pain from nonnociceptive stimuli, is a clinical presentation of central sensitization. It has been reported that the presence of allodynia is common during a migraine attack; however, factors leading to the development of allodynia are not well understood. Both the duration and severity of migraine headache have been hypothesized to contribute to the development of allodynia.

Method

This retrospective analysis included 792 patients in the double-blind period of a phase 3, placebo-controlled, randomized clinical trial of an investigational acute treatment for migraine (MAP0004/LEVADEX®). Baseline information on pain level was recorded by patients using an electronic diary, and baseline allodynia information was obtained using a standard questionnaire. Correlations between the percentage of patients that experienced allodynia, the severity of migraine, and the duration of migraine were analyzed by Fisher's exact test and chi-square test where indicated.

Results

At baseline, 53% of all patients experienced allodynia. The presence of allodynia did not change in relation to the duration of the migraine (chi-square *P*=.2182), regardless of migraine severity (moderate baseline pain, chi-square *P*=.1807; severe baseline pain, chi-square *P*=.5830). Patients reporting a severe level of migraine pain experienced significantly more allodynia (58.4%) than patients with a moderate level of pain (48.2%; Fisher's exact *P*=.0053).

Conclusions

According to these results, the presence and development of allodynia is associated with the severity of migraine. The data do not support a relationship between the duration of migraine and the presence of allodynia. This retrospective analysis suggests that migraine severity is a significant factor in determining whether a patient will experience central sensitization.

Study supported by MAP Pharmaceuticals, Inc.

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Acceptance & Commitment Therapy: efficacy study for an outpatient, group-based treatment of veterans with chronic, noncancer pain

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

Purpose

The American Psychological Association (Division 12) recently reported that there is "strong" research support for **Acceptance & Commitment Therapy** (ACT) for chronic pain. As of late 2011, there were 11 studies demonstrating that ACT improves outcomes in public health service employees (Dahl, Wilson, & Nilsson, 2004), patients in tertiary care (Vowles & McCracken, 2008), university-based outpatient clinic patients and veterans (Vowles, Wetherell, & Sorrell, 2009), pediatrics (Wicksell et al, 2009), and self-help book readers (Johnston et al, 2010). The purpose of the current research study was to determine whether an ACT outpatient, group-based treatment benefited veterans who suffer from chronic, noncancer pain.

Method

The current 10-week ACT group was developed utilizing 2 different established protocols (Dahl, 2005; Vowles & Sorrell, 2007) and an empirically supported self-help workbook (Dahl & Lundgren, 2006). To minimize bias, a convenience sample of 50 veterans aged 29-79 years old who participated in an ACT pain group therapy protocol as an outpatient at a Midwestern VA Medical Center between February 16, 2010-November 9, 2010 were evaluated. In order to participate in these groups, participants had to complete a preliminary pain health education program. Veterans self-selected to participate in the ACT pain groups at the completion of the program. Veterans were free to withdraw at any time. All participants completed a pre- and post-intervention assessment that included the Readiness Questionnaire, the Brief Pain Inventory, the Oswestry Disability Index, the Coping Strategies Questionnaire-Catastrophizing Scale, the Chronic Pain Coping Inventory-Short Form, and the Brief Symptom Inventory-18.

10-week protocol:

1. Introduction to Group
2. Introduction to ACT
3. Controlling Your Pain
4. What Do You Value?
5. Cognitive Defusion
6. Practicing Mindfulness
7. Reaching Acceptance
8. Making a Commitment to Action
9. Facing Obstacles
10. Living Beyond Your Pain

Results

Paired-samples t-tests were conducted to evaluate the impact of the program on veterans' scores on the aforementioned assessment measures. There was a significant difference found between pre- (M=6.96, SD=1.99) and post-test measures (M=6.32, SD=2.35) of pain interference in work, $t(49)=2.51$, $P=.015$, $r=.11$, suggesting the program had a moderate to large effect in decreasing the amount of pain interference in work. A significant

difference was also found between pre- (M=6.68, SD=1.95) and post-test measures (M=6.04, SD=2.43) of pain interference in enjoyment of life, t(49)=2.17, *P*=.035, r=.09, suggesting the program had a moderate to large effect in decreasing the amount of pain interference in enjoyment of life.

There were significant differences found between pre- and post-test measures of illness-focused coping, including (pre-M=4.39, SD=1.59, post-M=3.96, SD=1.82) guarding, t(49)=2.41, *P*=.020, r=.05; (pre-M=4.58, SD=1.72, post-M=4.12, SD=2.03) pain-contingent resting, t(49)=2.10, *P*=.041, r=.04; and (pre-M=3.91, SD=1.77, post-M=3.19, SD=1.91) asking for help, t(49)=2.57, *P*=.013, r=.05. These findings suggest that the program had a small to moderate effect in reducing illness-focused coping strategies. A significant difference was also found in the pre-(M=3.84, SD=.24) and post-test (M=3.25, SD=.26) measures of seeking social support, t(49)=2.54, *P*=.014, r=.05, suggesting the program had a small to moderate effect in decreasing the use of this wellness-focused coping strategy.

There were significant differences in the pre- and post-test measures of several dimensions of distress, including (pre-M=9.88, SD=4.62, post-M=7.86, SD=4.54) somatization, t(49)=4.00, *P*=.000, r=.08; (pre-M=8.90, SD=5.17, post-M=7.04, SD=5.23) depression, t(49)=3.93, *P*=.000, r=.07; (pre-M=5.10, SD=2.46, post-M=4.38, SD=2.66) anxiety, t(49)=2.37, *P*=.022, r=.05; (pre-M=3.98, SD=3.15, post-M=3.04, SD=2.97) panic, t(49)=3.69, *P*=.001, r=.07; and (pre-M=27.86, SD=12.92, post-M=22.32, SD=13.42) global distress, t(49)=4.39, *P*=.000, r=.08. These findings suggest that the program had a moderate to large effect in reducing symptoms from several dimensions of distress.

Conclusions

The findings of the current study may be due to modules being focused on specific core processes, such as Valued Living and Control as Being the Problem, and less on material related to willingness to accept, specifically defusing language and self-as-context. Future studies may want to present core processes more fluidly rather than in distinct modules. The current findings support past research which has found ACT to be an effective, principle based intervention used to treat a variety of disorders. Future studies may want to compare outcomes for group-based, ACT and CBT interventions with veterans who suffer from chronic pain.

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Cognitive Behavioral Therapy: efficacy study for an outpatient, group-based treatment of veterans with chronic, noncancer pain

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

Purpose

According to the American Psychological Association (Division 12), there is "strong," long-standing research support for CBT to treat chronic pain, especially for fibromyalgia (Goldenberg, Kaplan, & Nadeau, 1994), low back pain (Turner & Clancy, 1988), rheumatoid arthritis pain (Bradley et al, 1987), osteoarthritic knee pain (Keefe, et al, 1990), and headaches (Holroyd et al, 1991). Furthermore, meta-analytic comparisons (Morley, Eccleston, & Williams, 1999; Hoffman et al, 2007) have shown CBT to be highly efficacious. The purpose of the current research study was to determine whether a CBT outpatient, group-based treatment benefited veterans who suffer from mixed idiopathic chronic, noncancer pain.

Method

The 12-week Cognitive Behavioral Therapy (CBT) pain group was implemented utilizing a manualized "Treatments that Work" protocol (Otis, 2007). To minimize bias, a convenience sample of 46 veterans aged 33-81 years old who participated in the CBT pain group therapy protocol as an outpatient at a Midwestern VA Medical Center between November 3, 2009-September 2, 2010 were evaluated. In order to participate in these groups, participants had to complete a preliminary pain health education program. Veterans self-selected to participate in the CBT pain groups at the completion of the program. Veterans were free to withdraw at any time. All participants completed a pre- and post-intervention assessment that included the Readiness Questionnaire, the Brief Pain Inventory, the Oswestry Disability Index, the Coping Strategies Questionnaire-Catastrophizing Scale, the Chronic Pain Coping Inventory-Short Form, and the Brief Symptom Inventory-18.

12-week protocol (Otis, 2007):

1. Education on chronic pain
2. Theories of pain and diaphragmatic breathing
3. Progressive muscle relaxation and visual imagery
4. Automatic thoughts and pain
5. Cognitive restructuring
6. Stress management
7. Time-based activity pacing
8. Pleasant activity scheduling
9. Anger management
10. Sleep hygiene
11. Relapse prevention and flare-up planning
12. Review, termination, and feedback

Results

Paired-samples t-tests were conducted to evaluate the impact of the program on veterans' scores on the aforementioned assessment measures. There was a significant difference in the pre- (M=6.74, SD=2.60) and post-test (M=5.91, SD=2.80) measures of pain interference of sleep, t(45)=2.33, *P*=.024, r=.05, suggesting the program had

a small to moderate effect in decreasing the amount of pain interference on sleep. There was also a significant difference in the pre- (M=12.13, SD=6.82) and post-test (M=10.46, SD=7.23) measures of catastrophizing, t(45)=2.05, *P*=.046, r=.04, suggesting the program had a small to moderate effect in decreasing the use of catastrophizing as a coping strategy. A significant difference was found in the pre- (M=4.30, SD=2.00) and post-test (M=5.01, SD=1.77) measures of relaxation, t(45)=-2.58, *P*=.013, r=.06, suggesting the program had a moderate effect in increasing the use of relaxation as a coping strategy. In addition, a significant difference was found in the pre- (M=4.98, SD=2.89) and post-test (M=4.11, SD=3.00) measures of anxiety, t(45) =2.24, *P*=.030, r=.05, suggesting the program had a small to moderate effect in decreasing anxiety. Differences in pre- (M=3.11, SD=1.30) and post-test (M=3.57, SD=1.09) measures of readiness to change approached significance, t(45)=-1.97, *P*=.055, r=.04, suggesting the program may have a small effect in increasing readiness to change. There were no significant differences found between pre- and post-test measures of disability, illness- or wellness-focused coping strategies, or other dimensions of distress.

Conclusions

This study offers empirical support for the Otis (2007) manual, and the use of a CBT paradigm in the treatment of veterans with chronic, noncancer pain. The findings of the current study are consistent with key components of the intervention, including maladaptive thinking, cognitive restructuring, different relaxation techniques, and sleep hygiene. The current study also supports past research which has found CBT to be an empirically supported treatment for anxiety disorders (Barlow, Raffa, & Cohen, 2002). Future studies may want to compare outcomes from group-based, CBT and ACT interventions in the treatment of veterans with chronic or persistent pain.

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ACT vs CBT: comparative outcomes for outpatient group-based treatments of veterans with chronic, noncancer pain

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

Purpose

Past research has shown that ACT compares favorably with CBT in the treatment of chronic or persistent pain among university-based outpatient clinic patients and veterans (Vowles, Wetherell, & Sorrell, 2008). Several other studies have compared ACT to CBT/CT among different populations, including cancer patients (Branstetter et al, 2004), government employees (Flaxman, 2006), university students with anxiety or depression (Forman, 2007), general public with mood and interpersonal problems (Lappalainen et al, 2007), and people with clinical depression (Zettle et al, 2009; Zettle & Hayes, 1986). However, research comparing ACT and CBT to treat chronic, noncancer pain among predominately veterans is lacking.

Method

To minimize bias, a convenience sample of 96 veterans aged 29-81 years old who participated in pain groups at a Midwestern VA Medical Center between November 3, 2009-November 4, 2010 were evaluated. In order to participate in these groups, participants had to complete a preliminary pain health education program. Veterans self-selected to participate in either the ACT or CBT pain groups at the completion of the program. Veterans were free to withdraw at any time. The CBT group was based on an empirically supported, manualized protocol (Otis, 2007). The ACT group was based on an amalgamation of established protocols (Dahl, 2005; Vowles & Sorrell, 2007) and a self-help workbook (Dahl & Lundgren, 2006). All participants completed a pre- and post-intervention assessment that included the Readiness Questionnaire, the Brief Pain Inventory, the Oswestry Disability Index, the Coping Strategies Questionnaire-Catastrophizing Scale, the Chronic Pain Coping Inventory-Short Form, and the Brief Symptom Inventory-18.

Results

The outcome analysis was a 2 x 2 repeated measures multivariate analyses of variance. There was no significant interaction effect of intervention and time, Wilks' λ=.790, F(15, 80)=1.420, *P*=.158. There was no significant main effect for intervention, Wilks' λ=.904, F(15, 80)=.564, *P*=.894, which indicates that CBT and ACT were not significantly different on the dependent measures aforementioned. There was a significant main effect for time, Wilks' λ=.707, F(15, 80)=2.214, *P*=.012, partial eta squared=.293. Significant univariate main effects (*P*<.003) for time were obtained for different several dimensions of distress, including (pre-M=9.27, SD=4.585, post-M=7.87, SD=4.248) somatization, F(1, 94)=12.244, *P*=.001, partial eta squared =.115; (pre-M=8.04, SD=5.078, post-M=6.59, SD=4.943) depression, F(1, 94)=14.760, *P*=.000, partial eta squared =.136; (pre-M=5.04, SD=2.659, post-M=4.25, SD=2.821) anxiety, F(1, 94)=10.591, *P*=.002, partial eta squared =.101; and (pre-M=25.63, SD=13.065, post-M=21.48, SD=12.814) global distress, F(1, 94)=16.592, *P*=.000, partial eta squared =150. These findings suggest that distress levels for both groups decreased over time, but both CBT and ACT have the same moderate effect in decreasing distress. There were no significant univariate main effects (at the *P*<.003 level) for time for readiness to change, F(1, 94)=5.026, *P*=.027; disability, F(1, 94)=2.509, *P*=.117; catastrophizing, F(1, 94)=7.286, *P*=.008; and coping strategies, such as guarding, F(1, 94)=7.524, *P*=.007 and asking for help, F(1, 94)=6.964, *P*=.010.

Conclusions

No significant differences were found between CBT and ACT in the treatment of veterans with chronic pain. However, both interventions over time significantly reduced distress. Future studies may want to explore in what order chronic pain patients could be exposed to both interventions. Future studies may also want to explore an ACT/CBT integrated therapy provided both are approached from a similar philosophical and theoretical framework (see Ciarrochi & Bailey, 2008). However, a treatment model based on Lazarus and Folkman's (1984) Transaction Model of Stress and Coping may serve as a bridge between ACT and CBT by using their goodness-of-fit hypothesis.

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Pain Resource Nurse training program

June Dahl[1], Carol Curtiss[1], Debra Gordon[1], Jeannine Brant[1], Karen Stevenson[1], Judith Paice[1], Marty Skemp Brown[1]
[1]University of Wisconsin School of Medicine and Public Health, Madison, WI 53706, USA, [2]Curtiss Consulting, Greenfield, MA, USA, [3]University of Washington, Seattle, WA, USA, [4]Billings Hospital, Billings, MT, USA, [5]Middleton VA Hospital, Madison, WI, USA, [6]Northwestern University, Chicago, IL, USA, [7]University of Wisconsin, Madison, WI, USA

Purpose

The overall goal was to assist nursing leaders to implement Pain Resource Nurse (PRN) programs in their practice settings. Training materials were designed to facilitate the conduct of PRN programs across the US for the purpose of promoting effective organizational change and thus improving the practice of pain management. The PRN program concept was created and implemented in the early 1990s by Drs. Betty Ferrell and Marcia Grant at the City of Hope National Medical Center. The purpose of the program was to promote a decentralized, cost-effective and unified approach to the implementation of high quality pain management throughout the organization. A PRN program can serve as the instrument for institutional change. PRNs support quality improvement by assuming an active role in guiding the management of pain and promoting practice changes that will improve the quality of care for all patients.

Method

This project had 3 major components: developing a core curriculum for training PRNs; conducting 2 national PRN train-the-trainer programs; evaluating the impact of the PRN Programs on participants themselves and on the clinical settings in which they practiced. A panel of experts experienced with development and implementation of PRN Programs created a curriculum and resource tool-kit to assist nurses in developing PRN Programs in their hospitals. It consisted of 8 educational modules with objectives, power point slides, references and test questions. A case study was integrated into the power point slides. A 9th module focused on implementation of the PRN role with important information about the skills necessary to function as change agents and champions with a realistic description of the challenges that are faced by PRNs. The materials represented the first national PRN core curriculum training materials. They were disseminated via 2 national in-person train-the-trainer sessions held in late 2008 and again in 2009.

Results

A total of 105 nurses from 54 hospitals participated in the 2 programs Average pretest scores on a knowledge, attitude, practice survey of participants improved from 79% to 89% following the 2-day training programs. Participants scored the quality of the training programs as 4.9 on a 1-5 scale with 1 being poor and 5 excellent. Participants were surveyed at 6 and 12 months after the conferences to assess their success in implementing PRN programs in their settings. In the 12 months after the train-the-trainer sessions they held 54 PRN conferences that engaged 3,341 nurses. Eighty percent of those who held conferences stated that the PRN Program had an impact of the quality of pain management in their organization. They cited nurse manager and administration support as important facilitators of their efforts. Time and funding were cited as barriers.

Conclusions

A train-the-trainer approach appears to be an effective strategy for disseminating basic information about pain assessment and management and methods for improving the quality of care. The nurses reported that the programs had a positive impact on the quality of pain management in their practice settings. As is characteristic of other quality improvement initiatives, support from administrative leadership and provision of resources were reported to be critical

to facilitation of follow-up efforts. Time and funding were identified as major barriers to implementation of PRN programs.

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Assessing risk of alcohol-induced dose dumping with the use of a new extended-release hydrocodone formulation

Mona Darwish, Mary Bond, William Tracewell, Philmore Robertson, Jr
Teva Pharmaceuticals, Frazer, PA, USA

Purpose

Extended-release opioid formulations may offer advantages relative to immediate-release forms by decreasing dosing frequency. However, the requirement for increased drug load introduces the need to protect against intentional or accidental dose dumping since the rapid release of active drug may cause increased toxicity. A new extended-release hydrocodone tablet has been developed that employs OraGuard™ technology, a novel platform that is intended to resist dose dumping when taken with alcohol or when pulverized. This randomized, open-label, crossover study assessed the effect of increasing concentrations of alcohol on the pharmacokinetics of this extended-release hydrocodone formulation.

Method

Healthy subjects were randomized to receive extended-release hydrocodone 15 mg (under fasting conditions) with 240 mL of water or 240 mL of orange juice containing 4%, 20%, or 40% alcohol. Participants received each regimen once, separated by at least 5 days. Subjects received a single, 50-mg tablet of naltrexone to block opioid receptors and minimize opioid-related adverse events. Blood samples for pharmacokinetics were collected pre-dose and through 72 hours postdose. Pharmacokinetic parameters included peak plasma hydrocodone concentration (C_{max}) and area under the plasma hydrocodone concentration-vs-time curve to infinity ($AUC_{0-\infty}$). Safety was also assessed.

Results

Forty subjects were enrolled; 31 subjects completed all 4 dosing and sampling periods and 30 were evaluable for at least 1 pharmacokinetic comparison. The majority of subjects were men (90%) and white (87%), with a mean (SD) age of 30.3 (6.56) years. Geometric mean C_{max} with 0%, 4%, 20%, or 40% alcohol was 11.8 to 12.4 ng/mL with water, 13.2 ng/mL with 4% alcohol, 13.5 ng/mL with 20% alcohol, and 13.3 ng/mL with 40% alcohol. The geometric mean $AUC_{0-\infty}$ was 186.3 to 192.8 ng•hr/mL with water, 207.6 ng•hr/mL with 4% alcohol, 219.7 ng•hr/mL with 20% alcohol, and 212.9 ng•hr/mL with 40% alcohol. The 90% confidence intervals for the ratio of log-transformed C_{max} and $AUC_{0-\infty}$ fell within the bioequivalence limits of 0.8 and 1.25 for 4%, 20%, and 40% alcohol. No appreciable differences in the shapes of the mean plasma hydrocodone concentration-vs-time profiles were observed when extended-release hydrocodone was administered with up to 40% alcohol. No serious adverse events were reported, and the incidence of adverse events increased with increasing concentrations of alcohol: 25% with 4% alcohol, 57% with 20% alcohol, and 61% with 40% alcohol.

Conclusions

Extended-release hydrocodone tablets were resistant to dose dumping when administered with alcohol, even at high levels of alcohol exposure (40%). Systemic exposures (C_{max} and AUC) were similar when extended-release hydrocodone was administered with 4%, 20%, or 40% alcohol or with water. In addition, extended-release hydrocodone was generally well tolerated in these healthy, naltrexone-blocked subjects.

Sponsored by Cephalon, Inc, now a wholly owned subsidiary of Teva Pharmaceuticals.

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Effect of food intake on the pharmacokinetics of a novel extended-release hydrocodone tablet formulated with OraGuard™ technology

Mona Darwish, Mary Bond, Philmore Robertson, Jr, William Tracewell
Teva Pharmaceuticals, Frazer, PA, USA

Purpose

Hydrocodone, the most commonly prescribed opioid in the United States, is only available in the United States as immediate-release formulations in combination with other medications for the treatment of pain. A new extended-release hydrocodone tablet has been developed that employs OraGuard™ technology, a novel platform that is intended to resist dose dumping when taken with alcohol or when pulverized. Two randomized, open-label, crossover studies were conducted in healthy volunteers to assess the effect of food on the pharmacokinetics of the hydrocodone bitartrate extended-release tablet (Study 1, 15 mg; Study 2, 90 mg).

Method

Each participant received extended-release hydrocodone (15 mg or 90 mg) in both the fed and fasted states with 240 mL of water. Hydrocodone doses were separated by a minimum washout period of 5 (Study 1) or 14 days (Study 2). Subjects received a single, 50-mg tablet of naltrexone to block opioid receptors and minimize opioid-related adverse events. Blood samples were collected pre-dose and through 72 hours postdose. Pharmacokinetic parameters included peak plasma hydrocodone concentration (C_{max}) and area under the plasma hydrocodone concentration-vs-time curve from time 0 to infinity ($AUC_{0-\infty}$). Safety was also assessed.

Results

A total of 31 subjects completed Study 1 and 35 completed Study 2. In both studies, the shapes of the concentration-vs-time profiles and exposure through the time of C_{max} were similar for the fasted and fed states. In Study 1, the geometric mean C_{max} was 18.5 ng/mL in the fed state and 12.5 ng/mL in the fasted state. The geometric mean $AUC_{0-\infty}$ was 210.8 ng•hr/mL in the fed state and 193.5 ng•hr/mL in the fasted state. In Study 2, the corresponding C_{max} was 83.6 ng/mL in the fed state and 69.5 ng/mL in the fasted state, and $AUC_{0-\infty}$ was 1236.4 ng•hr/mL in the fed state and 1117.4 ng•hr/mL in the fasted state. In both studies, confidence intervals for AUC met bioequivalence criteria (0.8, 1.25) for the fed and fasted states (Study 1: $AUC_{0-\infty}$ 1.04, 1.11; Study 2: $AUC_{0-\infty}$ 1.06, 1.16), while those for C_{max} did not (Study 1: 1.35, 1.55; Study 2: 1.31, 1.51). C_{max} was 40%-45% higher under fed conditions in both studies. For both doses, exposure through the time of C_{max} was similar for subjects in the fed or fasted state. Adverse events were similar in fed and fasted states in Study 1 (36% vs 34%), but higher in the fasted state in Study 2 (16% vs 8%).

Conclusions

Despite the 40%-45% higher C_{max} in the fed state, early exposure up to the time of C_{max} was comparable to that in the fasted state. Both doses of extended-release hydrocodone were generally well tolerated in these healthy, naltrexone-blocked subjects. The higher C_{max} attained when extended-release hydrocodone was administered with food was not correlated with an increased incidence of adverse events in the healthy subjects who were naltrexone blocked. Because there were no noticeable differences in hydrocodone early exposure, the observed increase in the rate of absorption in the fed state may be of little or no clinical significance.

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Intramuscular drotaverine and diclofenac in acute renal colic: a comparative study of analgesic efficacy and safety

Amitabh Dash, Rituparna Maiti, Tejaswi Kumar, Puneet Arora
Department of Pharmacology, BHU, Varanasi, India

Purpose

To evaluate the analgesic efficacy and safety of intramuscular drotaverine hydrochloride vs diclofenac sodium in treatment of acute renal colic.

Method

We conducted a randomized, single-blind study comparing single intramuscular doses of drotaverine hydrochloride (80 mg) vs diclofenac sodium (75 mg) on 100 patients (50 in each arm) presenting to the emergency department (ED) with renal colic. Subjects with inadequate pain relief at 30 minutes received rescue intramuscular tramadol (100 mg). Pain intensity was recorded using a visual analog scale (VAS), which is the primary outcome measure of this study, before drug administration and 30 and 60 minutes afterwards. The drug effectiveness was defined as ≥50% decrease in pain intensity 60 minutes after intramuscular administration, without exacerbation during the following 2 hours. The need for rescue medication and the presence of adverse effects were considered as secondary outcome of the study.

Results

VAS decreased significantly ($P<.001$) with both drotaverine (52.4%) and diclofenac (49%) at 30 minutes. Reduction of VAS at 60 minutes was 61.3% with drotaverine in comparison to 60.4% with diclofenac. Forty-five patients (90%) in the drotaverine group and 44 (88%) in the diclofenac group found the therapy effective. The need for rescue medication was in 5 patients of the drotaverine group and 6 patients in the diclofenac group. There was no significant difference in safety profile in the study groups.

Conclusions

The efficacy and safety of drotaverine as analgesic in renal colic is noninferior to diclofenac and may be used as an alternative or add-on therapy to currently available options.

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Pharmacokinetic stability of hydromorphone extended-release: a population pharmacokinetic analysis in patients with chronic osteoarthritis pain

John Thipphawong[1], Krishna Devarakonda[2], Sathyan Gayatri[1]
[1]*Janssen Pharmaceuticals, Fremont, CA, USA,* [2]*Mallinckrodt Inc., Hazelwood, MO, USA,* [3]*Adamas Pharmaceuticals, Koramangala, Bangalore, India*

Purpose

The purpose of this study was to examine the population pharmacokinetics of hydromorphone extended-release (ER), a once-daily opioid formulation yielding sustained steady-state plasma levels over 24 hours, in patients with chronic osteoarthritis pain.

Method

This was a 12-week, fixed-dose (8 mg and 16 mg) clinical trial. Demographic and patient characteristic data from 407 patients (8 mg [n=212]; 16 mg [n=195]) were utilized to develop a population pharmacokinetic model to explore impact on steady-state clearance (CL/F). For each patient, 3 steady-state plasma samples were collected on each of 3 occasions (Weeks 1, 3, and 6). Several covariates were tested: sex, race, age, weight, height, body mass index (BMI), target joint, sedative use, prior opioid use, and radiographic index. The population pharmacokinetics model used forward addition (covariates added sequentially) to arrive at the full model, followed by backward elimination (each covariate of full model sequentially removed) to arrive at the final model.

Results

At Weeks 1, 3, and 6, mean hydromorphone plasma concentrations for 16 mg (1.55, 1.56, and 1.45 ng/mL) were approximately dose-proportional to 8 mg (0.78, 0.82, and 0.85 ng/mL). The typical value of CL/F was 484 L/h. Body weight and age were significant covariates ($P<.001$), suggesting potential impact on CL/F. At the median age of 58.5 years, every 10-kg increase in weight is predicted to increase CL/F by 5%, while at the median weight of 98 kg, each decade increase in age is predicted to decrease CL/F by 9%.

Conclusions

These findings are consistent with healthy volunteer data, and indicate that clearance of hydromorphone ER is predictable, stable over time, and not markedly impacted by most demographic characteristics.

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Abuse of extended-release (ER) and immediate-release oxycodone in Kentucky following introduction of reformulated ER oxycodone

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

Purpose

In August 2010, shipments of original OxyContin® (oxycodone HCl extended-release Tablets; OC) stopped and reformulated OxyContin (ORF) started. ORF tablets have physicochemical barriers to crushing and dissolving to deter tampering and reduce abuse and misuse. The objective of this study was to describe changes in routes of administration (ROA) and frequency of abuse of OxyContin, immediate-release (IR) oxycodone, and other opioids, particularly for non-oral ROA that require tampering, following the introduction of ORF in a sample of OxyContin abusers in rural Perry County, Kentucky. Source of opioids as well as prices paid were also explored.

Method

Structured interviews assessing opioid abuse, including past 30-day ROA and frequency, were completed by 189 OC abusers in rural Perry County, Kentucky. Participants reported retrospectively about their abuse in the pre-ORF period in August 2010, and concurrently about their abuse in the post-ORF period in interviews conducted December 2010 through September 2011. To anchor the questions, participants were asked about their use and abuse before the Black Gold festival, a well-known event in the area; the 2010 Black Gold festival date coincided with the ORF start date in August 2010. Substances examined included oxycodone (OC, ORF, other IR oxycodone), as well as heroin, methadone, buprenorphine, and other pharmaceutical opioids (eg, fentanyl, hydromorphone, morphine). Prevalence of abuse was defined as the number of participants reporting ≥1 day of abuse in the past 30 days. Frequency of abuse was defined as the mean days of abuse in the past 30 days among only those who reported abuse (nonusers excluded). Participants were asked about price paid and about the sources of first drug use for each opioid: spouse/partner, other family, friends, doctor/dentist, dealer, stolen, manufactured, or multiple sources.

Results

Most respondents reported abusing OC in the month prior to the introduction of ORF (74%). Among those respondents, before ORF introduction, the prevalence of past 30-day OC abuse was 2% for swallowing (average 4 days/month), 39% for snorting (15.2 days), and 41% for injecting (20.8 days). After ORF introduction, 60% reported past-30 day OC abuse compared to 33% for ORF. Abuse of ORF was mainly limited to oral ROA, with 22% reporting swallowing (6.8 days/month), 5% snorting (4.2 days), and only one participant by injecting (1 day). Prevalence of IR oxycodone abuse increased from 74% to 96% pre- to post-ORF. Prevalence of IR oxycodone abuse also increased pre- to post-ORF for each ROA: swallowing: 10% to 30%, snorting: 47% to 70%, and injecting: 31% to 51%. The frequency of IR oxycodone abuse increased slightly for injecting (18.4 to 20.4 days) and decreased slightly for swallowing (14.7 to 12.6 days) and snorting (15.9 to 14.7 days). Only 10 participants (5.3%) reported heroin abuse pre-ORF and 1 participant reported abuse post-ORF. Only 19.1% of the sample had a valid prescription for pain medication at the time of the interview and the most common source for first time use was not a prescription. Approximately half obtained their first OC, ORF, and IR oxycodone from a dealer (53.2%, 44.3%, and 43.4%, respectively); friends were the next most common source: OC (29.3%), ORF (47.4%), and IR oxycodone (31.2%). Among participants reporting the price per pill for OC post-ORF (n=135), the average price was $64.85 (SD=35.34), and was greater than the price per pill for ORF ($37.74, SD=21.71; n=65); pre-ORF, the price per pill for OC was $82.16 (SD=36.10, n=118). The reported price of IR oxycodone was $23.21 (SD=10.56, n=112) in the pre-ORF period and $21.27 (SD=12.14; n=115) in the post-ORF period.

Conclusions

In this sample, the prevalence of non-oral ORF abuse was lower than that of OC abuse before ORF introduction. The relative price of ORF compared to OC further suggests decreased desirability of ORF. After introduction of ORF, there was an increase in the prevalence of IR oxycodone abuse through all ROA and a slight increase in the frequency of abuse via injection. Heroin abuse was uncommon and did not increase post-ORF. These results suggest that OC abusers were less likely to abuse ORF via non-oral ROA that require tampering than OC or IR oxycodone.

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Incidence of restless legs syndrome in patients presenting with neuropathic pain

Joseph DiDuro
NeuroTCA, PHOENIZ AZ, USA

Purpose

Restless legs syndrome (RLS), characterized by an irresistible urge to move the legs, is usually associated with unpleasant sensations located mainly in the calves and around the ankles. However, RLS is diagnosed in only 8% to 12% of patients reporting RLS symptoms to their primary care physician. We postulated that RLS might be overlooked by clinicians when a comorbidity such as neuropathic pain (NP) is the primary complaint. NP is widely recognized as one of the most difficult pain syndromes to diagnose and treat. Although the complexity and subjective nature of both syndromes complicates their evaluation, various patient self-report instruments are clinically helpful in evaluating these patients. The objective of this study is to examine what percentage of patients that report neuropathic pain symptoms also report symptoms of RLS.

Method

A prospective analysis of consecutive patients with neuropathic pain was performed between November 2011 and May 2012 in southern Arizona. A self-completed Subjective Peripheral Neuropathy Questionnaire (SPNQ) identified neuropathy symptoms in this group. The Restless Legs Syndrome Rating Scale (RLSRS) of the International Restless Legs Syndrome Study Group was also offered to patients with leg and foot symptoms.

Results

191 patients were screened positive for neuropathy symptoms over the 6 month study period. Of that group, 22 patients (11.5%) also reported RLS symptoms via the RLSRS. Grades of RLS were: Very Severe 5 (22.7%), Severe 3 (13.6%), Moderate 10 (45.5%), Mild 4 (18.2%). This subgroup consisted of 14 women (63.6%), median age of 69.5 (range 48-89). Sleep disturbance was also a common complaint in the patients with RLS.

Conclusions

Symptomatic RLS is a common finding and is under diagnosed in patients with neuropathy who seek treatment primarily for pain. Recognition of this comorbidity would allow treatments specific to the underlying condition and more favorable outcomes.

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Patient satisfaction with fentanyl sublingual spray in opioid-tolerant patients with breakthrough cancer pain

Richard Rauck[1], Neha Parikh[2], Larry Dillaha[2], Jerry Barker[3], Lowell Reynolds[4]
[1]Center for Clinical Research, Winston-Salem, NC, USA, [2]INSYS Therapeutics, Inc., Phoenix, AZ, USA, [3]Baylor Research Institute, Fort Worth, TX, USA, [4]Loma Linda University, Loma Linda, CA, USA

Purpose

Breakthrough cancer pain (BTCP) is associated with decreased satisfaction with around-the-clock opioid therapy. The objective of this analysis was to examine patient satisfaction with a sublingual formulation of fentanyl, fentanyl sublingual spray, during open-label titration and double-blind treatment in a randomized, placebo-controlled study.

Method

Opioid-tolerant patients with 1-4 episodes of BTCP per day were included. During a 26-day, open-label titration phase (N=130), a successful dose (100 mcg-1600 mcg) was established that provided effective analgesia for 2 consecutive BTCP episodes. During a 26-day double-blind phase (n=96), patients received 7 units of study medication and 3 units of placebo. The Treatment Satisfaction Questionnaire for Medication (TSQM) was administered at baseline to assess satisfaction with previous BTCP medication and at end of titration to assess satisfaction with fentanyl sublingual spray. Global evaluation (GE) of study medication was performed 30 and 60 minutes postdose during double-blind treatment.

Results

All TSQM domains increased from baseline to end of titration, with effectiveness (mean [SE]: 48.8 [1.6] to 75.2 [1.2]) and global satisfaction (55.1 [1.8] to 75.4 [1.4]) showing greatest improvement. Satisfaction with symptom relief improved to 88%, from 27% with previous BTCP medication. Mean GE scores were significantly improved at 30 and 60 minutes with fentanyl sublingual spray vs placebo ($P<.0001$). Seventy-eight patients (60.0%) during titration and 47 (48.9%) during double-blind treatment reported ≥1 adverse event (AE). Common AEs were nausea (13.1%) and somnolence (8.5%) during titration and nausea (7.1%), peripheral edema (5.1%), and hyperhidrosis (5.1%) during double-blind treatment. Most (88%) AEs were mild or moderate in severity.

Conclusions

These data indicate markedly improved satisfaction among patients receiving fentanyl sublingual spray relative to previous BTCP medications.

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Effective dose titration of fentanyl sublingual spray in patients with breakthrough cancer pain: results from the open-label phase of a double-blind, placebo-controlled study

Richard Rauck[1], Janet Bull[2], Neha Parikh[3], Larry Dillaha[3], Lisa Stearns[4]
[1]Center for Clinical Research, Winston-Salem, NC, USA, [2]Four Seasons Hospice and Palliative Care, Hendersonville, NC, USA, [3]INSYS Therapeutics, Inc., Phoenix, AZ, USA, [4]The Center for Pain and Supportive Care, Scottsdale, AX, USA

Purpose

Breakthrough cancer pain (BTCP) is commonly managed with formulations of transmucosal fentanyl. A novel sublingual formulation of fentanyl, fentanyl sublingual spray, has been developed to enhance the rate and extent of fentanyl absorption and potentially the onset of analgesia. This analysis presents results from the 26-day open-label titration phase of a phase 3, randomized, double-blind, placebo-controlled study.

Method

Opioid-tolerant patients with 1-4 episodes of BTCP per day were enrolled. For randomization into double-blind treatment, patients must have successfully titrated to a dose (100 mcg-1600 mcg) that provided effective analgesia for 2 consecutive BTCP episodes. The Treatment Satisfaction Questionnaire for Medication was assessed at screening to determine satisfaction with previous BTCP medication and at the end of titration to determine satisfaction with fentanyl sublingual spray.

Results

Of 130 patients undergoing titration, 98 (75%) achieved a successful dose, with the majority of patients (73%) achieving successful doses ranging from 600 mcg to 1200 mcg. The median dose was 800 mcg, and the most common doses were 800 mcg (24.5%) and 1200 mcg (20.4%). Of 32 patients (24.6%) that withdrew from titration, only 3 (2.3%) were unable to establish an effective dose. At the end of titration, 89% were satisfied, very satisfied, or extremely satisfied with fentanyl sublingual spray, compared with 41% with their previous BTCP medication. Notably, 90% were at least satisfied with the onset of effect of fentanyl sublingual spray vs 21% in relation to previous BTCP treatment. Seventy-eight patients (60%) reported ≥1 adverse event (AE). Thirty-three AEs (25.4%) were considered probably related to treatment, the most common being nausea (6.2%) and somnolence (4.6%).

Conclusions

These data demonstrate that in patients with BTCP, fentanyl sublingual spray can be safely titrated to an effective dose, and many prefer this treatment over previous BTCP medications.

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Is discomfort with pain management linked to provider job stress? A pilot study of VA clinical providers.

Beth Dinoff, Patricia Pilkinton, Dutton Traci, Yuriy Ustinov, Lindsey Jacobs
Tuscaloosa VA Medical Center, Tuscaloosa, AL, USA

Purpose

Chronic pain is one of the most complex problems treated by VA clinical providers. An estimated 50% of veterans present to the primary care clinic for treatment of chronic pain. In 2009, a new VHA Pain Management Directive was issued to develop a comprehensive approach to pain management. This policy outlines pain management as a national priority and establishes the "stepped-care" model as the mechanism to provide for the management of most pain conditions. The stepped-care model provides for a continuum of care that begins with the development of a competent workforce within the primary care setting. Secondary consultation in pain management is required to be timely and collaborative.

Within the VA, research data has not been collected on providers' awareness of the stepped-care model for treating chronic pain. Nor has job stress and job satisfaction been investigated in healthcare professionals using this new model. VA medical centers treat a wide variety of patients with varying pain needs, including elderly veterans and veterans who may be dealing with physical disabilities, mental illnesses, substance abuse issues, and polytrauma. This study examines current pain management resources for assessing and treating the veterans seen, and we explore the correlations among scales developed for measuring knowledge of the new directive, comfort with pain management, agreement opioid prescription practices, problems, job stress, and job satisfaction. The data from this study will be used to improve the quality of chronic pain management available by identifying specific areas where advanced training and education may be needed.

Method

After obtaining Institutional Review Board approval as an exempt study, credentialed providers in psychology, medicine, pharmacy, and nursing were invited to participate in a voluntary anonymous online survey of pain management practices using SurveyMonkey. Demographic information was obtained, including degree (MD, PhD, NP, PharmD), years of practice in current role, sex (male, female, prefer not to answer), and number of pain patients seen weekly. The questionnaire was designed to address provider knowledge of key elements in effective pain management as identified in the VA Pain Management Directive, provide a needs assessment for developing a pain program in this facility, measures of job satisfaction and job stress, problems encountered when treating chronic pain within the VA system, future training priorities, comfort with treating chronic pain, and willingness to use opioids in treating patients' pains. Questions were derived from the International Pain Management Association's *Integrated Need Assessment* and other published literature. Statistical analyses were performed on the aggregate/de-identified data. Questions generally utilized a 4 or 5 point Likert-like scale with the exception of the demographic information and true-false knowledge questions. Individual items were summed to form the outcome scales of problems, comfort, opioid use preferences, knowledge, job stress, and job satisfaction. Scales were correlated and examined for statistical significance at $P<.05$ using JMP (SAS Institute Inc.).

Results

Approximately 90 providers were emailed login information for participating in the anonymous survey. Sixteen clinical providers responded to the survey. Because the sample size was smaller than expected, descriptive data were examined to determine the representativeness of the sample within our VA. We found that the sample included a proportionate representation of the population queried; therefore, we continued with planned analyses.

Over half of the participants were male (56%). Medical degrees were held by half of the participants, and 25% had a PhD or PsyD. Advance practice nursing degrees were held by 19%, and 6% had a doctoral degree in pharmacy. Most of the respondents (63%) saw less than 15 patients with chronic pain per week, although 25% of respondents saw 15 to 30 patients, and 13% saw 31 to 45 patients with chronic pain weekly. Treatment recommendations most frequently utilized were NSAIDS and antidepressants. Priorities for future education endorsed included treating pain in veterans with drug abuse histories and use of nonpharmacologic interventions.

A significant positive correlation was obtained between the numbers of problems endorsed and amount of job stress reported (r=.59, P=.04), indicating that as providers encountered challenging problems (eg, veterans with addictions or abuse histories, documentation requirements), they became more stressed in their occupation (eg, encountering difficulties in relationships with co-workers; and having too great an overall volume of work to complete). A significant negative correlation was found between willingness to use opioid medications and overall comfort in taking care of veterans having chronic pain (r=-.58, P=.02). Therefore, as providers became more comfortable working with pain conditions and challenging patients, they became less distressed about using opioid medications and less impacted by fear of potential legal action. In addition, providers voiced feeling less coerced into prescribing opioid pain medications.

Conclusions

This study reveals that VA providers experience challenges in the day-to-day management of veterans with chronic pain, and those challenges are impacting their overall job-related distress. Few studies, address job stress of VA providers. And, no studies could be located that relate job stress with the management of chronic pain conditions. Results suggest that when providers are not adequately prepared to work with the complexities of chronic pain management they are likely to begin to feel distressed about their overall work, even when treating pain patients is only a small percentage of their daily work. Future studies are recommended.

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Attitude of physicians in training towards opioids for long-term pain management

Ike Eriatior, Justin Estess, Jackson Walters
University of Mississippi Medical Center, Jackson, MS, USA

Purpose

The recent decades helped to illuminate the problem of chronic pain, and ushered in an era of increased opioid (narcotic) use for the treatment of pain. The prescription of opioids has increased significantly, and so have the public health problem. Currently the abuse of prescription opioids has surpassed that of heroin and cocaine combined, and about 40 people die daily in the USA from prescription opioids. Knowledge and skills to balance the availability of opioids for pain management and prevent abuse becomes critical. A significant proportion of pain patients are managed at the primary care level. We carried out a survey in a university hospital, following IRB approval, to examine the opinions and concerns of physicians in training in such specialties regarding long term use of opioids for pain management.

Method

93 trainees including those in Emergency Medicine, General surgery, Psychiatry, Internal Medicine, Family medicine and Neurology, and 16 medical students completed a pen and paper questionnaire. Participants were randomly selected to complete the survey and were approached at departmental meeting based on available lists.

Results

66% were males, 65% were Caucasians and 60% were married. 91% were less than 40 years old. 45% treated chronic pain on a regular basis. 21% felt comfortable treating chronic pain, while 34% felt it depended on the situation. 81% reported feeling uncomfortable prescribing long term narcotics for patients.

There was no significant relationship between treating chronic pain on a regular basis and being comfortable prescribing long term narcotics (P=.3). Females were more likely to feel uncomfortable prescribing long term narcotics (likelihood ratio, P=.02). However, trainees who felt comfortable managing chronic pain were significantly more likely to also feel comfortable prescribing long term narcotics. The most commonly listed concern with prescribing long term narcotic was chemical dependency or addiction (37%), closely followed by escalating opioid doses (35%). Legal environment was cited only by 3.4%.

Conclusions

Opioid use and misuse continue to be a significant medical and societal problem. The majority of practitioners in training continue to feel uncomfortable prescribing long-term opioids for patients. The most common current concern amongst such practitioners relates to chemical dependency and addiction. Further education and training directed towards such areas of concern can help to approach the problem of opioid abuse and misuse in a logical and scientific fashion.

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Pharmacist review of standard pharmaceutical therapies utilized prior to pain clinic referral

Susan Fry, Paula Carlson, Janelle Sellers
Veterans Affairs Nebraska/Western Iowa Health Care System – Grand Island Division, Grand Island, NE, USA

Purpose

The primary objective was to determine the appropriateness of referrals made by primary care providers in an ambulatory care clinic to a specialty pain clinic. The secondary objective included reviewing medication changes made by the interdisciplinary pain team at the initial pain clinic visit. An additional objective was to determine the amount of time it takes for a patient to be seen in pain clinic after referral from the primary care provider.

Method

The study was a retrospective case study. Patient charts were accessed through the Computerized Patient Record System (CPRS). The targeted cohort included patients with a pain clinic appointment from July 1, 2010 to July 1, 2011. Only initial consults were included in the study. Clinic visits in which patients were seen for follow up were excluded.

Data was collected on medications used prior to the pain consult and medication changes made at the initial pain clinic visit. Pain diagnosis was retrieved from the problem list in CPRS and must have been entered on the day of referral or prior. Time to referral was defined as the days between referral and initial visit in the pain clinic.

Criterion for assessment of standard medication therapies in pain management were taken from *Practice Guidelines for Chronic Pain Management*, from the American Society of Anesthesiologists and American Society of Regional Anesthesia and Pain Medicine.

Results

A total of 61 patients were reviewed who had attended pain clinic for an initial visit from July 1, 2010 to July 1, 2011. The average age of patients seen was 58 years old (23-95). A total of 57 patients (93.4%) had a diagnosis of musculoskeletal pain, 28 patients (45.9%) neuropathic pain, 17 patients (27.9%) with a diagnosis of pain not placed in any category, and 1 patient (1.6%) with pain related to immune disease. Nine patients (32.1%) with a diagnosis of neuropathic pain were not on any neuropathic pain medications prior to referral. Three patients (5.3%) with a diagnosis of musculoskeletal pain were not on any medications known to benefit musculoskeletal pain. Seventeen patients (48.6%) that were on neuropathic medications prior to referral had their dose maximized or scheduled. The average time for a patient to be seen in the clinic was 41 days (2-133) after referral.

Conclusions

Almost half of patients referred from an ambulatory care clinic to a specialty pain clinic were not utilizing standard therapies prior to referral. The majority of these patients were diagnosed with neuropathic pain. For those with neuropathic pain the most common intervention by the pain clinic was to maximize the dose of the neuropathic medication. A pharmacist can assess the appropriateness of referrals related to utilization of standard therapies. Implementation of these recommendations may lead to a decrease in inappropriate referrals, improvement in pain control, increased access for patients refractory to standard therapies, as well as improve utilization of resources.

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Simultaneous use of methylphenidate and opioids in the treatment of chronic pain patients

Jane Glanzer
West River Anesthesiology Consultants, Rapid City, SD, USA

Purpose

History and science are clear; the simultaneous use of stimulants (eg, methylphenidate) and opioids have, for over a century, been reported to be a superior combination for pain relief. It was found that the addition of methylphenidate enhanced the opioid effect. The objective of this study was to determine if there is a relationship between the addition of methylphenidate to opioids on mood, sleep, activity, fatigue and daytime sleepiness, and dosage of opioids and chronic pain.

Method

This was a retrospective chart review and analysis conducted on chronic pain patients on methylphenidate and opioids simultaneously. This data was obtained between October 2011 and June 2012 in a Midwestern chronic pain clinic. The 3D Assessment Functional Progress Questionnaire (FPQ) and self-report were completed pre and post methylphenidate. The FPQ measures effect of pain on mood (ie, level of anxiety, depression, and irritability) and impact of pain on activities of daily living.

Results

Fifteen patients were included in the retrospective study. Mood was reported as improved in 67% of the patients, and the FPQ results showed an overall improvement of mood by 31%. Sleep was reported as improved by 73% of the patients, and results of the FPQ for sleep was improved by 24%. In addition, decreased daytime sleepiness was reported by 80% of the patients. Activity was reported improved in 73% of the patients, and those activities included cooking, painting, and household maintenance. Opioid dosage was either reduced or not increased in 67% of the patients.

Conclusions

The majority of chronic pain patients who were prescribed methylphenidate in addition to opioids had an increase in mood, improved sleep, increased activity, and less fatigue and daytime sleepiness. In addition, some patients were able to either reduce or avoid increases in opioid dosages. A larger randomized controlled study of methylphenidate in combination with opioids is warranted.

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Hydroxyvitamin D levels below 25 ng/mL are associated with increased osteoarthritis symptoms and decreased pressure pain threshold in a clinical sample with chronic knee pain

Toni L. Glover[1], Burel R. Goodin[1], Ann L. Horgas[1], Christopher B. King[1], Kimberly Sibille[1], Charles Peloquin[1], Joe R. Riley, III[1], Roland Staud[1], Larry A. Bradley[2], Roger B. Fillingim[1,3]
[1]*University of Florida, Gainesville, Florida, USA,* [2]*University of Alabama at Birmingham, Birmingham, Alabama, USA,* [3]*North Florida/South Georgia Veterans Health System, Gainesville, Florida, USA*

Purpose

Vitamin D deficiency is a widespread problem correlated with several health conditions, including chronic pain. Research in our lab established vitamin D as a mediator of race differences in experimental pain. A clinically meaningful threshold value associating vitamin D and chronic pain outcomes has yet to be determined. Experts conservatively suggest values <10 ng/mL denote severe vitamin D deficiency, 10ng/mL-19 ng/mL indicate moderate insufficiency, and 20 ng/mL-29 ng/ml signify mild insufficiency. The purpose of this study was to determine a clinically useful vitamin D threshold level predictive of individuals' reported chronic pain-related symptoms and response to evoked experimental pain.

Method

The sample consisted of 94 (75% female) racially diverse (48 African Americans/Blacks and 52% Whites) community-dwelling middle-aged and older adults (mean age 56 years) with chronic knee pain, regardless of radiographic evidence of osteoarthritis (OA). Serum was collected for vitamin D analysis by high performance liquid chromatography (total 25-hydroxyvitamin D=25(OH)D2 plus 25(OH)D3). Participants completed the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and underwent pressure algometry at the knee to determine thresholds for pressure pain (PPT).

Results

Results showed a vitamin D threshold level of <25 ng/mL was most effective for demonstrating differences in WOMAC and PPT as a function of vitamin D insufficiency. Relative to vitamin D levels >25 ng/mL, vitamin D levels <25 ng/mL were significantly related to increased WOMAC total scores ($F_{1,90}$=5.46, *P*=.02) and diminished PPT ($F_{1,90}$=11.54, *P*=.001) indicating greater self-reported OA symptoms (pain, stiffness, physical dysfunction) and increased pain sensitivity to mechanical stimulation, respectively.

Conclusions

These findings support a relationship between low levels of vitamin D and chronic knee pain. Furthermore, vitamin D levels <25 ng/mL may provide a clinical threshold used to treat vitamin D insufficiency with the goal of mitigating chronic pain.

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ConZip™ tramadol hydrochloride formulation considerations in chronic pain management

Arshi Kizilbash[1], Benjamin Schwartz[2], Laurel Mengle-Gaw[2], Jason A. Gross[1]
[1]*Cipher Pharmaceuticals, Mississauga, Ontario, Canada,* [2]*The Camden Group, St. Louis, Missouri, USA*

Purpose

- To assess the relative bioavailability of ConZip™ capsules vs Ultram® ER tablets in 3 separate studies
- To assess the tolerability of ConZip™ 200 mg capsules and Ultram® ER 200 mg tablets

Method

Methods: Each study had an open-label, randomized, crossover design. In the single (300 mg) and multidose (200 mg once daily for 7 days) studies, healthy adult fasted subjects (n=36 and 50 enrolled, respectively) received ConZip™ capsules and Ultram® ER. In the 4-way food interaction study (n=32 enrolled), subjects received a single dose of 300 mg ConZip™ capsules and Ultram® ER under fasting or fed conditions. For each study, blood samples were sequentially collected to determine concentrations of tramadol and its metabolite, o-desmethyltramadol (M1), using validated LC/MS/MS methods. Primary PK parameters were assessed by ANOVA.

Results

Results: Respectively, 32 and 38 subjects completed the single dose and multidose studies, and 16 subjects completed all 4 periods of the food interaction study, with an additional 9 subjects completing at least 2 periods. Based on the PK analysis for tramadol and M1, ConZip™ capsules and Ultram® ER are bioequivalent under fasting conditions. Both formulations have a similar T_{max} of 10 to 12 hours. However, an optimal tramadol plasma concentration was obtained more rapidly with ConZip™ capsules (within one hour vs 4 hours). ConZip™ capsules were bioequivalent when dosed under fasted or fed conditions, while Ultram® ER has a significant food effect. ConZip™ capsules were at least as well-tolerated as Ultram® ER across each study; the most commonly reported AEs were nausea, constipation, headache, dizziness, and somnolence.

Conclusions

Conclusions: ConZip™ capsules more quickly achieved therapeutic plasma concentrations compared to Ultram® ER tablets, without the food interaction seen with other tramadol ER tablet formulations, and appeared to be at least as well tolerated.

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Augmented central pain processing in vulvodynia

Johnson Hampson[1], Barbara Reed[1], Richard Gracely[2], Daniel Clauw[1], Hope Haefner[1], Richard Harris[1]
[1]*University of Michigan, Ann Arbor, USA,* [2]*The University of North Carolina, Chapel Hill, USA*

Purpose

Vulvodynia (VVD), a chronic pain condition associated with painful intercourse, tampon use, and/or spontaneous vulvar pain, occurs in approximately 7%-10% of women in the United States, yet little is known about its pathophysiology or etiology. Recent data suggest that women with VVD have lower pain thresholds (ie, hyperalgesia) in the vulvar region, and also in peripheral regions such as the thumb, deltoid, and shin (ie, generalized hyperalgesia). This global decrease in pain thresholds suggests that central factors may play a role in symptom expression in these participants. CNS activation resulting from evoked experimental pain stimuli applied to a region distant from the vulva (ie, the thumb) was compared among 3 age- and sex-matched groups: VVD, fibromyalgia (FM), and HC. We hypothesized that the enhanced brain response seen in FM participants in the pain matrix regions may also be present in individuals with VVD, if these 2 pain conditions have similar pathobiology. We also hypothesized that women with VVD, in comparison to HCs without vulvar pain, would exhibit increased activation in brain regions that respond to painful stimulation. Further as an exploratory analysis we wanted to identify brain activation differences between previously suggested VVD subgroups such as generalized (beyond the introitus) or localized, provoked (pain only due to external stimuli) or unprovoked and primary (since first tampon use or first intercourse) or secondary (those whose pain developed later).

Method

Functional MRI scans were performed using a 3 Tesla General Electric scanner. For each participant the functional scans were acquired using multislice, forward spiral fMRI acquisition (TR 2500ms, TE 30ms, flip angle 90°, FOV 22cm, number of slices 48, slice thickness 3.0mm, voxel size 3.44x3.44x3) and slice-time corrected. During thumb stimulation, pressures were applied discretely to the left thumb using a remote stimulation device. A $1cm^2$ rubber probe was positioned over the thumb by a plastic housing and activated by a pneumatic system. Vulvar stimulation was applied using a vulvodolorimeter modified for fMRI. Preprocessing of fMRI images were performed using the SPM5 software package (Statistical Parametric Mapping). Identified ROIs were extracted using the Marsbar toolbox and exported to SPSS (Statistical Analysis Software Statistics 19, Chicago, IL), to explore for outliers and to examine individual responses to pressure pain.

Analysis 1 Comparison of VVD, FM, and HCs: A whole brain ANOVA was performed to compare activations across all 3 groups (VVD, FM, and HCs).

Analysis 2 Comparison of VVD participants vs HCs: A 2 sample t-tests analysis comparing VVD and HC for either thumb or vulvar pressure was performed for the whole brain.

Analysis 3 Comparison of proposed subgroups of VVD cases: Using SPSS, ROIs identified as having significantly more activity in women with VVD as compared to HC during thumb pressure stimuli (from analysis 2), were tested using an independent sample t-test comparison of participants meeting criteria for previously proposed VVD subgroupings.

Results

Both VVD and FM participants displayed enhanced pressure pain sensitivity. The mean pressures applied to the vulva for slightly intense pain were significantly lower for VVD participants compared to healthy controls (VVD: 0.31 ± 0.22

kg, HCs: 0.63±.43 kg, *P*=.01). There was also a trend towards lower pain threshold values for the thumb pressure stimuli (VVD: 4.62±1.62 kg, HCs: 5.78±2.28 kg, *P*=.10). Similarly, the mean pressures to the thumb among FM participants were significantly lower than that of the healthy controls (FM: 3.11±1.57 kg, HCs: 5.78±2.28 kg *P*<.001).

Analysis 1 VVD and FM participants display augmented brain activity in response to thumb pressure: Comparing VVD, FM, and HCs, greater activity at the insular cortex was detected in both the pain groups. Both VVD and FM patient groups had overlapping insular activity (*P*<.005).

Analysis 2 Augmented brain activation is present in VVD participants: Comparing VVD and HCs during slightly intense pressure stimuli to the thumb, VVD patients showed significantly increased brain activity in several pain regions, including the insula, dorsal mid cingulate, posterior cingulate and thalamus ventral posterolateral nuclei (*P*<.05).

Analysis 3 Differential BOLD activity in response to pressure stimulation in proposed *subgroups of VVD*: Thumb pressure ROIs from Analysis 2 showed significantly higher brain activity in the posterior cingulate region in primary VVD participants compared to secondary VVD participants (*P*=.03). Significantly higher brain activity was also noted at the posterior cingulate region in the provoked-only pain participants (ie, pain during intercourse, tampon insertion, etc.) compared to that of participants who also had unprovoked pain (*P*=.02). Pain-related activation during vulvar stimulation was significantly greater at the precuneus region in participants with provoked-only pain compared to those who reported unprovoked pain (*P*<.001).

Conclusions

The present study is consistent with our hypothesis and previous research indicating hyperalgesia and augmented central pain processing in VVD. Overlapping activation at the insula cortex in VVD and FM participants suggests that these 2 chronic pain states may share a common neurobiological pathophysiology. Augmented brain activation seen in VVD patients in response to stimulus remote from the vulva suggests central nervous system pathology in this disorder. Differing central activation among primary vs secondary VVD and those with provoked vs unprovoked pain suggest the presence of distinct VVD subgroups; groups that might differ in physiology, natural history and/or treatment response.

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Aging out of child-centered pediatric into adult-oriented healthcare: chronic pain as a key component in the transition of patients with cerebral palsy

April Zhang[1,2], Maxine Kuroda[1,3], R. Norman Harden[1,3]
[1]*Center for Pain Studies, The Rehabilitation Institute of Chicago, Chicago, Il, USA,* [2]*Northwestern University Feinberg School of Medicine, Chicago, Il, USA,* [3]*Northwestern University Department of Physical Medicine and Rehabilitation, Chicago, Il, USA*

Purpose

Pain is a critical factor for quality of life and physical and mental functioning, yet very little is known about pain in persons who have a lifelong disability such as cerebral palsy (CP). Furthermore, as persons with CP age and transition from pediatric into adult health care, there is evidence that services become substantially diminished and little attention is paid to the clinical assessment and management of pain. This study examined many different features of pain and function reported by children, adolescents, and adults with CP in order to help determine factors that affect pain as persons with CP age.

Method

This cross-sectional study included persons with CP (ages 4+) at all levels of motor severity seen in the outpatient clinics at the Rehabilitation Institute of Chicago. Following informed consent, patients were asked to complete age-appropriate forms relating to functional independence and pain intensity and location: Functional Independence Measure (FIM), Visual Analog Scale (VAS) for current pain intensity, Wong-Baker (WB) FACES pain rating scale, and a body location pain chart. The physician rated level of gross motor impairment (GMFCS). Accompanying conditions such as cognition and sensory and speech deficits were also recorded. If patients were cognitively unable to self-report, forms were completed by an accompanying caregiver.

The primary objectives of this study were descriptive and presented as mean±standard deviation for continuous variables. Differences were tested by the Student's t test and 1-way ANOVA, with associations evaluated by Pearson r or by Spearman rho, as appropriate. Multivariable linear regression was used to model current pain intensity from relevant predictors while controlling for potential confounding variables. All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS for Windows, version 17.0, Chicago, IL, 2009).

Results

The sample consisted of 15 children (mean age 8.5±2y), 18 adolescents (mean age 16.7±3.1y), and 17 adults (mean age 33.3±11.2y) for a total of 50 persons with CP (48% male, 52% female), with 14% GMFCS level I, 24% GMFCS level II, 26% GMFCS level III, 24% GMFCS level IV, and 12% GMFCS level V. 70% of the subjects had intact or age-appropriate cognition. The majority of the subjects reported pain in some form (67% children, 89% adolescents, 94% adults). Adults reported a greater number of painful body locations than children (P=.035). WB FACES pain ratings and current pain intensity measured by the VAS did not differ by age or by GMFCS. FIM scores decreased with increasing GMFCS level I-V (P<.001). In adults, FIM and current pain intensity were positively correlated (P=.036), as were FIM and WB FACES pain ratings to a slightly lesser extent (P=.091). In a multivariable linear regression model controlling for age and sex, GMFCS strongly predicted (P=.050) and FIM moderately predicted (P=.189) current pain intensity in adolescents and adults.

Conclusions

Pain is highly prevalent in persons with CP of all ages. There does not appear to be age-related changes in pain intensity, suggesting that the presence of pain should be addressed from an early age. Of note, our results show that as persons with CP age from youth to adulthood, functional independence and level of motor impairment become more important predictors of pain. Adults with greater functional independence reported higher levels of pain intensity. As young adults with CP transition into adult healthcare, attention should be focused on those who are more functional to ensure continued care and pain management.

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Is gender a factor for placebo analgesic response in the knee osteoarthritis pain model?

Meryem Saracoglu[1,2], Kelly Comstock[1], Joseph Graciosa[1], Amy Kirsling[1], Maxine Kuroda[1,2], Bruni Hirsh[1], R. Norman Harden[1,2]
[1]Rehabilitation Institute of Chicago, Chicago, IL, USA, [2]Northwestern University Department of Physical Medicine and Rehabilitation, Chicago, IL, USA

Purpose

Knee osteoarthritis (KOA) is a leading cause of chronic disability in the elderly in the United States. The symptoms of KOA, a chronic painful condition, is affected by many biopsychosocial factors, such as gender and pain perception. Pharmaceutical clinical trials that assess chronic pain frequently use the single blind placebo lead-in phase to mitigate the placebo response. Many of these trials identify conflicting findings regarding pain perception differences in the placebo analgesic response by gender. The objective of this study was to evaluate whether there is a placebo analgesic effect on chronic KOA pain levels in women and men.

Method

Data on the first 30 participants with chronic KOA pain (20 women and 10 men) were abstracted from an ongoing double blind placebo controlled pharmaceutical trial testing the efficacy of milnacipran (Savella) in treating chronic KOA pain. Prior to randomization, subjects entered into a single blind placebo lead-in on Day 4. Data from the single blind placebo lead in period (Days 4 to 13) were analyzed from the baseline and follow-up visit to evaluate the impact of gender differences on the placebo analgesic response.

At the baseline visit, all subjects received identical placebo pills, although being told the pill was either placebo or active study drug. Before and after they took the placebo, subjects were individually and collectively (males vs females) compared for their subjective average perception of pain using the Visual Analogue Scale (VAS) and McGill Pain Questionnaire Short Form (MPQ-SF).

Student's t-test and linear regression model were run to compare the data from the baseline and end of the single blind lead-in phase. The Statistical Package for the Social Sciences (SPSS for Windows, version 17.0, Chicago, IL, 2009) was used for all analyses.

Results

Women and men did not differ in age (55.1±9.6 and 55.4±7.3 years, respectively), body mass index (BMI) (34.6±7 and 33.8±6.3, respectively) and in duration of pain (8.5±8.9 years and 6.6±6.6 years, respectively). In contrast, females had an increased placebo analgesic response, while males had a decreased response during the single blind placebo lead-in. Mean VAS scores decreased by 11.9±26.1 mm between baseline and follow up visits for female participants, but increased by 8.2±19.4 mm for male participants (P=.041). Mean MPQ-SF total scores decreased by 1.4±6.1 between visits for female participants, but the score increased by 6.4±4.6 for male participants (P=.001). Between the 2 visits, MPQ affective subscale scores decreased by 0.25±1.7 for the female participants but increased by 1.8±2.6 the male participants (P=.040). Similarly, MPQ sensory subscale scores decreased by 1.0±4.6 for the female participants, but increased by 3.8±2.7 for the male participants between the 2 visits (P=.005).

In multivariable linear regression models that controlled for age, race, pain duration, and BMI, only sex contributed to differences in VAS scores, in MPQ-SF total scores and in MPQ-SF sensory subscale scores between visits. However, age and BMI, in addition to sex, contributed to differences in MPQ-SF affective subscale scores.

Conclusions

Sensory and affective descriptors of pain are affected by different bio-psycho-social factors. Our data support an important role for gender differences in pain perception and its implication for the placebo effect. Our findings add to a better understanding of pain reporting, including perception and descriptive differences in placebo analgesic responses for the KOA model.

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Evaluation of patients seeking frequent pain management services within a community hospital emergency department

Kelly Struemph[1,2], Chris Herndon[2], Julia Schimmelpfennig[1]
[1]St. Elizabeth's Hospital, Belleville, IL, USA, [2]Southern Illinois University Edwardsville, Edwardsville, IL, USA

Purpose

This project will focus on the pain management utilization of Emergency Department resources at St. Elizabeth's Hospital, a 400-bed community teaching hospital in Belleville, Illinois. The purpose of this retrospective study is to evaluate the patient demographics and treatment modalities employed during ED visits for pain management services.

Method

Following institutional review board approval, patients were identified by a computerized dispensing device medication summary of all scheduled pain medications that were administered in the ED during the months of April 2011 through June 2011. From this, any patient greater than 18 years of age with greater than 4 separate ED visits was included in the study. Patient demographics, chief complaint, treatment modalities and disposition of patients were collected for each visit.

Results

Seventy-one ED visits were evaluated for 13 patients. The top chief complaints reported were abdominal pain, chest pain, and headache. The mean number of days between visits was 11 (SEM 1.2). Only 4% of visits received a urine drug screen and at no visits was it documented that the ILPMP was reviewed. At 89% of visits patients received IV/IM opioid treatment with a mean morphine equivalent of 17.1 mg per visit. Patients with third party insurance were more likely to be admitted to the hospital (P=.002). There was no difference between genders or prescribing physicians in provisions of discharge medications (P=.48 and .433, respectively)

Conclusions

The results may not be generalizable to patients seeking frequent ED services for pain at other institutions. Planned interventions at our institution include obtainment of dedicated PDMP access for triage nursing staff, training of all ED physicians and nurses on PDMP use and evaluation, development of policies regarding urine drug screening and imaging and case management follow-up with primary care providers.

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Simultaneous quantitative determination of opioid dependency treatment drugs in human urine using ultra performance liquid chromatography paired with tandem quadrupole mass spectrometry

Michelle Wood[1], Allan Traynor[2], Crystal Holt[3], Russell Watts[1]
[1]Waters Corporation, Manchester, UK, [2]Waters Corporation, London, UK, [3]Waters Corporation, Pleasanton, CA, USA

Purpose

To develop and validate a single, simple, and rapid UPLC-MS/MS method for the quantitative determination of the opioid dependency treatment drugs methadone, buprenorphine and dihydrocodeine, in human urine.

Method

Quantitative analysis was performed on methadone (METH), buprenorphine (BUP), and dihydrocodeine (DHC) and 2 drug metabolites: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) and norbuprenorphine (NBUP) with 5 internal standards: methadone-D9; buprenorphine-D4; dihydrocodeine-D3; 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine-D3; norbuprenorphine-D3; dihydrocodeine-D6. All authentic urine samples, calibrators and quality controls (QCs) were prepared by enzymatic hydrolysis followed by a simple liquid/liquid extraction procedure. Chromatography was achieved using a Waters Acquity UPLC® system. Analytes were separated on a Waters Acquity UPLC HSS T3 (2.1 mm x100 mm, 1.8 µm) column using a gradient elution over 5 min with a mixture of 5 mM ammonium acetate containing 0.025% formic acid in water (A) and methanol (B). A Waters TQD mass spectrometer was used for analysis with electrospray ionisation in positive mode (ESI+). Two MRM transitions were monitored for each compound and each transition was optimised to achieve maximum sensitivity.

Results

Responses were linear for all compounds over the investigated range ie, 25 ng/mL-25000 ng/mL for METH and EDDP, 25 ng/mL-2500 ng/mL for DHC, 2.5 ng/mL-250 ng/mL for BUP and NBUP. Precision (intra- and interassay) and accuracy were good with CV's for spiked QC samples <14% and 96%-115%, respectively. The use of the liquid/liquid extraction was demonstrated to be very efficient and gave reproducible recoveries ie, >84% for all analytes. All compounds were shown to be stable in extracted samples over 24 hours. Limits of detection were 0.5 ng/mL for EDDP, 1 ng/mL for METH & DHC and 2 ng/mL for BUP & NBUP. Matrix effects were assessed by spiking blank extracted patient samples (n=7) with all compounds and comparing the responses against the equivalent concentration for a solvent standard solution. Average matrix effects were found to be acceptable for METH, EDDP & DHC. More significant effects were observed for BUP & NBUP (-39% and +19.3%, respectively), consequently deuterated internal standards were included throughout to minimise the impact of the matrix on data quality. The method was applied to the analysis of clinical patient samples (n=58) for METH, EDDP, BUP & NBUP which were previously analysed by 2 separate, established and validated HPLC-MS/MS methods; all samples showed good agreement. No suitably quantified patient samples could be obtained for DHC, however samples containing DHC (n=20) that had been qualitatively analysed using thin layer chromatography were obtained and analysed using the newly developed method. The qualitative results showed good correlation.

Conclusions

The developed method provides a simple, sensitive and robust solution for the quantitation of opioid dependency treatment drugs in human urine. The use of a single assay, suitable for the simultaneous analysis of all of the drugs of interest, alleviates the issues involved in switching between methodologies for the different drugs, offers significant time-saving benefits and a 50% reduction in sample preparation time.

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Maternity support vest for pregnancy-related low back pain: a randomized controlled pilot study

Simone Sin Man Ho[1], Winnie Wai Man Yu[2], Terence Tzu Hsi Lao[1], Daniel HK Chow[2], Joanne Wai Yee Chung[3]
[1]*The Chinese University of Hong Kong, Hong Kong, Hong Kong,* [2]*The Hong Kong Polytechnic University, Hong Kong, Hong Kong,* [3]*The Hong Kong Institute of Education, Hong Kong, Hong Kong*

Purpose

Although pregnant women often perceive low back pain (LBP) as a normal physiological process, studies showed that LBP experienced during pregnancy may become more intense after delivery and even chronic in nature. LBP is the most common musculoskeletal problem during pregnancy. As many as 50%-70% of pregnant women experience pregnancy-related low back pain (PLBP) and/or pregnancy-related pelvic girdle pain (PPGP). Common treatments recommended by healthcare professionals include heat applications, ergonomic advice, exercises, physiotherapy, analgesics, and support belts. Women are reluctant to taking medications for the fear of potential harm to the fetus, and compliance to physiotherapist treatments is poor especially for women in the workforce. Many pregnant women self-manage their back discomfort by wearing support garments as they are easily accessible and widely advocated. While some studies reported that support garment wearing have reduced LBP, others identified undesirable effects of skin irritation, excessive heat and pressure, and adjustment problem. To date, scientific research relating to the design and development of maternity support garments is lacking. The clinical efficacy of these garments remains elusive with limited solid research evidence to substantiate its putative beneficial effects.

The purposes of this study were to develop design criteria for maternity support garments, to develop a garment prototype, and to evaluate the feasibility of recruitment and the efficacy of a new prototype of maternity support vest (MSV) on PLBP in a randomized controlled pilot study. This abstract will present the findings of the pilot study only since it is part of a larger study.

Method

This study was conducted in 3 phases; exploratory phase, developmental phase, and evaluative phase. In the exploratory phase, interviews and wear trials were completed to elicit responses of 10-14 pregnant women using 8 maternity support garments in terms of comfort, ease to put on and take off and aesthetics. Material tests were performed on the same 8 garments to determine the physical properties. The above studies aimed to identify the design criteria for developing maternity support garments. Furthermore, a longitudinal study of 29 pregnant women was undertaken to investigate various biomechanical parameters during the 3 trimesters to identify which biomechanical parameters may be used to assess the biomechanical effect of garment prototype. In the developmental phase, a functional-designed MSV prototype was developed mainly based on the new design criteria. In the evaluative phase, 9 subjects were randomly assigned to a 7-week MSV and exercises group and a control group (exercises only) in a longitudinal prospective randomized controlled trial to provide preliminary data for future larger scale trial. Pregnant women who were primigravida at gestational week 28 with singleton pregnancy were recruited in the antenatal clinic of a large local university hospital. The primary outcomes were pain intensity using Numeric Rating Scale (NRS) and functional status measured by Roland-Morris Disability Questionnaire (RMDQ). The secondary outcomes included pregnancy outcomes, compliance rate, biomechanical parameters include centre of pressure and sagittal lumbar curve, and garment comfort evaluation. The primary outcomes were assessed at baseline (T_0) and weeks 1 (T_1), 4 (T_2) and 7 (T_3).

Results

The data shows a progressive decreasing trend in present pain intensity in the intervention group (NRS=2.0±2.2 (T_0) to 1.5±1.9 (T_3)). This pain reduction was accompanied by some improvement in the functional status (RMDQ scores=7.3±4.3 (T_0) to 5.0±7.4 (T_3)). On the contrary, there is a progressive increasing trend in present pain intensity in the control group (NRS=.8±.8 (T_0) to 2.8±2.2 (T_3)), despite a slightly improved functional status (RMDQ scores=8.2±3.3 (T_0) to 7.2 ±3.3 (T_3)). No between-group differences were observed on pregnancy outcomes including delivery week, mode, fetal body weight, and Apgar scores. Treatment compliance was considered high since most women wore the MSV prototype for an average of 5 times per week for 9 hours per day during the 7 weeks of intervention period. No adverse effects were reported by the intervention group. No obvious trend was noted in the biomechanical parameters. It is probable that the biomechanical effects were not sufficiently large to be detected in a small sample. Alternatively, this may indicate that there are perhaps other important biomechanical factors that may explain the pain reduction. The comfort evaluation showed high overall comfort scores.

Conclusions

This study demonstrated the feasibility of a randomized controlled trial using MSV among pregnant women during the third trimester. Preliminary findings suggest that long term wearing of MSV as an adjunct to exercises may improve pain intensity and functional status over exercises alone for pregnant women with PLBP. The new maternity support vest prototype seems to be a safe, comfortable, usable and promising intervention for pregnancy-related low back pain.

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The effects of nurse-initiated early pain management program (NIEPMP) for acute back pain in Emergency Medicine Ward: Pilot study

Ching Ying Yau, Carmen Wing Han Chan, Simone Sin Man Ho
The Chinese University of Hong Kong, Hong Kong, Hong Kong

Purpose

Disability related to chronic low back pain has been identified as one of the major medical and social problems. Early activation of pain management program using biopsychosocial model has demonstrated to be effective in reducing disability and chronicity of low back pain. However, there are limited studies relating to back pain management in emergency room. Studies concerning psychosocial components and nursing input were very limited in AED. These include back pain related emotions such as anxiety. Nursing input such as providing health education and reassurance can help ease some anxiety and make patients psychologically more ready to be discharged home. However, such biopsychosocial model of care for back pain patients, which acknowledge the influence of psychosocial factors on the development of chronicity and disability, is seldom addressed in the emergency setting. This pilot study examines the feasibility of recruitment and the efficacy of a nurse-initiated early pain management program (NIEPMP) for adults with acute low back pain patients in the Emergency Medicine Ward (EMW). The 4 objectives are to assess the effects of NIEPMP on prevention of disability, pain relief, anxiety reduction, and promotion of patient satisfaction in EMW.

Method

This study adopts a pretest, posttest, repeated measures, randomized controlled trial. Subjects are selected from patients presenting to the AED of a regional hospital in the Kowloon Central Cluster. They are admitted to EMW after 5pm (after the service hour of physiotherapy) and waiting for physiotherapy next day. The NIEPMP was based on a combined intervention of physiological therapeutic component (heat therapy) and psychosocial therapeutic component (health education booklet). The primary outcome measure was the Roland and Morris Disability Questionnaire (RMDQ). Secondary outcome measures were: Visual Analog Scale (VAS) for pain intensity and patient satisfaction, and short Form from the Spielberger State-trait Anxiety Inventory (STAI). Eligible participants were randomly assigned to interventional group (n=10) or control group (n=10). Pretest data (T0) were collected as soon as consent was obtained. After randomization, the interventional group received NIEPMP delivered by researcher individually as soon as they admitted EMW. Posttest data (T1) were collected immediately after NIEPMP. 3 telephone follow-up were carried out at 1-week (T2), 1-month (T3) and 3-month (T4) intervals.

Results

Thirteen patients were randomly assigned to NIEPMP or usual care in this prospective randomized controlled trial to provide preliminary data to inform future trial of larger scale. There was no significant difference in RMDS, pain intensity and satisfaction (VAS) at T1 and only a lower SF-SSTAI Score was found in the NIEPMP group (m=17.88(SD=1.81) vs m=15.80(SD=2.25)) at T1. However, at T2, T3 and T4, the data showed a greater decreasing trend in RMDS, pain intensity (VAS) and SF-SSTAI in the NIEPMP group than the control group.

Conclusions

This study demonstrated the feasibility of a randomized controlled trial of NIEPMP in EMW. Preliminary findings suggest that NIEPM may reduce anxiety level, pain intensity, and physical disability in patients with acute low back pain.

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Effects of facilitated swaddling for controlling procedural pain in premature neonates: a randomized controlled trial

Simone S.M. Ho, Lai Ping Ho, Doris Y.P. Leung
The Chinese University of Hong Kong, Hong Kong, Hong Kong

Purpose

Preterm neonates are exposed to multiple painful medical interventions in neonatal intensive care units (NICU) but pain assessment and control remains suboptimal. Clearly it is important to develop strategies to ameliorate pain caused by medical procedures among neonates. Pharmacological approach is widely accepted analgesia for neonate in NICU during painful procedures. Owing to the concern of early opioid exposure in preterm infants, effective nonpharmacological interventions that are easy to administer are therefore essential and preferred methods of analgesia for less painful procedures such as heelstick and suctioning. Swaddling, motor containment of infants to maintain a flexed position with a blanket, is still a common practice in many countries. Recently, the use of swaddling in clinical studies among healthy and full term infants showed beneficial effects of decreased pain scores. However, there are few research into swaddling as a pain relief intervention to control heelstick procedural pain among premature neonates. We investigated the effect of facilitated swaddling to control procedural pain among premature neonates.

Method

54 premature neonates between 30-36 6/7 gestation age from NICU were randomly assigned to facilitated swaddling (N=27) and control (no intervention, N=27). Written informed consents were obtained from parents. Assessment of pain was performed pre, during, immediate, 2, 4, 6, and 8 minutes after heelstick procedure using the Premature Infant Pain Profile (PIPP). The PIPP is a composite measure of 7 indicators including heart rate (HR) and oxygen saturation (SaO_2), 3 facial responses to pain, behavioral state and gestational age. PIPP has demonstrated high level of reliability and validity.

Results

The results showed that the changes in PIPP scores were significantly lower in the intervention compared to the control group over time ($P<.001$). The changes in HR and SaO_2 in the intervention group were significantly lower than that of the control group at all measured time points ($P<.001$). Notably, both HR and SaO_2 of the swaddled neonates resumed to the baseline level at 2 minutes whereas the physiologic outcomes of the control group reached a stable state at an extended period of 6 to 8 minutes respectively. No adverse effects were observed. The results suggest that facilitated swaddling was effective in controlling procedural pain of heelstick among premature neonates. It has been suggested that the motor containment provides stimulation across the proprioceptive, thermal and tactile sensory systems that may reduce pain through gate control mechanisms.

Conclusions

Swaddling seems to be a simple, safe, effective, low cost, and nonpharmacological pain relief intervention and may be used among preterm neonates during heel stick procedures in the clinical setting.

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A correlation data analysis of psychotropic medication use in patients on buprenorphine, methadone, or combination opioid therapy

Cameron West, Amadeo Pesce, Murray Rosenthal, Maria Guevara, Angela Huskey, Perla Almazan, Charles Mikel, Robert West, Sergey Latyshev, David Masters-Moore
Millennium Research Institute, San Diego, USA

Purpose

Methadone and buprenorphine are part of the arsenal of opioids used to treat patients with chronic pain. Patients suffering with chronic pain often have comorbidities due to the biopsychosocial effects of pain on the patient's quality of life. Depression and anxiety are common comorbidities, and it is unknown whether pain typically precedes depression and anxiety or if depression and anxiety predispose a patient to chronic pain. In addition, certain psychotropic medications are sometimes used to treat various pain types such as neuropathic pain. To date, there have been no studies examining the relationship between chronic opioid therapy, including methadone and buprenorphine, with use of anxiolytic and antidepressant medications. The purpose of the analysis was to examine the correlation between detection of the specific opioids buprenorphine and methadone or combination opioid therapy and the detection of psychotropic medications, specifically antidepressants and benzodiazepines, in patients with chronic pain.

Method

Over 300,000 urine specimens from patients were tested for the presence of opioids and commonly prescribed psychotropics using liquid chromatography-tandem mass spectrometry (LC-MS/MS) at Millennium Laboratories between November 2011 and February 2012. De-identified specimens from patients on buprenorphine monotherapy, methadone monotherapy, and combination opioid therapy were considered. The buprenorphine and methadone monotherapy groups were further sorted into 2 groups:
1) where only the opioid and/or metabolite were observed and 2) where additional nonreported opioids were detected in addition to the prescribed opioid. Specimens positive for psychotropic medications were tabulated and compared among the cohorts.

Results

26.7% of specimens (n=3930 of 14,710) that tested positive for prescribed buprenorphine monotherapy were positive for psychotropics whereas 38.1% of specimens (n=897 of 2355) that tested positive for prescribed buprenorphine monotherapy, but were also positive for one or more nonprescribed opioids, were positive for psychotropics. For methadone the rates were 42.7% (n=1751 of 4098) and 48% (n=386 of 805), respectively. 46.4% of specimens (n=30,898 of 66,659) with reported combination opioid therapies were positive for psychotropics. This analysis is limited because specimens were tested according to physician requests and therefore not all specimens were tested for all compounds. Furthermore, it is unknown for which indications the medications were prescribed. Specifically, it is unknown whether any patients prescribed buprenorphine or methadone were being treated for opioid dependence.

Conclusions

Buprenorphine monotherapy was accompanied by the lower use of psychotropic drugs than methadone monotherapy. Those patients on methadone monotherapy or combination therapy were more likely than those on buprenorphine monotherapy to be positive for psychotropic drugs. Treatment of chronic pain is challenging and multi-

faceted, particularly with opioid therapy. Objective information regarding concomitant use of psychotropics may be helpful in clinical decision making, particularly to prevent drug-drug interactions, duplication of therapy, and identify misuse, abuse or addiction that can result in referral to treatment.

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Analgesic dose-response relationship between 200-mg and 400-mg single doses of ibuprofen: a meta-analysis

Shyamalie Jayawardena, Paul Butkerait
Pfizer Consumer Healthcare, Madison, NJ, USA

Purpose

Ibuprofen is a peripherally acting nonsteroidal anti-inflammatory drug (NSAID) available as an over-the-counter (OTC) agent for analgesia. Based on the current OTC dosing instructions for ibuprofen, adults and children 12 years and older may take 1 tablet (200 mg) every 4 to 6 hours while symptoms persist or for up to 10 days. If pain does not respond to 1 tablet, 2 tablets (400 mg) may be used; however, the maximum dose should not exceed 6 tablets (1200 mg total) within a 24-hour period unless directed by a doctor. The oral surgery model (third molar extraction) is an acute pain model frequently used to assess analgesic effects of NSAIDs. The purpose of this meta-analysis was to investigate the analgesic dose-response relationship between 200-mg and 400-mg doses of immediate-release ibuprofen in oral surgery studies.

Method

This meta-analysis was based on Total Pain Relief scores over 6 hours (TOTPAR6), which is the maximum labeled dosing interval for OTC ibuprofen. Pain relief was measured using a categoric scale from 0 (no pain relief) to 4 (complete pain relief) at prespecified timepoints. Studies considered for inclusion in the meta-analysis were identified through an extensive search of Pfizer internal databases and external databases (eg, MEDLINE through June 2011). Studies that met the following criteria were included: double-blind, placebo-controlled studies conducted in the oral surgery setting that evaluated 200- and/or 400-mg single doses of immediate-release ibuprofen and included sufficient information to obtain estimates of treatment differences and associated standard errors. Studies evaluating all formulations of immediate-release ibuprofen were included. Although some formulations have been shown to provide faster onset of action (eg, liquid gelatin capsules), all marketed formulations were assumed to provide similar overall extent of pain relief. A separate analysis was conducted for each comparison (400-mg vs placebo, 200-mg vs placebo, and 400-mg vs 200-mg), using only those studies that concurrently evaluated the doses being compared. In the statistical model, study term was used as a random effect.

Results

The search identified 931 clinical studies. After manual review for inclusion criteria, 38 unique studies were included in the meta-analysis. Of these studies, 13 evaluated 200-mg ibuprofen, 32 evaluated 400-mg ibuprofen, and 7 evaluated both 200- and 400-mg doses of ibuprofen. Twenty-one of these studies were internal Pfizer studies (4 evaluated 200-mg ibuprofen, 17 evaluated 400-mg ibuprofen, and 2 evaluated both 200- and 400-mg doses of ibuprofen). The pooled estimate for the treatment difference for the 400-mg (n=2890) vs placebo (n=1486) comparison was 9.58 (95% CI: 8.80-10.36). Of the 32 studies included in this comparison, none had a confidence interval that crossed zero. The pooled estimate for the treatment difference for the 200-mg (n=1036) vs placebo (n=653) comparison was 6.89 (95% CI: 5.42-8.35). Of the 13 studies included in this comparison, only 1 had a confidence interval that crossed zero. Both the 400-mg and 200-mg vs placebo comparisons were statistically significant ($P<.001$). For the 400-mg (n=716) vs 200-mg (n=714) comparison, the pooled estimate for the treatment difference was 1.39 (95% CI: 0.41-2.37). This comparison was also statistically significant ($P=.013$). Both the 400-mg and 200-mg doses of ibuprofen were well tolerated across all studies, and the incidence of adverse events was similar between both doses.

Conclusions

Both doses of ibuprofen provided significantly better overall pain relief compared with placebo over the 6-hour period studied. For the 400-mg and 200-mg vs placebo comparisons, the confidence intervals for the pooled estimates did not overlap, indicating that 400-mg ibuprofen provided significantly better overall pain relief compared with 200-mg ibuprofen. These results were confirmed by data from the 7 studies that simultaneously evaluated both doses of ibuprofen. The results of this meta-analysis are consistent with other reports in the literature on the efficacy and safety of OTC ibuprofen for pain relief following oral surgery.

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Concomitant opioid and methylphenidate use in patients with chronic pain

Yutong (Joy) Jiang[1], Joseph Ma[1,2], Brookie Best[1,3], Candis Morello[1,4], Rabia Atayee[1,2], Amadeo Pesce[5,6]
[1]*University of California San Diego (UCSD), Skaggs School of Pharmacy and Pharmaceutical Sciences, La Jolla, CA, USA,* [2]*Doris A. Howell Palliative Care Services, San Diego, CA, USA,* [3]*UCSD Department of Pediatrics, Rady Children's Hospital, San Diego, CA, USA,* [4]*Diabetes Intense Medical Management Clinic, Veterans Affairs San Diego Healthcare System, La Jolla, CA, USA,* [5]*Millennium Research Institute, San Diego, CA, USA,* [6]*Department of Pathology and Laboratory Medicine, UCSD School of Medicine, La Jolla, CA, USA*

Purpose

High doses and/or multiple opioids are sometimes used for the management of moderate to severe pain, particularly in patients with chronic pain. Opioid-induced sedation can be a serious adverse effect in patients on chronic opioid therapy, leading to decreased daily function and/or quality of life. Evidence suggests that methylphenidate can be used to manage opioid-induced sedation. However, sparse data exist regarding methylphenidate and opioid use in nonterminal patients with chronic pain. The purpose of this retrospective data analysis was to examine concomitant opioid and methylphenidate use by testing urine specimens of nonterminal patients with chronic pain. These observations may provide insight for urinary medication monitoring of methylphenidate.

Method

Urine specimens collected by healthcare professionals between September 2011 and May 2012 were analyzed at Millennium Laboratories using Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS). This retrospective data analysis was performed using de-identified test results that were examined for physician-reported prescribed methylphenidate, oxycodone, oxymorphone, hydrocodone, hydromorphone, morphine, fentanyl, and methadone. For each of these opioids, specimen data were separated into those with reported prescriptions for methylphenidate and an opioid vs a baseline population who were taking an opioid, but not methylphenidate. Concomitant vs baseline population frequencies were compared. Percent differences of reported opioid use in the concomitant population were calculated to correct for baseline frequencies in order to determine the opioids most associated with methylphenidate use. Urine specimens were then analyzed for detected concentrations of each opioid, methylphenidate and its metabolite, ritalinic acid, to assess for presence of reported medications. Detection rates were compared to baseline detection rates in the total cohort population. Frequencies were calculated using specimens collected from a subject's first visit only.

Results

Methadone was the most common opioid used with methylphenidate in patients with chronic pain. Compared to the baseline population, methadone use was 130% higher in the methylphenidate group vs the baseline group. In contrast, hydrocodone was the only opioid used less with methylphenidate compared to the baseline population, with a 16.8% lower use rate. The detection rates of reported as prescribed opioids in urine specimens were found to be slightly higher in the concomitant population vs the baseline population, with the percent use ranging from 0.41%-7.23% higher. The detection rate of opioids ranged from 70.2%-88.3% in the baseline population and 71.1%-88.9% in the concomitant population. The overall detection rate of methylphenidate and ritalinic acid in urine samples of subjects with reported methylphenidate use was 50.6% and 71.3% respectively. In the concomitant population compared to the baseline population, methylphenidate and ritalinic acid detection rates were the following: methadone (higher detection rate of 21.9% and 14.6%, respectively), fentanyl (24.3%, 8.3%), morphine (25.5%, 13.6%), and oxycodone (5.7%, 4.5%). A lower detection rate for both methylphenidate and ritalinic acid was observed in oxymorphone (lower by -43.5%, 19.8% respectively) and hydrocodone (-76.3%, -6.9%) users.

Hydromorphone had a higher detection rate of methylphenidate (percent difference of 7.4%) but a lower detection rate of ritalinic acid (percent difference of -3.8%). The limitations of this retrospective analysis are that the following factors are not known: 1) the indication for which methylphenidate was prescribed (eg for the side effects of opioids or an attention deficit disorder) or 2) if the methylphenidate was prescribed to be taken regularly or as needed. Furthermore, tests were performed by physician request, and therefore not all specimens were analyzed for all compounds.

Conclusions

Of the opioids examined, methadone was the most common opioid used in combination with methylphenidate; this may be due to the opioid-induced sedation associated with methadone. Urinary detection in specimens with reported prescriptions for opioids showed detection is consistent with reported prescriptions (range 71%-89%). Detection of methylphenidate is less consistent with its reported prescriptions. However, a portion of all reported prescribed medications is undetected overall, suggesting that inconsistencies exist between intended and actual use of certain medications. Considering the potential for medication misuse of these controlled substances, healthcare professionals should consider closely monitoring medication use in patients prescribed these medications.

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Retrospective study of false-positive percent for urine drug screening by immunoassay

Kamisha Johnson-Davis[1,2], JoEtta Juenke[2], Lutsia Jensen[3], Chantry Clark[3], Paul Brown[3], Gwendolyn McMillin[1,2]
[1]University of Utah Health Sciences Center, Salt Lake City, Utah, USA, [2]ARUP Institute for Clinical and Experimental Pathology, Salt Lake City, Utah, USA, [3]ARUP Laboratories, Salt Lake City, Utah, USA

Purpose

Urine drugs screens are often ordered by clinicians to identify drug use or exposure in the emergency department or other medical settings, to monitor patient adherence to prescribed drug therapy; and to support various forensic applications. Urine drug screens are frequently performed by immunoassay on routine chemistry analyzers due to ease of use, relatively low cost, rapid result turnaround time, and ability to detect several drugs and drug classes. However, immunoassays are limited in sensitivity and specificity when compared to complex analytical methods such as chromatography coupled to mass spectrometry. Immunoassay drug screens are prone to interferences and can produce false-negative and false-positive results, due largely to the cross-reactivity profiles of the capture antibodies. For example, immunoassays may or may not detect metabolites or structurally similar compounds. Immunoassay specificity varies among commercial vendors, thus cut-offs for specific compounds within a drug class, are not standardized. In addition, urine adulteration may lead to false-negative results. Consequently, it may be important to follow-up a positive or negative drug screen result obtained by immunoassay, with confirmatory testing, based on the clinical scenario. The purpose of this retrospective study was to evaluate the performance of the in-house urine drug screen, to accurately detect positive patient samples for different drugs. The screen can detect several drugs and drug classes, which include: amphetamine, methamphetamine, barbiturates, benzodiazepines, cocaine, ecstasy (MDMA), methadone, propoxyphene, opiates (morphine, codeine, dihydrocodeine, hydrocodone, hydromorphone, oxycodone and oxymorphone), phencyclidine (PCP), marijuana (tetrahydrocannabinol; THC).

Method

All results for a urine drug screen with reflex to confirmation test were collected over a 6-week period, and de-identified. Reagents from Microgenics were used for the oxycodone assay and the Syva EMIT® II Plus reagents were used for the rest of the drugs in the screen. The screen was performed on the Beckman AU400e random access automated clinical analyzer. Urine drug screens (cutoff, ng/mL) performed include: amphetamine and methamphetamine (300), barbiturates (200), benzodiazepines (200), cocaine (150), MDMA (500), methadone (150), propoxyphene (300), opiates (300), oxycodone (100), PCP (25), and THC (20). Percent positivity - for each immunoassay were determined. Agreement with previously validated GC-MS or LC-MS/MS confirmatory methods was also determined, in order to assess the true positivity percent vs the percent of false-positive results (positive by screen but negative by confirmation). False-negative results were not investigated. False-positive amphetamine/methamphetamine/MDMA specimens were further analyzed by full-scan GC-MS on the Agilent 6890N gas chromatograph with Agilent 5973N mass selective detector, with an amu range of 55 - 425. Drug identification was made by comparison to retention times, mass pattern matches, and library match.

Results

There were 1504 de-identified results collected, of which 1145 were positive for at least one of the immunoassays performed (76%). Confirmation results demonstrated that 53 (4.6%) of the samples that tested positive by screen were false-positives and tested negative by confirmation testing. The percent of positive samples for the following immunoassays: barbiturates, cocaine, methadone, propoxyphene, and PCP were relatively low, <5%. In addition, the percent of false-positive samples for the following immunoassays: cocaine, methadone, propoxyphene, and PCP were 0% and barbiturates were 3.6%. The percent of positive samples were 6.8% for

amphetamine/methamphetamine/MDMA, 12.8% for benzodiazepines, 29.9% for opiates, and 18.0% for THC. There were 41.7% false-positive samples for amphetamine/methamphetamine/MDMA, 0% for benzodiazepines, 2.0% for opiates (including oxycodone), and 0% for THC immunoassays.

To investigate the high false-positive percent for amphetamine/methamphetamine/MDMA, an additional study was performed and 311 additional patient samples that screened positive for this assay were collected. After comparing the screen results to confirmation data, it was discovered that out of 311 samples, 175 samples were confirmed positive (56.3%) and 136 were confirmed negative, which were false-positives (43.7%). Out of the 136 that were false-positives by immunoassay screen, 70 specimens were false-positives for MDMA, 48 were false positives for amphetamine/methamphetamine. The false-positive specimens were further analyzed by full-scan GC/MS, to determine if there were other drugs present in the specimen that may have caused the false-positive results. Based on this analysis, 3 specimens were positive for phentermine, 2 were positive for ephedrine/pseudoephedrine, 12 were positive for bupropion, and 1 was positive for trazodone. The cross-reactivity profiles of the immunoassays and independent publications from other laboratories suggests potential to cross-react with bupropion, ephedrine, phentermine, pseudoephedrine, and support the data in this study.

Conclusions

Based on the results from this retrospective study, immunoassay drug screens could accurately detect true positive patient samples for most of the drugs in the screen and had percent false-positives <5%. On the contrary, some immunoassay tests were more prone false-positives, such as, amphetamine/ methamphetamine/MDMA. Upon further investigation, the amphetamine/methamphetamine /MDMA assays were susceptible to false-positive results, explained in part by bupropion, phentermine, ephedrine/pseudoephedrine, and trazodone. Confirmation testing is necessary, especially for immunoassay tests that are prone to false-positive or false-negative results, when quantitative results are important for interpretation (eg opiates), and when results are inconsistent with clinical expectations.

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The economic burden of prescription opioid tampering in the United States

Jeffrey Vietri[1], Ashish Joshi[2], Jack Mardekian[2], Alexandra Barsdorf[2]
[1]*Kantar Health, Princeton, NJ, USA,* [2]*Pfizer Inc, New York, NY, USA*

Purpose

Prescription opioid medications have an established role in pain management, providing relief to those with acute pain and allowing many with moderate to severe chronic pain to lead more comfortable and productive lives. However, abuse of these medications is a tremendous problem in the US. Over 12 million people used or misused prescription pain relievers in the past year, and almost 15,000 died from overdose of prescription opioids. In addition to the human costs, the economic costs resulting from abuse and misuse of prescription opioids are estimated to be billions of dollars annually.

While oral overconsumption of opioids is common among abusers, tampering with opioids by chewing, or crushing to enable abuse by other routes such as IV injection or snorting is also common among abusers. One approach that may reduce prescription opioid abuse while safeguarding appropriate use is to develop formulations that incorporate tamper-resistant technologies (TRTs). In order to accurately gauge the benefit that opioid medications with TRTs could provide, a better understanding of the impact of the tampering of prescription opioids within the US general population is necessary. This study surveyed a nationally-representative sample to quantify the economic costs associated with prescription opioid abuse.

Method

Participants from the US National Health and Wellness Survey (NHWS) were invited to complete a screening survey assessing use, misuse, and abuse of prescription opioid medications in the preceding 3 months. For this study, abuse was defined as taking a prescription opioid medication for the purpose of getting high. Those identified as prescription opioid users and abusers were directed to an extended version of the survey where they provided more information on their use of these drugs, including the frequency they took the medication to get high and whether they tampered with the medication (eg, crushed, chewed, etc). Respondents also indicated the number of physician visits, ER visits, hospitalizations, and days of drug rehabilitation due to opioid use and not due to opioid use during the same 3 months. Direct healthcare costs for physician visits, ER visits, and hospitalizations were estimated by multiplying the reported frequency of each type of healthcare resource use by the 2010 median unit cost in the Thompson Reuters MarketScan database for each type of service. Drug rehabilitation costs were estimated using mean unit costs from the Alcohol and Drug Services Study Cost Study, inflated to 2010 dollars. Generalized linear models (GLMs) were used to quantify the opioid-specific direct medical costs. GLMs specified a negative binomial distribution and log-link function, and covariates included age, race, employment status, household income, alcoholism, psychological comorbidities, and Charlson comorbidity index (CCI). Models of costs within abusers also included tampering and frequency of abuse as predictors.

Results

A total of 25,864 were screened for prescription opioid use, and 1206 respondents reported either use or abuse and provided usable data in the extended survey. Abusers who tampered with opioid drugs (n=107) and abusers who did not tamper (n=118) were younger, had lower CCI scores, and were less likely to be white than nonabusers (prescription opioid users who did not abuse or misuse opioids, n=981). Relative to nontampering abusers, tampering abusers were more likely to abuse opioids more than 2 days per week, were more likely to be male, less likely to be white, and had higher CCI scores. Annualized mean opioid-related direct medical costs were estimated at $22,110

for tampering abusers, $2,816 for nontampering abusers, and $306 for nonabusers ($P<.05$ for all pairwise comparisons). Annualized median opioid-related direct medical costs were estimated at $3,018 annually for tampering abusers, in contrast to zero dollars ($0) for both nontampering abusers and nonabusers.

In multivariable models, annual opioid-related medical costs were strongly associated with abuse. Within abusers, tampering ($P<.01$), more frequent abuse ($P<.01$), and minority race ($P<.05$) were associated with higher opioid-related medical costs. The adjusted annual incremental cost of tampering was estimated at $9,707 relative to respondents who abused the medication only in its original form.

Conclusions

Abuse of prescription opioid medication is associated with greatly increased opioid-specific healthcare costs relative to appropriate medical use of these medications. The direct medical cost of abuse varies widely among abusers; those who tamper incur even higher costs than those who only abuse these drugs in their original form. Replacing conventional prescription opioids with those with TRTs may reduce the impact of prescription opioid abuse due to tampering on healthcare utilization and associated costs.

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Pain improvement project with small test of changes using simple tools and education

Helen Kim, Jill McCormick, Pamela McGill, Christina Lolachi
Kaiser Permanente Riverside Medical Center, Riverside, CA., USA

Purpose

During the 2010 Kaiser Permanente nursing summit, pain management was identified as a focus for improving patient care. Representatives from different physician specialties, nursing leadership, education, and staff were selected to form a steering committee dedicated to improve pain management for the hospitalized inpatient population at our facility.

Our goal is to improve and promote effective pain management through a consistent and standardized method of pain assessment, documentation, and communication.

Method

Our team studied other hospitals in our organization with consistently high pain management scores on the Hospital Consumer Assessment of Healthcare Providers and Systems survey (HCAHPS). Kaiser Permanente Baldwin Park had initiated a similar project with good success and kindly shared their teaching tools with our facility. Further modifications were made to these tools by our team to meet our needs.

We first implemented 2 bedside patient teaching tools that would encourage communication between the patient and healthcare providers, as well as patient's active involvement of their care. Each bedside tool included the Wong-Baker faces scale, proven to be reliable and valid in the assessment of a patient's pain level. This scale was placed in close proximity to the patient, allowing them to track their own pain level. The bedside teaching tool also included a pain management agreement between the patient and nursing staff which reviewed the responsibilities and expectations of both the nurse as well as the patient, with the end goal of better pain control through enhanced communication.

We also implemented a bedside medication flow sheet listing the commonly used pain medications, with their mode of action, and side effects. The nursing staff is also able to list their current pain medications on this tool, with dose given, and the next dose. This further promoted communications between patient and healthcare provider. To collect preliminary data, nursing students were used to survey the patients on the units where these studies were being implemented.

Results

Preliminary in-house data collection shows that patient perception of their pain management care has improved. Currently available HCAHPS data on pain management also reflects this positive trend at Kaiser Riverside.

Indirectly, as a result of these small tests of change, nursing staff noted that patients were less likely to use their call button to ask about their pain medications, communication was improved between patient and staff members, and patient understanding of their pain management treatment plan was enhanced.

The staff has become more engaged in pain management problem solving and is more likely to approach pain specialists.

Conclusions

Our goal was to improve and promote effective pain management through a consistent and standardized method of pain assessment, documentation, and communication. Though this study is still ongoing, our preliminary data seems to show that our tests of change appear to be effective in reaching our end outcome in providing interactive and enhanced pain management care of our hospitalized patients at Kaiser Permanente Riverside.

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Development of the chronic pain acceptance Self Rating Scale: results of the Expert Review Rounds

Audrey Kinzel, Laurie Hellsten, Randy Duncan
University of Saskatchewan, Saskatoon, Saskatchewan, Canada

Purpose

Acceptance of chronic pain is an approach embraced by some individuals allowing them to live their lives meaningfully and purposefully, even though they experience pain. The purpose of this multiphase research study is to accumulate psychometric (ie, validity and reliability evidence) for the Chronic Pain Acceptance Self Rating Scale (CPASRS) and to develop related treatment interventions to facilitate the management and treatment of chronic pain. The CPASRS will provide chronic pain professionals/clinicians a valid and useful measure by which to identify current acceptance related attitudes, beliefs, emotions, and behaviours held by the client. This information will allow the clinician to tailor the intervention to the client thus increasing treatment efficiency whereby client distress will reduce while increasing quality of life. Phase one of the study involves a series of item content reviews by measurement and chronic pain experts. Following revisions based on the experts' comments and quantitative assessment results of item fit, a focus group will offer feedback and suggestions resulting in further revisions. A pilot study will be conducted which will refine the scale further. Longer term plans are to develop interventions to be used primarily by psychologists but also physicians and rehabilitation specialists to facilitate management of chronic pain. The overall goal is to facilitate the clients' development of acceptance related pain strategies that will, over time, increase quality of life while reducing distress for the individual. With such knowledge, the effectiveness and efficiency of chronic pain treatment will increase and associated financial costs lowered.

Method

The purpose of the expert content reviews (phase 1) was to judge the relevance and representativeness of the proposed CPASRS items. The first step delineated key constructs and specify the scale content. This step involved multiple strategies, including review of relevant theories and research and examination of existing scales. A concise definition of each aspect/subscale of chronic pain acceptance was developed which demarcated the boundaries of each domain. Following this, 60 items were developed specifically for the domain definitions. To accumulate evidence of content validity for the scale, the items and domain definitions are being subjected to 2 rounds of review (first round involving psychometricians is complete and second round with psychometricians and chronic pain professionals is underway). Experts receive the scoring package and instructions. Using a scale ranging from 0 (No Fit) to 4 (Excellent Fit), experts judge how well each item represents (ie, fits) subscale definition it was developed for. Experts then judge how comprehensively the proposed items sample the subdomains and asked to judge: (a) whether scoring protocol is likely to identify individuals who may benefit from treatment; (b) whether scales are likely to identify individuals who have increased in their acceptance of their pain as indicated by their score on the CPASRS and in what areas, and (c) utility of the scale in overall treatment for clients. Judges then provide suggestions for item revisions and return the their rating scale package to the researchers. Results of the review direct the subscale and item revisions.

Results

Eleven psychometric experts were asked to complete the reviews and 6 experts accepted the invitation. The experts (2 males and 4 females) rated each of the items according to how well the item met the domain definition it was intended to measure. Experts evaluated the fit of 8 items intended for the Thoughts/Cognitions subscale, 11 items designed for the Support subscale, 28 items intended to assess the Attitude subscale, 8 items designed for the Behaviours subscale, and 5 items intended to measure participants' Emotions. Following the compilation and summary

of the judges' qualitative feedback, the numerical ratings were inputted into the Excel computer program and analyzed using the methods outlined by Hellsten and Rogers (2009). Results were then compared for consensus and convergence in order to determine the items that best fit the subscale definitions. Although each judge rated the items numerically, the most valuable part of the rating process to date has been the suggested modifications, revisions, and the judges' comments. Due to the substantial suggested revisions, the decision was made to revise (ie, revise, add, and delete) the scale according to the qualitative feedback rather than utilize the quantitative ratings which lost much of their meaning once modifications to the items were made. Qualitative feedback ranged from simple suggestions to improve item clarity to specific comments regarding the overlap of domain definitions. Judges also suggested that some items may better fit alternative scales. Judges also recommended the addition of 14 items to the scale. Both psychometricians and professionals in chronic pain are currently reviewing the resulting 72 items as part of the second expert review panel. Due to the clarification and refinement obtained in this first review, it is expected that the results of the second review will demonstrate more constructive quantitative findings and additional item modifications.

Conclusions

Acceptance of chronic pain is an approach allowing individuals to live meaningfully and purposefully with their pain. Knowledge about an individuals' level of acceptance and related constructs is predicted to facilitate appropriate interventions to assist the individual living with their pain. The CPASRS will provide this information. The development of a psychometrically strong, self-report instrument, which the CPASRS will be, is pre-requisite to further research examining acceptance and determining intervention. The current round of expert review has provided valuable data and it is expected that following the second round of review, items comprising the CPASRS will possess content validity.

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Rescue medication use in the acute treatment of migraine during MAP0004 pivotal trial

Donald Kellerman, Shashidar Kori, Biao Lu
MAP Pharmaceuticals, Mountain View, CA, USA

Purpose

This posthoc analysis evaluated the use of rescue medication in the acute treatment of migraine episodes reported during a randomized, placebo-controlled, double-blind trial of MAP0004, an investigational, orally inhaled dihydroergotamine (DHE). The effectiveness of the acute treatment of migraine can be evaluated by the extent of rescue medication use (RMU). RMU is required when headache symptoms persist or recur 2-24 hours after the initial abortive treatment and is a good indication of the duration of relief provided by the initial treatment. Therefore, in this study we compared the use of rescue medicine after inhaled DHE treatment to that of placebo.

Method

RMU was permitted in this study if migraine symptoms were not relieved 2 hours after study drug administration. RMU in the MAP0004 and placebo treatment groups were adjusted for baseline pain scores and compared according to demographic and baseline disease characteristics (eg, age, gender, race, migraine history, baseline pain severity). The relationship between RMU and migraine symptom endpoints was also assessed.

Results

This posthoc analysis included 794 patients randomized (1:1) to receive double-blind treatment with MAP0004 or placebo. The primary results of the study were previously published (Aurora et al, Headache, 2011). Patients were well matched for demographic and baseline characteristics. Patients receiving MAP0004 experienced statistically significant migraine symptom reduction compared with patients receiving placebo. RMU in the double-blind period was consistently lower with MAP0004 than with placebo at 2 hours (4% vs 8%, $P=.0261$), 4 hours (19% vs 37%, $P<.0001$), 24 hours (36% vs 54%, $P<.0001$), and 48 hours (42% vs 59%, $P<.0001$) after study drug administration. RMU was also significantly lower with MAP0004 than with placebo across demographic and baseline characteristics. Among patients who reported pain relief at 2 hours, MAP0004-treated patients had significantly lower RMU at 4, 24, and 48 hours than placebo-treated patients. The overall adverse event rate was comparable to that of placebo.

Conclusions

In this study, RMU was significantly lower with MAP0004 than with placebo overall and across demographic and baseline characteristics.

Study supported by MAP Pharmaceuticals, Inc.

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Efficacy of MAP0004 in treating severe migraine

Shashidar Kori, Emilee Connors, Jay Zhou, Biao Lu, Borland Scott
MAP Pharmaceuticals, Mountain View, CA, USA

Purpose

The treatment needs of migraine patients are often unmet by available therapies, due in part to the incapability to completely relieve symptoms consistently across a broad spectrum of migraine attacks. MAP0004, an investigational drug that delivers dihydroergotamine (DHE) systemically via oral inhalation, was superior to placebo for the acute treatment of migraine in a Phase 3 trial. A subgroup analysis of subjects with severe migraine pain at baseline during the double blind period is reported here.

Method

The effectiveness MAP0004 vs placebo in the acute treatment of severe migraine was assessed through statistical analysis performed by Fisher's exact test.

Results

Severe baseline pain was reported in 366 of the 794 subjects. Subjects with severe migraine pain treated with MAP0004 experienced statistically significant pain relief ($P<.05$) as early as 10 minutes and at all subsequent prescheduled evaluation time points compared to placebo. These subjects were significantly pain free ($P<.05$) by 60 minutes and at all subsequent time points following treatment compared to placebo. Sustained pain relief and sustained pain free values, both between 2 and 24 hours and 2 and 48 hours, were statistically significantly higher for MAP0004 relative to placebo. Headache recurrence over 24 hours occurred in 6.2% of severe migraine subjects treated with MAP0004 compared to 18% when treated with placebo.

Conclusions

In summary, this analysis describes the baseline presentation of the severe migraine patient population and shows that MAP0004 was effective in the acute treatment of severe migraine in this Phase 3 trial.

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Prevalence registry of small fiber testing in the evaluation of neuropathic pain

Todd Levine, David Saperstein
Phoenix Neurological Associates, Phoenix, Az, USA

Purpose

Neuropathic pain is one of the most common reasons for patients to seek medical attention. Despite thorough evaluations, to include nerve conduction studies, electromyography and medical imaging, many patients remain without a definitive diagnosis. Potential diagnoses in such cases include small fiber neuropathy, fibromyalgia and complex regional pain syndrome (CRPS). The quantification of epidermal nerve fibers from a skin biopsy is an established technique for identifying small fiber neuropathy (SFN). A decreased epidermal nerve fiber density (ENFD) is 88% sensitive and 92% specific for a diagnosis of SFN. Recent, small retrospective series have suggested that a significant percentage of patients with fibromyalgia and CRPS may have SFN.. In order to increase our understanding of the utility of ENFD testing in assessing patients with neuropathic pain, we have created a multicenter, national registry.

Method

Techniques to determine ENFD and SFN have been available for many years. Three millimeter punch biopsies are taken from affected areas on the patient's skin. The biopsies are processed for immunohistochemical staining with antibodies against protein gene product (PGP) 9.5, a pan-axonal marker. This allows visualization and quantification of unmyelinated C fibers in the epidermis. If the ENFD is decreased, as compared with established normative data, then a diagnosis of SFN is supported.

The registry will collect clinical information from patients of private practice and academic clinicians who submit skin biopsies to one of the 3 participating labs: Corinthian Reference Labs, Washington University, or Kansas University. Clinical information collected will include the nature of the patient's pain, the patient's diagnosis before and after the biopsy, coexisting diseases, concurrent pain medications, and whether the results of the biopsy affect the patient's clinical care.

Results

The registry will collect data from 2012 through the end of 2013, representing the largest population-based study of patients with unexplained neuropathic pain. There is a need to understand how often patients with painful conditions like CRPS or fibromyalgia have objective evidence for SFN. The identification of a SFN is an important step in the evaluation of these patients as there are a number of diagnosable conditions that are known to cause SFN that would not ordinarily be evaluated in patients with CRPS or fibromyalgia. Thus we believe that the identification of the population of patients with SFN and painful conditions will lead to a more specific and often treatable diagnosis and may help elucidate the underlying pathophysiology of CRPS or fibromyalgia.

Conclusions

Through this multicenter, national registry of patients referred in for skin biopsies for evaluation of their painful conditions we hope to identify, in a large cross sectional population, the incidence of small fiber neuropathy in patients with CRPS and fibromyalgia. Participation in this registry is open to all physicians ordering skin biopsies for neuropathic pain. Additional sites are being sought.

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Early evaluation of patient characteristics, hospital length of stay and costs among users of tapentadol IR and oxycodone IR

Jay Lin[1], Wing Chow[2], Myoung Kim[2], Marcia Rupnow[1]
[1]*Novosys Health, Flemington, NJ, USA,* [2]*Janssen Scientific Affairs, Raritan, NJ, USA*

Purpose

Pain is a prevalent condition in the United States with substantial economic implications. Pharmacologic treatment for moderate to severe pain includes opioid therapy; however, treatment-emergent side effects may limit their use. Tapentadol-immediate release (TAP IR) is a centrally acting analgesic with 2 mechanisms of action, μ-opioid receptor agonism and norepinephrine reuptake inhibition, indicated for the relief of moderate to severe acute pain in adults. Clinical trials demonstrated at equianalgesic doses TAP IR is associated with a better tolerability profile than oxycodone IR (OXY IR) while providing similar pain relief. Yet, published data on the associated economic effect, including hospital length of stay (LOS) and costs are limited. The purpose of this study was to evaluate the LOS and costs between TAP IR and OXY IR treated patients.

Method

A retrospective analysis of patients (≥18 years) taking TAP IR or OXY IR between 6/1/2009 to 7/31/2011 selected from the OptumInsight Clinformatics™ Data Mart managed care claims database was conducted. This database contains longitudinal patient-level details and is a nationally representative integrated medical and pharmacy claims-based database of 15 million covered lives. Patients were assigned to TAP IR or OXY IR cohort based on their initial drug usage (index event). They were required to have continuous health plan coverage 60 days before (baseline period) and after (follow-up period) the index event. TAP IR patients were matched to OXY IR patients (1:1) using a combination of exact match of key patient characteristics and propensity score matching with patient demographics and clinical characteristics as covariates. Logistic regression was used to generate the propensity scores. T-test and chi-squared test were employed to evaluate the differences in demographics and clinical characteristics between patients treated with TAP IR or OXY IR.

Results

At baseline, among the unmatched cohorts, patients who used TAP IR (N=17,539) were older (47.18 vs 43.63 year, *P*<.0001), slightly more were female (62.08% vs 52.27%, *P*<.0001) and health plans were more often point-of-service or exclusive provider organizations compared with patients who used OXY IR (N=85,821). Patients taking TAP IR were more likely treated for major joint replacement/lower limb reattachment (22.25% vs 15.27%) or spinal fusion (4.41% vs 4.05%) during hospitalizations at baseline. With the exception of osteoarthritis (12.59% vs 14.31%, *P*<.0001; TAP IR and OXY IR, respectively), a significantly greater proportion of TAP IR patients (*P*<.0001) had pain-related conditions, including back pain (38.27% vs 29.35%), neck pain (17.91% vs 14.11%), and fibromyalgia pain (8.81% vs 5.04%) in comparison to OXY IR patients. After patient matching, TAP IR patients (n=10,185) and OXY IR patients (n=10,185) were similar in age (mean=46.11), gender (female=57.81%), Charlson Comorbidity Index score (mean=.17), health plan type and healthcare resource utilization at baseline. During the 60-day follow-up period, within the matched cohorts, patients who took TAP IR had a significantly shorter mean per patient hospital LOS (0.21 vs 0.35 days, *P*<.0001), lower mean number of hospitalizations (mean=.07 vs 0.10, *P*<.0001), and lower total healthcare costs ($13,450 vs $15,466, *P*=.0001) than patients who received OXY IR. The higher index opioid Rx cost of TAP IR ($190 vs $150, *P*<.0001) was more than offset by the differences in total healthcare costs.

Conclusions

The characteristics of patients who took TAP IR were different from patients who took OXY IR in many respects, including age, gender, conditions requiring hospitalizations and pain-related conditions. When patients were matched on similar characteristics, patients taking TAP IR had a lower number of hospitalizations, shorter hospitalized length of stay and lower total healthcare costs than patients who received OXY IR. Additional studies are needed to further delineate the real-world economic benefits of using TAP IR vs a traditional μ-opioid receptor agonist.

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Real-world evaluation of adverse event related outcomes in hospitalized patients using tapentadol IR vs oxycodone IR

Jay Lin[1], Wing Chow[2], Samir Mody[2], Marcia Rupnow[1]
[1]*Novosys Health, Flemington, NJ, USA,* [2]*Janssen Scientific Affairs, Raritan, NJ, USA*

Purpose

Opioid analgesics are the mainstay of pain management among postsurgical hospitalized patients, although treatment-limiting side effects are common and may result in suboptimal pain management. Tapentadol-immediate release (TAP-IR) is a centrally acting analgesic with 2 mechanisms of action, μ-opioid receptor agonism and norepinephrine reuptake inhibition, indicated for the relief of moderate to severe acute pain in adults. Clinical trials demonstrated at equianalgesic doses TAP IR is associated with a better tolerability profile than oxycodone IR (OXY IR) while providing similar pain relief. Real-world use of TAP IR may differ from OXY IR, which may impact the comparative analysis of patient outcomes. The purpose of this study was to evaluate the real-world frequency of adverse events, as determined by use of medications for treatment of adverse effects, between TAP IR and OXY IR treated hospitalized patients with similar patient and admission characteristics.

Method

A retrospective analysis of hospitalized patients (≥18 years) selected from the Premier Perspective™ database between 6/1/2009 and 9/30/2011 who received at least one prescription for TAP IR or OXY IR was conducted. Premier Perspective™ database is the largest integrated inpatient drug utilization database comprised data collected from over 600 hospitals nationwide. The database contains patient level details including demographic and hospital characteristics as well as drug utilization details, diagnosis and procedures codes, admission and discharge dates for each inpatient episode. TAP IR users were matched to OXY IR users (1:3) using a combination of exact match of key patient characteristics and propensity score matching with patient demographics and clinical characteristics as covariates. Logistic regression was used to generate the propensity scores. T-test and chi-squared test were employed to evaluate the differences in demographics, clinical characteristics, admission characteristics, and adverse event rates among hospitalized patients using TAP IR or OXY IR.

Results

Among the unmatched cohorts, patients who used TAP IR (N=2977) were older (mean=61.68 vs 55.15), more often female (69.77% vs 59.37%), and were more often treated in the Southern US at rural and smaller hospitals compared with those who used Oxy IR (N=549,148). Additionally, a greater proportion of TAP IR patients had prior opioid treatment compared with OXY IR patients (94.5% vs 89.5%, respectively). Among all prior opioid treatment used, Schedule II opioids were the most common and included oxycodone mono- or combination products. After patient matching, TAP IR patients (n=1,858) and OXY IR patients (n=5,574) were similar in age (mean=62.20 vs 61.77, *P*=.30), gender (female=70.72% vs 70.72%, *P*=1.00) and Charlson Comorbidity Index score (mean=.66 vs 0.67, *P*=.58). The majority of matched patients in either cohort were admitted for elective surgery (65.45% vs 62.68%) for primarily knee joint (29.44% vs 29.44%, *P*=1.00) or hip joint (11.95% vs 11.95%, *P*=1.00) replacement by an admitting orthopedic surgeon. A greater proportion of TAP IR patients vs Oxy IR patients received anti-nausea medication (51.29% vs 41.32%, p<0.0001), and/or medication for constipation (23.36% vs 16.59%, *P*<.0001) prior to initiation of the corresponding pain medications. However, after initiation of corresponding medications for pain, a smaller proportion of TAP IR patients vs those who received OXY IR were prescribed with medication to treat nausea (29.87% vs 33.98%, *P*=.0011) and/or constipation (27.50% vs 34.93%, *P*<.0001). Other adverse events, including vomiting, dizziness, headache, somnolence, and pruritus were identified by the corresponding ICD-9 codes from either

patients' admission or discharge diagnosis codes. These event were generally low (<5.0%) and their frequencies were not significantly different between TAP IR and OXY IR patients either prior to or after pain medication initiation.

Conclusions

The majority of TAP IR patients underwent an elective knee or hip replacement surgery. Prior to the initiation of TAP IR or OXY IR, a greater proportion of TAP IR patients received treatment for gastrointestinal side effects compared with those who received OXY IR, but a lower percentage of them required such treatments after initiation of their corresponding pain medications. This study suggests that hospitalized patients who use TAP IR may benefit from its better tolerability profile than those who use a traditional μ-opioid receptor agonist. TAP IR may offer an effective alternative pain management option among postoperative hospitalized patients.

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Efficacy, safety, and tolerability of a single-tablet combination of ibuprofen-famotidine: results in patients who require nonsteroidal anti-inflammatory drugs for osteoarthritis, rheumatoid arthritis, or chronic pain

Michael Schiff[1], Mark Genovese[2], Alfonso Bello[3], Amy Grahn[4], Merrell Magelli[4], Alan Kivitz[5]
[1]University of Colorado School of Medicine, Greenwood Village, Colorado, USA, [2]Stanford University Medical Center, Palo Alto, California, USA, [3]Illinois Bone and Joint Institute, Glenview, Illinois, USA, [4]Horizon Pharma, Inc., Northbrook, Illinois, USA, [5]Altoona Center for Clinical Research, Duncansville, Pennsylvania, USA

Purpose

Gastrointestinal (GI) toxicity remains a major concern with nonsteroidal anti-inflammatory drugs (NSAIDs) used in the treatment of osteoarthritis (OA), rheumatoid arthritis (RA) and chronic pain. Current national and international guideline recommendations for gastroprotective strategies in NSAID users include co-therapy with gastroprotective agents (eg, prostaglandin analogues, proton pump inhibitors [PPIs], H2 receptor antagonists [H2RAs]) or NSAIDs with a lower GI risk (eg, coxib) (Wilcox et al, *Clin Gastroenterol Hepatol*, 2006; Chan et al, *Am J Gastroenterol*, 2008; Rostom et al, *Aliment Pharmacol Ther*, 2009). Despite guideline recommendations, most patients at increased GI risk are not prescribed a gastroprotective strategy, and decreased patient adherence to co-therapy is associated with significantly increased risk of ulcer or bleeding (Abraham et al, *Gastroenterology*, 2005; Goldstein et al, *Clin Gastroenterol Hepatol*, 2006; Abraham et al, *Am J Gastroenterol*, 2008). A combination tablet of ibuprofen (IBU) plus a high-dose H2RA (famotidine [FAM]) may decrease IBU-induced ulcer disease and improve compliance in patients who require chronic NSAIDs for osteoarthritis (OA), rheumatoid arthritis (RA), or chronic pain (Weinblatt et al, *Arthritis Rheum*, 2010). The objective of this evaluation was to determine if a single-tablet combination of IBU (800 mg) and famotidine (26.6 mg) (HZT-501, DUEXIS®, Horizon Pharma, Inc., Deerfield, IL) administered 3 times per day (TID) would significantly decrease upper GI ulcers as compared to IBU alone in patients who require chronic NSAIDs for OA, RA, or chronic pain.

Method

Two multicenter, phase 3, 24-week, parallel-group, double-blind, randomized trials of HZT-501 given 3 times daily, were undertaken (REDUCE-1 and REDUCE-2) to evaluate the efficacy, as measured by endoscopically-diagnosed upper GI ulcers, and safety of HZT-501 compared with IBU. Patients were randomized in approximately a 2:1 ratio, to treatment with either HZT-501 or IBU. Patients were stratified on 2 risk factors for ulcer development: 1) concomitant use of low-dose aspirin (LDA) (≤325 mg daily) and/or other anticoagulant medication; and 2) history of an upper GI ulcer. Patients 40-80 years old expected to require daily NSAID therapy ≥6 months with no history of ulcer complications, negative H. pylori test, and baseline endoscopy (EGD) showing no ulcers and <5 erosions in the upper GI tract were enrolled. Concomitant LDA (≤325 mg daily) and oral anticoagulant therapies were permitted. Study EGDs were done at 8, 16, and 24 weeks of therapy. The primary efficacy endpoint was gastric ulcers identified at endoscopy during the 24-week study period. An endoscopic diagnosis of ulcer required unequivocal depth and diameter of ≥3 mm. Subgroup analyses were conducted by NSAID indication (OA, RA, and chronic pain).

Results

REDUCE-1 and REDUCE-2 enrolled 906 and 627 patients, respectively. The total number of patients was 1533, of which 1022 patients received HZT-501 and 511 patients received IBU. The NSAID indication subgroups of interest included 761 patients for OA+RA and 521 patients for chronic pain in the primary analysis population. The mean age was 55.5±9.2 years in HZT-501 and 55.7±9.4 years in IBU and 67.1% and 69.9% of patients were female in the HZT-501 and IBU treatment groups, respectively.

The crude proportion of upper GI ulcers in all patients was 11.0% in patients receiving HZT-501 and 21.9% in patients receiving IBU ($P<.0001$).The crude proportion of upper GI ulcers in the OA+RA subgroup was 11.9% in patients receiving HZT-501 and 20.2% in patients receiving IBU ($P=.002$) and the crude proportion of upper GI ulcers in the chronic pain subgroup was 9.9% in patients receiving HZT-501 and 23.9% in patients receiving IBU ($P<.0001$). These results demonstrate that HZT-501 reduced NSAID-associated upper GI ulcers overall and in the subsets of patients taking NSAIDs for OA, RA, and chronic pain.

The incidence of TEAEs was balanced across both treatment groups, except for dyspepsia, which was statistically lower for HZT-501 (4.7%) compared with IBU (8.0%) ($P=.009$); this observation is in line with the known activity of FAM. SAEs were reported in 3.2% and 3.3% of patients in HZT-501 and IBU, respectively, and discontinuations due to TEAEs occurred in 6.7% and 7.6% of patients in HZT-501 and IBU, respectively.

Conclusions

HZT-501 reduces NSAID-associated upper GI ulcers overall and in the subset of patients taking NSAIDS for OA, RA and chronic pain. TEAEs were similar across treatment groups, with the exception of dyspepsia, which was lower for HZT-501 vs IBU. Combination therapy may improve adherence and compliance in patients taking NSAIDs±LDA who require gastroprotection.

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AYX1 investigational drug candidate prevents the development and the maintenance of pain after incisional, inflammatory or neuropathic injury

Julien Mamet[1], Michael Klukinov[2], Tony Yaksh[3], Shelle Malkmus[3], Samantha Williams[3], Bradley Taylor[4], Renee Donahue[4], Frank Porreca[5], Jennifer Xie[5], Janice Oyarzo[5], Timothy Brennan[6], Alberto Subieta[6], Scott Harris[1], Donald Manning[1], William Schmidt[7], David Yeomans[2]
[1]Adynxx, Inc., San Francisco, CA, United States Minor Outlying Islands, [2]Stanford University, Stanford, CA, United States Minor Outlying Islands, [3]UCSD, San Diego, CA, United States Minor Outlying Islands, [4]University of Kentucky, Lexington, CA, United States Minor Outlying Islands, [5]University of Arizona, Tucson, AZ, United States Minor Outlying Islands, [6]University of Iowa, Iowa City, IA, United States Minor Outlying Islands, [7]NorthStar Consulting, LLC., Davis, CA, United States Minor Outlying Islands

Purpose

The persistence of pain following surgery or trauma limits recovery, physical rehabilitation and the return to a normal quality of life. AYX1 is an investigational drug candidate specifically developed for preventing the development and maintenance of postsurgical pain and accelerating physical recovery with a single intrathecal administration prior to surgery. AYX1 has recently completed a phase 1 clinical study in healthy volunteers and a phase 2, proof-of-concept study in surgical patients is planned to launch at the end of 2012. The current work describes the pharmacology of AYX1 in preclinical models of postsurgical pain that supports the feasibility of its therapeutic profile and its clinical development.

Method

Postsurgical pain arises from a combination of mechanical/incisional, inflammatory and often nerve trauma. Early in the development of pain following such injury, there are waves of gene regulation in DRG and spinal cord neurons leading to long-term sensitization and the maintenance of pain over time. These transcriptional events involve the sequential and interdependent regulation of almost all classes of encoding pain genes, including receptors, ion channels, secondary messengers, enzymes, neurotransmitters and proteasome-ubiquitin factors. The transcription factor EGR1 is a molecular switch acting at the epicenter of this plasticity: its activation immediately after an injury triggers the waves of gene regulation necessary for maintaining neuronal sensitization in the DRG-spinal ne2rk. AYX1 is a DNA decoy drug candidate (small synthetic, dsDNA molecule) that acts by mimicking the genomic binding sequence for EGR1 and consequently blocking its function around the time of injury. AYX1 was delivered once as a single 0.02mL (rat, Sprague Dawley) or 1mL (dog, Beagle) bolus intrathecal injection around the time of surgery. AYX1 efficacy was evaluated by its capacity to prevent pain, measured as mechanical hypersensitivity using Von Fey hairs. For biomarker studies, L4-6 DRG and spinal cord segment were collected 3h following a plantar incision, RNA extracted and AYX1 marker genes analyzed by RT-PCR. Animal models were performed as previously described in the literature. All experiments were approved by appropriate animal care and use committees.

Results

The current body of work demonstrates that a single intrathecal delivery of AYX1 around the time of an inflammatory (CFA model), incisional (Brennan model) or neuropathic (Spared Nerve Injury model) injury in rats produces a dose-dependent prevention of persistent mechanical hypersensitivity with no evident effects upon motor function. AYX1 effect was maintained until pain resolved in vehicle-treated animals. The analysis of spontaneous pain-related behavior (weight bearing incapacitance) demonstrated that AYX1 improved functional recovery following nerve injury. Finally, biomarker analysis of AYX1 activity in the DRG and spinal cord of rats and dogs suggest its pharmacology is conserved across animal species.

Conclusions

Pharmacological studies in complementary preclinical models showed that AYX1 therapeutic profile has the potential of improving the management of acute pain following surgery and preventing the maintenance of persistent/chronic pain. At a functional level, AYX1 treatment reduces physical disability following surgery. This works supports the current clinical development plan of AYX1 in surgical patients.

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Concomitant opioid and sleep medication use in patients with pain

Lindsey Mann[1], Joseph Ma[1,2], Brookie Best[1,3], Candis Morello[1,4], Rabia Atayee[1,2], Amadeo Pesce[5,6]
[1]*University of California, San Diego (UCSD), Skaggs School of Pharmacy and Pharmaceutical Sciences, La Jolla, CA, USA,* [2]*Doris A. Howell Palliative Care Services, San Diego, CA, USA,* [3]*UCSD Department of Pediatrics, Rady's Children's Hospital, San Diego, CA, USA,* [4]*Diabetes Intense Medical Management Clinic, Veterans Affairs San Diego Healthcare System, La Jolla, CA, USA,* [5]*Millennium Research Institute, San Diego, CA, USA,* [6]*Department of Pathology and Laboratory Medicine, UCSD School of Medicine, La Jolla, CA, USA*

Purpose

Patients with chronic pain or post-operative pain frequently experience sleep disturbances. Animal models suggest painful stimuli increases gamma-amino butyric acid (GABA) reuptake in the synapses and decreases the amount available to cause a depressant effect resulting in sleep. While sedation is a common adverse effect of opioids, opioids can also disturb the sleep cycle by increasing awakenings at night. Lack of sleep sensitizes pain, resulting in a positive-feedback loop in which lack of sleep and increased pain continue to worsen. Zolpidem is a nonbenzodiazepine hypnotic indicated for use in insomnia, and it binds to the GABA-A chloride channel, circumventing the lack of GABA in the case of painful stimuli. The purpose of this retrospective analysis was to determine which opioids were commonly used with zolpidem and other sleep medications in a population of patients with chronic pain.

Method

This retrospective analysis used de-identified urine specimens analyzed using liquid chromatography tandem mass spectrometry (LC-MS/MS) at Millennium Laboratories, Inc. from the period of November 2011 to May 2012. Specimens from single-visit patients and specimens with creatinine values greater than or equal to 20 mg/dL were included in the analysis (total pain population). The urine specimens that were tested for zolpidem were divided into 2 cohorts: 1) those whose providers reported zolpidem as prescribed, and 2) those whose providers did not report zolpidem as prescribed. The prevalence of detection of additional medications (opioids, tricyclic antidepressants, skeletal muscle relaxants, GABA analogues, nonopioid analgesics, benzodiazepines, barbiturates, and alcohol) in urine specimens from these 2 cohorts was tabulated and compared to the prevalence of detection of the same medications in the total pain population to obtain a relative percent difference in medication use in the 2 zolpidem cohorts as compared to the total pain population. Analysis was done using Microsoft Excel® 2010 and OriginPro 8.6.

Results

Of the specimens tested in this retrospective data analysis, 5257 had zolpidem listed as a reported prescription. Of these results, 74.2% had detectable urine concentrations. 83.2% of the patient specimens with reported prescribed zolpidem were also positive for opiates concomitantly, with the most common being hydrocodone/hydromorphone (61.2%) and oxycodone/oxymorphone (53.7%). Compared to the population of all specimens tested for any opiate, hydrocodone/hydromorphone positive specimens were 29.7% higher, and oxycodone/oxymorphone positive specimens were 18% higher in those who reported prescribed zolpidem. 23.9% of the patient specimens with reported prescribed zolpidem and opiates present also showed the presence of benzodiazepines. The most commonly detected benzodiazepine was alprazolam, with a higher presence of 58.1% compared to the total population.

Among the patient specimens in the cohort without reported prescribed zolpidem (n=66,662), 4.7% of tested were positive for the presence of zolpidem. The medications most frequently concomitantly present with zolpidem in the second cohort were similar to the first cohort that reported prescribed zolpidem, with 79.7% of patients also taking an

opiate. Oxycodone/oxymorphone and hydrocodone/hydromorphone were the most commonly found at 33.8% and 33%, respectively. Oxycodone/oxymorphone was detected at 13.8% greater compared to the total pain population, while hydrocodone/hydromorphone was detected at 1.1% greater. Benzodiazepines were detected in 23% of the specimens with opioids present in addition to zolpidem detected without a reported prescription. Alprazolam use was 67.9% greater in the second cohort compared to the total population. In subjects with detectable zolpidem in urine, alcohol use was higher among those who did not report prescribed zolpidem than in those who did report prescribed zolpidem (6.1% and 3.1%, respectively).

Conclusions

A higher prevalence of opioid use, specifically hydrocodone/hydromorphone and oxycodone/ oxymorphone, was observed in zolpidem-positive patient specimens. The increase in concomitant benzodiazepine and alcohol use in patients using zolpidem may create a higher risk for adverse outcomes and drug-drug interactions. The overall detection of zolpidem, along with other pain related medications, may provide support for continued urinary monitoring.

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The effect of lower-dose, submicron particle NSAIDs on peak pain relief in patients with acute pain

Garen Manvelian[4], Bill McCarberg[1,2], Stephen Daniels[3]
[1]*Kaiser Permanente, San Diego, California, USA,* [2]*University of California San Diego, San Diego, California, USA,* [3]*Premier Research Group Limited, Austin, Texas, USA,* [4]*Iroko Pharmaceuticals, Philadelphia, Pennsylvania, USA*

Purpose

Nonsteroidal anti-inflammatory drugs (NSAIDs) are well-established and effective in the management of acute pain. However, commercially available NSAIDs are associated with dose-dependent risks for the development of cardiovascular, gastrointestinal (GI), and renal adverse events. The FDA has issued a Public Health Advisory that NSAIDs should be administered at the lowest effective dose for the shortest duration consistent with individual patient treatment goals (Available at: http://www.fda.gov/Drugs/ DrugSafety/Postmarket DrugSafetyInformationforPatientsandProviders/ ucm150314.htm). Lower-dose, submicron particle NSAIDs are being developed using proprietary SoluMatrix™ technology and are designed to offer effective pain relief at lower doses. Two separate Phase 2 clinical trials were conducted to evaluate the efficacy and safety of investigational, submicron particle oral diclofenac and naproxen in a validated postsurgical pain model. Data from these studies show that submicron particle oral diclofenac and naproxen demonstrated good efficacy for the primary efficacy endpoint, sum of total pain relief (TOTPAR) at 12 h, compared with placebo. The results for the secondary efficacy endpoint, peak pain relief, are reported here.

Method

Both Phase 2 trials were multicenter, randomized, double-blind, single-dose, placebo-controlled studies in which patients underwent extraction of ≥2 impacted third molars under local anesthesia. Within 6 h following extraction, patients with moderate to severe pain intensity (a score of >50 mm on a 100 mm Visual Analog Scale [VAS]) were randomized to treatment. Patients received a single dose of submicron particle diclofenac (18 or 35 mg) or naproxen (200 mg or 400 mg), an active comparator (reference compound or celecoxib 400 mg), or placebo. Key inclusion criteria included healthy adults between 18 and 50 years old that weighed ≥45 kg and had a body mass index ≤35 kg/m^2. Key exclusion criteria included patients with a history of clinically significant intolerance to any study drug or its ingredients or any history of peptic ulcers or GI bleeding. Peak pain relief was defined as the maximum of the reported pain relief during the entire assessment period for each patient. Patients assessed their pain relief relative to study entry (Time 0) using a 5-point categorical scale rating the amount of pain relief they had relative to the starting pain: none=0, a little=1, some=2, a lot=3, and complete=4. The primary efficacy endpoint for these studies was (TOTPAR) over 12 h.

Results

Overall, >450 patients were randomized across the 2 studies, with >200 patients for each study. As secondary endpoints, a higher proportion of patients receiving lower dose submicron particle diclofenac (18 and 35 mg), naproxen (200 mg and 400 mg), or reference compound treatments rated their pain relief as "some," "a lot," or "complete" during the 12h following randomization compared with placebo ($P \leq .001$):

- Submicron particle diclofenac Phase 2 trial
    - Submicron particle diclofenac 18 mg 83.7% (41/49)
    - Submicron particle diclofenac 35 mg 84.3% (43/51)
    - Celecoxib 400 mg 58.8% (30/51)
    - Placebo 25.5% (13/51)

- Submicron particle naproxen Phase 2 trial
    - Submicron particle naproxen 200 mg 84.0% (42/50)
    - Submicron particle naproxen 400 mg 94.1% (48/51)
    - Naproxen 250 mg 82.0% (41/50)
    - Naproxen 500 mg 90.2% (46/51)
    - Placebo 41.2% (21/51)

Safety and tolerability were generally comparable among the submicron particle NSAID treatment groups, comparators (celecoxib or reference compound), and placebo.

Conclusions

The data reported from this postsurgical pain model demonstrate that patients treated with investigational, lower dose, submicron particle oral diclofenac and naproxen experienced good peak pain relief compared with placebo. Submicron particle NSAIDs were generally well tolerated. These results suggest that lower dose submicron particle NSAIDs could be effective in the management of pain and warrant further evaluation in Phase 3 trials.

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Evaluation of pharmacist interventions for patients with chronic noncancer pain in the primary care setting.

Michele Matthews[1,2], Edgar Ross[2], Lori Tishler[2], Elizabeth Scanlan[2], Laura Lourenco[1], Robert Jamison[2]
[1]*Massachusetts College of Pharmacy and Health Sciences, Boston, MA, USA,* [2]*Brigham and Women's Hospital, Boston, MA, USA*

Purpose

Chronic pain has become a global public health problem, affecting one out of every 3 people within their lifetimes. At its worst, it can also cost its sufferers their work productivity and even their daily functioning. It is imperative that proper pain assessment and management be performed to reduce the severity of pain and improve quality of life and functioning for patients with chronic pain. In order to meet this challenge, an interdisciplinary team approach is necessary to provide the comprehensive care that chronic pain patients require. With an estimated 70 million people in the United States undertreated for painful conditions, it is important to implement innovative clinical services to target this healthcare disparity. With pharmacists having extensive drug therapy knowledge, they play a vital role in identifying drug-related problems and providing recommendations that can assist patients with attaining their treatment goals while monitoring the risks of drug therapy. Additionally, the services that pharmacists provide can allow for ambulatory care clinics to increase the number of patients that are treated and can decrease clinic staff burden. The pharmacist's role in various ambulatory care settings has been well documented; however, evidence to support pharmacist-directed chronic pain management programs in the primary care setting is lacking. The objective of this study was to identify pharmacist interventions for patients with chronic noncancer pain in the primary care setting.

Method

Patients referred to the Chronic Pain Management Clinic by primary care physicians within the Brigham and Women's Hospital (BWH) Phyllis Jen Center for Primary Care were included in this analysis. Patients who were <18 years old, did not have a diagnosis of chronic noncancer pain, or had chronic noncancer pain for <3 months were excluded. Through the use of the BWH electronic longitudinal medical record (LMR) system, various patient demographics were identified, including age, gender, ethnicity, and type of chronic pain. The types of pharmacist intervention and recommendation acceptance rates were analyzed. Additionally, for patients on chronic opioid therapy, the following parameters were assessed to identify improvement in opioid misuse risk assessment and/or management after pharmacist intervention: Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) score, Current Opioid Misuse Measure (COMM) score, implementation of opioid treatment agreements, regular assessment of drug-related adverse effects, and urine toxicology screens.

Results

A total of 80 patients had been referred to the pharmacist-directed Chronic Pain Management Clinic since May 2011. The median patient age was 55 years (26-85), and slightly more patients were female (53.8%). Forty-three percent of patients were Caucasian, with the remainder of patients being African American (38.8%) or Hispanic (17.6%). Most patients were diagnosed with chronic low back pain (62.2%) followed by osteoarthritis (10.2%), chronic abdominal pain (10.1%), and fibromyalgia (7.7%). Most patients had pain in more than one location (65%). Patients with comorbid depression and/or anxiety represented 77.8% of the population. Almost half of the patients had a history of substance abuse, and among them, 70% had a history of polysubstance abuse. Less than 20% of patients reported a family history of substance abuse. The most common drug-related problems identified in this population were untreated indication (36.8%), nonadherence to therapy (29.2%), adverse drug reaction (15.7%), and improper drug/dose selection (13.5%). A total of 228 pharmacist recommendations were provided to the patients' primary care

providers with a 91% acceptance rate. With regard to opioid misuse risk assessment and management, the number of patients who completed the SOAPP-R and COMM questionnaires increased significantly as did the implementation of opioid analgesic treatment agreements and routine urine drug testing.

Conclusions

This retrospective analysis justifies the integral role that pharmacists have in chronic pain management and supports the integration of a pharmacist-directed clinic within the primary care setting. Future analysis will be conducted to correlate pharmacist recommendations and acceptance rates with improvement in pain and functioning.

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A randomized, double-blind placebo-controlled study to determine the effectiveness of Theramine and a low dose ibuprofen on the management of chronic back pain

William Shell[1,2], David Silver[1,2], Lawrence May[1,2], Debbie Bullias[1,2], Stephanie Pavlik[1,2], Fred McCall[1,2]
[1]*Targeted Medical Pharma, Inc., Los Angeles, CA, USA,* [2]*Physician Therapeutics, Los Angeles, CA, USA*

Purpose

Back pain is a common problem in the United States and can become chronic with considerable pain and debilitation. Many current drug treatments such as NSAIDs (nonsteroidal anti-inflammatory drugs) and narcotic analgesics are associated with significant side effects, including gastrointestinal (GI) hemorrhage, kidney and heart disease and the potential for addiction. Medical Foods present an alternative therapeutic approach for back pain with an improved side effect profile. Medical Foods were regulated as drugs prior to 1972 and are defined in the 1988 FDA Orphan Drug Act. They are enterally administered, use ingredients the FDA regards as GRAS (generally regarded as safe), require physician supervision and address specific nutritional deficiencies related to a specific disease or condition.

The primary objective of this study was to compare the efficacy of Theramine, an amino-acid based prescription medical food on chronic back pain when taken with or without a low-dose NSAID: ibuprofen.

Method

A total of 127 patients were randomized to one of 3 treatment arms: low-dose ibuprofen (n=42); Theramine (n=42); or the combination of Theramine and ibuprofen (n=43) for a 28-day period. Eligible patients reported the presence of back pain >6 weeks. Patients underwent a washout period during which oral anti-inflammatory or other analgesic medicines were discontinued. Aspirin ingestion (325 mg/d) was allowed for nonarthritic conditions. Acetaminophen was given as rescue therapy for pain at 650 mg-1000 mg every 4-6 hours for a total daily dose <4 gm.

Pain was assessed using the Roland-Morris Disability Questionnaire, Oswestry Disability Index and a Visual Analog Scale at baseline and at Day 28. Blood was drawn for laboratory analysis including C-Reactive Protein (CRP), Interleukin-6 (IL-6), and liver function (alkaline phosphatase, AST and ALT) at both time points. An amino acid panel was also drawn at baseline and Day 28 on 25 patients selected from each treatment group. On day 7 and 14, the evaluation of VAS and patient breakthrough medication usage was collected.

Patients randomized to the ibuprofen group were given 400 mg/d in the morning with a 2-capsule dose of L-alanine (placebo twice daily). In the Theramine group, subjects were given a 2-capsule dose Theramine twice daily and a single capsule of L-alanine (placebo) in the morning. The group receiving combination therapy (Theramine and ibuprofen) received a 2-capsule dose of Theramine twice daily and 400 mg of ibuprofen in the morning. Both the active and placebo capsules were administered in a double-blind fashion.

Results

At baseline, there were no statistically significant differences in low back pain as assessed by Roland-Morris Disability Index (RM), Oswestry Disability Index (OST), or for levels of inflammatory markers.

On the RM the percent change from baseline to Day 28 was statistically significant ($P<.01$) showing improvements in pain ratings for both the Theramine and the combined (Theramine with ibuprofen) groups compared with the ibuprofen alone group (0.73, -50.3, -63.1 respectively).

On the OST the percent change from baseline to Day 28 was statistically significant ($P<.01$) for both the comparison of Theramine and combined groups vs the ibuprofen alone group (-4.52, -41.9, -62.2 respectively) and for the comparison of combined group vs Theramine ($P<.05$).

For both the inflammatory markers C-Reactive Protein (CRP) and IL-6 the percent change for both the Theramine and combined groups showed statistically significant reductions ($P<.01$) compared to the ibuprofen alone group. For CRP the combined group compared to the Theramine group showed a statistically significant ($P<.05$) reduction. It should be noted that CRP and IL-6 levels in the ibuprofen group increased over baseline.

Laboratory blood tests also confirmed greater functional improvement for both the Theramine group and combined group compared to patients taking ibuprofen alone. The percent change in liver enzyme levels was not significant among the treatment groups except for alanine transaminase (ALT), which was reduced in the Theramine group (-11.5%) and combined group (-8.1%). Administration of Theramine resulted in an increase in blood concentrations of the amino acid precursors associated with the important neurotransmitters involved in the modulation of pain. Rescue medications were used in 76% of the patients in the ibuprofen vs 18% in the Theramine group ($P<.01$) and 12% of the combined group ($P<.01$). There were no adverse events or complications among any of the groups during this 28 day study.

Conclusions

The prescription medical food Theramine was shown to be safe and effective in relieving back pain compared to ibuprofen alone without causing any serious side effects. When administered as an adjunct to ibuprofen, Theramine mitigates the inflammatory effects seen with ibuprofen alone. Theramine may provide a safe alternative to traditional pharmaceuticals prescribed in the management of chronic back pain.

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Explaining pain mechanisms to patients: a good starting point?

A. Breck McKay
Fifth Quadrant Research Group, Brisbane, Queensland, Australia

Purpose

Pain, ache, sore, and *hurt* are abstract words used and heard every day. These words are abstruse, indefinite, and have no sharable lexicon to allow people to understand the actual meanings of the pain words between individuals or healthcare professionals. We only have our own unique past memories for our brain's 'pain perception' to compare to, as we experience noxious inputs, so we need a better communication method. So how can we simply explain 'pain perception' to patients using simple concepts they understand? Very easily... by using the Loeser/Bonica Onion skin model and the AstraZeneca Pathophysiology of Pain Booklet and going step by step from periphery to cerebral cortex. By using the descriptive input pathways from A beta, A delta and C fibre (touch, pressure, thermal, mechanical and chemical) receptors, it is possible to develop a shared lexicon of pain experiences between persons.

Method

We look at how a switch/microphone (receptor) turns on an electric current (nerve) and acoustic feedback (dorsal horn) moderates it and that output, on reaching the midbrain, activates 'suffering' and then 'turns on the light' (pain perception) in the cerebral cortices. The switch (peripheral nociceptors and mechanoreceptors) start the electric input (axon impulse) that passes up the cables (nerves) to the spinal cord (dorsal horn) where the sensory A beta (touch, pressure etc) and A-delta—nociceptive—(thermal and mechanical) and C fibre—polymodal—(high intensity mechanical, chemical and thermal) inputs interact causing modulation (amplification, impedance, attenuation, excitation, interactions). If this becomes unbalanced, acoustic feedback can occur and the outputs may become unrelated to the inputs. The resultant dorsal horn output passes to the midbrain where it interacts with the autonomic vestibular regulation mechanism giving rise to the excess autonomic outputs = the 'suffering' of pain (or dysautonomia).

Above the midbrain the electrical inputs turn on the light bulb by activating many different brain areas which then compare the current input patterns to known past experiences, thus forming the "pain perceptions" as being of a remembered type, as per past similar pain experience. None of this can be known or understood by any other person, because pain perception is an exclusive sensory and emotional experience for each person, based on accumulated unique past experiences.

Results

The model evolved gradually over 4-5 years while explaining pain to 3000 chronic low back pain patients using the booklet. The model consists of nociception consisting of 9 types of switches (toggle, slide, push, pull, turn, electronic, auditory, nuclear, and organic), which feed into A-delta and C fibres, and when they turn on (acting like a microphone), the impulse goes up to the dorsal horn (amplifier). At the dorsal horn the A-delta and C-fibre inputs pass through more switches at the Rexed layers. A-beta inputs and the dorso-lateral funiculus (DLF) from above, reduces the effects of the A-delta and C-fibre within these Rexed layers and the impulses get 'damaged' and 'out of balance' ; which is like amplification and 'acoustic feedback' where the output is very 'noisy'.

This noise then passes to the midbrain, stimulating the autonomic vestibular control centre...(responsible for blood pressure, sleeping, eating, hormones, alertness, sleep control) and this is also affected by the integration of sight, sound, smell direct inputs from above and is called Pain.

'Suffering' is the combined output from this autonomic centre via the sympathetic and parasympathetic systems affecting the whole body, as well as activating the endocrine system via the hypothalamus and the releasing Orexin/Hypocretin which alters sleep and creates excess hunger, thus sleep deprivation (often labelled as 'depression'), and weight gain in chronic pain.

The afferents while passing to many cerebral areas, stimulate the hippocampus, amygdala and multiple brain centres to create a composite pattern or 'pain perception' based on comparison to the person's past unique, experience memory base. The overall outcome is 'pain perception' = 'Light coming on' and then 'pain behaviour' follows to try and modify that which is felt/perceived, by simple body position changes!

These follow Loeser's 4 stages: Nociception, Pain, Suffering and Pain Behaviour.

Conclusions

Explaining *pain, ache, sore*, and *hurt* concepts to patients with no medical lexicon is virtually impossible. This simple model set was evolved during the author's patient interaction. Pain perception is just like "turning on a light" at the "switch"/"microphone" that sends a current to the "amplifier" (dorsal horn) and the upward current triggers the "suffering" (via autonomic nervous system) and the brain checks its memory and the "light turns on" (= pain perception).

After listening to the description, the patient's usual answer was...."I easily understood that. Why have none of the doctors bothered to tell me before?"

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Lifestyle Redesign® for chronic headaches

Susan McNulty, Soma Sahai-Srivastava
University of Southern California, Los Angeles, CA, USA

Purpose

Individuals with headaches have an underlying genetic vulnerability to headaches and lifestyle factors which can cause headaches. Occupational Therapy is a healthcare profession aimed at preventing illness and disability and promoting adaptation to life changes through participation in meaningful occupations. The aim of this study was to determine the effectiveness and of a preventive lifestyle-based occupational therapy intervention in improving patient's knowledge of lifestyle factors related to headaches, their ability to adapt behaviors, and to decrease the overall number of headaches and negative effect on headaches on quality of life.

Method

A case series study was conducted examining effects of a lifestyle headache treatment program. Patients included 12 men and women aged 15-63 (mean age 40 years), recruited from the Neurology department at USC University Hospital with a diagnosis of headache. Patients participate in 8 individual or group sessions for 1-1.5 hours/week. Sessions include topics such as Lifestyle Balance, Regular Eating/Sleep/Exercise Routines, Dietary Triggers, Ergonomics, Stress Management, Sensory Processing & Environmental Triggers, How to Manage Headaches in the Moment, and Pain Communication. Outcome measures include: Migraine Disability Assessment Scale (MIDAS), which measures disability caused by headaches, Migraine Specific Quality of Life Questionnaire (MSQ v.2.1) with 3 separate measures (RFR, RFP, EF) and the Headache Impact Test (HIT-6) which measure the impact of migraine on health related quality of life, and The Headache Management Self-Efficacy Questionnaire (HMSE) which measures an individual's belief that they are able to do the things necessary to prevent headaches.

Results

Outcomes for individual and group participants were not found to be significantly different for the MIDAS, MSQ v.2.1, and HMSE with *P*-values of .86: .69, .69, .55: .52 respectively. As a result outcome data for individuals and groups were combined to analyze overall effectiveness of the program. Outcomes rescored after 8 individual or group sessions from result in a statistically significant (*P*-value less than .05) improvement from the HIT-6 (*P*=.004) which measures the impact of headaches on quality of life and the HMSE (*P*-value=.03) which measures the individual's belief that they are able to do the things necessary to prevent headaches. Patient improvements in the MIDAS and MSQ v.2.1 were found, but not to a significant level.

Conclusions

A lifestyle-oriented occupational therapy intervention has beneficial effects for patients diagnosed with headaches and can significantly improve headache related Quality of Life and Self-Efficacy measures in addition to showing a trend towards improvement of all other outcome measures. The lack of significance in some measures is likely due to small sample size, limited time for patients to incorporate lifestyle changes and loss of final outcome measures from patient noncompliance. No significant difference between group and individual services outcomes were found in the MIDAS, MSQv.2.1, and HMSE measures which demonstrates the versatility of the program in group or individual format.

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Prescribing practices in hospice patients with adult failure to thrive or debility

Leah Sera[1], Mary Lynn McPherson[1], Holly Holmes[2]
[1]*Department of Pharmacy Practice and Science, The University of Maryland School of Pharmacy, Baltimore, MD, USA,*
[2]*Department of General Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA*

Purpose

Debility and adult failure to thrive are complex syndromes of functional decline that are not a process of normal aging. Despite being a common admitting diagnosis, there is very little published literature on medication management in hospice patients admitted with a diagnosis of failure to thrive or debility. The purpose of this study was to describe medication prescribing practices in hospice patients with either of these primary diagnoses by characterizing prescribed medications by name and by pharmaceutical class, and determining whether the patient or hospice organization provided each medication.

Method

A retrospective review of a patient information database compiled by a national hospice organization was conducted. Patients were included in the study if they were admitted to hospice with a primary diagnosis of failure to thrive or debility. We included patients who were admitted to hospice on or after January 1, 2010, and were discharged by death on or before December 31, 2010. We evaluated medication orders in the hospice database, which included drug name, dosage form, dosing frequency, start dates and discontinuation dates, as well as whether the hospice provided the medication.

Results

Overall 293 patients and 5209 medication entries were evaluated. The most commonly prescribed drugs were acetaminophen, lorazepam, morphine, atropine, prochlorperazine, haloperidol, docusate, aspirin, and bisacodyl. The most commonly prescribed pharmacological classes were opioid and nonopioid analgesics, anxiolytics, anticholinergics, antihypertensives, laxatives, antidepressants, and vitamins/supplements. The hospice organization provided over 90% of medications in these pharmacological classes, with the exception of laxatives, antidepressants, antihypertensives, and vitamins/supplements. Less than 5% of opioid and nonopioid analgesic, anxiolytics, anticholinergics, antipsychotics, and stool softeners were discontinued prior to death. The most commonly discontinued drug classes were anti-infectives, cholinesterase inhibitors, lipid lowering agents, diuretics, and appetite stimulants.

Conclusions

Recognized clinical components of failure to thrive syndrome include cognitive impairment, malnutrition, and depression. Hospice often provided antidepressants, but infrequently provided appetite stimulants and drugs treating dementia. The most commonly provided drugs were those used for symptoms associated with most end stage diseases.

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The 100 most commonly prescribed drugs in a population of hospice patients

Leah Sera[1], Mary Lynn McPherson[1], Holly Holmes[2]
[1]*Department of Pharmacy Practice and Science, The University of Maryland School of Pharmacy, Baltimore, MD, USA,*
[2]*Department of General Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA*

Purpose

Medications are used in hospice patients to palliate common symptoms in terminal illness including pain, dyspnea, nausea, delirium, and depression. In general, the prescribing of medications for chronic comorbid conditions decreases at the end of life, while prescribing of medications used to palliate symptoms increases. The purpose of this study is to determine the 100 most commonly prescribed medications in a population of hospice patients.

Method

A retrospective review of a patient information database compiled by a national hospice organization was conducted. We evaluated demographic information (patient age, sex, race, and primary state), admitting diagnosis, length of stay, and medication information. Medications were grouped by pharmacological class. We evaluated the 100 most frequently prescribed drugs.

Results

Overall 4252 patients and 80,441 medications were evaluated. Medication classes used for symptom management were most commonly prescribed. The 6 most common drugs (acetaminophen, morphine, haloperidol, lorazepam, and prochlorperazine) were all included in the symptom management medication kits provided to most patients at admission. Other drugs prescribed for over 10% of patients included albuterol, docusate, bisacodyl, scopolamine, senna , furosemide, aspirin, ipratropium , omeprazole, magnesium, oxycodone, fentanyl, metoprolol, hydromorphone. Opioid and nonopioid analgesics, anxiolytics, anticholinergics, and antipsychotics were prescribed to over 60% of patients at some point during admission. Other frequently prescribed medication classes were laxatives, antihypertensives, bronchodilators, and acid reducers.

Conclusions

These commonly prescribed drug classes largely correlated with those considered essential by the International Association of Hospice and Palliative Care. Medications which are preferentially prescribed in any organization depend on many factors, including efficacy, safety, availability, and cost. The results of this research will be beneficial in the development of educational materials for healthcare professionals and patients.

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Identification and resolution of actual and potential drug-related problems in a hospice population

Mary Lynn McPherson, Joy Chou, Erin McCartin, Hsiao-Ting Wang
University of Maryland School of Pharmacy, Baltimore, MD, 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 nonprescription 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.

This pilot project was a preliminary, retrospective study with the following aims:

1. Review a sampling of clinical pharmacy notes written after reviewing the medication regimen of patients admitted to a hospice program and categorize the drug-related problems recorded.
2. Review a small cohort of these patient records to determine for what percentage the nurse case manager acknowledged the clinical pharmacy recommendations, and what percentage of recommendations were eventually implemented.

Method

Hospice of the Chesapeake is a not-for-profit hospice providing services in Maryland (USA). A clinical pharmacist reviews the medication regimen for all patients admitted to the hospice program, and generates clinical pharmacy note identifying actual or potential drug related problems, and suggested action steps. This note is entered into the patient's electronic medical record, accessible to the nurse case manager who is responsible for reacting to the note and documenting outcomes as appropriate. The University of Maryland IRB approved this project.

Patients admitted during the first full weeks of January, April, July, and October 2011 were included in this phase of the project. Drug-related problems as reported by the clinical pharmacist were tabulated and categories into 11 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 (eg, a potential drug related problem) or specific (eg, 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. For each drug-related problem identified by the pharmacist an analysis of subsequent action steps was conducted. This included note of any documentation in the nurse's notes regarding the recommendations, and eventual changes to the medication regimen consistent with the recommendations.

Results

150 clinical pharmacy notes were written during the 4 study week periods. Of this cohort, 62% of the patients were female; the average age of all patients was 76.5 years. Cancer was the primary admitting diagnosis (44% of patients), followed by debility/failure to thrive (18.7% of patients), and the remaining diagnoses represented 37.3% of the population.

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 (170, 44%), followed by drug w/o indication (150, 41%), formulary issues (33, 8%), inappropriate drug selection (13, 3%), drug allergy implications (11, 2%), underdose (4, 1%), drug interaction (4, 1%), and need for additional therapy (1, <1%).

Secondary analysis included 45 patients with demographics consistent with the larger cohort. A total of 183 drug related problems (DRP) were identified; 165 (90%) consultative and 18 (10%) specific.

111 (61%) of drug related problem recommendations were accepted and changes were to drug regimen; 61% of consultative recommendations were accepted and 56% of specific recommendations. However, only 73 (40%) of drug related problems were documented in nurse's 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 (eg, antihypertensive and antidiabetic medications). Over 60% of the recommendations to reduce or stop these medications were implemented. Drug use without indications (eg, supplements) was also a large category of DRP's; over half of these recommendations were accepted.

One area of improvement is nursing documentation in acknowledgement of DRPs and resolution.

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Improvement in knowledge and skills of hospice nurses in pain management and palliative care with an online training program

Mary Lynn McPherson, Joanne Hilburn, Francoise Prade
University of Maryland School of Pharmacy, Baltimore, MD, USA

Purpose

Hospice nurses must possess excellent skills in the assessment, management and monitoring of patients with advanced illness, both pain and nonpain symptoms. The aim of this study was to compare knowledge, attitudes, and self-perceived skills within 15 content domains in pain and palliative care by comparing results of a survey before and after completing an online training program.

Method

The Hospice and Palliative Care Nurses Association in the US developed a series of slide presentations developed for the education of hospice and palliative care nurses on basic pain and symptom management. With permission, these slides were divided into modules, narrated and posted to an online learning system, along with self-assessment and post-assessment activities in each module. The content was divided into 15 domains. Nurses from hospice program across the United States were invited to participate in this online course. The course became available November 2009; 643 nurses started the course and 410 nurses completed it by July 1, 2011. Participants also rated their self-perceived need for improvement in each domain before the course, and rated their self-perceived ability to perform in each domain after the course. A students t-test was used to compare aggregate pre- and post-course results ($P<.05$=statistical significance).

Results

The 15 content domains included pathogenesis of pain, pain assessment, analgesic selection, routes of opioid administration, opioid conversion calculations, opioid titration, selecting/dosing/adverse effects of adjuvant analgesics, physical dependence/tolerance/addiction, assessing and treating pain in special populations, nondrug management of pain, identification of nonpain symptoms, etiologies of nonpain symptoms, medication management of nondrug symptoms, nondrug management of nonpain symptoms, education of patient/family. There was no change in participant's attitudes about the importance of being skillful in 14 of the 15 domains; the majority opinion pre-course was that these were important skills, and this was rated similarly postcourse. Self-perception of skill was significantly improved in all 15 areas by the end of the course. In knowledge, there was a favorable trend in performance in all 15 areas by the end of the course, with 8 of the 15 showing statistical significance. Participants were asked in the pre-course survey if they felt there was room for improvement in each domain; on average 69% responded there was "moderate" or "very much" room for such. In the postcourse survey participants, on average 80% of responded felt the course improved their skills by a "moderate" or "very much" amount.

Conclusions

By all measures, this online training program was successful at improving hospice nurses knowledge in 15 content domains, self-perceptions of skill in each area, and overall improvement.

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Strengthening the pharmacists role in managing chronic opioid therapy

Bronwyn Boyes, Joan Meyer
MediCom Worldwide, Inc, Morrisville, PA, USA

Purpose

Pain affects approximately one in 3 American adults. The annual healthcare costs associated with chronic pain is momentous (about $635 billion) in medical treatment and lost productivity and it causes more suffering and disability than heart disease or cancer.

Chronic pain is an ongoing challenge receiving national attentiveness in the form of national drug control policy, FDA mandated risk evaluation and mitigation strategy (REMS), healthcare policy reform, and clinical guidelines. Many barriers exist in treating chronic pain, especially when utilizing chronic opioid therapy. Pharmacists are often the first port of call for patients seeking relief from their pain and, therefore, could play a vital role in the assessment, education, monitoring, and treatment of chronic pain. Although all healthcare professionals must have knowledge of the pharmacological options available to help treat pain, pharmacists have a particularly significant role because they are highly trained in medication management, as well as being easily visible and accessible members of the healthcare team.
This educational webinar series was developed by an expert team of pain management pharmacists to address the growing and vital role pharmacists can play in the healthcare system including monitoring pharmacotherapy and the education of patients as well as other members of the multidisciplinary healthcare team, minimizing patient risk using clinical tools to improve assessment and monitoring of pain and drug-related aberrant behaviors and how to use a "universal precautions" approach to enhance the process of assessment and monitoring.

Method

A 4-part webinar series was developed with the assistance of an expert panel of pharmacists and needs assessment surveys conducted by MediCom Worldwide, Inc., to a growing pharmacist membership group of Emerging Solutions in Pain (ESP). ESP was launched in 2005 with a leading cadre of pain management experts to address some of the most critical issues in pain management. ESP is a forerunner in providing robust, value-added and award-winning pain education in an array of convenient multimedia formats. ESP also works in partnership with Southern Illinois University Edwardsville (SIUE), Southern Illinois University (SIU) School of Medicine, St. Louis University, and other key pain associations to extend the distribution of pain education across the largest number of healthcare providers possible.
A live webinar format was chosen to provide a large amount of knowledge in a limited amount of time. The audience interactive format enabled an opportunity for open discussion on challenging issues in chronic pain management. The case vignettes provided an actual problem or situation to provoke controversy and debate. A registration process with a pre-activity assessment aided in obtaining participants' attitudes, knowledge and practices in pain management. Finally, to ensure maximal and cost-effective distribution of this critical information, the live meetings were adapted into interactive self-study programs on the ESP website for 1 year. The overall objective of this webinar series was to increase the knowledge and resources to pain pharmacists and patients to minimize the risks that are often associated with opioids and improve clinical outcomes.

Results

A total of 1473 pharmacists completed an evaluation form following participation in the educational initiative. The respondent population contained similar numbers of RPh and PharmDs (38% each) with a smaller portion of BPharm

(21%) and CPHT (3%). A statistically significant change occurred in the 3 domains of pharmacists' confidence, knowledge and change outcomes from pre-education to post-education surveys ($P<.0001$).

The most significant changes in knowledge occurred in the following:
• Information regarding the Risk Evaluation and Mitigation Strategy (REMS) relating to opioids
• The role of the pharmacist in pain management
• Multidisciplinary pain management team approach
• Multimodal and pharmacological analgesic therapy
• Identification and significance of aberrant drug related behaviors
• Risk assessment terminology and tools.

Although a high proportion of respondents did not correctly identify red flag signs of aberrant drug taking behaviors relating to chronic opioid therapy. The most highly rated sources of education were live followed by internet CE programs

Conclusions

Pharmacists play a vital role in managing pain, from the initial patient assessment, to patient education and ongoing patient monitoring. Currently there exists a gap in pharmacists' knowledge and their pain-related decision making. To this end, this educational webinar series was designed by pharmacists for pharmacists to improve knowledge, access to essential pain management resources and patient education support materials. The results from an evaluation of this educational initiative show an improvement in confidence and knowledge of pharmacists to make evidence-based care choices for their patients.

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KP511: a novel opioid pain therapy with reduced abuse potential and improved safety

Travis Mickle, Sven Guenther, Gouchen Chi, Jaroslaw Kanski, Andrea Martin, Bindu Bera
KemPharm, Inc., North Liberty, Iowa, USA

Purpose

Opioids have been around for over a century now. They play an important role in the treatment of moderate to severe pain. With an increasing market for pain therapies, diversion and abuse of opioids have escalated as well. As a result, physicians and payers have expressed a need for less abusable pain treatments.

Method

Typical approaches to reduce abuse potential have been through formulation, which have demonstrated drawbacks. KP511 is a prodrug composed of hydromorphone and a nontoxic ligand. When taken as directed, the prodrug is metabolized after oral administration to release the active opioid. KP511's inherent molecular properties provide a differential and preferred way to address narcotic abuse.

Results

Preclinical studies suggest that KP511 exhibits unique abuse deterrent properties by significantly limiting the narcotic exposure upon intranasal and intravenous administration and being resistant to chemical and physical extraction methods. Additionally, studies in rats have indicated that KP511 limits the exposure to the active opioid at high doses and may thus be the first opioid derivative with oral abuse prevention and overdose protection.

Another benefit of KP511 is its potential to prevent or reduce Opioid Induced Constipation (OIC) that afflicts many patients. Unlike peripheral μ-opioid receptor antagonists intended to compensate for the constipatory effects of concomitantly administered opioid pain therapies, KP511 appears to not cause OIC, because it is biologically inactive and does not interact with the enteric μ-opioid receptors. This theory was confirmed by a motility study in rats.

Conclusions

KP511 is a novel opioid derivative with anti-abuse properties, tamper resistance, potential reduction of OIC and possible oral overdose protection.

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Monitoring oxycodone use in patients with chronic pain: analysis of oxycodone and metabolite excretion in oral fluid and urine

Kathleen Moy[1], Brookie Best[1,2], Joseph Ma[1,3], Candis Morello[1,4], Rabia Atayee[1,3], Amadeo Pesce[5,6]
[1]University of California San Diego (UCSD), Skaggs School of Pharmacy and Pharmaceutical Sciences, La Jolla, CA, USA, [2]UCSD Department of Pediatrics, Rady Children's Hospital, San Diego, CA, USA, [3]Doris A. Howell Palliative Care Service, San Diego, CA, USA, [4]Diabetes Intense Medical Management Clinic, Veterans Affairs San Diego Healthcare System, San Diego, CA, USA, [5]Millennium Research Institute, San Diego, CA, USA, [6]Department of Pathology and Laboratory Medicine, UCSD School of Medicine, La Jolla, CA, USA

Purpose

Oxycodone is a semisynthetic opiate agonist used to treat moderate to severe pain. Oxycodone is N-demethylated by cytochrome P450 (CYP) 3A to its predominant metabolite, noroxycodone, and O-demethylated by CYP2D6 to its minor and active metabolite oxymorphone. The presence of medication may be monitored by quantitation of oxycodone and its metabolites in oral fluid, plasma and urine. Oral fluid medication monitoring has advantages over urine and plasma medication monitoring in its ease of collection, minimal invasiveness and reduced susceptibility to tampering and adulteration. Oral fluid is also purported to have a close correspondence to plasma concentrations due to a passive diffusion process from plasma to oral fluid. However, limited data are available characterizing oxycodone and its metabolites in oral fluid. The purpose of this retrospective data analysis was to evaluate oxycodone metabolism using oral fluid specimens and to compare concentrations in oral fluid and urine.

Method

Urine and oral fluid specimens collected from patients with chronic pain in accordance with routine patient care procedures were received at Millennium Laboratories between March 2012 and June 2012, and analyzed using liquid chromatography-tandem mass spectrometry (LC-MS/MS) to quantitate oxycodone, noroxycodone and oxymorphone concentrations. Only those de-identified test results of patients with reported prescriptions for oxycodone and no reported prescriptions for oxymorphone were included in the retrospective data analysis. Urine specimens with a creatinine concentration less than 20 mg/dL were excluded. Urine specimens and oral fluid specimens with an oxycodone, noroxycodone, or oxymorphone concentration below the lower limit of quantitation were excluded. Final sample size was 849 oral fluid specimens and 27,974 urine specimens. Statistical analyses were carried out with Microsoft Excel® 2010 and OriginPro 8.6.

Results

A frequency distribution of oxymorphone concentrations in oral fluid reveals a Gaussian distribution which is truncated on the lower end when using a quantitation limit of 1 ng/mL, which may lead to false negatives in oral fluid monitoring for oxycodone. The geometric mean metabolic ratio (MR) of noroxycodone to oxycodone in oral fluid was 0.11, while the geometric mean MR in urine was 1.7. The geometric mean oxycodone concentration in oral fluid was 860 ng/mL (range, 1.5-8,600,000 ng/mL), while the geometric mean noroxycodone concentration was 98 ng/mL (range, 2.3-8,800 ng/mL). Fifty-four of the oral fluid specimens (6%) had oxycodone concentrations between 10,000 and 9,000,000 ng/mL. The geometric mean oxycodone concentrations were approximately 3 times greater in urine compared to oral fluid (2,500 ng/mL vs 860 ng/mL), while noroxycodone concentrations were approximately 40 times greater in urine compared to oral fluid (4,350 ng/mL vs 98 ng/mL). The geometric mean MR in oral fluid decreased with increasing concentrations of oxycodone.

Conclusions

Oxycodone is predominant over noroxycodone in oral fluid (similar to plasma), while the reverse relationship exists in urine. Much greater oxycodone concentrations were found in oral fluid than have been reported in plasma (up to a 1000-fold difference). Possible explanations include medication residue in the mouth (recent medication use) or active secretion into saliva. The current data suggest that in oral fluid testing for oxycodone, concentrations of noroxycodone are typically only ~10% of the parent drug, and as such, an oral fluid drug test should be highly sensitive, capable of detecting very low concentrations of the metabolite.

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Lumbar sympathetic block with botulinum toxin type B for complex regional pain syndrome: report of 2 cases

Francis Nahm[1], Eunjoo Choi[1], Hye-Young Kim[2], Pyung-Bok Lee[1]
[1]*Seoul National University Bundang Hospital, Seongnam, Republic of Korea,* [2]*Seoul National University Hospital, Seoul, Republic of Korea*

Purpose

The lumbar sympathetic block (LSB) is an effective method for sympathetic mediated pain in the lower extremity. To prolong the sympathetic blocking, sympathetic destruction with alcohol or radiofrequency has been used. However, our clinical experience has shown that the effect of sympathetic destruction in CRPS patients lasts for only a short period. The pre-ganglionic sympathetic nerves are cholinergic, and the botulinum toxin (BTX) inhibits the release of acetylcholine at the cholinergic nerve terminals. Moreover, BTX type B has greater affinity for sympathetic nerve than BTX A. Based on these background, we performed the LSB with BTX type B in the patients with CRPS.

Method

LSB was performed in 2 patients with CRPS chain using 0.25% levobupivacaine 5 mL plus BTX type B 2500 IU under the fluoroscopic guidance.

Results

The patients who received LSB using BTX type B experienced the improved coldness and pain at the lower limb for 2 months. The patients did not suffer from any adverse effect from the injection of BTX type B.

Conclusions

We conclude that BTX type B can produce efficacious and durable lumbar sympathetic block effect.

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Single-entity hydrocodone extended-release: disability and satisfaction

Srinivas Nalamachu[1], Martin Hale[2], Richard Rauck[3], Cynthia Robinson[4]
[1]*International Clinical Research Institute, Overland Park, KS, USA,* [2]*Gold Coast Research, LLC, Weston, FL, USA,* [3]*Carolinas Pain Institute, Center for Clinical Research, and Wake Forest University School of Medicine, Winston-Salem, NC, USA,* [4]*Zogenix, Inc., Emeryville, CA, USA*

Purpose

Hydrocodone (HC) is available only in combination with nonopioid analgesics, such as acetaminophen or ibuprofen, which may prevent titration of HC to effective levels due to dose-limiting toxicity of the nonopioid component. HC bitartrate extended-release (HC-ER; Zohydro™, Zogenix, Inc., San Diego, CA) is a single-entity HC therapy currently being evaluated for treatment of chronic moderate-to-severe pain in patients requiring long-term, continuous opioid therapy; the availability of HC-ER would provide another hydrocodone option for treatment of such pain without the dose-limiting effect of a nonopioid component. The overall objective of this study was to evaluate the long-term tolerability and efficacy of HC-ER in subjects with moderate-to-severe chronic pain.

Method

This multicenter study included an open-label conversion/titration (C/T) phase (≤6 weeks) and a treatment phase (≤48 weeks) in opioid-experienced subjects with chronic pain. After screening (n=938), subjects who entered the C/T phase (n=638) were converted to HC-ER using initial doses 20%-30% less than the equivalent dose calculated by the Opioid Conversion Table. HC-ER dose was titrated until a stable level was reached. During the treatment phase, subjects (n=424) received their individualized HC-ER dose and up to 2 tablets of hydrocodone bitartrate 5 mg/acetaminophen 500 mg daily for breakthrough pain. The Oswestry Disability Index (ODI) was used to assess subject disability. Overall subject satisfaction was measured using the Subject Global Assessment of Medication (SGAM). No hypothesis testing was conducted.

Results

At screening, mean ODI score was 41.2%±14.9%, within the lower limit for severe disability (>40%-60%). Mean ODI score improved to 31%±14.5% at baseline and was maintained at week 48 (n=285) or study termination (34.1%±17.3%), scoring near the midpoint of moderate disability (>20% to 40%); changes were -10.2%±13.4% and -6.8%±14.5%, respectively. SGAM scores showed that only 20.5% of subjects who entered the treatment phase were "very much" or "completely" satisfied with their treatment at screening; this increased to 82.3% at baseline and 72.7% at study end. In contrast, 27.4% of subjects were "not at all" or "a little bit" satisfied with their previous opioid treatment at screening, compared with 1.2% at baseline and 7.9% at study end. The safety of HC-ER was consistent with the profile of other opioids (details reported separately).

Conclusions

ODI and SGAM scores improved from screening to baseline and were largely maintained throughout the subsequent treatment period. HC-ER appeared to reduce disability and increase overall satisfaction in subjects with chronic pain who require around-the-clock opioid therapy.

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Hydromorphone extended-release in chronic neuropathic pain

Srinivas Nalamachu[1], Martin Hale[2], Arif Khan[3]
[1]*International Clinical Research Institute, Overland Park, KS, USA,* [2]*Gold Coast Research, LLC, Weston, FL, USA,* [3]*Northwest Clinical Research Institute, Bellevue, WA, USA*

Purpose

The benefits of opioid therapy in patients with chronic neuropathic pain warrant further investigation. The purpose of this study was to analyze the efficacy and safety of hydromorphone extended-release (ER) in patients with neuropathic vs non-neuropathic low back pain (LBP), who participated in a previously published double-blind, randomized withdrawal study.[1]

Method

Patients were initially converted from prior opioid therapy to once-daily hydromorphone ER and titrated to a stable effective dose (12 mg-64 mg) over 2-4 weeks; patients successfully achieving a stable dose were randomized to continued treatment with hydromorphone ER or placebo for 12 weeks. Immediate-release hydromorphone tablets (2, 4, or 8 mg) were allowed as rescue medication. For this subanalysis, outcome measures, including an 11-point pain intensity numeric rating scale (NRS) and Roland Morris Disability Questionnaire (RMDQ), were analyzed separately for patients with non-neuropathic and neuropathic LBP (classified using the Quebec Task Force Classification of Spinal Disorders).[1]

Results

The study was completed by 67/173 (38.7%) patients with non-neuropathic LBP and 43/94 (45.7%) patients with neuropathic LBP randomized to the double-blind phase. Baseline characteristics were similar between groups. Mean (SD) screening NRS pain scores were 6.6 (1.75) and 6.7 (1.82) in non-neuropathic and neuropathic patient groups, respectively. The final titrated dose of hydromorphone ER was 36.3 mg and 38 mg, respectively. Both patient groups showed significant ($P<.001$) reductions in pain intensity during conversion/titration; baseline mean (SD) NRS scores for randomized patients at the start of double-blind treatment were 3.2 (0.99) and 3.1 (1.09) for neuropathic and non-neuropathic groups, respectively. In both patient groups, those treated with hydromorphone ER maintained improvements in pain intensity over the double-blind period vs placebo as demonstrated by Week 12 mean (SD) NRS scores (non-neuropathic: 3.7 [1.79] for hydromorphone ER and 5.1 [2.13] for placebo, $P<.001$; neuropathic pain: 3.8 [1.72] and 4.6 [2.07], respectively, $P=.006$). Similarly, improvements in RMDQ scores were maintained at Week 12 with hydromorphone ER vs placebo in both patient groups as demonstrated by mean (SD) change from baseline (non-neuropathic pain: -0.3 [5.38] for hydromorphone ER and 2.2 [5.58] for placebo, $P=.002$; neuropathic pain: 1.3 (4.52) and 3 (4.72), respectively, $P=.037$). Adverse events were generally similar between patient groups.

Conclusions

This analysis indicates that hydromorphone ER was similarly effective in treating neuropathic or non-neuropathic chronic LBP.

Reference: Hale M, Khan A, Kutch M, Li S. Once-daily OROS hydromorphone ER compared with placebo in opioid-tolerant patients with chronic low back pain. *Curr Med Res Opin.* 2010;26(6):1505-1518.

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An open-label study to evaluate the efficacy and safety of hydromorphone extended-release (ER) in patients with chronic neuropathic pain

Srinivas Nalamachu[1], Donna Ruck[1], Christy Akright[1], Sam Fasbinder[1], Ritvik Bansal[2]
[1]*International Clinical Research Institute, Overland Park, KS, USA,* [2]*Texas A&M University, College Station, TX, USA*

Purpose

Hydromorphone extended-release (ER) is an opioid formulation administered once daily as around-the-clock medication to control moderate to severe chronic pain in opioid-tolerant patients. The purpose of this study was to examine the efficacy and safety of once-daily hydromorphone ER in patients with chronic neuropathic pain.

Method

In this single-center, open-label, 12-week study, opioid-tolerant patients were converted from their previous opioid and titrated to adequate analgesia with hydromorphone ER over 2 weeks. The primary efficacy measure was change from baseline on question #5 ("average pain") of the Brief Pain Inventory (BPI) scale, assessed at Week 12. The Pain Quality Assessment Scale (PQAS) and the Global Assessment of Treatment Satisfaction (GATS) were included as secondary endpoints. All patients provided written informed consent; this study received approval from an Institutional Review Board.

Results

Overall, 30 patients (mean age, 58 y; 67% male; mean daily morphine equivalent dose: 163.7 mg) were enrolled and received ≥1 dose of hydromorphone ER. Patients were initially converted to a mean daily hydromorphone ER dose of 18.1 mg and subsequently titrated to a mean daily dose of 26.4 mg. BPI "average pain" decreased from 5.7 at baseline to 4.5 at Week 12. The PQAS decreased from 104 at baseline to 79 at Week 12. The majority of patients (73%) were either very satisfied or satisfied with their treatment. The most common adverse events were dizziness (n=4), headache (n=2), and nausea (n=2). No serious adverse events were reported.

Conclusions

These findings indicate that patients with chronic neuropathic pain can be safely and effectively converted and maintained on hydromorphone ER. Additional placebo-controlled studies are needed in this patient population.

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The National Breakthrough Pain Survey: multivariate predictors of functional status, pain interference and disability

Arvind Narayana[1], Nathaniel Katz[2], Alicia Shillington[3], Judith Stephenson[4], Russell Portenoy[5]
[1]*Teva Pharmaceuticals Ind. Ltd, Frazer, PA, USA,* [2]*Tufts University School of Medicine, Boston, MA, USA,* [3]*EPI-Q Inc., Oak Brook, IL, USA,* [4]*Health Core, Inc., Wilmington, DE, USA,* [5]*Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, New York, NY, USA*

Purpose

Breakthrough pain (BTP) is a transitory exacerbation of moderate to severe pain that occurs on a background of controlled persistent pain. Prior studies suggest an association between BTP and relatively poor pain control, physical/emotional functioning and overall quality of life. These findings require confirmation through multivariate analysis of larger patient samples, which can distinguish the unique impact of BTP from other medical and psychosocial comorbidities. The National Breakthrough Pain Survey (NBTPS) applied a standardized interview in a large commercially-insured population and determined that 80.4% and 77.2% of patients with noncancer and cancer pain, respectively, reported BTP. The current report presents the findings of the NTBPS interview with regards to impairments in patient functional status, pain interference, and disability associated with BTP.

Method

Adult current members of an affiliated health plan were eligible if they had ≥2 claims at an interval ≥3 months with an ICD-9-CM diagnostic code suggesting a chronic pain condition (cancer or noncancer) and ≥3 opioid prescription claims consistent with chronic use. Patients were contacted by phone and, upon consent, responded to demographic and disease/treatment-related questions, a structured interview for BTP, and questionnaires to assess quality-of-life, mood, and functioning (SF-12, Brief Pain Inventory [BPI], Sheehan Disability Scale [SDS]). Patients with uncontrolled baseline pain were excluded. Comorbidity severity was extracted from claims using the Deyo-modified Charlson Comorbidity Index. Univariate associations were assessed by Pearson *r* and Cohen's *d*. Parameters with effect sizes of ≥.3, and/or with *P* values of <.1 were generally considered for multivariable model inclusion after examining for potential multicollinearity. Models were constructed using ordinary least squares regression analysis.

Results

Of the 2198 patients who completed the survey, 919 did not meet criteria for clinically significant chronic pain, were included in the control group and were not included in these analyses. There were 1134 with chronic noncancer pain (no BTP in 222 and BTP in 912) and 145 with chronic cancer pain (no BTP in 33 and BTP in 112). BTP in overall group which included both cancer and noncancer pain was associated with an increase in pain interference (*B*=.907, *P* <.0001) controlling for demographics, level of baseline pain, anxiety and depressed symptoms. Those with BTP reported poorer functioning on the SF-12 physical component scale (*B*=4.627, *P*<.0001) controlling for demographics, anxiety, depressed symptoms, and comorbidities, as well as higher disability (SDS) (*B*=2.499, *P*<.0001), controlling for demographics, level of baseline pain, anxiety and depressed symptoms. In the subset of patients with BTP, which included cancer or noncancer patients, BTP intensity also accounted for an increase in overall pain interference (*B*=.374, *P*<.0001) and incremental deficits in physical functioning (*B*=-1.442 , *P*=.003). Although BTP intensity was not associated with increased disability, number of BTP days per week was associated with higher disability (*B*=.27, *P*=.034). Associations were independent of comorbidities, baseline pain severity, demographics, presence of cancer pain, or pain mechanism (neuropathic/nociceptive).

Conclusions

This is the largest survey of patients with BTP and its consequences, and demonstrates that BTP is highly associated with negative impact on function and disability when other potential influences are controlled. These findings add to the epidemiologic literature on BTP and highlight the need for effective strategies to manage it.

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The cost associated with breakthrough pain: findings from the National Breakthrough Pain Survey

Arvind Narayana[1], Nathaniel Katz[2], Alicia Shillington[3], Judith Stephenson[4], Russel Portenoy[1]
[1]Teva Pharmaceuticals Ind. Ltd, Frazer, PA, USA, [2]Tufts University School of Medicine, Boston, MA, USA, [3]EPI-Q Inc, Oak Brook, IL, USA, [4]HealthCore Inc, Wilmington, DE, USA, [5]Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, New York, NY, USA

Purpose

Breakthrough pain (BTP) is a transitory exacerbation of moderate to severe pain that occurs on a background of controlled persistent pain. It is highly prevalent and associated with impairments in functioning and quality of life. Although these characteristics suggest that high costs may be incurred by those with BTP, little is known about the economic consequences. The National Breakthrough Pain Survey (NBTPS) applied a standardized interview in a large commercially-insured population and examined the payer's perspective by evaluating the costs associated with BTP and related patient-reported impairments.

Method

Adult members of an affiliated health plan were eligible if they had ≥2 medical claims at an interval ≥3 months with an ICD-9-CM diagnostic code suggesting a chronic pain condition (cancer or noncancer) and ≥3 opioid prescription claims consistent with chronic use. Patients were contacted by phone and those who consented completed questionnaires by interview. Patients were classified as reporting BTP, not reporting BTP and controls. Comorbidity severity was assessed from medical claims using the Deyo-Charlson Comorbidity Index. Total all-cause medical and pharmacy costs (in US dollars) were determined from administrative claims data for the 12 month period prior to the date of the survey, adjusted for health plan region and type of health plan (HMO, PPO). Univariate associations with cost were assessed by Pearson's and Cohen's effect size. Parameters with effect sizes ≥.3 and/or with *P* values of <.1 were considered for multivariate model inclusion after examining for potential multicollinearity. Generalized linear models with a gamma distribution and logarithmic link function were constructed due to the skewed nature of the healthcare cost data.

Results

Of the 2198 patients who completed the survey, 1279 had controlled persistent pain and could be assessed for BTP; 1024 (81.1%) of these patients had BTP. Those who did not meet criteria for controlled baseline pain were not included in analysis. A control group contained 919 patients. Cancer pain accounted for 145 (11.3%) of the total pain cohort. The mean (SD) unadjusted total annual healthcare cost of patients with BTP was $39,115 ($66,410) compared with $33,992 ($55,843) for those without BTP, an annual mean difference of $5,123 per patient. BTP was associated with an increase in the mean total annual healthcare cost of 23.8% over those without BTP (*P*=.0083), after controlling for health plan and patient demographics, comorbidity severity, cancer pain, neuropathic pain, severity of baseline pain, history of prior surgery, treatment by a pain specialist and patient-reported pain interference. In terms of pharmacy costs, patients with BTP had unadjusted mean (SD) annual costs of $12,481 ($20,476), compared with $7,593 ($10,931) among those without BTP, an increase of $4,888 annually. After controlling for health plan and patient demographics, comorbidity severity, neuropathic pain, cancer pain, history of prior surgery, treatment by a pain specialist, level of baseline pain and patient-reported pain interference, BTP was associated with an increase in pharmacy costs of 28.9% compared to those without BTP (*P*=.0049). For patients with BTP, separate models showed that history of prior surgery was most highly associated with total healthcare costs and neuropathic pain was most highly associated with pharmacy costs.

Conclusions

This is the first study reporting cost implications of BTP in a large, commercially-insured population. Patients with BTP had significantly higher total healthcare and pharmacy costs compared with the costs of non-BTP patients, even after adjusting for covariates including demographics, comorbidities, baseline pain severity and other healthcare utilization.

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Physical pain interference and nonmedical prescription opioid use: a 3-year epidemiologic study of US adults

Scott Novak[1], Cristie Glasheen[1], Carl Rowland[2], Ashish Joshi[3]
[1]RTI International, RTP, NC, USA, [2]Pfizer, Inc, Cary, NC, USA, [3]Pfizer, Inc, New York, NY, USA

Purpose

The nonmedical use (NMU) of prescription opioids, which involves use that is not as directed by a legally authorized prescriber, is a significant public health problem in the United States. An important gap in knowledge is that very few studies have examined whether those reporting self-reported physical pain are at higher risk for NMU. Much of the previous research has been limited to cross-sectional data or brief clinical assessments less than 1 year. This study used a 3 year longitudinal assessment to: (1) Characterize the longitudinal course of pain over 3 years and its association to the NMU of prescription opioids; (2) Assess whether the prospective associations differed by levels of use (eg, use that did not meet the Diagnostic and Statistical Manual Version 4.0r clinical criteria for abuse/dependence vs use among those meeting criteria for disordered use based on abuse/dependence).

Method

Data were drawn from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a national survey of 34,653 U.S. adults interviewed with a standardized structured clinical interview in 2001-2002 (Wave 1; W1) and re-interviewed approximately 3 years later (Wave 2; W2). Physical pain interference was measured at each wave by the SF-12 scale item based on pain interference with normal work in the past month (Ware, 1990). The response options for the Likert scale are based on a 5-point scale (ie, not at all, a little bit, moderately, quite a bit, and extremely). The 5 items were collapsed into 3 categories (High Pain based on the response options of quite a bit or extreme interference, Moderate Pain based on the response option of moderate interference, and None/Negligible Pain Interference based on the response options of not at all or a little bit of work interference due to pain). The cross-tabulation of the 3 response options at W1 and W2 yields 9 distinct patterns over the 2 waves. There are 3 stable cells in which the respondents endorsed the same level of interference at each wave (stable High Pain, stable Moderate Pain, and stable None/Negligible pain). The remaining 6 cells capture transitions between waves, such as transitions involving increases in pain interference from W1 to W2 (eg, None/Negligible Pain at W1 and Moderate Pain at W2), or decreases in pain interference between waves (eg, High Pain at W1 and None/Negligible Pain at W2).

Results

The overall prevalence of High pain interference was 11% and 9% at W1 and W2. Most of the sample (65%) reported stable pain interference states over a 3-year period, primarily is the Low/Negligible Pain interference (50%) category. While 65% of the sample reported stable pain from W1 to W2, the remaining 35% reported a change in pain status over the 3-year period. About 2% of the total sample reported None/Negligible Pain interference at W1 and moved to High Pain Interference at W2. Conversely, 3% of the entire sample moved from High Pain Interference at W1 to Low/Negligible Pain Interference at W2. About 15% was new onset pain interference (ie, None/Negligible Pain Interference at W1 to either High Pain or Moderate Pain Interference at W2). Conversely, 13% was remitted pain (eg, reporting of any pain interference category other than Non/Negligible at W1 and then reporting None/Negligible pain at W2). Overall, stable High Pain Interference at both waves was associated with advanced age (aged 55 or older), white race (relative to other races), and male sex. In terms of the factors associated with the NMU of prescription opioids at W2, those with stable High Pain Interference reported the highest level of NMU of prescription opioids (3.5%), followed by new onset pain interference (None/negligible Pain Interference at W1, and any pain interference at W2, 2.9%), remitted pain (None/negligible Pain Interference at W2, any pain interference at

W1, 2.1%), and stable None/negligible Pain Interference (1.2%). Changes in mood (eg, onset of new mood disorder between waves), anxiety (onset of anxiety disorder between waves), and marital status (divorce) were associated with W2 NMU of prescription opioids.

Conclusions

Understanding the underlying impact that pain has on the NMU of prescription opioid medications may help identify those at greatest risk for NMU of opioid medications prescribed with the intent of treating legitimate pain.

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Methods of acquiring prescription opioid pain medications for abuse: trends and characteristics from a national epidemiologic study from 2004 to 2010

Scott Novak[1], Cristie Glasheen[1], Carl Rowland[2], Ashish Joshi[3]
[1]RTI International, RTP, NC, USA, [2]Pfizer, Inc, Cary, NC, USA, [3]Pfizer, Inc, New York, NY, USA

Purpose

The nonmedical use (NMU) of prescription opioids, which involves use that is not as directed by a legally authorized prescriber, is a significant public health problem in the United States. Numerous studies have shown that social routes of diversion, such as friends and relatives, are among the most common method of obtaining prescription pain medications for NMU. Yet, epidemiological data also indicate that a sizeable proportion of NMU occurs via direct routes, whereby the medication was prescribed to a patient by a licensed prescriber and then diverted for nonmedical use. The current study examines differences between social and prescriber routes of diversion for (Aim 1) NMU consumption practices and (Aim 2) co-occurring risk and protective factors among NMUs in the general population.
The nonmedical use (NMU) of prescription opioids, which involves use that is not as directed by a legally authorized prescriber, is a significant public health problem in the United States. Numerous studies have shown that social routes of diversion, such as friends and relatives, are among the most common method of obtaining prescription pain medications for NMU. Yet, epidemiological data also indicate that a sizeable proportion of NMU occurs via direct routes, whereby the medication was prescribed to a patient by a licensed prescriber and then diverted for nonmedical use. The current study examines differences between social and prescriber routes of diversion for (Aim 1) NMU consumption practices and (Aim 2) co-occurring risk and protective factors among NMUs in the general population.

Method

A total of 455,729 individuals aged 12 or older completed computerized self-assessments for the US National Surveys on Drug Use and Health (NSDUH, 2004-10). The NSDUH is a repeated cross-sectional survey, with replicate samples each year. Statistical methods were used to account for the clustered design of NSDUH (via SUDAAN®). The methods of acquisition were classified based on their last reported method of acquisition among past-year NMUs of prescription opioids.

Results

Interestingly, trend analyses revealed that the percentage of past year NMU of prescription opioids did not evolve to epidemic proportions as suggested by the media. Instead the prevalence was actually fairly stable between 2004 and 2010, where about 4% of the total population reported NMU of prescription pain relievers in any given year. Within this population of NMUs, approximately 66% reported indirect methods of obtaining medications-namely via friends and family. In contrast, 19.4% reported direct methods of obtaining prescription pain relievers for NMU through a single doctor (17.1%) or multiple doctors (2.3%). Those meeting the Diagnostic and Statistical Manual (version 4.0r) clinical criteria for abuse/dependence on prescription opioids were more likely to report prescriber as the methods of acquisition than social methods of acquisitions (Aim 1). Those most likely to report obtaining medications for NMU via a prescriber compared with social methods (Aim 2) include: those with previous drug arrests, having prior illicit drug use histories, age 35+ (relative to those age 34 or younger), male (relative to females), and white race (relative to non-whites).

Conclusions

This study demonstrates that the method of acquiring prescription opioids for NMU is associated with specific personal characteristics and co-occurring risk factors. Learning more about diversion can inform prevention efforts that may reduce the NMU of prescription drugs, and specifically prescription opioid pain medications. These findings suggest that unique prevention and intervention efforts are needed, given the unique constellation of risk factors.

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C-II opioid medication rewrite program

Marylee O'Connor, Philip Eulie, Wafa Samara
U.S. Department of Veterans Affairs, Mather, CA, USA

Purpose

The CII rewrite program was developed to ensure patient's received their monthly opioid medication for chronic noncancer pain in a timely consistent fashion to reduce pseudo-addictive behaviors. The purpose of the program is to improve overall pain management, provide record of patient request for CII medications and decrease delay in receiving medications.

Method

The solution was to implement a system that would control the point of entry for patients requesting their CII medications, ensure proper controls are in place for safe and responsible prescribing of opioids, identification of at-risk patients who need further intervention for problems such as substance abuse and to allow a consistent and uniform criteria for all patients who are currently prescribed CII opioids. This program allows consistent use of controls consistent with safe and responsible prescribing such as Narcotic Agreement Forms (opioid contract), routine urine toxicology screens that are scheduled randomly, and a review of Statewide databases for patients that may be receiving controlled substances from physicians and providers outside the VA system. This program works by referral in the VA healthcare system and patient's receive medications the same day every month, ie, Oct 30, Nov 30, Dec 30... Patients are instructed to call a set telephone number dedicated to this program one calendar week before their next medication request is due. Once they call and request their medications their information is sent to a Pharmacist who acts as a provider and they review the patient's current urine toxicology screens, current narcotic agreement, EKG if patient is on high dose Methadone and also does a chart review to ensure no emergency room visits or other drug seeking behavior has occurred. The Pharmacist then prescribes the CII opioid as indicated in the referral and makes recommendations as indicated.

Results

This process has eliminated up to 95% the patients making multiple points of contact in order to get their monthly CII prescriptions , such as using the pharmacy call center, the appointment call center, local clinic telephones, RN case manager telephones, and or walk ups to the pharmacy/ provider. It has also eliminated 100% of the duplicate work and chaos that was previously associated with stable CII patients receiving their medications. This process is an effective way to monitor and safely prescribe opioids (C-II's) for chronic noncancer pain.

Conclusions

Pain has been recognized as an unmet clinical need. In pain management settings, as many as 90% of patients have been reported to receive opioids for chronic pain management. It has been called the 5th vital sign. The increasing need for adequate pain control and the use of opioids has been unaccompanied by systems and technologies that will help us control pain and employ such opioids safely. This program meets both the needs of the patient and the provider in order to assure safe and responsible prescribing of opioids.

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A single-dose crossover study of fentanyl sublingual spray, oral transmucosal fentanyl citrate (OTFC), and fentanyl citrate injection (IV) in healthy volunteers

Neha Parikh, Venkat Goskonda, Ashok Chavan, Larry Dillaha
INSYS Therapeutics, Inc., Phoenix, AZ, USA

Purpose

Several transmucosal immediate-release fentanyl preparations are available for breakthrough cancer pain. Sublingual delivery of fentanyl, formulated as fentanyl sublingual spray, offers potential for more rapid absorption and higher bioavailability of fentanyl compared with other transmucosal preparations. This study evaluated rate of absorption and bioavailability of fentanyl sublingual spray compared with oral transmucosal fentanyl citrate (OTFC) and fentanyl citrate injection (IV) under fasted conditions.

Method

This phase 1, single-dose, 3-treatment crossover study evaluated rate of absorption and bioavailability of fentanyl sublingual spray 400 mcg vs OTFC 400 mcg and fentanyl citrate injection (IV) 100 mcg under fasted conditions. Healthy subjects received 3 single-dose treatments with a 7-day washout between doses. Pharmacokinetic parameters were evaluated pre-dose, at 5, 10, 20, 30, and 40 minutes, and at various time points through 36 hours.

Results

Forty subjects enrolled, and 21 completed the study. Mean maximum plasma concentration (C_{max}) for fentanyl sublingual spray (0.81 ng/mL) was 33% higher than for OTFC (0.61 ng/mL) and 13% lower than for IV fentanyl (0.93 ng/mL). Mean area under the concentration-time curve from time zero to infinity (AUC_{inf}) was 5.76 ng•h/mL, 4.18 ng•h/mL, and 1.76 ng•h/mL for fentanyl sublingual spray, OTFC, and IV fentanyl, respectively. Mean absolute bioavailability of fentanyl sublingual spray (F=.76) was greater than that of OTFC (F=.51). Median time to maximum plasma concentration (T_{max}) was 1.50 hours, 2 hours, and 0.17 hours for fentanyl sublingual spray ($P<.05$ vs OTFC), OTFC, and IV fentanyl, respectively. At 5 minutes postdose, mean plasma fentanyl concentration for fentanyl sublingual spray (0.168 ng/mL) was 21% of mean C_{max} vs 0.2% of mean C_{max} for OTFC (0.00146 ng/mL). Fentanyl concentrations at 5 minutes for fentanyl sublingual spray were 115-fold greater than for OTFC. Fifteen (38%) subjects reported mild adverse events, most commonly lightheadedness (n=3), dizziness, vomiting, headache, and sublingual burning (n=2 each).

Conclusions

The rate and extent of fentanyl exposure is substantially greater following administration of fentanyl sublingual spray compared with OTFC.

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Efficacy and safety of daily and as needed dosing of oral methylnaltrexone for the treatment of opioid-induced constipation in patients with chronic noncancer pain

John Peppin[1,2], Richard Rauck[3], Robert Israel[4], Shirley Huang[5], Enoch Bortey[5], Robert Rolleri[5], Paterson Craig[5], William Forbes[5]

[1]Pain Treatment Center of the Bluegrass, Lexington, KY, USA, [2]The Center for Bioethics, Pain Management and Medicine, Lexington, KY, USA, [3]Carolinas Pain Institute, Winston-Salem, NC, USA, [4]Progenics Pharmaceuticals, Inc, Tarrytown, NY, USA, [5]Salix Pharmaceuticals, Inc, Raleigh, NC, USA

Purpose

The treatment of chronic, noncancer pain with opioids may be complicated by dose-limiting opioid-induced constipation (OIC), impacting quality of life and pain control. Methylnaltrexone (MNTX) is a peripherally acting, selective μ-opioid receptor antagonist approved in >50 countries worldwide as a subcutaneous (SC) injection for the treatment of OIC in patients with advanced illness when response to laxative therapy has been insufficient (RELISTOR®). Oral MNTX represents a potential new therapy for the treatment of OIC in subjects with chronic pain of noncancer origin. The purpose of this analysis was to evaluate the efficacy and safety of daily dosing (QD) and dosing as needed (PRN) of MNTX administered as an oral formulation in a Phase 3, multicenter, double-blind, placebo (PBO)-controlled, parallel-group study.

Method

803 subjects were randomized to receive PBO or oral MNTX tablets 150, 300, or 450 mg for 12 weeks (4 weeks QD followed by 8 weeks of PRN dosing). During the PRN dosing phase subjects were instructed to use the study drug as needed, but no more than once daily. To be included, subjects with chronic, noncancer pain and a history of OIC were required to be taking ≥50 mg oral morphine equivalents/day. The primary endpoint was the average percentage of doses per subject resulting in a rescue-free bowel movement (RFBM) within 4 hours (h) of dosing during the 4-week QD dosing period. Rescue-free was defined as no laxative use within 24h prior to a bowel movement. An additional secondary endpoint assessed the weekly percentage of doses per subject resulting in RFBM within 4h of dosing during the overall 12-week study (QD and PRN phases). Data were also analyzed to determine the proportion of subjects with ≥3 RFBMs/wk, with an increase of ≥1 RFBM/wk over baseline, for at least 9 weeks out of 12 weeks (a measure of durability).

Results

Demographic and baseline characteristics were similar among groups. For the primary endpoint, a significantly greater proportion of subjects in the 300 mg and 450 mg dose groups experienced RFBMs within 4h of dosing compared with PBO ($P<.01$ and $P<.0001$, respectively) over the 4 weeks of QD dosing. The mean proportions of RFBMs within 4 hours of all doses during the 4-week QD dosing period were 18%, 21%, 25%, and 27% in the placebo and oral MNTX 150, 300, and 450 mg groups, respectively. Significant differences between PBO and oral MNTX were observed as early as Week 1. Significant improvements in RFBMs established during the 4-wk QD phase were maintained throughout the 8-wk PRN dosing phase. The proportion of subjects with ≥3 RFBMs/wk, and an increase of ≥1 RFBM/wk, increased from baseline for at least 9 weeks out of 12 weeks of treatment. The 450 mg dose demonstrated statistical significance over placebo (45.5% vs 33.3%, $P=.01$). Overall, a mean of 6.4 active doses was administered at Week 4 (QD phase) vs 6.1 for PBO. At the end of the PRN phase (Week 12), a mean of 4.4 active doses was administered vs 4.5 for PBO. The incidences of adverse events (AEs) during the 4-week QD and 8-week PRN periods were similar between PBO and the MNTX groups: most common AEs (≥3%) were abdominal pain (QD: 7% PBO, 6% all MNTX; PRN: 4% PBO, 1% all MNTX), nausea (QD: 6%, 5%; PRN: 4%, 3%), flatulence

(QD: 5%, 4%; PRN: 0%, 1%), diarrhea (QD: 2%, 3%; PRN: 2%, 3), and urinary tract infection (QD: 0%, 1%; PRN: 4%, 3%).

Conclusions

The rapid onset and consistency of effect of oral MNTX, established during the 4-week QD dosing phase, was demonstrated to be durable during the 8-week PRN dosing phase, despite a reduction in the overall weekly dose. An evaluation of responders, using a definition of efficacy intended for chronic daily dosing, demonstrated improvements with a dosing paradigm that included both QD and PRN dosing. The safety profile of oral MNTX during the 12-week study was similar to PBO.

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Rate of cross over to problematic opioid us and associated costs among opiate analgesic-treated chronic noncancer pain patients within a commercially insured population

Jacqueline Pesa[1], Hyong Un[2], Peter Kardel[3], Joseph Tkacz[3], Joseph Volpicelli[4], Lien Vo[1], Charles Ruetsch[3]
[1]*Janssen Scientific Affairs, LLC, Raritan, NJ, USA,* [2]*Aetna, Blue Bell, PA, USA,* [3]*Health Analytics, LLC, Columbia, MD, USA,* [4]*Institute for Addiction Medicine, Inc, Plymouth Meeting, PA, USA*

Purpose

While the incidence of ICD-9 diagnosed opioid dependence (ie, addiction) among opioid analgesic treated chronic pain (OAT-CP) patients ranges between 3%-5% across clinical trials(1) and administrative health plan claims-based studies,(2) use of self-reported behavioral indicators to identify opioid dependence and problematic opioid use yields reported rates as high as 50%.(3) Two proxies of problematic opioid use that potentially indicate elevated patient tolerance and/or loss of control over opioids include: rapid dose escalation and multiple opioid prescribers.(4-5) Case finding based on these proxies of problematic opioid use may identify patients in need of intervention similar to those with an addiction diagnosis. The purpose of this study was to estimate the incidence of problematic opioid use among a commercially insured OAT-CP patient population using proxies of problematic opioid use in addition to the diagnosis of opioid addiction. Service utilization and cost of care were used to characterize differences between a control group of patients without evidence of problematic opioid use and/or addiction and those exhibiting problematic opioid use based on behavioral proxies.

Method

Data for this study came from Aetna and covered calendar years 2009-2011. In order to be selected, a patient must have had ≥3 medical claims with a primary diagnoses for chronic pain and/or lower back pain, osteoarthritis, or diabetic peripheral neuropathy during a 3-month period (preceded by 6 months without this same diagnosis) and evidence of 90 days or greater supply of opioids filled within 180 days of the index date (index date defined as the start of opioid therapy). All patients were required to have continuous eligibility with full benefits over the course of the 18-month study, which included a 6-month pre-index period and 12-month post-period. The final study sample (n=4254) were grouped according to their problematic opioid use status: opioid addiction diagnoses present (addiction), problematic opioid use present (POU), or reference group (no addiction). The addiction group was then divided into its constituents: 1) presence of ICD-9 diagnosis of opioid dependence/abuse; or 2) no opioid dependence diagnosis, but ≥1 fill for Suboxone/Subutex. Similarly, the POU group was divided into its constituent groups based on the presence of: 1) multiple opioid prescribers; 2) rapid opioid dose escalation; or 3) both 1 and 2. We report the percentage of patients identified as "crossing over" to addiction or problematic opioid use as determined by group affiliation (addiction and POU groups), describe and compare across groups using ANOVA and independent sample t-tests on pre-and post-index values for demographics, risk factors (for addiction), comorbidities, healthcare service utilization and costs.

Results

The rate of cross-over to problematic opioid use was 44%. The addiction group (n=236, 5.5%) was the smallest group while the POU group (n=1654, 38.8%) was much larger. The reference group, no addiction (n=2364, 55.6%) accounted for the majority of the study sample. The addiction, POU and no addiction groups differed on age ($F(2,4252)=59.80$ $P<.001$) with the addiction group the youngest (42.1 years) and the no addiction group the oldest (48.6 years). During the pre-period, there were no significant differences between groups on the Charlson Comorbidity Index ($F(2,4252)=1.49$, $P=.22$). The addiction group had significantly more opioid fills than the no addiction group during the pre-period ($F(2,4252)=11.38$, $P<.05$), and both the addiction group and POU groups had

a significantly greater number of opioid fills than the no addiction group in the post-period ($F(2,4252)=95.18$, $P<.001$). This same pattern held for post-period total daily supply of opioids. Examining all prescription medications filled, there was a statistically significant main effect for group ($F(2,4252)=11.68$, $P<.001$), with the POU group having a greater number of fills than both no addiction and addiction groups. There was a statistically significant main effect for hospital admissions ($F(2,4252)=18.60$, $P<.001$), with the POU group utilizing more hospital admissions than the no addiction group ($P<.001$). Finally, the number of physician visits differed between groups ($F(2,4252)=22.51$, $P<.001$) with the addiction group and POU group utilizing more than the no addiction group.

Conclusions

The rate of OAT-CP patients diagnosed with opioid dependence confirm previous findings (<5%), however; over a third of the study sample evidenced problematic opioid use. During pre-period, the POU group was similar to the no addiction group, but behaved analogous to the addiction group during post-period. Illness and service utilization indicators were significantly higher for addiction and POU compared to no addiction group, while the POU group had highest total cost of care. Broadening the criteria for identifying problematic opioid use may have value to health plans and providers interested in improving outcomes and containing costs among this population.

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Healthcare service utilization and costs among chronic pain patients identified with problematic opioid use in a commercial health plan

Joseph Tkacz[2], Jacqueline Pesa[1], Hyong Un[3], Joseph Volpicelli[4], Peter Kardel[2], Lien Vo[1], Charles Ruetsch[2]
[1]Janssen Scientific Affairs, LLC, Titusville, NJ, USA, [2]Health Analytics, LLC, Columbia, MD, USA, [3]Aetna, Blue Bell, PA, USA, [4]Institute for Addiction Medicine, Inc, Plymouth Meeting, PA, USA

Purpose

In recent years, addiction, overdose and problematic use of prescription opioid analgesic medications have increased(1). As those addicted to opioids are at greater risk of increased use of high-cost venue healthcare services, crime, and death,(3) it is incumbent upon clinicians, and health plans, to monitor patients on chronic opioid therapy for appropriate dose adherence. In particular, it may be useful to identify patients rapidly developing tolerance and other addiction related behaviors.(4) To our knowledge, no previous study has quantified the burden of cross over to problematic opioid analgesic use in terms of healthcare service utilization and costs. The purpose of this study was to analyze insurance claims data in order to: 1) identify chronic pain patients diagnosed with opioid abuse and/or addiction; 2) identify chronic pain patients displaying evidence of problematic opioid use (regardless of addiction diagnosis status); and, 3) compare healthcare service utilization and expenditures between these 2 patient groups and a control group.

Method

Aetna provided medical, pharmacy, and membership data for individuals with chronic pain and an opioid prescription fill during calendar years 2009 to 2011. From this broader database, the following inclusion criteria were required: 1) ≥3 claims of either low back pain, osteoarthritis, or diabetic peripheral neuropathy spanning ≥3 months or a single diagnosis of chronic pain during the case finding period; 2) a 6-month pain diagnosis naïve period prior to the initial diagnosis (index date); 3) ≥90 days' supply of opioids prescribed within 180 days of the index date (index date + 90 days); and 4) continuous eligibility for the entire measurement period (including the 6-month pre-index and 1-year post-index). Participants (n=4254) were placed into one of 3 groups: 1) "problematic opioid use group" (n=1645), defined by the presence of either a pattern of doctor shopping (receiving opioid prescriptions from 5 or more different prescribers within 12 months [5]) and/or opioid dose escalation (50% increase in opioid dose in the first 3 months of treatment, or 100% increase in dose during the 12-month post-period); 2) "diagnosed opioid addiction group" (n=236), as indicated by an ICD-9 diagnosis of opioid dependence (addiction) or abuse, or a buprenorphine fill; 3) "control group" (n=2364) patients who did not meet any of the problematic opioid use criteria. OLS regression compared groups on healthcare service utilization and cost change scores between the annualized 6-month pre-period and the 1-year post-period. Alpha level was set at $P<.05$ for all analyses.

Results

The mean age of the sample was 47.4 (±9.7) years, with an equal distribution in both gender and geographic region of residence within the United States. The mean Charlson Comorbidity Index score for the sample during the pre-period was 0.03 (±0.23), indicating low prevalence of comorbid conditions. In the 1-year post-period, there were significant group differences on 14 of the 15 measured service utilization and cost variables, with the control group showing the lowest values for 12 of the 14 variables. The problematic opioid use group and the diagnosed opioid addiction group had higher healthcare service utilization and costs in the post-period compared with the control group on: mean number of opioid fills (20.4 and 21.4 vs 16.5, $P<.001$), mean number of inpatient hospital visits (0.95 and 0.64 vs 0.41, $P<.001$), and mean number of emergency room visits (0.11 and 0.31 vs 0.04, $P<.001$). This increase in utilization was reflected in higher total cost for the problematic opioid use group and diagnosed opioid

addiction group compared to the control group ($39,631 and $29,101 vs $26,717 , *P*=.001). OLS models of change in service utilization and costs from pre- to post-periods revealed that the diagnosed opioid addiction group incurred significantly higher prescription costs ($796, *P*=.009), higher emergency room costs ($449, *P*=.039), and more physician office visits (1.43, *P*=.025) and associated costs ($1,147, *P*=.040) compared to the control group. Additionally, the problematic opioid use group incurred significantly more prescription fills (5.2, *P*<.001) and associated costs ($444, *P*=.002), emergency room admissions (0.18, *P*<.001) and associated costs ($477, *P*<.001), inpatient admissions (0.48, *P*<.001), days (0.59, *P*<.001), and associated costs ($8,203, *P*<.001), physician office visits (1.37, *P*<.001) and associated costs ($1,017, *P*<.001), total medical costs ($12,288, *P*<.001), and total healthcare costs ($12,731, *P*<.001) compared to the control group.

Conclusions

Chronic pain patients with problematic use of opioid analgesics demand more services and incur greater costs than nonproblematic users. The incidence of diagnosed opioid addiction was similar to previously reported studies; however, the group displaying potentially problematic opioid use made up nearly one-third of the study sample and used more services and had the highest healthcare spending. These findings point to the need for closer monitoring of such patients and potentially intervention. Further, these results suggest that focusing on the diagnosis of addiction underestimates the impact of problematic opioid use on healthcare service utilization costs.

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A comparison of opioid utilization patterns and areas for quality improvement in a Medicaid and commercial population

Jacqueline A. Pesa, Anisha M. Patel, Andrew Howe, Samir H. Mody
Janssen Scientific Affairs, LLC, Raritan, NJ, USA

Purpose

The rapid increase in opioid use in the US coupled with the challenge of appropriate and effective treatment of pain drives the need for improved understanding of patterns of opioid utilization. The objective of this analysis is to demonstrate the utility of a Medication Use Evaluation Tool in assessing real-world utilization of long acting opioids (LAOs) and chronic short acting opioids (SAOs) and identifying related areas for improvement in the management of the commercial and Medicaid populations.

Method

This analysis was performed using the Chronic Opioid Medication Use Evaluation (MUE) software, designed to analyze retrospective pharmacy claims data. Commercial data included pharmacy claims contributed by 37 plans representing 24.1 million lives. Medicaid data was from one state covering 600,000 lives. Patients selected had ≥1 claim for a LAO and/or chronic SAO (ie, evidence of ≥60 days of continuous therapy with a SAO) from July 1, 2008 to June 30, 2009. Analyzed measures included: most frequently utilized opioids, daily average consumption (DACON), potential markers for misuse such as number of patients with ≥2 prescribers and number of patients filling at ≥2 pharmacies, percentage of patients with concomitant GI medication usage, percentage of patients with >3.1gm/day acetaminophen (APAP).

Results

A total of 10,681 and 25,788 patients with a claim for a LAO and/or chronic SAO were identified from the Medicaid and commercial samples, respectively. Among chronic SAO users, 91% (n=5,147) in the Medicaid sample, and 85% (n=11,730) in the commercial sample had no concomitant LAO claim (minimum 60-day overlap). The most commonly prescribed LAOs for Medicaid and commercial patients, respectively, were morphine CR/ER/SR (33% and 21%), fentanyl transdermal (26% and 23%), and oxycodone CR (18% and 36%). The DACONs for both morphine CR/ER/SR (2.3, 2.4) and oxycodone CR (2.6, 2.8) in the Medicaid and commercial samples, respectively, were above the recommended daily use. There was a higher percentage of Medicaid than commercial patients with ≥2 unique prescribers for LAO and/or chronic SAO (42.1% vs 26.6%). Additionally, 31% of Medicaid patients filled prescriptions at ≥2 pharmacies, and 4.2% filled prescriptions at 4+ pharmacies. Average daily doses between 3.1-4 gm/day of APAP in chronic SAO users were observed for 5.8% and 4.9% of commercial and Medicaid enrollees, respectively. Concomitant use of prescription GI medications with or after opioid therapy was evident for 13% and 11% LAO patients, and 18% and 19% chronic SAO patients in the commercial and Medicaid sample, respectively.

Conclusions

In this analysis of opioid utilization in the commercial and Medicaid populations, areas of further investigation and potential improvement were identified. Tools such as the Opioid MUE can be used by health plans to better understand treatment-use patterns and support targeted education efforts for providers and patients, and facilitate long-term monitoring of practice patterns and quality of care.

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Utilization of opioids in commercially insured and Medicare patients with painful diabetic peripheral neuropathy

Anisha M. Patel, Jacqueline A. Pesa, Samir H. Mody, Marcia FT Rupnow
Janssen Scientific Affairs, LLC, Raritan, NJ, USA

Purpose

Peripheral neuropathy is a common complication in 30%-50% of diabetic patients, contributing up to 27% of direct healthcare costs for diabetes management. Approximately 11%-26% of these patients develop chronic pain. Practice guidelines recommend the use of long-acting opioids, as a part of a multimodal treatment plan in the event that approved first-line agents (eg pregabalin) provide inadequate analgesia. Additionally, 50% of older patients with long-standing type 2 diabetes are affected by diabetic peripheral neuropathy, yet few studies have examined opioid treatment use in different age-groups within this population. Therefore, the objective of this analysis is to describe real-world utilization of long acting opioids (LAOs) and chronic short acting opioids (SAOs) in patients with painful diabetic peripheral neuropathy (pDPN) and to compare such patterns between younger and older patients.

Method

The Chronic Opioid Medication Use Evaluation (MUE) software was used to analyze retrospective pharmacy claims from the MarketScan Claims Databases, specifically the Commercial Claims and Encounters Database and the Medicare Supplemental and Coordination of Benefits Database. Patients with pDPN were identified if they had ≥1 pharmacy claim for pregabalin, an ICD-9-CM diagnosis code for diabetic peripheral neuropathy (250.6X or 357.2) during 360 days prior to the first pregabalin claim, ≥1 concomitant claim for a LAO and/or chronic SAO therapy (ie, ≥60 days of continuous therapy with a SAO) in the 360 days after the first pregabalin claim, and insurance eligibility from January 1, 2005 to March 31, 2009. Patients were required to have at least 1 pharmacy claim for pregabalin with a >30 day's supply after the first claim. Data was extracted for 12-months (3/24/2008 to 3/23/2009) from this pDPN sample for the current analysis. Patients were further grouped into younger (<65) and older (≥65) age cohorts. Various utilization measures were analyzed for the total pDPN sample and both cohorts (younger; older) including average day's supply, average daily dose (ADD), daily average consumption (DACON), opioid rotation defined as change in therapy within the same formulation group (eg, LAO to another LAO), opioid switching defined as switch from one opioid molecule and/or formulation to another (eg, chronic SAO to LAO), and acetaminophen (APAP) use.

Results

A total of 482 unique pDPN patients (60% in the younger; 40% in the older group) with 3137 claims for a LAO and/or chronic SAO were identified (mean age=56 and 75 years, respectively). Chronic use of a SAO was observed for 56% of pDPN patients; of these, 88% had no concurrent LAO claim (minimum 60-day overlap). Among concomitant LAO and chronic SAO users, oxycodone CR was most commonly used in combination with chronic use of SAOs (14%). The most frequently filled LAOs in the younger and older cohorts were oxycodone CR (32%, 45%), fentanyl transdermal (25%, 26%), and morphine CR/ER/SR (24%, 19%), respectively, with an average day's supply of 31.6, 31.5 and 30.5 days, respectively. Among the younger and older pDPN cohorts, the ADD for oxycodone CR was 166.9 mg and 77.4 mg, and for morphine CR/ER/SR was 125.1 mg and 71.9 mg, while the DACONs for oxycodone CR were 3.4 and 2.5, and for morphine CR/ER/SR were 2.5 and 1.8, respectively. Among the total pDPN sample, switching of opioid therapy was observed for 20% of patients, while opioid rotation was observed commonly in the chronic SAO users (14%). The ADD between 3.1-4 gm/day and ≥4 gm/day of APAP was observed for 5.2% and 1.9% of chronic SAO users.

Conclusions

This study presents a snapshot of real-world opioid use among painful diabetic peripheral neuropathy patients treated with pregabalin. The opioid use patterns in the younger and older patients were generally similar, with some differences in ADD and DACONs (higher ADD and DACON in younger oxycodone CR users). Monitoring drug utilization trends can assist healthcare decision-makers in managing this population and identifying areas for patient or physician directed quality improvement efforts.

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Tapentadol abuse: the first 18 months

Richard Dart[1], Edgar Adams[2,1], Becki Bucher-Bartelson[1], Gary Baker[3], Janet Pitner[3], Gary Vorsanger[3]
[1]*Rocky Mountain Poison and Drug Center, Denver, CO, USA,* [2]*Covance Market Access, Gaithersburg, MD, USA,* [3]*Janssen Scientific Affairs, LLC, Raritan, NJ, USA*

Purpose

Prescription opioid analgesics play an important role in the management of moderate to severe pain. An unintended consequence of these agents is the nonmedical use of prescription pain relievers. In 2008, nonmedical use of pain relievers among persons aged 12 years or older was second only to marijuana in the U.S. We describe the rates of abuse, misuse, and diversion of tapentadol immediate release [Nucynta®, CII], for the 18 months following launch in 2009.

Method

The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System measures rates of abuse, misuse and diversion throughout the U.S. Data from the Drug Diversion, Survey of Key Informants (SKIP), Poison Center, and Opioid Treatment Programs were analyzed to compare rates for tapentadol with other opioid analgesics from June 2009 through December 2010, utilizing both per 100,000 population (POP) and per 1000 Unique Recipients of Dispensed Drug (URDD) as denominators.

Results

Based on data from the SKIP program from June 2009 to December 2010, nonmedical use rates for tapentadol fluctuated between 0 and 0.572 per 1000 people who filled a prescription (URDD) and 0 and 0.015 per 100,000 population (POP), reflecting nonsignificant changes over time (P=.816 and P=.867, respectively). Data from Poison Centers, Outpatient Treatment Programs, and Drug Diversion programs also showed similar nonsignificant trends in population and exposure rates (all P-values >.05) during the observation period.

Conclusions

Since product launch, rates of abuse, misuse, and diversion of Nucynta have been low; however, continued monitoring of trends in the data are warranted.

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Trends in nonmedical use of Nucynta by college students

Richard Dart[1], Edgar Adams[2,1], Becki Bucher-Bartelson[1], Gary Baker[3], Janet Pitner[3], Gary Vorsanger[3]
[1]*Rocky Mountain Poison and Drug Center, Denver, CO, USA,* [2]*Covance Market Access, Gaithersburg, MD, USA,* [3]*Janssen Scientific Affairs, LLC, Raritan, NJ, USA*

Purpose

Prescription opioid analgesics play an important role in the management of moderate to severe pain. An unintended consequence of these agents is nonmedical use. In 2008, the prevalence of nonmedical use of pain relievers among persons aged 12 years or older was second only to marijuana in the U.S. We describe the rates and methods of nonmedical use of tapentadol immediate release [Nucynta®, CII] among college students following FDA approval in 2009.

Method

The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System College Survey Program is an online questionnaire collecting data from approximately 2000 self-identified college-aged students throughout the US administered during the spring, summer, and fall terms. Responses were analyzed for trends in the rate and method of nonmedical use of tapentadol compared with other opioid analgesics from June 2009 through March 2011.

Results

Nonmedical use of tapentadol was highest in 4Q2009 (0.66 per 1000 people who filled a prescription) and significantly decreased in the 4 subsequent survey periods ($P \leq .001$). Similarly, nonmedical use per 100,000 population rate was highest in 4Q2009 (0.013 per 100,000 population) and decreased, although not significantly to 0.004 in 1Q2011 ($P = .22$). The primary method of nonmedical use of tapentadol among college students is oral/transmucosal (78%) followed by inhalation and injection.

Conclusions

Since launch, rates of nonmedical use of Nucynta by college students were low and are decreasing over time. The initial levels of reported nonmedical use may represent a brief period of experimentation after introduction.

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Significance of an interdisciplinary pain program in a Veterans Affairs community

Jennifer Pruskowski, Kimberly Reno-Ly, Amit Singh, Jeffery Meyer, Kevin Brittain
William Jennings Bryan Dorn Veterans Affairs Medical Center, Columbia, South Carolina, USA

Purpose

The U.S. Department of the Veterans Benefits Administration 2011 Annual Fiscal Report ranked musculoskeletal pain as the sixth most prevalent service-connected disability. As the Veteran population increases, the instance of musculoskeletal pain could become even greater. In addition, even in the general population the prevalence of nonspecific chronic pain has been estimated to be as high as 55%. To meet the needs of this patient group, interdisciplinary pain programs have been created to address all facets of chronic pain. Preliminary studies have found these programs to be both therapeutic and cost effective. However, there is limited data available. The purpose of this study is to evaluate the Outpatient Interdisciplinary Pain Program (OIPP) in a Veterans Affairs Community

Method

This is a single-center, observational review to evaluate an OIPP. The Veterans Affairs OIPP team consists of a medical physician, a pain psychologist, a physical therapist, an occupational therapist, a biofeedback practitioner, a registered nurse, a chaplain, and a pharmacist. Patients were only included in this study if they were actively enrolled in the OIPP. Their enrollment included participation in an 18-day program spread over 6 weeks during which they were required to attend group sessions with each of the team members. Patients were evaluated at baseline and discharge. Objective outcomes included opioid and benzodiazepine use (in daily morphine and lorazepam equivalents), and emergency room admissions due to pain. Self-reported outcomes were obtained through the use of pain intensity ratings, a pain outcomes questionnaire, a pain catastrophizing scale, a Oswestry disability index, a patient health questionnaire, a fear avoidance beliefs questionnaire, and patient satisfaction. Functional measures included a 6 minute walk test, and the use of assistive devices.

Results

Since the introduction of the OIPP in January 2011, 35 patients have successfully completed the program. Preliminary results showed significant improvement in pain intensity, pain outcomes, and the 6 minute walk test (in feet). In addition, the patients exhibited improvements in mobility, increased daily living activities, and vitality when referring to the pain outcomes questionnaire. Most important, 100% of the patients would recommend the OIPP to a friend.

Conclusions

In our unique population, Veterans view the interdisciplinary program very favorably. The majority of outcomes are trending in a clinically favorable direction. However, with additional enrollment and follow-up these results could improve significantly. Changes have already been implemented to replace incomplete or insensitive measures with better alternatives, and studies have begun to determine the appropriate number of sessions needed. It is hoped that with further study and refinements, the program will be able to dramatically improve the quality of patients' lives.

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Variability in metabolism of imipramine and desipramine in the pain population using urinary excretion data

Kelley Ramey[1], Candis Morello[1,2], Joseph Ma[1,3], Brookie Best[1,4], Rabia Atayee[1,3], Amadeo Pesce[5,6]
[1]University of California, San Diego (UCSD), Skaggs School of Pharmacy and Pharmaceutical Sciences, La Jolla, CA, USA, [2]Diabetes Intense Medical Management Clinica, Veterans Affairs San Diego Healthcare System, La Jolla, CA, USA, [3]Doris A. Howell Palliative Care Service, San Diego, CA, USA, [4]UCSD Department of Pediatrics, Rady Children's Hospital, San Diego, CA, USA, [5]Millennium Research Institute, San Diego, CA, USA, [6]Department of Pathology and Laboratory Medicine, UCSD School of Medicine, La Jolla, CA, USA

Purpose

Imipramine is a tricyclic antidepressant (TCA) sometimes prescribed for the treatment of neuropathic pain. Although the primary use of tricyclic antidepressants (TCAs) for treatment of depression has decreased with the introduction of the selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), which have a more tolerable side effect profile compared to the TCAs, the TCAs remain an effective therapeutic option for certain types of depressive illnesses and neuropathic pain. Imipramine undergoes demethylation to the primary active metabolite, desipramine, via cytochrome P450 (CYP) 2C19, CYP1A2 and CYP3A4. Little to no data exists regarding urinary excretion ranges, which may be beneficial in assessing drug metabolism. The purpose of this retrospective data analysis was to characterize inter- and intrapatient variability of imipramine and desipramine metabolism in urine and evaluate concomitant medication detection, with particular attention to opioids.

Method

Between January 2011 and April 2012, urine specimens for patients being treated for chronic pain were analyzed using Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) at Millennium Laboratories. A retrospective data analysis was conducted using de-identified specimens that were tested for imipramine and desipramine to determine the urinary concentrations of these 2 analytes. Specimens with concentrations of less than the 50 ng/mL cutoff concentration of the parent drug or metabolite as well as dilute specimens with creatinine concentration of less than 20 mg/dL were excluded. Urinary concentrations were corrected for creatinine concentration and log transformed to normalize the distribution. The percent coefficient of variation (%CV) among the interpatient population was determined from the mean desipramine: imipramine metabolic ratio (MR) of the patient's first-visit specimen, while intrapatient variability was calculated as the mean %CV of MR for each patient with 2 or more urine specimens. Among the interpatient population, various potential causes of MR variability were evaluated, including age, gender, urinary pH, concomitant medications, and CYP2C19 inhibitors and inducers. Use of oxycodone, hydrocodone, oxymorphone, hydromorphone, morphine, and methadone, as well as other medications reported in the medication list, were evaluated for their effect on MR. All data analyses were performed using Microsoft Excel® and Origin Pro 8.6.

Results

600 unique de-identified urine specimens had a geometric mean MR of 1.47 and a %CV of 170.6%, while the intrapatient population, assessed from 137 patients, had a geometric mean MR of 1.35 and a %CV of 38.9%. Of these 600 patient specimens, only 105 had imipramine listed in their prescribed medications list. Factors that did not affect the imipramine MR were gender, CYP2C19 inhibitors or inducers and urine pH ($P>.05$). The young age group (18-36 years) had a significantly higher mean geometric MR than the middle (37-66 years) and older (67-90 years) age groups (1.93 vs 1.45 vs 1.22, $P<.05$). About 1/3 of specimens were positive for 1 or more of the following medications: hydrocodone, oxycodone, hydromorphone or oxymorphone, while about 14% were positive for morphine and 9% were positive for methadone. Evaluation of the individual opioids for their impact on imipramine

MR produced no significant results. However, patients on imipramine with no reported opioid use had a significantly lower geometric mean MR than the opioid-reporting population (1.03 vs 1.51, $P<.05$). Furthermore, patients with 2 or more reported opioids had a significantly higher mean MR (1.71) than those with only 1 reported opioid (1.71 vs 1.45, $P<.05$). A slight, but not significant, increase in the mean MR was found in specimens positive for oxymorphone ($P=.07$) and hydromorphone ($P=.09$). Other common concomitant drugs, including gabapentin, soma, and benzodiazepines, did not affect the MR ($P>.05$).

Conclusions

Interpatient variability of imipramine metabolism was over 4-fold greater than intrapatient variability. Variability was not affected by gender, CYP2C19 inhibitor or inducer use, or urine pH. Younger age groups had a higher imipramine MR, while patients with no reported opioids had a lower MR than the opioid-reporting population. Specimens for oxymorphone and hydromorphone had a slight, but not significant, increase in MR. Other sources for variability may include the impact of genetic polymorphisms of CYP2C19, CYP1A2, CYP3A4 and CYP2D6 on imipramine metabolism. The numerous metabolic pathways for imipramine may give rise to its large interpatient variability.

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Single-entity hydrocodone extended-release for chronic pain

Richard Rauck[1], Martin Hale[2], Srinivas Nalamachu[3], Cynthia Robinson[4]
[1]*Carolinas Pain Institute, Center for Clinical Research, and Wake Forest University School of Medicine, Winston-Salem, NC, USA,* [2]*Gold Coast Research, LLC, Weston, FL, USA,* [3]*International Clinical Research Institute, Overland Park, KS, USA,* [4]*Zogenix, Inc., Emeryville, CA, USA*

Purpose

Hydrocodone is only available in combination with nonopioid analgesics, such as acetaminophen, which may prevent titration of hydrocodone to therapeutic levels. Hydrocodone bitartrate extended-release (HC-ER; Zohydro™, Zogenix, Inc., San Diego, CA), the first single-entity hydrocodone formulation, will provide another option for treatment of moderate-to-severe chronic pain without the dose-limiting effect of acetaminophen. The overall objective of this study was to evaluate long-term safety and efficacy of HC-ER in subjects with moderate-to-severe chronic pain.

Method

This multicenter, open-label study comprised a conversion/titration (C/T) phase (≤6 weeks) followed by a treatment phase (≤48 weeks) in opioid-experienced subjects with chronic pain. During C/T, subjects (n=638) were converted to HC-ER using initial doses 20%-30% less than the equivalent dose calculated by the Opioid Conversion Table. HC-ER dose was titrated until stabilized. During the treatment phase, subjects (n=424) received their individualized HC-ER dose and up to 2 tablets of HC bitartrate 5 mg/acetaminophen 500 mg daily. Safety was the primary endpoint. Efficacy endpoints included change in pain intensity (PI) score (0-10 numerical rating scale) and selected Brief Pain Inventory (BPI) questions about pain severity, relief with medication, and interference with activities. No statistical testing was performed.

Results

638/938 (68%) of screened subjects were enrolled; 424/638 (66%) and 285/424 (67%) completed the C/T and treatment phases, respectively. Daily PI score improved from screening to end of treatment (mean±SD change, -2.3±2.5). Changes in BPI scores from screening to end of treatment showed improvement in pain severity, relief achieved with medication, and interference with activities. The most common adverse events (AEs) during the C/T phase were constipation (72/638; 11%) and nausea (68/638; 11%). The most common AEs during the treatment phase were constipation (53/424; 13%) and back pain (47/424; 11%). The most frequent AEs that led to study discontinuation (DAEs) in the C/T phase were nausea (10/638; 2%), somnolence (9/638; 1%), insomnia (7/638; 1%), lethargy (7/638; 1%), and headache (7/638; 1%). The most frequent DAEs in the treatment phase (each 2/424; 0.5%) were constipation, upper abdominal pain, and cognitive disorder. Four deaths occurred; all were considered unrelated or unlikely to be related to HC-ER. No trends in laboratory parameters or vital signs were evident.

Conclusions

HC-ER exhibited a safety profile consistent with that of other opioids and appeared effective for managing chronic pain. HC-ER may provide a new opioid option for subjects with chronic pain not satisfied with their current treatment.

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Oral methylnaltrexone for the treatment of opioid-induced constipation in patients with noncancer pain

Richard Rauck[1], John Peppin[2,3], Robert Israel[4], Jennifer Carpenito[4], Jeffrey Cohn[5], Shirley Huang[5], Enoch Bortey[5], Craig Paterson[5], William Forbes[5]
[1]Carolinas Pain Institute, Winston-Salem, NC, USA, [2]The Pain Treatment Center of the Bluegrass, Lexington, KY, USA, [3]The Center for Bioethics, Pain Management and Medicine, Lexington, KY, USA, [4]Progenics Pharmaceuticals, Inc, Tarrytown, NY, USA, [5]Salix Pharmaceuticals, Inc, Raleigh, NC, USA

Purpose

Opioid use for chronic, noncancer pain may be complicated by dose-limiting opioid-induced constipation (OIC), impacting quality of life and pain control. Methylnaltrexone (MNTX) is a peripherally acting, selective μ-opioid receptor antagonist approved in >50 countries worldwide as a subcutaneous (SC) injection for the treatment of OIC in patients with advanced illness (RELISTOR®).Oral MNTX represents a 1st in class and potentially new oral therapy for the treatment of OIC in subjects with chronic, noncancer pain. The purpose of this study was to evaluate the safety and efficacy of MNTX administered in an oral formulation in a phase 3, double-blind, placebo (PBO)-controlled, parallel-group, dose ranging, multicenter study.

Method

804 subjects were randomized to receive PBO or oral MNTX tablets 150, 300, or 450 mg for 12 weeks (4 weeks QD followed by 8 weeks PRN dosing). Subjects were taking ≥50 mg oral morphine equivalents/day for ≥1 month for chronic, noncancer pain and had a history of OIC. Primary endpoint was the average proportion of rescue-free bowel movements (RFBMs) per subject within 4 hours (h) of dosing during the 4-week QD dosing period. Rescue free was defined as no laxative use within 24h prior to bowel movement. Key secondary endpoints were 1) proportion of subjects with ≥3 RFBMs/week and ≥1 RFBM/week increase from baseline for ≥3 of 4 weeks and 2) change in weekly RFBMs from baseline during QD dosing.

Results

Demographic and baseline characteristics were similar between groups. For the primary endpoint, a significantly greater proportion of subjects in the 300 and 450 mg dose groups experienced RFBMs within 4h of dosing compared with PBO over the 28 days of QD dosing. These findings were maintained throughout the entire 12 weeks including QD and PRN phases. Significant differences were also seen for ≥3 RFBMs/week with an increase of ≥1/week over baseline at the 300 mg and 450 mg doses during the 28 day QD dosing. Analyses based on the primary endpoint demonstrated a linear dose response for the 3 active doses ($P<.0001$) over 28 days of QD dosing. For the first dose, significant differences were seen in the 150 mg (34%), 300 mg (41%), and 450 mg (42%) treatment groups for RFBM at 24h post first dose compared with subjects receiving PBO (23%) ($P=.0200$, $P=.0002$, $P<.0001$, respectively). The incidence of adverse events (AEs) was similar among treatment groups and PBO: most common AEs (≥3%) were abdominal pain (6.0% PBO, 6.8% all MNTX), nausea (5.5%, 4.7%), flatulence (4.5%, 4.0%), and diarrhea (2.0%, 3.3%).

Conclusions

Oral MNTX 150 mg, 300 mg, and 450 mg QD significantly increased the proportion of RFBMs and decreased time to first RFBM in a dose-dependent manner in patients with OIC.

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Cardiac safety of oral methylnaltrexone in healthy subjects and noncancer pain patients with opioid-induced constipation

Richard Rauck[1], Robert Israel[2], Shirley Huang[3], Enoch Bortey[3], Robert Rolleri[3], Craig Paterson[3], Pam Golden[3], William Forbes[3]
[1]Carolinas Pain Institute, Winston-Salem, NC, USA, [2]Progenics Pharmaceuticals, Inc, Tarrytown, NY, USA, [3]Salix Pharmaceuticals, Inc, Raleigh, NC, USA

Purpose

Oral methylnaltrexone (MNTX), a peripherally acting, selective μ-opioid receptor antagonist (PAMORA), represents a potentially new oral therapy for treatment of opioid-induced constipation (OIC) in patients with chronic noncancer pain. Methylnaltrexone is currently approved in >50 countries as a subcutaneous (SC) injection for treatment of OIC in patients with advanced illness when response to laxative therapy has been insufficient (RELISTOR®). Patients with chronic, noncancer pain taking long-term opioids are at increased risk of cardiac events compared with matched controls not taking opioids, likely confounding interpretation of non-controlled studies. Accordingly, the cardiac safety of oral MNTX was evaluated in a randomized, controlled, pivotal study of oral MNTX in subjects with chronic, noncancer pain taking opioids and in 2 thorough QT studies in healthy subjects.

Method

Cardiac safety of oral MNTX was assessed during the randomized, controlled study by examining cardiac safety-related adverse event rates and changes in ECG findings. In this trial, 804 subjects with a history of OIC and taking chronic opioids (≥50 mg oral morphine equivalents/day) for noncancer pain were randomized to receive PBO or oral MNTX tablets 150 mg, 300 mg, or 450 mg for 12 weeks (4 weeks QD followed by 8 weeks PRN dosing). During the PRN dosing phase subjects were instructed to take the study medication no more than once daily. In 2 thorough QT studies in healthy subjects, the effects of single doses of MNTX (SC [n=207], 0.15, 0.3, and 0.5 mg/kg; IV infusion [n=56], 0.3 and 0.64 mg/kg) on QTc interval and ECG parameters were compared with a positive control and placebo.

Results

In the pivotal trial, demographic and baseline characteristics were similar among groups. The median daily morphine equivalent dose was 132 mg in the PBO group and 150 mg in the MNTX groups. Oral MNTX 300 mg and 450 mg QD significantly increased the proportion of rescue-free bowel movements (RFBMs) and decreased time to first RFBM in a dose-dependent manner, and efficacy was comparable to that reported in clinical studies of SC MNTX in similar subjects. No deaths occurred in placebo or treatment groups. The number of severe adverse events potentially of cardiac origin was low and similar between PBO and treatment groups. In the placebo group, there was one report of atrial flutter and 2 reports of "noncardiac chest pain" (each following a normal cardiac workup); none at 150 mg/day; 2 reports of chest pain at 300 mg/day (the first, atypical chest pain with no cardiac etiology identified on workup; the second, musculoskeletal), and none at 450 mg/day. No myocardial infarctions were reported in any group. Similarly, when cardiac safety related treatment-emergent adverse event rates were analyzed, 12 subjects reported at least one cardiac-safety-related adverse event; incidence rates were 1.5% in the placebo group and 1.5% in the all-MNTX group. Similar proportions of PBO- and MNTX-treated subjects experienced shifts from normal baseline ECG findings to abnormal post-baseline findings (31.8% vs 37.7%, respectively). Among the 3 doses in MNTX-treated subjects, there was no evidence of dose-dependence of cardiac adverse event rates. In the 2 thorough QT studies, no effects on QT/QTc prolongation, secondary ECG variables, or wave form morphology were observed at therapeutic or supratherapeutic MNTX doses, consistent with clinical findings in the pivotal oral MNTX trial.

Conclusions

Findings from the pivotal oral MNTX trial demonstrated no increased risk of cardiac adverse events or ECG changes associated with oral MNTX relative to placebo, either overall or dose-related, in this patient population with OIC. These results are consistent with the findings in 2 thorough QT studies demonstrating no significant effects of therapeutic or supratherapeutic MNTX doses on QTc interval or other ECG findings in healthy subjects. Overall, the data demonstrated no increased cardiac safety risk with oral MNTX treatment in this opioid-treated chronic noncancer pain patient population.

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Single-entity hydrocodone extended-release for chronic low back pain

Richard Rauck[1], Srinivas Nalamachu[2], James Wild[3], George Walker[4], Cynthia Robinson[5], Charles Davis[6]
[1]Carolinas Pain Institute, Center for Clinical Research, and Wake Forest University School of Medicine, Winston-Salem, NC, USA, [2]International Clinical Research Institute, Overland Park, KS, USA, [3]Upstate Clinical Research Associates, Williamsville, NY, USA, [4]Private practice, New Orleans, LA, USA, [5]Zogenix, Inc., Emeryville, CA, USA, [6]CSD Biostatistics, Inc., San Diego, CA, USA

Purpose

Hydrocodone is only available in combination with nonopioid analgesics, such as acetaminophen, that may prevent titration of hydrocodone to therapeutic levels. Hydrocodone bitartrate extended-release (HC-ER; Zohydro™, Zogenix, Inc., San Diego, CA), the first single-entity hydrocodone formulation, will provide another option for chronic pain treatment without the dose-limiting toxicity of acetaminophen. The overall objective of this study was to examine the efficacy of HC-ER in opioid-experienced adults with moderate-to-severe chronic low back pain (CLBP).

Method

This trial comprised an open-label conversion/titration (C/T) phase (≤6 weeks) followed by a placebo-controlled, randomized, double-blind treatment phase (12 weeks). After screening (n=828), subjects converted from their current opioid to HC-ER using initial doses 20%-30% less than the equivalent dose calculated with the Opioid Conversion Table. HC-ER dose was titrated during the C/T phase (n=510) to a stabilized dose (20 mg-100 mg twice daily). During the treatment phase, subjects (n=151 per group) received the stabilized HC-ER dose or placebo; 183 subjects completed the study. Subjects were permitted ≤2 tablets/day of hydrocodone bitartrate 5 mg/acetaminophen 500 mg. The primary efficacy endpoint was mean change in average pain intensity (PI) score from baseline to day 85 using a 0-10 numerical rating scale. A key secondary endpoint was treatment response, defined as treatment phase completion with ≥30% average PI score improvement from screening to day 85. Changes in least and worst PI scores and rescue medication were assessed. Efficacy data were recorded in electronic subject diaries.

Results

Demographic and baseline characteristics were generally similar between groups. The mean (± SD) change in average PI score from baseline to day 85 was significantly lower in the HC-ER group vs the placebo group (0.48±1.56 vs 0.96±1.55; P=.008). Significantly more subjects in the HC-ER group than the placebo group were responders (68% vs 31%; P<.001). Mean PI score increases from baseline were significantly less with HC-ER vs placebo for worst pain (0.42±1.76 vs 1.03±1.79; P=.002) and least pain (0.50±1.43 vs 0.98±1.47; P=.004). Mean total daily rescue medication use during the treatment phase was lower in the HC-ER group vs placebo (6±3.4 vs 7.5±3.9 mg). Subjects in the HC-ER group were less likely to discontinue treatment (P≤.001) than those in the placebo group. The overall pattern and nature of adverse events experienced by subjects taking HC-ER were consistent with those expected with other opioid medications.

Conclusions

HC-ER is effective and well tolerated for the treatment of CLBP in this subject population.

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Cardiac safety of subcutaneous methylnaltrexone: results from a pooled safety analysis and a case-control analysis in noncancer pain patients with opioid-induced constipation

Richard Rauck[1], Robert Israel[2], Shirley Huang[3], Enoch Bortey[3], Robert Rolleri[3], Craig Paterson[3], Pam Golden[3], William Forbes[3]
[1]Carolinas Pain Institute, Winston-Salem, NC, USA, [2]Progenics Pharmaceuticals, Inc, Tarrytown, NY, USA, [3]Salix Pharmaceuticals, Inc, Raleigh, NC, USA

Purpose

Methylnaltrexone (MNTX) is a peripherally-acting, selective μ-opioid receptor antagonist (PAMORA) that is currently approved as a subcutaneous (SC) injection for treatment of opioid-induced constipation (OIC) in patients with advanced illness when response to laxative therapy has been insufficient (RELISTOR®). Patients with chronic, noncancer pain taking long-term opioids are at increased risk of cardiac events compared with matched controls not taking opioids, likely confounding interpretation of non-controlled studies. The purpose of this analysis was to evaluate the cardiac safety of SC MNTX using 2 approaches: 1) an analysis of the pooled safety data from 2 randomized, double-blind, placebo-controlled studies in subjects with noncancer pain taking opioids, and 2) a case-control analysis from long-term, open-label administration of SC MNTX.

Method

Data on the pooled cardiac safety of SC MNTX relative to placebo were analyzed from 2 randomized, controlled studies: a 4-week, double-blind phase of a 12-week, Phase 3 study in which patients received SC MNTX 12 mg every other day (QOD), SC MNTX 12 mg every day (QD), or placebo (PBO); and one Phase 2, 4- or 7-day, double-blind study in which patients received SC MNTX 12 mg QD or PBO. A total of 316 patients received at least one dose of SC MNTX and 177 received at least one dose of PBO. Cardiac safety-related adverse event rates and changes in ECG findings were analyzed. For the case-control analysis of cardiac-related adverse events, patients in the 8-week, open-label phase of a 12-week, Phase 3 study, and patients in a 48-week, open-label safety study, were included. Prior data documenting an increased event rate of cardiac events in patients maintained on chronic opioid therapy suggest that 4 events would be likely to occur in the 667 combined patient exposure years from these 2 open-label studies. For the selection of controls, therefore, a 4:1 matching ratio was used, ie, 4 controls were matched to each case compared to the general population. Days on therapy was divided into 4 categories (based on quartiles), with the lowest days on study therapy serving as an internal reference.

Results

In the pooled double-blind, placebo-controlled studies, demographic and baseline characteristics were similar between groups. At baseline, cardiovascular disease was present in 42.9% and 40.5% of patients in the PBO and SC MNTX groups, respectively. Mean daily opioid use, expressed as oral morphine equivalents, was 193.9 (201.7) mg and 194.5 (170) mg in the PBO and SC MNTX groups, respectively. No deaths occurred in the PBO or SC MNTX groups. There were no reported serious adverse events of myocardial infarction, cardiac failure congestive, or cerebrovascular accident in either the PBO or SC MNTX groups. Mean changes from baseline were small for all ECG parameter results in the PBO and SC MNTX groups, and no clinically significant changes in QTc interval were observed in the PBO or SC MNTX groups, consistent with findings from 2 thorough QT studies in healthy subjects. Findings from the case-control analysis of patients maintained on long-term, open-label therapy indicated that the occurrence of potential cardiac-related events was not associated with days on study therapy. Events of a cardiac origin, therefore, appeared to be occurring at random and were not associated with duration of exposure.

Conclusions

These findings indicate that when studied under controlled, double-blind conditions, the cardiac safety of SC MNTX is similar to PBO in patients with OIC and noncancer pain. Long-term, open-label data indicate that the duration of exposure does not correlate with the incidence of cardiac events. Overall, the data demonstrate no increased cardiac safety risk with SC MNTX treatment in this noncancer pain patient population.

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Characteristics and use patterns of chronic hydrocodone users

Brad Rice[1], Thomas Samuelson[1], Howard Birnbaum[1], Nathaniel Katz[2]
[1]*Analysis Group, Inc., Boston, MA, USA,* [2]*Analgesic Solutions, Natick, MA, USA*

Purpose

Hydrocodone/acetaminophen is the most frequently-prescribed pain treatment, however little has been studied about the types of patient characteristics associated with long-term "chronic" use. This analysis identifies the frequency of chronic hydrocodone therapy and assesses use patterns and characteristics of chronic users compared to others (ie, acute or subacute users).

Method

Patients, ages 18-64 and initiating hydrocodone from 2006-2009 were selected from a nationwide, privately-insured, de-identified administrative claims database. Among these hydrocodone users, those having continuous continuously eligible for insurance benefits were included in the final analytic sample (n=424,810). Patients with an average daily dose exceeding 20 mg during any 90-day period in the 15 months following hydrocodone initiation were identified as "chronic" users. Hydrocodone users without a 90-day period exceeding this threshold were considered nonchronic. Characteristics of chronic and nonchronic users were compared descriptively using chi-square and t-tests.

Results

8355 users, 2% of the sample, were identified as chronic users. Chronic users averaged 16.0 mg/day (vs 0.7) during the 15-month evaluation period, filling over 6-times more hydrocodone prescriptions than nonchronic users (12.5 vs 1.9), at higher doses (68.3% vs 36.2% at >5 mg). Additionally, chronic users were more likely to receive prescriptions for nonhydrocodone short-acting opioids (50.2% vs 24.8%). Seventy-five percent of chronic users had ≥1 diagnosis of back pain, neuropathic pain, and/or osteoarthritis. Finally, chronic users had more indirect pain-related diagnoses such as insomnia (6.1% vs 3.0%) and mental health conditions (29.6% vs 17.6%); hip/knee replacements or spinal surgeries (15.2% vs 1.7%); and liver-related conditions (3.7% vs 2.5%). (All comparisons significant at $P<.0001$.)

Conclusions

These findings suggest that many hydrocodone/acetaminophen patients receive high doses for a sustained period and that chronic users have higher incidence of certain comorbidities, including liver-related conditions potentially associated with sustained acetaminophen use. Knowledge regarding the characteristics and treatment patterns of chronic hydrocodone users may help inform clinicians and optimize pharmacotherapy including consideration of extended-release opioid use in this population.

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Self reports of prescription opioid abuse and diversion in 2 samples of nondependent, recreational opioid users

Beatrice Setnik[1], Carl Roland[1], Veerainder Goli[1,2], Glenn Pixton[1], Naama Levy-Cooperman[3], Ira Smith[3], Lynn Webster[4]
[1]Pfizer Inc, Cary, NC, USA, [2]Duke University Medical Center, Durham, NC, USA, [3]INC Research, Toronto, ON, Canada, [4]Lifetree Clinical Research, Salt Lake City, UT, USA

Purpose

Prescription (Rx) opioid abuse and diversion are significant health concerns in both the United States (US) and Canada. In both countries, there is a pressing need to better understand behavioral patterns of abuse and diversion among the populations who abuse Rx opioids. To compare and characterize a range of behaviors relating to Rx opioid abuse and diversion, the Recreational Prescription Opioid Abuse questionnaire was given to 2 samples of self-reported, nondependent recreational opioid users in Utah, US and Ontario, Canada.

Method

Healthy adults, 18-55 years old, who self-reported nondependent recreational opioid use were invited to participate in 2 abuse liability clinical trials, one in Salt Lake City, Utah, the other in Toronto, Ontario. The trials were designed to assess the abuse potential of EMBEDA® and as part of the trial screening process participants were asked to complete the Recreational Prescription Opioid Abuse questionnaire. This questionnaire is designed to capture Rx opioid abuse and diversion behaviors using a multiple choice answer format. The US trial (NCT01380093) and the Canadian (CDN) trial (NCT01595867) were both IRB approved. Patients were advised of study anonymity and that responses would not determine study eligibility. The CDN trial specifically recruited users with experience of intranasal administration of opioids. Questionnaire results were summarized as percentages with the denominator being the number of responses.

Results

Questionnaires were completed by 80 US and 174 CDN participants. Approximately half of participants (48% US, 56% CDN) reported smoking cigarettes. In both samples, 63% of participants cited use of opioids for nonmedical purposes "a few times a month". In the US cohort, age of onset was most commonly between 12 and 18 years (63%) while in the CDN cohort, age of onset was more evenly distributed amongst the age categories, with 19 to 24 years being the most common (35%). The predominant reason for initial use of Rx opioids in the US cohort was "to treat pain" (55% US, 26% CDN) while CDN participants cited to "feel high or stoned" (59% CDN, 38% US). Oxycodone, Tylenol with codeine, and morphine were commonly abused among both samples, however a notable difference in opioids used between the 2 samples was the substantially greater US use of hydrocodone (91% US, 11% CDN). Similarly, the use of Tylenol with codeine was greater in CDN participants (59% CDN, 31% US). Participants reported taking prescription opioids via various methods with swallowed whole, crushed and snorted, and chewed/crushed and swallowed as the most prevalent. Over the past year, the most common route of administration to get high in the US cohort was swallowing whole (87%) while the CDN cohort cited snorting (92%). Diversion of opioids for recreational use was similar between samples with most users reporting family and friends as their source of opioids. Both samples reported marijuana and alcohol as the drugs most commonly co-administered with opioids.

Conclusions

A range of similar behavioral patterns with respect to Rx opioid abuse and diversion was captured by the Recreational Prescription Opioid Abuse questionnaire in 2 differing samples of nondependent, recreational opioid

users in the US and Canada. Differences in route of administration data reflect differences in eligibility requirements between studies and differences in regional availability of opioid formulations may influence the opioids selected for abuse. Further characterization of these populations is warranted.

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Transforming care for low back pain (LBP) in the primary care setting

J.B. Jones[1], Thomas R. Graf[1], Melissa S. Stahl[1], Christa A. Bruce[1], Marcia Rupnow[2], Virginia Lerch[1], Walter F. Stewart[1]
[1]*Geisinger Health System, Danville, PA, USA,* [2]*Janssen Scientific Affairs, Raritan, NJ, USA*

Purpose

LBP is the second most common reason for primary care visits in the U.S. Most episodes resolve within weeks. However, 5%-10% of patients have persistent recurrent or chronic pain problem that often results in excessive use of health care that might otherwise be avoidable. We hypothesized that shared decision-making (SDM) for LBP during primary care encounters would improve patient satisfaction and other outcomes, enhance appropriate use of care, and reduce medical costs. We describe the design and implementation of a web-based application incorporating patient survey and electronic health record (EHR) data to facilitate SDM in the primary care setting.

Method

The LBP application, denoted "eLowBackPain," collects patient-reported data, processes these and EHR data, and displays content to facilitate SDM. During an encounter, the LBP questionnaire automatically appears on a second touchscreen monitor when the nurse opens the patient's EHR in the exam room. The questionnaire is completed after the nurse leaves. Decision rules process patient data and display specific LBP recommendations. A visual display application consisting of 4 tabs appears for joint viewing when the provider opens the patient's EHR. The tabs include a summary of the patient data, tailored physical exam, guideline-based recommendations and nuanced talking points tailored to the patient, a compiled progress note, and other content. eLowBackPain is currently being tested in a RCT in 5 Geisinger primary care practices. Eligible adult patients include those who are being seen for LBP. We will enroll 100 into the usual care arm and 200 into the eLowBackPain arm.

Results

To date, a total of 91 patients in 5 practice sites had a LBP encounter, were randomized, and completed a usual care encounter (n=53) or encounter with the eLowBackPain application (n=38). Providers used eLowBackPain 55% of the time. This compares to traditional alerts evoked during encounters that are used by the providers 0% to 20% of the time. We will present preliminary comparative data using an intention-to-treat design on the primary measures of interest including: measures of appropriate care, patient satisfaction with care, and patient pain level and functioning at 3 months.

Conclusions

While the EHR represents an important opportunity to transform how health care is delivered, we expect that the most profound changes will occur through flexible, robust, and highly functional web applications that interface with and complement the current but somewhat limited functionalities of the EHR.

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Pain characteristics, pain treatments and patient-reported outcomes (PROs) among patients diagnosed with cancer: an analysis using a national survey data

Anisha M. Patel[1], Kathy Annunziata[3], Carmela Benson[2], Marcia Rupnow[1]
[1]Janssen Scientific Affairs, LLC, Raritan, NJ, USA, [2]Janssen Scientific Affairs, LLC, Titusville, NJ, USA, [3]Health Sciences Practice, Kantar Health, Princeton, NJ, USA

Purpose

Pain is the most burdensome symptom of cancer yet, it remains a secondary focus in the overall cancer patient care model. Among cancer survivors, pain can persist even after successful treatment of the disease, and continue to negatively affect patient functionality and well-being. This study aims to evaluate pain characteristics and pain treatments, medical-resource utilization (MRUs) and other patient-reported outcomes (PROs) among cancer patients.

Method

Respondents to the 2011 US National Health and Wellness Survey (NHWS), a self-administered online questionnaire of 75,000 adults, indicating any cancer diagnosis in the past were included in the study. NHWS collected self-reported data on demographics; pain severity, frequency, and intensity; pain treatments, side-effects, and satisfaction with current medication; MRUs ie, Emergency Department (ED) visits, hospitalization and physician-office visits in the past 6 months; and other PROs including work-productivity and daily-activity impairment due to health. Respondents rated pain severity as "mild", "moderate" or "severe"; pain intensity in the past week was measured on a 11-point numeric rating scale (0=no pain to 10=pain as bad as you can imagine), and satisfaction with medication was graded using a 7-point categorical scale (1=extremely dissatisfied to 7=extremely satisfied).

Results

Among 7883 cancer patients (mean age=62 years; 51.2% males; 86.4% whites; 36.5% employed), skin (37.2%), prostate (13.9%), and breast (12.3%) cancer were the most common conditions. A total of 3507 (44.5%) cancer patients reported pain in the past year, of them, 2987 (85.2%) indicated diagnosis of pain; and 1536 (51.4%) of those diagnosed were currently using a prescription medication to treat their pain. Arthritis (45.4%), back (40.5%) and joint (28.7%) pain were top-3 diagnosed pain conditions, and 13% of these cancer patients reported diagnosis of neuropathic pain. When respondents were asked about their current pain, they frequently reported back (56%), arthritis (49.7%) and joint (48.7%) pain as the cause of pain in the past month, 68.5% rated their pain as moderate-to-severe, and 54.9% reported daily pain and an average pain intensity of 5.1. Sleep difficulties (26.4%) and insomnia (16.9%), depression (19.8%), and anxiety (16.6%) were common pain-related comorbidities in these patients.

Among current prescription users, 20.1% and 47.5% indicated using a strong or weak opioid, respectively, to treat their pain; over one-third were treating their back pain. Constipation (55.4%), sleepiness (37.6%), dizziness (25.3%), trouble thinking clearly (23.1%), and nausea (19.9%) were frequently reported side-effects among the opioid users. Adjuvant medications included anticonvulsants (3.5%-7.2%), muscle relaxants (0.2%-6.5%), and antidepressants (0.5%-4.2%). Less than half of these patients (44%) reported satisfaction with their current pain medication (45.1% for strong opioids; 44.8% for weak opioids).

As for MRUs, 14.5% had an ED visit, 12.3% were hospitalized and 93.3% had a physician-office visit in the past 6 months. Additionally, 34.8% of these cancer patients reported high daily-activity impairment (ie, >40% impairment); and 20.1% of those employed reported high work-productivity impairment (ie, >31% impairment) due to health.

Conclusions

This analysis suggests that pain is prevalent among cancer patients and majority of these patients rate their pain as moderate-to-severe. We also noted an under treatment of pain in cancer, high prevalence of gastrointestinal and CNS side-effects, and a low satisfaction among the treated patients. These factors can be a major barrier to adequate pain alleviation, accounting for an unmet need in the cancer pain population. Further analysis will elucidate the impact of cancer pain on other PROs.

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Low back pain episodes of care: patient characteristics and health care

Lianna Weissblum[1], Robert Bailey[2], James Muller[1], Carmella Benson[2], Marcia Rupnow[2], Rachel Feldman[1]
[1]*The Moran Company, Arlington, VA, USA,* [2]*Janssen Scientific Affairs, LLC, Raritan, NJ, USA*

Purpose

Low back pain (LBP) is a condition that presents in many healthcare settings with varying degrees of intensity, and often recurs. LBP is common among working age adults, and results from diverse etiologies, many of which may never be fully diagnosed, even while the pain is treated. The costs associated with the treatment of LBP have been previously evaluated and recognized as an area of care that potentially requires improved management. Due to the high incidence of LBP and the associated healthcare costs, payers and policy makers have proposed the development of an episode of care (EOC) payment methodology for LBP. This study explored the use of administrative claims data in empirically defining EOCs related to LBP to profile the costs and patterns of care for different types of LBP episodes. This study may be of interest to the payer community and others interested in improving the cost, quality, and outcomes of LBP management.

Method

Adult (age 18-64 years), noncancer LBP EOCs were identified using the 2005-2009 Thomson Reuters MarketScan® Commercial Claims and Encounters Database. The beginning of an EOC was marked by a claim with a LBP diagnosis and a pain prescription from the World Health Organization Pain Ladder (WHOPL) within 30 days. WHOPL rungs categorize pain medication strength; Rung 1 includes nonopioids, Rung 2 includes opioids for mild to moderate pain, and Rung 3 includes opioids for moderate to severe pain. EOCs continued from diagnosis or prescription until there were at least 60 days with no LBP claims. Each EOC was placed into a WHOPL rung group determined by the highest rung drug received and was used as a surrogate for pain severity. Patients were grouped by EOC length into single acute (SA) (one <90 day episode), and chronic (at least one episode ≥90 days) populations. Three LBP patient groups were identified with sufficient volume to warrant in-depth analysis: SA; Chronic Non-neuropathic (CNN); Chronic Neuropathic (CN). Neuropathic pain included sciatica, myelopathy, and spinal stenosis. EOC costs included primary insurance, secondary insurance, and beneficiary shares. All costs were adjusted to December 2011 dollars using the Consumer Price Index-Urban medical services component. Costs were classified as LBP service costs or non-LBP service costs. LBP services included all prescription drugs, outpatient services, and inpatient stays with a LBP diagnosis. Non-LBP services included all other prescription drugs, outpatient services, and inpatient stays without a LBP diagnosis.

Results

Overall, the proportions of females in the SA/CNN /CN samples were 53%/57%/56%, respectively. Mean age in the SA/CNN/CN samples were 44.6/47.1/48.5 years. In the SA population, mean age increased slightly as rung increased. Mean age decreased as rung increased for CNN/CN. In SA, mean days per EOC did not vary greatly by rung (R-mean days) (R1-32, R2-29, R3-33). In both chronic populations, mean days per EOC increased as rung increased (CNN R1-189, R2-254, R3-432 and CN R1-167, R2-223, R 3-383). CN EOCs were the most expensive across the 3 rungs ($4,795-$18,890) followed by CNN episodes ($4,460-$17,760) and SA episodes ($1,085-$3,701). The proportion of LBP related costs for each EOC were: SA 40%-44%; CNN 58%-64%; CN 46%-53%. The percentage of non-LBP costs decreased as rung increased.

The majority of LBP costs were for outpatient services across all groups and rungs, and as rung increased the proportion of inpatient services increased (SA-R1 2%, R2 8%, R3 16%; CNN-R1 1%, R2 5%, R3 6%; CN-R1 2%, R2 7%, R3 12%). The majority of non-LBP costs were outpatient service costs across all groups and rungs. SA episodes had the largest percentage of non-LBP outpatient costs (73%-77%). The percentage of non-LBP outpatient costs was similar for CN/CNN(56%-59%). A small proportion of non-LBP costs were inpatient costs in all populations increasing with rung. The percentage of non-LBP costs associated with nonpain drugs, decreased as rung increased, and was highest for the CN/CNN (33%-42%). The most common non-LBP conditions diagnosed during LBP EOCs were musculoskeletal related, as well as injury and poisoning including fractures, and arthropathy.

Conclusions

These findings suggest LBP represents a significant cost burden to employers and to the US healthcare system overall. Regardless of the chronicity, severity, and type of LBP, more than half of healthcare costs in an episode of LBP are non-LBP related. These observations suggest a potentially complex relationship between LBP and other concomitant conditions. Further study is warranted to understand this relationship and to identify potential ways to lower costs, improve care, and outcomes. These observations may inform healthcare policy makers developing new payment methodologies as to what patient related factors impact healthcare costs in a LBP episode.

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Concomitant use of opioids and ketamine in patients with pain

Pamela H. Saarikoski[1], Joseph D. Ma[1,2], Brookie M. Best[1,3], Candis M. Morello[1,4], Rabia S. Atayee[1,2], Amadeo J. Pesce[5,6]

[1]University of California San Diego (UCSD), Skaggs School of Pharmacy and Pharmaceutical Sciences, La Jolla, CA, USA, [2]Doris A. Howell Palliative Care Service, San Diego, CA, USA, [3]UCSD Department of Pediatrics, Rady Children's Hospital, San Diego, CA, USA, [4]Diabetes Intense Medical Management Clinic, Veterans Affairs San Diego Healthcare System, La Jolla, CA, USA, [5]Millennium Research Institute, San Diego, CA, USA, [6]Department of Pathology and Laboratory Medicine, UCSD School of Medicine, La Jolla, CA, USA

Purpose

Ketamine is a potent *N*-methyl-D-aspartate (NMDA) receptor channel blocker that is clinically prescribed for analgesia, as an adjuvant to opioids or when opioids provide minimal pain relief. Chronic opioid use can produce hyperalgesia, via over activation of the NMDA receptor, resulting in increased analgesic requirements and opioid tolerance. In this scenario, patients may benefit from adding ketamine to the treatment regimen. However, little is known about the general use and effectiveness of ketamine in nonterminal, chronic pain patients. The purpose of this analysis was to determine opioid and ketamine concomitant use and detection rates in urine specimens of a chronic pain population. In addition, effects of possible confounding variables of age, gender and urine pH on urinary ketamine and metabolite concentrations were examined. These observations may help to identify current patterns of concomitant opioid use with ketamine and increase understanding of ketamine metabolism.

Method

This was a retrospective data analysis of de-identified urine specimens from a population of patients treated for pain between September 2011 and May 2012. These specimens were analyzed at Millennium Laboratories using liquid chromatography-tandem mass spectrometry (LC-MS/MS) to determine urinary concentrations of commonly prescribed opioids in the presence or absence of ketamine or norketamine metabolite. Specimens with a creatinine concentration less than 20 mg/dL, ketamine and norketamine concentrations below the lower limit of quantitation (LLOQ) of 50 ng/mL and a concentration for each opioid below its specific LLOQ were excluded from analysis. Detection rates of concomitant opioid and ketamine use were compared to baseline detection rates in the total patient population. Provider-reported medication lists were also examined for these opioids. Inter-patient variability of the urinary metabolic ratio (MR) of norketamine to ketamine was evaluated from specimens collected from a patient's first visit and potential differences in MR due to patient age, urine pH or gender were also determined. Statistical analyses were carried out with Microsoft Excel® 2010 and OriginPro 8.6.

Results

From a population of patients with chronic pain, 85,758 de-identified urine specimens were tested for ketamine. After removal of duplicate patient visits, 90 single-visit patients were found to have a positive urine test result for ketamine and/or norketamine. The most common opioid detected with ketamine was fentanyl with a +119.5% higher detection rate compared to the baseline population. Other opioids with higher concomitant detection rates compared to the baseline population were methadone (+100.4%), morphine (+79.1%), codeine (+62.9%), oxymorphone (+57.9%), oxycodone (+31.0%), buprenorphine, (+30.6%) and hydromorphone (+16.6%). Conversely, hydrocodone showed a lower urine detection rate compared to the baseline pain population (-17.8%). Upon comparing concomitant opioid and ketamine presence in urine and provider-reported opioid prescriptions, 42.2% had one detected concomitant opioid (55.3% reported prescribed), 25.6% had 2 detected concomitant opioids (34.8% reported prescribed of both opioids), 17.8% had 3 detected concomitant opioids (18.8% reported prescribed of all 3 opioids), and 3.3% had 4

concomitant opioids (0% reported prescribed of all 4 opioids). The most common concomitant opioid detected with fentanyl was hydrocodone (50%). The interpatient variability was calculated from 84 patients with single visits resulting in a geometric mean MR of norketamine to ketamine of 0.823 (95% CI: 0.67-1.01). The %CV of the MR between patients was 128%. No statistically significant correlations were found between the MR of norketamine to ketamine and patient age, gender or urine pH.

Conclusions

Among the specimens tested for ketamine, low overall detection rates were observed, and when observed, the presence of ketamine was commonly associated with at least one opioid. Detection rates of many opioids with ketamine were higher than detection rates in the baseline population. The most common concomitant opioids detected were fentanyl, methadone and morphine. This is consistent with ketamine's expected use as an analgesic adjuvant in patients with severe or intractable pain as well as its potential role to prevent or reverse opioid tolerance or hyperalgesia. Patient-specific variables did not contribute to interpatient MR variability.

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Factors predicting the initiation of a discussion regarding the risks and safe use of long-acting/extended-release opioid therapy: results from a national survey

Gregory Salinas, Caroline Robinson, Maziar Abdolrasulnia
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. However, following a decade of standard setting and research on pain control, healthcare practitioner assessment and management of patient pain continues to be inadequate. While evidence-based guidelines emphasize thorough patient assessment, prompt recognition of patient pain, frequent monitoring, multimodal analgesic therapies, and patient input, implementing these recommendations is often hindered by physician misconceptions and attitudes about opioids and abuse. The purpose of this study was to identify the factors involved in physicians' decisions to initiate a discussion with their patients about the risks and safe use of long-acting/extended-release (LA/ER) opioids.

Method

After a thorough literature review was conducted to ascertain the current attitudes and practice of physicians regarding opioid therapies, an online survey was designed and nationally distributed to primary care physicians (PCPs) in October 2011. Data collected from 201 PCPs were compiled for descriptive analysis and then analyzed to determine differences among various demographic groups. Logistic regression was used to determine the main predictors of physicians' initiation of a discussion regarding the risks and safe use of LA/ER opioid therapy.

Results

Half of surveyed PCPs do not always discuss the risks and safe use of LA/ER opioids with their patients when providing a new prescription, although most have positive attitudes regarding doing so. Additionally, PCPs may not fully the factors which place a patient at risk for opioid abuse, as there was often wide disparity in whether or not discussions about opioid risk would be initiated with varying patient types. A main factor when deciding to initiate a discussion is whether the patient and physician have a trusting and lengthy relationship, which is a decision model which could lead to many patients not getting the counseling that they need. The primary predictors of initiation of discussions regarding risks and safe use of LA/ER opioids are whether the physician's colleagues, office, and staff expect them to have discussions and if they find such actions important.

Conclusions

These data highlight many gaps in the care of patients with chronic pain that can be addressed by educational, informational, or policy interventions. Foremost, attention may need to be placed on training to improve physician comfort with talking about the caveats of opioid therapy with their patients. Information and education on how to use screening and monitoring tools (eg, Opioid Risk Tool, urine drug screening) should be provided for PCPs. Furthermore, hands-on activities using realistic case-based approaches should be utilized in continuing education in order to provide experience for physicians in determining a patient's risk for opioid abuse and misuse.

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Nine-year study of patterns of marijuana and cocaine use seen in urinary drug testing of patients with chronic back pain and opioids followed in primary care

Jerome M. Sampson
North Florida / South Georgia VA Medical Center, Gainesville, FL, USA

Purpose

What can we learn about long term urine drug testing in chronic pain patients who test positive for marijuana and/or cocaine? Could pain be a trigger? These patients sign pain agreements when taking opioids to abstain from drug use and consent to periodic urinary drug testing. If inappropriate drug use is discovered patients are subject to discontinuance of opioids. Urinary drug testing is becoming more common but there is no consensus on when, how often, or what to do with a positive result. Patients change physicians, pharmacists, and domicile; are we prepared?

Method

This was a retrospective study from 2003 to 2011 of 200 patients initially on opioids for chronic nonmalignant pain followed in 2 primary care teams. Patients were taken from a Pharmacy print out of those receiving opioids for greater than 3 months. The electronic medical record was used to review the laboratory results and patterns.

Results

One hundred forty-four (n=144) had a diagnosis of back pain, Fifty-six (n=56) were being treated for other causes including headache and joint pains. Out of those with back pain 56 (n=56) were positive for marijuana and/or cocaine; (n=27) with marijuana, (n=19) with cocaine, and (n=11) with both. Urinary drug testing in 1 year may have been -none, once, twice, multiple, with the most 16 times. Positive screens were not usually sent for confirmation nor were patients automatically sent for further evaluation or treatment of drug use. Over the years, qualitative positive urinary drug screen patterns could be seen.

Conclusions

Without urinary drug testing, the use of marijuana or cocaine would not likely have been discovered. Patients with one positive urine screen were more likely to have a second one. Cocaine was harder to stop than marijuana. When both were found in the urine, cocaine was more often seen. Further studies are recommended including optimal testing and results of drug treatment on pain and further drug use in this pain population.

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Neurobiological and psychological benefits of exercise in chronic pain and PTSD

Erica Scioli[1,2], Daniel Forman[1,3], Terence Keane[1,2], John Otis[1,2], Kelly Allsup[1,4], Ann Rasmusson[1,2]
[1]VA Boston Healthcare System, Boston, MA, USA, [2]Boston University School of Medicine, Boston, MA, USA, [3]Harvard Medical School, Boston, MA, USA, [4]New England Geriatric Research, Education and Clinical Center, Boston, MA, USA

Purpose

Chronic pain and posttraumatic stress disorder (PTSD) are highly comorbid, disabling conditions. Research has shown that exercise in healthy participants and/or rodents increases plasma levels of neuropeptide Y (NPY) and the GABAergic neuroactive steroid allopregnanolone (ALLO). Both NPY and ALLO play critical roles in pain gating at the spinal and supra-spinal levels, are lower in PTSD, and correlate negatively with PTSD symptoms. This pilot study was designed to 1) determine if there are antinociceptive and anti-stress benefits of exercise in chronic pain/ PTSD, and (2) delineate the role of low NPY and ALLO in the interrelated pathophysiology of these conditions.

Method

This research assessed the effects of aerobic and anaerobic exercise on NPY and ALLO levels, stress system steroids known to impact NPY and ALLO system function, endorphins, and changes in pain sensitivity in 2 groups: male and female veterans with a) PTSD along with chronic pain, b) healthy, trauma exposed, comparison participants. A symptoms-limited cardiopulmonary exercise test was performed in accordance with guidelines published by the American College of Cardiology. During exercise, the rates of oxygen (O2) consumption and carbon dioxide (CO2) production were calculated from continuous recordings of expired ventilation rate, and expired fractions of O2 and CO2. Blood sampling from an intravenous line was performed prior to exercise and during the last minute of each exercise workload for measurement of NPY and ALLO. Measures of pain, pain tolerance (via the cold pressor test), distress, and perceived exertion were made 30 minutes before and 30 minutes after testing.

Results

The pilot sample (N=12) was 58.3% male (n=7), 41.7% female (n=5) with mean age of 38 years; 42% identified themselves as Black, 33% White, 8% Asian, and 16.7 as "other: (ie, Native American and Indian). Half of the participants had PTSD and comorbid chronic pain; the rest were trauma-exposed but healthy. We found medium to large effect size differences between these groups in baseline and exercise-induced changes in self-reported pain, pain threshold, and pain tolerance. The levels of GABAergic neuroactive steroids (allopregnanolone, pregnanolone, and androsterone) increased in all participants in association with exercise, but were consistently ~40%-75% lower and did not increase as much in response to exercise in the PTSD/chronic pain participants. NPY levels are currently being measured.

Conclusions

This is the first study of exercise-associated increases in the anti-stress, anti-nociceptive compounds NPY and GABAergic neuroactive steroids in persons with comorbid chronic pain and PTSD compared to healthy trauma-exposed participants. The preliminary data suggest that Pain/PTSD participants have reduced release of the anti-stress/anti-nociceptive GABAergic neuroactive steroids, which could contribute to both chronic pain and PTSD symptoms. We are currently investigating whether engagement in a chronic exercise regimen can increase the capacity for release of such beneficial hormones and reduce pain and PTSD symptoms.

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Changes in number of spontaneous adverse event reports of drug abuse, intentional drug misuse, medication error, and overdose after reformulation of OxyContin®

Nelson E Sessler, Todd F Baumgartner, Paul M Coplan
Purdue Pharma, Stamford, CT, USA

Purpose

OxyContin® (oxycodone HCl extended-release [ER]) Tablets were reformulated to be more difficult to crush and to form a gel when dissolved. In August 2010, Purdue Pharma stopped shipments of the original OxyContin formulation (OC) and started reformulated OxyContin (ORF) shipments. The objective of this study was to assess changes in the number of spontaneous adverse event reports of drug abuse, intentional drug misuse, medication error, and overdose following distribution of the reformulated product.

Method

A search of the Purdue Adverse Event Reporting Database (ARGUS) was performed to identify all spontaneous adverse event case reports associated with ER oxycodone containing a preferred term associated with drug abuse, intentional drug misuse, overdose, or medication error. OxyContin cases received by Purdue in Jan-Dec 2010 that were OC cases because they occurred prior to ORF or mentioned the original formulation were compared to those received from Jan-Dec 2011 that were ORF cases. OxyContin cases received on, or after, 27Sep2010 involving unknown formulation of ER oxycodone or OxyContin were designated as ORF. No changes were made to the procedures for documenting and characterizing reports in the adverse event reporting system, except for characterizing the formulation of OxyContin, during the course of this study.

Results

The total number of reported cases for OxyContin with a preferred term related to drug abuse, intentional drug misuse, overdose, and medication error declined 36%, from 1272 in 2010 to 819 in 2011. The number of unique cases with a drug abuse preferred term declined 44% (894 vs 499) with terms associated with fatal outcome declining 71% (48 vs 14). The number of unique cases with an overdose preferred term declined 50% (240 vs 120) with terms associated with fatal outcome declining 51% (162 to 79). The number of unique cases with a medication error preferred term declined 16% (155 vs 131), with terms associated with fatal outcome declining 50% (8 vs 4). The number of unique cases with an intentional drug misuse preferred term did not change, and terms with fatal outcome declined from 2 to 1. The total number of U.S. retail pharmacy prescriptions dispensed for OxyContin has declined slightly over the 2010-2011 periods.

Conclusions

The pharmacovigilance adverse event reporting system may be useful for monitoring the impact of the introduction of new formulations designed to be abuse-deterrent on actual patterns of misuse and abuse in the real-world setting. Analysis of AE reports received by Purdue indicates reductions in the number of AE cases for extended-release oxycodone associated with drug abuse, overdose and medication error, and reductions in associated fatalities, occurring after OxyContin tablets were reformulated. Reporting of adverse events to the sponsor is voluntary and spontaneous and therefore reflects an unknown and potentially variable subset of the adverse experiences occurring in the US population.

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Effects of reformulating extended-release oxycodone on fatal adverse event reports

Nelson E Sessler, Jared M Downing, Hrishikesh Kale, Barbara Harding, Todd F Baumgartner, Paul M Coplan
Purdue Pharma, Stamford, CT, USA

Purpose

Physicochemical barriers to crushing and dissolving were incorporated into the reformulation of OxyContin® (oxycodone HCl extended-release) Tablets to deter tampering and with the intention of reducing abuse and misuse. In August 2010, shipments of original OxyContin (OC) from the manufacturer to wholesalers ceased and shipments of reformulated OxyContin (ORF) started. The effects of the reformulation on fatal adverse event reports have not previously been characterized. This study assessed changes in the number of fatal post-marketing spontaneous adverse event reports associated with OxyContin from the year before (3Q2009 to 2Q2010) to the first year after (3Q2010 to 2Q2011) and the second 3 quarters after (3Q2011 to 1Q2012) introduction of ORF. Trends for all fatal reports, fatal reports involving overdose, and fatal reports involving overdose plus abuse were assessed separately using reports that included information on date of death.

Method

A search of Purdue's Adverse Event Reporting Database (ARGUS) was performed to identify all fatal reports that originated in the United States, involved extended-release oxycodone, and were reported during 3Q2009 to 1Q2012. We created criteria to identify whether fatal cases were overdose-related (eg, drug availability, environmental/clinical information, and laboratory/autopsy report results) or drug abuse-related (eg, tablet manipulation, theft/diversion, doctor/pharmacy shopping, addiction/rehabilitation history, and illicit drug use information). Fatalities were analyzed by 3-month quarters. Fatalities with a date of death reported prior to ORF (3Q2009-2Q2010) were compared to those reported in the first year after ORF (3Q2010-2Q2011) and the second 9-months after ORF (3Q2011-1Q2012). We focused analysis on fatal reports that included a date of death because time trends in mortality cannot be ascertained from cases where a date of death is unknown, and the date of receipt of a report does not necessarily correlate with the date of death. To assess the impact of lag in timing of reporting of spontaneous events when compared to the actual date of death, an analysis of the reporting lag was also conducted. No changes were made to the procedures for documenting and characterizing reports in the adverse event reporting system, except for characterizing the formulation of OxyContin, during the course of this study.

Results

Between 3Q2009 and 1Q2012, there were a total of 753 fatal case reports, of which 344 (46%) included date of death information. In the remaining 56% of fatal case reports, there was no information on the date of death. The number of all fatal case reports in the year prior to reformulation averaged 39 (95% CI: 35-43) per quarter, declined by 5% in the year after ORF to 37 cases (95% CI: 35-39) per quarter, and declined by 66% to 13 cases (95% CI: 1-26) per quarter between 3Q2011 and 1Q2012. The number of overdose fatal case reports in the year prior to reformulation averaged 26 (95% CI: 23-30) per quarter, declined by 19% in the year after ORF to 21 cases (95% CI: 19-23) per quarter, and declined by 80% to 5 cases (95% CI: -4-14) per quarter between 3Q2011 and 1Q2012. The number of overdose fatal case reports with abuse mentioned in the year prior to reformulation averaged 24 (95% CI: 20-27) per quarter, declined by 33% in the year after ORF to 16 cases (95% CI: 13-18) per quarter, and declined by 82% to 4 cases (95% CI: -2-10) per quarter between 3Q2011 and 1Q2012. Assessing the time lag in case reporting from 6 prior 6-month periods, on average 24% of cases were received at least 3 months after the 6-month period in which the death occurred, suggesting that the number of cases in the second 9-month period

ultimately may increase by 24% over time. In 1Q2012, there were 8, 1, and 0 cases of all fatal reports, overdose fatal reports, and overdose plus abuse fatal reports, respectively.

Conclusions

There was a reduction in the number of fatal adverse event cases associated with OxyContin reported to the sponsor after reformulation of OxyContin, particularly those occurring at least one year after the reformulation was introduced, and for fatal cases of overdose with mention of abuse. Delayed reporting of cases may account for a small part, but not all, of the observed reduction in reported fatalities. Reporting of adverse events to the sponsor is voluntary and spontaneous and therefore reflects an unknown and potentially variable subset of fatalities occurring in the US population.

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Patient Global Impression of Change (PGIC) and Brief Pain Inventory-Short Form (BPI-SF) assessments with Tapentadol Extended Release (ER) for painful diabetic peripheral neuropathy (DPN)

Aaron Vinik[1], Douglas Shapiro[2], Keith Karcher[2], Bernd Lange[3], Christine Rauschkolb[2], Mila Etropolski[2]
[1]EVMS Strelitz Diabetes Research Center, Norfolk, VA, USA, [2]Janssen Research & Development, L.L.C., Raritan, NJ, USA, [3]Grünenthal GmbH, Aachen, Germany

Purpose

In this randomized-withdrawal, placebo-controlled study (NCT01041859) of tapentadol ER for moderate to severe, chronic, painful DPN, patients were titrated to an optimal dose of tapentadol ER (100 mg-250 mg bid) during a 3-week, open-label period.

Method

Patients with ≥1-point reduction in pain intensity (11-point numerical rating scale) were then randomized to receive placebo (n=152) or their optimal dose of tapentadol ER (n=168) during a 12-week, double-blind, maintenance phase.

Results

At double-blind endpoint, the distribution of PGIC scores was significantly better with tapentadol ER vs placebo, with approximately 66% of tapentadol ER patients reporting their pain was either very much improved or much improved compared to approximately 45.3% of patients receiving placebo ($P<.001$ for the overall distribution). From the open-label start to double-blind endpoint, tapentadol ER was associated with a significant reduction in the mean (SD) pain intensity subscale score of the BPI-SF (placebo, -2.3 [2.33]; tapentadol ER, -3 [2.16]; $P=.003$) vs placebo. The mean (SD) change in the pain interference score of the BPI-SF from open-label start to double-blind endpoint was -2.6 (2.38) for placebo and -3 (2.07) for tapentadol ER ($P=.05$). Nausea (21.1%) and vomiting (12.7%) were the most common TEAEs (≥10%) with onset or worsening in intensity during the maintenance phase in the tapentadol ER group.

Conclusions

Compared with placebo, tapentadol ER (100 mg-250 mg bid) provided significant improvements in PGIC and BPI-SF scores for the management of moderate to severe, chronic, painful DPN.

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Efficacy and tolerability of Tapentadol Extended Release (ER) in patients with chronic, painful diabetic peripheral neuropathy (DPN): results of a Phase 3, randomized-withdrawal, placebo-controlled study

Aaron Vinik[1], Douglas Shapiro[2], Christine Rauschkolb[2], Bernd Lange[3], Keith Karcher[2], Deborah Pennett[2], Mila Etropolski[1]
[1]EVMS Strelitz Diabetes Research Center, Norfolk, VA, USA, [2]Janssen Research & Development, L.L.C., Raritan, NJ, USA, [3]Grünenthal GmbH, Aachen, Germany

Purpose

This Phase 3, randomized-withdrawal, placebo-controlled study (NCT01041859) evaluated the efficacy and tolerability of tapentadol ER for the management of neuropathic pain associated with DPN.

Method

Adult patients with moderate to severe, painful DPN with symptoms for ≥6 months and ≥3-month history of analgesic use for painful DPN were titrated to an optimal dose (balancing efficacy and tolerability) of tapentadol ER (100 mg-250 mg bid) during a 3-week open-label period. At the end of the titration period, patients with ≥1-point reduction in pain intensity from the beginning to end of titration were randomized (1:1) to receive placebo or their pre-determined optimal dose of tapentadol ER for 12 weeks (double-blind, fixed dose, maintenance phase). The primary efficacy endpoint was mean change in average pain intensity (recorded twice daily [average pain during previous 12 hours]; 11-point NRS) from the start to Week 12 (LOCF) of the double-blind maintenance phase. Treatment-emergent adverse events (TEAEs) were recorded.

Results

A total of 358 patients completed the open-label titration period; 318 patients (placebo, n=152; tapentadol ER, n=166) were randomized and received ≥1 dose of study medication. At the start vs Week 12 of double-blind maintenance, respectively, mean (SD) pain intensity was: tapentadol ER, 3.70 (1.78) vs 4.01 (2.23); placebo, 3.35 (2.17) vs 4.83 (2.60). Mean (SD) change in average pain intensity from the start to Week 12 of the double-blind maintenance phase was: tapentadol ER, 0.28 (2.042); placebo, 1.30 (2.428) (least-squares mean difference for tapentadol ER vs placebo, -0.95 [95% CI: -1.415 to -0.493]; $P<.001$ favoring tapentadol ER). TEAEs (≥10%) reported in the tapentadol ER group during double-blind maintenance were nausea (21.1%) and vomiting (12.7%).

Conclusions

Tapentadol ER (100 mg-250 mg bid) was effective and well tolerated for the management of moderate to severe, neuropathic pain associated with DPN in adults.

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A pooled analysis evaluating efficacy and tolerability of Tapentadol ER for chronic, painful diabetic peripheral neuropathy (DPN)

Sherwyn Schwartz[1], Mila Etropolski[2], Douglas Shapiro[2], Christine Rauschkolb[2], Aaron Vinik[3], Bernd Lange[4], Kimberly Cooper[2], Ilse Van Hove[5], Juergen Haeussler[1]
[1]Cetero Research, San Antonio, TX, USA, [2]Janssen Research & Development, L.L.C., Raritan, NJ, USA, [3]EVMS Strelitz Diabetes Research Center, Norfolk, VA, USA, [4]Grünenthal GmbH, Aachen, Germany, [5]Janssen Research & Development, Beerse, Belgium

Purpose

The efficacy and tolerability of tapentadol ER were evaluated using pooled data from 2 randomized-withdrawal, placebo-controlled, phase 3 studies (NCT00455520; NCT01041859) of similar design in patients with moderate to severe, chronic, painful DPN.

Method

In each study, patients were titrated to their optimal dose of tapentadol ER (100 mg-250 mg bid) during a 3-week, open-label (OL) titration period. Patients who had tolerated tapentadol ER and had ≥1-point improvement in pain intensity (11-point NRS) from the start to end of titration were randomized to placebo or tapentadol ER (dose determined during titration) for a 12-week, double-blind (DB) maintenance period. Average pain intensity over the previous 12 hours was recorded twice daily. The primary efficacy endpoint was mean change in pain intensity from the start to Week 12 (LOCF) of DB maintenance.

Results

Mean (SD) pain intensity for the overall population (n=1034) was 7.29 (1.38) at the start of OL titration and decreased to 4.15 (2.10) at the end of titration. With placebo (n=343) and tapentadol ER (n=360), respectively, mean (SD) pain intensity scores were 3.48 (2.02) and 3.67 (1.85) at the start of DB maintenance and 4.76 (2.52) and 3.77 (2.19) at Week 12; mean (SD) changes from the start to Week 12 of DB maintenance were 1.28 (2.41) and 0.08 (1.87), indicating that pain intensity worsened with placebo but was relatively unchanged with tapentadol ER. The least-squares mean difference for the change from start to Week 12 of DB maintenance for tapentadol ER vs placebo was -1.14 (95% CI: -1.435 to -0.838; $P<.001$). AEs led to treatment discontinuation for 16.3% (169/1040) of patients during OL titration and 8.2% (28/343) of patients receiving placebo and 14.2% (51/360) of those receiving tapentadol ER during DB maintenance.

Conclusions

Results of this pooled analysis support those of the individual studies and indicate that tapentadol ER was effective and well tolerated for managing moderate to severe, chronic, painful DPN.

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Pain assessment in recovery: a pilot study.

Zainab Ali Sherazi[1,2], Anand Rajasekaran[1]
[1]*Central Manchester University Hospital NHS Foundation Trust, Manchester, UK,* [2]*University of Manchester, Manchester, UK*

Purpose

Assessment and management of acute postoperative pain in recovery is an interesting and challenging clinical scenario which requires diligent attention to regular pain intensity and pain relief evaluation. Pain is measured using validated tools including Numerical Rating Scale (NRS), Verbal Rating Scale, and the Visual Analogue Scale. Similarly, pain relief requires a quantifying measure such as the Total Pain Relief Score (TOTPAR)[1]. The aim of this pilot study was to study the suitability of TOTPAR scale in assessing the effect of pain treatment in comparison to the NRS.

1. Cooper SA, Beaver WT. A model to evaluate mild analgesics in oral surgery outpatients. *Clin Pharmacol Ther.* 1976;20:241-249.

Method

This observational study was piloted in recovery rooms of the theatres in Manchester Royal Infirmary. All patients undergoing surgery under a general anaesthetic were included while those receiving a central neuraxial or plexus blocks were excluded. Standard recovery observations including pain scores were recorded. If pain scores were >5, intravenous opioids were administered and NRS and TOTPAR were assessed at regular intervals till discharge. Age, gender, presence of chronic pain, type of analgesic provided, side effects experienced, and length of stay were also recorded.

Results

Thirty nine patients (n=70) had NRS and TOTPAR scores recorded. There was a mild negative correlation between NRS and TOTPAR scores. A formal test of whether the slope of the regression line was nonzero generated *P*-values of .008, .000, and .184 (sig 0.05) at 15, 30, and 45 minutes after treatment respectively in a simple linear regression analysis. Interestingly, the length of stay had a mild positive correlation with the pain relief scores and pain scores; however this was not statistically significant. This may be due to the observer bias and logistical factors involved. Multivariate analysis showed that age, gender and chronic pain did not act as confounders on the length of stay.

Conclusions

NRS and TOTPAR scores are reliable tools for the assessment of acute postoperative pain and analgesic efficacy. TOTPAR can be reliably used for the assessment of the effectiveness of pain relief. A NRS score of >5 is the only discharge criteria and using a TOTPAR score of 50% may enable early patient discharge. This requires adequate patient education, staff training and further research. Using more than one tool may increase reliability of assessment, reduce risk of under or over treatment, reduce the amount of opioid used and thereby their side effects.

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Safety and tolerability of oral methylnaltrexone in chronic noncancer pain patients with opioid-induced constipation

Neal Slatkin[1], Richard Rauck[2], Robert Israel[3], Enoch Bortey[4], Paterson Craig[4], William Forbes[4]
[1]*City of Hope Medical Center, Duarte, CA, USA,* [2]*Carolinas Pain Institute, Winston-Salem, NC, USA,* [3]*Progenics Pharmaceuticals, Inc, Tarrytown, NY, USA,* [4]*Salix Pharmaceuticals, Inc, Raleigh, NC, USA*

Purpose

Opioid-induced constipation (OIC) is one of the most frequent and distressing adverse effects of opioid therapy, and represents a major limiting factor in achieving adequate analgesia in patients with chronic, noncancer pain. Therapies targeting the effects of the opioids on the gut should not cross the blood-brain barrier in order to avoid reversal of analgesia or precipitation of opioid withdrawal syndrome. Methylnaltrexone (MNTX) is a peripherally acting, selective μ-opioid receptor antagonist approved in >50 countries worldwide as a subcutaneous (SC) injection for the treatment of OIC in patients with advanced illness when response to laxative therapy has been insufficient (RELISTOR®).Oral MNTX represents a potentially new therapy for the treatment of OIC in subjects with chronic, noncancer pain that does not appear to compromise analgesia. The purpose of this study was to evaluate the safety, efficacy, and potential effects on analgesia of oral MNTX tablets in a phase 3, multicenter, double-blind, placebo (PBO)-controlled, parallel-group study.

Method

804 subjects were randomized to receive PBO or oral MNTX 150 mg, 300 mg, or 450 mg tablets, allocated in a 1:1:1:1 ratio, for 12 weeks (4 weeks QD dosing followed by 8 weeks PRN dosing). For inclusion in the study, adult subjects with chronic, noncancer pain and a history of OIC were required to be taking ≥50 mg oral morphine equivalents/day for ≥14 days. Safety assessments included: treatment-emergent adverse events, changes from baseline in total Objective Opioid Withdrawal Scale (OOWS) scores, total Subjective Opioid Withdrawal Scale (SOWS) score, and changes from baseline in pain intensity scores, assessed on an 11-point Numeric Rating Scale (0=None, 10=Worst Pain Possible; based on pain experienced during the last 24 hours). Efficacy endpoints were rescue free bowel movements (RFBMs) within 4 hours of dosing and RFBMs/week over the first 4 weeks.

Results

Demographic and baseline characteristics were similar between treatment groups. The mean (SD) daily morphine equivalent dose was 218.7 (217.4) mg in the MNTX groups and 207.4 (199.7) in the PBO group, with the most common opioid medications being oxycodone (33.9% all MNTX, 32.8% PBO), morphine (29.4%, 28.9%), and hydrocodone/acetaminophen (23.9%, 16.9%). In MNTX (n=602) and PBO (n=201) subjects, completion rates during the 4-week QD dosing period were 90.0% and 89.6%, respectively. In MNTX (n=527) and PBO (n=167) subjects continuing in the 8-week PRN dosing period, completion rates were 88% and 85.6%, respectively. Across the entire 12-week study, the most common reasons for discontinuation were subject request (6.5%) and lost to follow up (5%) in the MNTX groups and subject request (8.5%) and protocol violation (7%) in the PBO group. The incidence of adverse events (AEs) was similar between the MNTX groups and PBO: most common AEs (≥5%) were abdominal pain (8% all MNTX, 8.5% PBO), nausea (6.8%, 9%), and diarrhea (6%, 3.5%). The majority of AEs in both treatment groups were rated by investigators as either mild or moderate in severity. The incidence of serious adverse events in the MNTX and PBO groups was 2.5% and 4%, respectively. None was considered by investigators to be related to the study drug. At the end of the study, the MNTX groups experienced little or no change from baseline in the OOWS score, and there was not a statistically significant difference from placebo on this measure. Similar findings were observed for SOWS scores. Primary and secondary endpoints of RFBMs within 4 hours of dosing and RFBMs/week were statistically significant ($P<.01$) for the 300 mg and 450 mg groups vs placebo. Throughout the

course of the study, there were minimal changes from baseline in pain intensity scores regardless of the treatment group.

Conclusions

Oral MNTX 150 mg, 300 mg, and 450 mg tablets appear safe and are generally well-tolerated across 12 weeks of therapy. While significantly active in achieving the efficacy endpoints, adverse events in the MNTX arms were similar to those observed with placebo. The lack of effects on opioid withdrawal scores and analgesia are consistent with the peripheral mechanism of action of oral MNTX.

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Case study: rotation of opioid-adrenergic agent combinations

Howard Smith
Albany Medical College, Albany, NY, USA

Purpose

Opioids and adrenergic agonists have demonstrated efficacy and tolerability for chronic noncancer pain when used independently, combined as 2 separate agents, or combined by the action of single molecule with opioid and adrenergic effects (eg, tapentadol). However, there is limited literature describing the rotation from one opioid-adrenergic agent combination to another. The objective of this study was to present a case illustrating the rotation of a patient from an opioid agonist and a serotonin-norepinephrine reuptake inhibitor (SNRI) to a single molecule that combines opioid agonist and adrenergic agonist mechanisms.

Method

A woman aged 57 years had been diagnosed with fibromyalgia 7 years earlier. Despite treatment with orally administered milnacipran 50 mg twice daily and oxycodone controlled release 10 mg twice daily (BID), she experienced mild to moderate cognitive difficulties, sleep disturbances, fatigue, and widespread pain. Physical examination revealed tenderness in 12 of 18 standard areas according to American College of Rheumatology 1990 criteria; other physical examination findings were normal. Several considerations affected the strategy for conversion to more effective therapy. First, opioid rotation typically involves conversion to an equianalgesic opioid dose using standardized tables.[1] However, standardized tables do not account for the adjuvant effects of a separate adrenergic agonist or an opioid with adrenergic properties. Second, the current combination of opioid agonist plus SNRI had been selected to avoid pharmacokinetic drug-drug interactions (PK-DDIs) because oxycodone undergoes metabolism by cytochrome P450 (CYP450) enzymes, whereas milnacipran does not. Similar caution against PK-DDIs must be exercised when selecting the combination of opioid agonist and adrenergic agonist for rotation; for example, a posthoc analysis has assessed safety outcomes in patients taking SNRIs metabolized by CYP450 enzymes in combination with oxymorphone, which undergoes metabolism via glucuronidation.[2] For this patient, milnacipran and oxycodone controlled release were replaced with orally administered tapentadol extended release 100 mg BID on an empiric basis.

Results

The rotation from oxycodone plus milnacipran to tapentadol was well tolerated; symptoms of pain and fatigue improved by approximately 30%.

Conclusions

Successful rotation from one opioid-adrenergic agent combination to a single agent that combines both mechanisms of action can be successful as an empiric process guided by equianalgesic opioid dosing and consideration of PK-DDIs.

References

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Case study: use of universal precautions to identify and manage aberrant drug-related behavior

Howard Smith
Albany Medical College, Albany, NY, USA

Purpose

In recent years, increased opioid prescribing for the management of chronic noncancer pain has been accompanied by an increase in opioid abuse, overdose, and deaths. Clinical practice guidelines recommend several strategies to mitigate these risks, including thorough initial assessment with a full history (including patient and family history of substance abuse), physical examination, and validated substance abuse risk-assessment tools; consideration of nonopioid and nonpharmacologic therapy; patient commitment to a clearly explained controlled substance agreement; cautious, individualized opioid selection, dosing, and titration; routine compliance monitoring; and a plan for response to evidence of aberrant drug-related behaviors. The Centers for Disease Control and Prevention coined the expression "universal precautions" to describe the need to apply a protocol to all patients when it is impossible to reliably distinguish at-risk patients; some pain authorities believe that this approach is necessary for risk mitigation in chronic opioid therapy. The case presented here illustrates the value of a universal precautions approach to preventing, identifying, and responding to aberrant drug-related behaviors indicative of opioid misuse.

Method

An otherwise-well woman aged 68 years complaining of chronic, aching, axial low back pain had been treated over several years with nonpharmacologic interventions, nonsteroidal antiinflammatory drugs, and muscle relaxants before her pain increased and function diminished to the point that opioid analgesia was considered. She was opioid-naïve, aside from a few short-term prescriptions of hydrocodone/acetaminophen for unrelated acute pain problems. Personal and family histories were unremarkable for substance abuse. In the clinician's subjective impression, this patient was at low risk for substance abuse. A controlled substance agreement was explained to the patient, who by signing the agreement, agreed to be monitored for compliance using initial and routine urine toxicology and pill counts. Initial urine screening toxicology was negative for opioids and commonly abused substances. The patient was prescribed a 5-day supply of oxymorphone extended release (ER) 5 mg twice daily as an initial trial of chronic opioid therapy. Frequent follow-up for dose titration was planned until dose stabilization; thereafter, once-monthly visits were planned for reassessment and prescription refills, which were dependent on compliance with the controlled substance agreement.

Results

Before starting chronic opioid therapy, the patient complained of grade 7-8 pain (0=no pain, 10=worst imaginable pain). After the first 5 days, she reported persistent but diminished pain of 5-6 severity; her oxymorphone ER dose was increased to 10 mg twice daily, which reduced her pain to grade 3-4; her dose remained stable thereafter. The patient also reported improved function and facility with all activities of daily living. Six months after starting opioid therapy, her urine toxicology was negative for oxymorphone (ordered specifically), other opioids, and commonly abused substances. The test was repeated with the same outcome. Eight months after starting opioid therapy, her urine toxicology was again negative for oxymorphone and other opioids. After 2 abnormal urine tests, consistent with the terms of the controlled substance agreement, the patient was asked to account for these results. She divulged 2 potential causes. First, she sometimes took extra tablets when in more severe pain, causing her supply to run out a few days before her next visit and urine test. Second, she believed that her grandson sometimes stole some of her pills. She did not report either problem until asked to explain her abnormal urine test because she felt embarrassed to

admit her uncertainty regarding how much of the tablet shortage was due to inadequate analgesia and how much was due to theft.

Conclusions

Aberrant drug-related behavior became evident when a universal precautions approach was applied with this apparently low-risk patient. Clinical strategies to mitigate the risk of opioid abuse fundamentally involve a questioning of trust in the physician-patient relationship and may seem unnecessary in some patients who give the impression of low risk. However, this case illustrates that a universal precautions approach facilitated the identification of inadequate pain control, with possible family dysfunction and substance abuse in a family member. Bringing these issues to light provided therapeutic opportunities that would have otherwise been missed.

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Integrated analysis of efficacy of a once-daily gastroretentive formulation of gabapentin in patients with postherpetic neuralgia who are at least 75 years old

Wendy Smith[1], Anita Gupta[2], Richard L Rauck[3], Gordon A Irving[4], Michael Sweeney[1]
[1]Depomed, Inc., Menlo Park, CA, USA, [2]Pennsylvania Symptom Management and Palliative Care, Philadelphia, PA, USA, [3]Carolinas Pain Institute, Winston-Salem, NC, USA, [4]Swedish Pain and Headache Center, Seattle, WA, USA

Purpose

Gabapentin TID, a first-line treatment for postherpetic neuralgia (PHN), is associated with a high incidence of somnolence and dizziness. In addition to preventing efficacious dosages from being reached, these side effects are especially problematic for older individuals, who are at greater risk for falls. A once-daily gastroretentive formulation of gabapentin (G-GR), which for patients in the fed state remains in the stomach for approximately 8 hours, was approved for the treatment of PHN. This formulation minimizes dizziness and somnolence, which in turn allows patients to reach a dosage that is therapeutically efficacious.

Method

Integrated efficacy analyses were performed on 2 placebo-controlled, Phase 3 studies in patients with PHN. The analysis included 333 patients randomized to receive 1800 mg G-GR and 340 patients randomized to receive placebo, both taken with the evening meal. The primary efficacy assessment was the change in "average pain for the past 24 hours" as assessed by the Numeric Pain Rating Scale (NPRS), with scores recorded every morning from Baseline to Week 10. Secondary efficacy assessments included the percentage of responders, Patient Global Impression of Change (PGIC) at Week 10, and change from Baseline to Week 10 in average daily sleep interference score (SIS). Subgroup analyses were performed based on age: ≥75 years and <75 years. Missing values were imputed using last observation carried forward (LOCF) methodology.

Results

A total of 179 patients—94 in the G-GR group and 85 in the placebo group—were 75 years and older. The mean absolute change in NPRS score was significantly greater with G-GR than with placebo (−2.2 vs −1.4; *P*=.032). A greater proportion of G-GR patients achieved a ≥30% response compared with placebo (52% vs 29%; *P*=.002). According to the PGIC instrument, at Week 10, significantly more patients in the G-GR arm felt "Very Much" or "Much" improved compared with patients in the placebo group (*P*=.001). The change in Sleep Interference Score (SIS) was also significantly greater for patients who received G-GR than for those who received placebo (−2.4% vs −1.3; *P*<.0017). AEs affected 44% of patients in the G-GR arm vs 52% of patients in the placebo arm. There was no significant increases in the incidence of AEs were observed for patients ≥75 years compared with all patients (dizziness, 12% vs 10.9%; somnolence, 5% vs 4.5 %; and peripheral edema, and 4% vs 3.9%, respectively). For patients ≥75 years, serious AEs occurred in 0.8% of patients in each arm. No adverse events were deemed by investigators to be related to study drug.

Conclusions

G-GR can be an effective treatment option for PHN, including for the very elderly (≥75 years). G-GR had similar safety and efficacy profiles in very elderly patients compared with the overall population.

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ThermaCare HeatWraps for lower back pain and muscle stiffness

Jerrold Petrofsky[1], Lee Berk[1], Gurinder Bains[1], Geraldine Doyle[2], Shijie Chen[2], Jill Stark[2]
[1]*Loma Linda University, Loma Linda, CA, USA,* [2]*Pfizer Consumer Healthcare, Madison, NJ, USA*

Purpose

Lower back pain (LBP) is among the most common and costly healthcare problems. More than 80% of the US population experiences LBP at some point during their lifetime. The present study assessed the efficacy of ThermaCare Heatwraps on relieving pain and reducing back stiffness, and evaluated the stopwatch methodology for measuring onset of analgesic effect in a population with acute LBP.

Method

Subjects of 18-55 years old with atraumatic primary muscular LBP were randomized into one of 2 primary efficacy groups: ThermaCare treatment group (n=26) and oral placebo group (n=25). Endpoints included: pain relief (PR) hourly for 8 hours (0=no relief to 5=complete relief), time weighted sum of PR scores from 0-8 hours [TOTPAR 0-8], time to "first perceptible" pain relief (FPR), time to meaningful pain relief, muscle stiffness (0=no stiffness to 100=most possible stiffness), and global improvement.

Results

There was a statistically significant increase in pain relief over 8 hours for the ThermaCare group compared to the oral placebo group. The TOTPAR 0-8 was significantly higher for the ThermaCare group than the oral placebo group (22 vs 11.5; $P<.001$). The time to confirmed FPR and time to meaningful PR were significantly shorter for the ThermaCare group compared to the placebo group (median of 96.5 minutes vs >240 minutes and 215.7 minutes vs >240 minutes, respectively; $P<.05$ for both comparisons). The hourly back stiffness improvement from baseline was significantly better at all post dosing time points except for the 4th hour with the ThermaCare group compared to the oral placebo control.

Conclusions

In conclusion, ThermaCare Heatwraps provide clinically significant faster pain relief and back stiffness improvement over the 8 hours compared to oral placebo. The double stopwatch is a viable approach for assessing the onset of analgesia in low back pain.

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Medication changes initiated after palliative care consult in hospitalized patients: a focus on analgesic category and route of administration

Shelley Stevens, Scott Lagasse, Scott Donelenko
North Florida/South Georgia Veterans Health System, Gainesville and Lake City, FL, USA

Purpose

Patients nearing death are frequently continued on standard medical care, an effort that may inadvertently worsen end of life issues. Hospice and palliative care services provide a unique interdisciplinary approach for the patient whose goals are no longer curative in nature, shifting the focus from interventional medical techniques to pain relief, comfort, and enhancing quality of life. While it has been shown that palliative programs can improve end of life care, literature for appropriate medication prescribing in hospice patients is scarce. The purpose of this study is to retrospectively evaluate medication changes implemented after palliative consultations at 2 Veteran's Affairs (VA) medical centers with a focus on opioid and nonopioid analgesics and route.

Method

An IRB and VA R&D approved retrospective chart review was conducted at the Malcom Randall and Lake City VA Medical Centers to assess changes in inpatient medication profiles as death nears. This is a sub-analysis of a more comprehensive retrospective chart review and focuses on the change in opioid and nonopioid analgesic medications and route in terminal patients. Chart review was completed for 60 randomly selected patients who received an inpatient palliative care consult and subsequently passed away on either VA's palliative care unit between June 30, 2010 and June 30, 2011. Medication administration records were evaluated through electronic medical records (Computerized Patient Record System). Outpatient consults and patients discharged to home hospice were excluded as medication profiles are more difficult to assess in these populations. Changes were evaluated by recording active medications up to one week prior to the hospice consult (day -7), the day after hospice consult (day +1), and the last day of life. Data collection included veteran age, terminal diagnosis, medication name and class, medication route of administration, and time in relation to date of consult and date of death.

Results

Average veteran age at time of death was 72.5 years and 59 of 60 study patients were male. The mean number of active analgesics per patient increased from 1.90 prior to consult (95% CI: 1.56-2.24) to 3.17 on the last day of life (95% CI: 2.84-3.49; $P<.001$). Opioids, specifically, increased from 0.95 per patient prior to consult (95% CI: 0.69-1.20) to 1.87 at death (95% CI: 1.67-2.07; $P<.001$). Prior to consult, oxycodone was the most common active opioid analgesic (52%, N=30), dropping to 16% (N=16) of all active opioid analgesics the day after consult. Codeine and hydromorphone also decreased as death neared. At death, hydromorphone and morphine were the most common opioid analgesics (37%, N=41; 31%, N=35, respectively); an increase was also noted in fentanyl and methadone as death neared. Prior to consult, 54% of opioid analgesics (N=31) were oral in route of administration, falling to 27% the day after consult and even further to 19% at death. There were no analgesics ordered for subcutaneous administration prior to consult. The most common opioid routes of administration at time of death were intravenous push (33%, N=37) and subcutaneous (28%, N=31). Nonopioid analgesics increased from 0.95 per patient prior to consult (95% CI: 0.74-1.16) to 1.30 at death (95% CI: 1.07-1.53; $P=.03$). The most common nonopioid analgesic at all study time periods was acetaminophen, representing 70% of active nonopioid analgesics at death. Like opioid analgesics, the number of oral nonopioid analgesics decreased as death neared. Besides acetaminophen, there was an increase in the number of active orders for oral, subcutaneous, and intravenous dexamethasone as death neared.

Conclusions

The overall increase in analgesics mirrors the palliative care goals of symptom management and comfort care. Palliative care providers may be more comfortable prescribing a range of analgesics, as reflected in the increase in variety of these medications as death neared. The shift away from oral administration as death neared highlights the importance of having an early plan for when patients develop difficulty swallowing secondary to terminal diagnoses and the dying process. Further, the increase in subcutaneous administration emphasizes this route as a readily available, simple, and effective option for delivering medications in patients without intravenous access and/or difficulty swallowing.

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Tamper-resistant properties of tapentadol extended-release tablets

Eric Galia[1], Yinka Williams[2], Ben Van Hove[3], Joseph Pergolizzi[4], Mila Etropolski[5]

[1]Pharmaceutical Development and Drug Delivery, Grünenthal GmbH, Aachen, Germany, [2]Janssen Research & Development, L.L.C., Spring House, PA, USA, [3]Janssen Research & Development, Beerse, Belgium, [4]Naples Anesthesia and Pain Associates, Naples, FL, USA, [5]Janssen Research & Development, L.L.C., Raritan, NJ, USA

Purpose

Oral extended-release opioid analgesic formulations contain higher doses of active ingredients than corresponding immediate-release formulations, which may make extended-release formulations more attractive for abuse or misuse. One property that may make extended-release opioid analgesics more appealing to potential abusers is how readily the dosage form can be manipulated to provide access to the active ingredients. Tapentadol, a centrally acting analgesic with both μ-opioid agonist and norepinephrine reuptake inhibitor activities, is available in an extended-release formulation (NUCYNTA® ER, Janssen Pharmaceuticals, Inc.) that received FDA approval in August 2011 for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Tapentadol extended-release (ER) tablets are formulated with a polyethylene oxide (PEO) matrix using a melt extrusion manufacturing process to produce hardened tablets of high mechanical strength that are resistant to crushing or extraction (INTAC® tamper-resistant technology, Grünenthal, Aachen, Germany). The results of a battery of analytical and physical characterization tests used to evaluate the tamper-resistant properties of PEO-based tapentadol tablets are summarized here.

Method

To evaluate the mechanical resistance of tapentadol PEO tablets to crushing, an attempt to crush each dose strength (50, 100, 150, 200, and 250 mg) was made using 4 different tools: 2 commercially available metal spoons, a professional metal pill crusher (Ocelco Inc.), a standardized pharmacopeia breaking force tester (USP <1217>), and a standardized hammer instrument (a 5-kg steel weight was dropped once onto the tablet from an 80-cm height [impact energy force = 39.2 Nm]). The resistance of frozen tablets (-20°C) to crushing with the standardized pharmacopeia breaking force tester was also evaluated. The tablet dimensions were then evaluated, and the tablets were inspected visually. A Quality Control (QC) dissolution method (performed using USP Apparatus 2 [Paddle] at 100 rpm in 900 mL of 0.050 M phosphate buffer pH 6.8) was used to evaluate the in vitro drug release profiles of control (untampered) tapentadol PEO tablets and tablets subjected to tampering with the pill crusher and the hammer instrument. The in vitro drug release profiles of control tapentadol PEO tablets (50, 100, 150, 200, and 250 mg) in a 40% ethanol solution were also evaluated. In addition, the resistance to extraction of control 250-mg tapentadol PEO tablets and tablets subjected to tampering by hammering were evaluated by shaking these tablets vigorously for 15 minutes and 1 hour in 10 different solutions (isopropanol, acetone, ethyl acetate, 40% ethanol, absolute ethanol, methanol, water, 0.1N HCl, 0.1N NaOH, and organic food corn oil). All tests were performed in triplicate.

Results

No deformation of the tapentadol PEO tablets was possible when using 2 spoons in an attempt to crush the tablets. With the pill crusher, only minimal deformation (and no breakage/pulverization) was observed for all dose strengths. Using the standardized pharmacopeia breaking force tester, all tapentadol PEO tablets at all dose strengths were resistant to crushing (breaking force >1,000 N), and tablets were only visibly deformed; frozen tablets were likewise resistant to crushing by the breaking force tester and deformed to a similar degree as unfrozen tablets. With the standardized hammer instrument, the hammered tablet was flattened but not pulverized or broken into pieces by the instrument. For tapentadol PEO tablets tampered with using the pill crusher, the mean in vitro release profile in standard QC medium was similar to control tablets. For hammered tablets, the mean release profile was somewhat

faster, but only 30% of the active ingredient was released after 30 minutes, which is only slightly higher than the maximum release allowed per manufacturing specifications. The mean in vitro release profile of control tapentadol PEO was slower in the 40% ethanol solution than in QC medium, indicating no dose dumping in either medium. At 1 hour, control PEO tablets were completely resistant to extraction in acetone, absolute ethanol, ethyl acetate, isopropanol, and organic food corn oil; the mean amount of extracted drug reached a maximum of 20% in 0.1N HCl, 0.1N NaOH, 40% ethanol, and water and 32% in methanol at 1 hour. For hammered PEO tablets at 1 hour, the mean amount of extracted drug was ≤11% in acetone, ethyl acetate, isopropanol, and organic food corn oil; ≤62% in 0.1N HCl, 0.1N NaOH, 40% ethanol, absolute ethanol, and water; and 86% in methanol.

Conclusions

Tapentadol PEO tablets were strongly resistant to crushing using the spoons, pill crusher, and breaking force tester and were flattened (not pulverized or broken into pieces) with the hammer, indicating mechanical resistance to tampering. In vitro dissolution testing showed the extended-release profile was largely maintained for control and hammered tablets, indicating that this formulation resists tampering and prevents immediate release of active ingredient. In extraction tests, tapentadol PEO was resistant to dissolution in 5 different solvents; the solvents that partially dissolved tapentadol PEO (methanol, 0.1N HCl, 0.1N NaOH, 40% ethanol, and water) would require additional steps to obtain pure drug.

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Street prices of prescription opioids diverted to the illicit market

Hilary Surratt[1], Steven Kurtz[1], Theodore Cicero[2], Richard Dart[3]
[1]*Nova Southeastern University, Coral Gables, FL, USA,* [2]*Washington University School of Medicine, St. Louis, MO, USA,* [3]*Rocky Mountain Poison and Drug Center, Denver, CO, USA*

Purpose

Prescription opioid abuse and diversion have become major public health problems in recent years, contributing to a wide range of health, social and economic consequences among affected populations. Within this context, there is an ongoing need to identify and examine new, proactive indicators to better characterize the prescription opioid abuse and diversion problem. In this regard, we implemented a national street price surveillance program with law enforcement investigators. Monitoring trends in street prices for prescription opioids may provide an indicator of drug availability, demand, and abuse potential within targeted geographic areas.

Method

We examined street prices of diverted prescription opioids using surveillance data from a nationwide ne2rk of law enforcement officers, collected as part of the Researched Abuse, Diversion, Addiction-Related Surveillance (RADARS®) System. Drug diversion investigators were surveyed quarterly during 2010 and 2011 regarding the street prices of diverted prescription opioids in their areas. We computed mean and median prices per milligram for the targeted prescription opioids in order to make standardized price comparisons across drug classes. Trends in price data over time were also examined.

Results

Street prices per milligram ranked as follows: hydromorphone (mean, $5.87; median, $5.00); oxymorphone (mean, $3.00; median, $2.00); methadone (mean, $1.30; median, $1.00); oxycodone (mean, $1.14; median, $1.00); hydrocodone (mean, $1.05; median, $1.00); morphine (mean, $0.95; median, $0.96); tramadol (mean, $0.14; median, $0.10); and, tapentadol (mean, $0.13; median, $0.10).

Conclusions

Our analyses yielded substantial differences in street price by opioid class. Higher street values appear to reflect greater drug desirability/demand among abuser populations. Street price appears to be a useful indicator of drug popularity among abuser groups.

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Buprenorphine/naloxone treatment

Tommy Swate
Houston, TX, USA

Purpose

Buprenorphine/naloxone can be used for opioid dependency treatment and chronic pain syndrome in a primary care setting. All patients had opioid tolerance and dependency. Chronic pain syndrome patients were differentiated from opioid dependency patients by their history and an identified mechanism for chronic pain. National guidelines recommend "in house induction" followed by multiple clinic visits with counseling. The requirement of "in house induction" has been reported as a barrier to buprenorphine/naloxone treatment. The optimal level of office visits and level of counseling in an outpatient primary care setting has not been established. The purpose of this study is to evaluate patient retention rates at 90 days using standard outpatient medical office visits with home unobserved induction protocol at 30, 60, and 90 days. The primary outcome was the number of opioid free patients remaining in treatment at 90 days.

Method

166 participants were either opioid-dependent or diagnosed with Chronic Pain Syndrome that were eligible for office based buprenorphine treatment. The initial physician visit included assessment, education, and a 30 day buprenorphine prescription with follow up at 30 days intervals. Instructions were given on home induction. Patient initiated dosing off site at a later time. Primary outcome was treatment status at 90 days. Attempts were made to contact drop out patients to determine the cause of discontinuing treatment.

Results

50 out of 82 opioid dependent patients (60%) remained in treatment after 90 days. 55 out of 84 chronic pain syndrome patients (65%) remained in treatment after 90 days. All remaining patients at 90 days had urine screens for opioid and Suboxone. The dropout rate for opioid dependent patients was 20 did not return for second visit and 11 did not return for third visit. The dropout rate for Chronic Pain Syndrome patients was 25 did not return for second visit and 10 did not return for third visit. 15 patients that dropped out of the program were able to be contacted. 11 of the 15 patients contacted gave economic or transportation problems as a reason for not returning for treatment. Factors other than medical services may play a role in the dropout rate. A majority of patients were successful in offsite induction.

Conclusions

The dropout rate of opioid dependent patients receiving buprenorphine/naloxone in an outpatient setting with home induction with follow up in 30, 60, and 90 days did not differ significantly from reported dropout rate with more intensive and extended therapy. Opioid agonist treatment can reasonably be the first line of treatment prior to expensive residential or intensive counseling. Program evaluation is vital for a number of reasons. Accountability is one of the critical areas of substance abuse treatment. Outcome evaluation is a must in order to determine the most effective and economical methods of treatment.

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Over 15 million patient uses of 5% lidocaine medicated plaster: an update on its safety profile

Daniela Bertarelli, Ingrid Tacken
Grunenthal GmbH, Aachen, Germany

Purpose

5% lidocaine medicated plaster was prescribed worldwide to approximately 15.25 million patients since the first marketing authorisation in 1999 until end of 2011. (This calculation is based on the assumption that patients applied on average 1.1 plasters per day[1] and the average duration of treatment is about 3 months.[1]) Prescriptions included postherpetic neuralgia (PHN), painful diabetic neuropathy, low back pain and chronic post-operative pain. Data are complemented by over 1400 patients treated in clinical trials. 5% lidocaine medicated plaster is indicated for the symptomatic relief of neuropathic pain associated with previous herpes zoster infection (post herpetic neuralgia, PHN) and recommended in international treatment guidelines.

Method

A pooled safety analysis of 3 clinical Phase III studies was performed to calculate adverse drug reaction (ADR) frequency.[2] Additionally, spontaneous safety reportings from consumers and healthcare professionals were collected for approximately 15.25 million patients (as of December 2011) who had been prescribed the lidocaine plaster between 1999 and end of 2011. Data include expected and unexpected ADRs.

Results

Based on clinical trials in patients suffering from PHN receiving 5% lidocaine medicated plaster, approximately 16% of patients experience an ADR.[2] All adverse reactions were predominantly of mild and moderate intensity.

On a background of 15.25 million patients exposed, adverse events were spontaneously reported that mainly consisted of skin reactions, application site reactions, or reports of drug inefficacy (for unapproved indications). The majority of AEs were nonserious in nature. Post authorization experience appears to be in line with the safety profile identified from the clinical development program.

Conclusions

The 5% lidocaine medicated plaster has been used in more than 15 million patients worldwide. The extensive post-marketing surveillance confirmed the favourable safety profile of 5% lidocaine medicated plaster in addition to published evidence on efficacy and safety from clinical trials. These findings support its first line position in the treatment of localized neuropathic pain after herpes zoster infection.

1. Ritchie et al. *Clin Drug Investig.* 2010;30(2):71-87.
2. SmPC. Versatis, version 13.0; Sep 2011.

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A review of duloxetine once-daily dosing for the management of chronic pain presented with major depression disorder

Robert Taylor[5], Joseph Pergolizzi[1,2], Srinivas Nalamachu[4], Robert Raffa[3]
[1]Johns Hopkins, Baltimore, MD, USA, [2]Georgetown University School of Medicine, Washington, DC, USA, [3]Temple University School of Pharmacy, Philadelphia, PA, USA, [4]International Clinical Research, Institute and Pain Management Institute, Overland Park, KS, USA, [5]NEMA Research Inc., Naples, FL, USA

Purpose

Chronic, inadequately treated pain and associated mood disorders are widespread throughout the United States. Failure to treat pain effectively can reduce patients overall quality of life and can be psychologically deteriorating. The association of depression with pain is very commonplace and failure to treat one or the other can prolong the duration and severity of the individual morbidities as well as contribute to additional complications. During pain management, some physicians are trying to relieve both pain and the psychiatric conditions by providing analgesics and adjuvant agents such as antidepressants or anxiolytics. However, this raises safety concerns relating to an increase potential for side-effects and drug-drug interactions. In addition, multiple drug regimens coupled with potential hospitalizations due to side effects can increase healthcare utilization and costs. Therefore, identifying one agent that could improve pain and mood outcomes would be welcomed.

Recently, the antidepressant duloxetine, which has been approved for MDD and generalized anxiety disorder (GAD), was further granted approval for treating the pain conditions of osteoarthritis, low back pain, fibromyalgia, and diabetic nerve pain. The exact mechanisms of duloxetine's antidepressant, analgesic, and anxiolytic properties are not fully known; however, it has been reported to be a selective dual neuronal serotonin (5-Hydroxytryptamine, 5-HT) and norepinephrine reuptake inhibitor. Duloxetine's dual indications may provide physicians with a single, viable treatment option for both pain and mood disorders. In light of its recent approval, we here review the evidence for the efficacy once-daily dosing of duloxetine for simultaneously improving both pain and associated mood disorders.

Method

Databases that were searched for relevant articles within the last 10 years included PUBMED, MEDLINE, EMBASE, Cochrane, and Google Scholar. The literature was searched for clinical trials, retrospective studies, and posthoc analysis studies published involving duloxetine used at the 60 mg dose. Pain conditions that were searched included diabetic peripheral neuropathy, fibromyalgia, low back pain, and osteoarthritis. Mood disorders that were searched included MDD and GAD.

Results

Studies of painful symptoms reported in mental health studies were the primary focus and were extracted from the literature. In addition, trials that focused specifically on pain outcomes or mood outcomes were also included. Articles that did not include a 60 mg/d daily dose as a study arm were excluded. Studies analyzing patients with mood disorders and pain generally documented greater improvements in patient reported outcomes for both pain and mood symptoms for duloxetine vs placebo. In addition, patients in these studies were more likely to enter remission for the underlying mood condition. Direct improvement of pain by duloxetine resulted in improved mood symptoms while improvement of mood marginally contributed to pain reduction. Overall global satisfaction as reported by patients and/or physicians was improved.

Conclusions

The studies reviewed report that duloxetine once-daily dosing can be an effective option for the management of a variety of chronic pain conditions associated with mood disorders. Since chronic pain and mood disorders are so intimately connected at the nerves and neurotransmitters, antidepressants may be a viable option to treat pain and depression simultaneously. Physicians may now be able to treat both conditions with one pharmacologic treatment. This has its advantages by reducing polypharmacy and drug-drug interactions, especially in elderly patients, in addition to potentially reducing medical costs and healthcare utilization.

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Essential oxygen oil for treatment of sport-related injuries

Robert Taylor[4], Joseph Pergolizzi[1,2], Robert Raffa[3]
[1]Department of Medicine, Johns Hopkins University, Baltimore, MD, USA, [2]Georgetown University School of Medicine, Washington, DC, USA, [3]Department of Pharmaceutical Sciences, Temple University School of Pharmacy, Philadelphia, PA, USA, [4]NEMA Research Inc., Naples, FL, USA

Purpose

Sports injuries can occur in people of all ages. Common injuries in adolescents include torn muscles, knee problems, torn ligaments, and injuries involving the spine and head. Geriatrics experience similar injuries including fractures, ligament injuries, and muscle or tendon injuries, with most related due to falls. Competitive and professional athletes are also at risk for mild to severe injuries with elite athletes often under pressure to recover quickly and return to competition. Effective pain management becomes essential for facilitating rapid and successful recovery.

Topical analgesics are an important product for localized rather than systemic pain relief. A novel product, essential oxygen oil (OxyRub™ essential oxygen oil, CreoMed, Naples, FL), has been clinically tested for use in a variety of acute and chronic pain syndromes among nonathletes. This product has been available as an over-the-counter topical analgesic in Europe for over a decade and has recently become available in the United States. This poster explores a variety of small clinical trials conducted in Europe involving the use of this topical analgesic in different populations of top athletes.

Method

Data from several small unpublished studies conducted in Europe was compiled and analyzed. The main criterion for study inclusion was subjects evaluated must have been athletes.

Results

Studies varied in design, patient populations, and endpoints. Some of the athletes examined included, rugby players, weightlifters, skiers, swimmers, soccer players, kick boxers etc. Patient Reported Outcomes varied in each study, but generally consisted of improvement of pain, improvement in recovery, enhancement of performance, improvement in hematomas and safety. Overall, essential oxygen oil was accepted by many of the athletes and it was indicated that many of the athletes were able to resume their sports activities more rapidly after injury. In addition, essential oxygen oil had a good safety profile, with mild skin irritation or erythema being the common side effects.

Conclusions

Essential oxygen oil is a topical analgesic product which appears to enhance recovery, relieve pain, and promote the diffusion and resolution of hematoma in several small studies and case reports of elite athletes. Essential oxygen oil is a topical analgesic which can be used in a wide range of acute and chronic pain syndromes and works well in the setting of post-performance massage therapy of competitive and professional athletes. The product worked well and was safe for a variety of athletes, from skiers to dancers to boxers, suggesting that it has a role in sports medicine.

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Corticotropin (ACTH) and cortisol serum concentrations help predict high dose opioid requirements

Forest Tennant
Veract Intractable Pain Clinic, West Covina, CA, USA

Purpose

To determine if abnormal, too high or too low, serum ACTH and cortisol concentrations help predict which intractable pain patients will require high opioid dosages. Severe pain may cause stimulation and even depletion of the hypothalamic-pituitary-adrenal axis (HPA) which can be assessed by determination of ACTH and cortisol serum concentrations.[1] If pain is severe and chronic enough to require high dosages of opioids for control, it should be reflected in abnormal ACTH and/or cortisol levels.

Method

Twenty-two (22) intractable pain patients were referred from their primary physicians in 2012 for pain treatment because they did not receive relief with standard opioid dosages which are defined here as less than 80 mg equivalence of morphine a day. Blood samples were taken at 8:00 am for determination of serum ACTH and cortisol concentrations. Opioid dosages were titrated upward over a 6-week period until the patient reported satisfactory pain relief and no impairment of activities of daily living such as dressing, ambulation, and socialization.

Results

Fifteen (15) of 22 (68.2%) patients had abnormal ACTH (6 high, 4 low), and/or cortisol (7 high, 3 low) serum concentrations. All these patients required a daily morphine equivalence dosage of over 150 mg. Only 1of 7 (14.3%) patients with normal serum ACTH and cortisol concentrations required this high a daily opioid dosage.

Conclusions

Serum concentrations of ACTH or cortisol that were abnormally high or low in this study required higher dosages of opioids to control pain. A serum level of ACTH and cortisol should be determined to identify intractable pain patients who will likely require high opioid dosages for control.

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Cytochrome P450 defects in high dose opioid patients

Forest Tennant
Veract Intractable Pain Clinic, West Covina, CA, USA

Purpose

To determine if cytochrome P450 defects are likely responsible for high dose opioid requirements in severe pain cases. The cytochrome P450 enzyme system is critical for the safe and effective metabolism of opioids.[1] Testing for CYP450 defects has recently become commercially available so that pain patients on high dose opioids can now be conveniently tested.

Method

Sixty-six (66) intractable pain patients who attended an outpatient clinic in May 2012 and who required over 150 mg equivalence of morphine a day for pain relief were genetically tested for these 3 enzymes: CYP2D6, CYP2C9, and CYP2C19. Samples were collected by buccal swab and analyzed at a commercial laboratory.

Results

Of the 66 patients, 55 (83.3%) had one or more CYP450 defects. No more than 20% to 30% of the general population has CYP450 defects. Twenty-one (21) of 66 (31.8%) had 2 defects and 6 (9.1%) had 3 defects.

Conclusions

This study suggests that CYP450 defects are responsible, in great part, for high dose opioid requirements. Now that CYP450 enzyme testing is commercially available, it is recommended that pain patients who require over 150 mg of morphine equivalence a day be tested to help establish the medical necessity for a high opioid dosage. Pain patients should not be given pejorative labels such as "drug seekers" prior to CYP450 enzyme testing.

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The life experiences of individuals with chronic pain on long term opioid therapy

Kathy Thornton[1], Melissa Garno[1], Jackson Rainer[1], Stephen Warner[1], Jim Routon[2], Cameron Durdenn[1]
[1]*Georgia Southern University, Statesboro, GA, USA,* [2]*East Georgia Regional Medical Center Pain Clinic, Statesboro, GA, USA*

Purpose

Although long term opioid therapy has been shown to have efficacy in treating chronic pain, it has also been implicated to have suppressive hormonal and immune effects and the potential for hyperalgesia. Few long term analgesic studies have measured nonanalgesia outcomes, and findings are conflicting. Due to a risk of impaired psychosocial or physical function and the lack of associated research, the purpose of our project was to explore the personal daily life experience of individuals with chronic pain who have been on long term opioid therapy.

Method

Participants were recruited from a local rural pain clinic. Inclusion criteria were individuals who experienced chronic pain, were taking opioid drugs for pain management for over 6 months and had no major comorbidities. Participants were majority male (55%), average age 50 years (range 33-65) and predominantly Caucasian (84%). A mixed methods design was used including in-depth phenomenological interviews, a demographic/pain survey questionnaire and the SF-32 questionnaire that measures health. We report results of the qualitative data here. The interviews were conducted to determine the personal life experience of being on long term opioid therapy for individuals with chronic pain. Interviews were audio taped and transcribed verbatim. Transcriptions were analyzed using the Colaizzi method. Transcriptions were coded to formulate meaning categories and then organized into clusters of themes to describe the phenomenon. Five university faculty in Nursing and Psychology collaborated to collect and analyze the data.

Results

The major structure that emerged from the clustered themes was a continuum of chaos/discord to hanging on and persevering. The themes and sub-categories included the following.

1. Experiencing pain: Bearing pain; Coping with some relief; Minimizing impact; Accepting pain as part of life; Accepting what is real.
2. Living with effects: Memory loss; Impaired concentration; Fatigue; Not able to sleep; Depression; Worsening pain; Risk of overdose.
3. Searching for relief: Why am I taking; What can I do; Effectiveness of other therapies.
4. Ego integrity: Frustration; Normality; Self Support; Faith in self.
5. Difficult rules: Taking as prescribed; Drug screens; Managing bottles.
6. Bias & stigma: Judged as addicted; Rejected; Discrimination; No understanding.
7. Control: Respect-Caution; Breakthrough pain; Choices; Distraction; Sleep; Routines;
8. Loss: Minimizing impact on daily life; Productivity; Social isolation.
9. Fears: No relief; Invasive treatments; Loss of function; Death; Disability; Uncertainty.
10. Impact of support: Family; Health care providers.

Participants lived with daily chaos due to: Lack of complete relief of pain and living with constant pain; Nonanalgesic effects of opioids; Lack of psychosocial support; Difficult rules to follow to receive the opioids; Being judged by family, friends and healthcare workers; Loss of productivity and social interactions; and Fears of not getting any relief of pain, losing control, loss of function, disability and death. Participants expressed that they attempted to persevere and

hang-on each day through: Developing a sense of self-support and faith in self; Redefining a new "normal;" Relying on supportive family when it was offered; Accepting what is "real" and pain as part of life; Daily planning to minimize impact on life; Seeking adjunctive therapies and using distraction techniques; Understanding why I am taking the drugs; Making choices; and Living with "some relief."

Conclusions

We discovered that participants experienced a level of chaos and altered functioning related to opioid therapy but were attempting to hang on to get through each day. Participants indicated that without opioids, they did not know how they could go on living with the pain. Health care providers need to consider the life experiences of these individuals and attempt to provide support and understanding, to become aware of their own potential bias, maintain a nonjudgmental approach in treating these patients, and consider that the use of opioid therapy for chronic pain is essential for these patients.

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TD-1211 demonstrates improvement in bowel movement frequency without impacting analgesia in a Phase 2b study of patients with opioid-induced constipation

Ross Vickery[1], Yu-Ping Li[1], Ullrich Schwertschlag[1], Neil Singla[2], Lynn Webster[3], Dan Canafax[1]
[1]*Theravance, Inc, South San Francisco, CA, USA,* [2]*Lotus Clinical Research, Inc, Pasadena, CA, USA,* [3]*Lifetree Clinical Research, Inc, Salt Lake City, UT, USA*

Purpose

Opioid-induced constipation (OIC) is a common and debilitating consequence of long-term opioid use. TD-1211 is an investigational, orally-administered, peripherally selective, multivalent inhibitor of the mu-opioid receptor designed with the goal of alleviating gastrointestinal side effects of opioid therapy without affecting analgesia. This study evaluated the safety, tolerability, and efficacy of 3 doses of TD-1211 compared to placebo.

Method

A 5-week, randomized, multicenter, double-blind, parallel-group study was conducted in chronic noncancer pain patients with OIC, defined as ≤5 spontaneous bowel movements (SBMs) per week over a 2-week baseline. For the first 4 days of dosing, patients randomized to TD-1211 received 5mg and on Day 5, remained at 5 mg or were dose-escalated to 10 mg or 15 mg for the remainder of the treatment period. Patients randomized to placebo received placebo for all 5 weeks. Throughout the study, patients were required to stop laxatives and bowel movement (BM) regimens, except protocol-permitted rescue bisacodyl use. Daily electronic diaries collected frequency, timing, and symptoms of BMs; use of laxatives and opioids; daily pain scores; and satisfaction/quality of life metrics. The primary efficacy endpoint was the change from baseline in weekly average complete spontaneous bowel movements (CSBMs) over weeks 2-5 of treatment. A key secondary endpoint was the change from baseline in weekly average SBMs over the same period.

Results

217 patients were randomized. The baseline daily opioid doses ranged from 30-1740 (mean=145) oral morphine equivalent units. All 3 doses of TD-1211 met the primary efficacy endpoint. The increase from baseline for placebo-treated patients was 0.8 CSBMs/week vs 2.5 for the TD-1211 15 mg treatment group (*P*=.0003), 2.6 for the 10 mg group (*P*=.0010), and 1.5 for the 5 mg group (*P*=.0413). The 15 mg and 10 mg groups were statistically significant for the key secondary endpoint. The increase from baseline for placebo-treated patients was 1.9 SBMs/week vs 3.7 for the TD-1211 15 mg treatment group (*P*=.0003), 3.4 for the 10 mg group (*P*=.0038), and 2.7 for the 5 mg group (*P*=.0739). In a pre-specified responder analysis, defined as ≥3 SBMs/week and an increase of ≥1 SBM/week from baseline for ≥3 weeks over weeks 2-5 of treatment, TD-1211 response was statistically significant vs placebo: 59% (*P*=.0401), 61% (*P*=.0222), and 70% (*P*=.0016) for the 5 mg, 10 mg, and 15 mg groups, respectively, compared to 39% for placebo. For another secondary endpoint, a 7-point global impression of change scale at end of therapy, 66% of patients receiving 15mg TD-1211 reported that their constipation was "better" or "much better," which was significantly higher than the 21% of patients receiving placebo (*P*<.0001). Results from patients on 5 mg and 10 mg also were statistically significant vs placebo. The most common adverse events reported for TD-1211 were abdominal pain (13% for TD-1211 vs 11% for placebo), nausea (9% vs 4%), diarrhea (9% vs 0%), and headache (5% vs 6%). The majority of GI-related adverse events were associated with treatment initiation, resolved within a few days, and were mild to moderate. Four patients experienced serious adverse events, none of which were treatment-related. There was no evidence of CNS opioid withdrawal or analgesic interference based on the Clinician Opioid Withdrawal Score, daily opioid use, or daily pain scores.

Conclusions

TD-1211 increased CSBM and SBM frequency and SBMs/week responder rates in chronic noncancer pain patients with OIC over 5 weeks of therapy and improved global impression of change at end of therapy. TD-1211 did not impact analgesia and was generally well tolerated. The data from this Phase 2b study support progression of TD-1211 into Phase 3 development for treatment of OIC.

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Undertreatment of pain among older adults: data from a national health survey

Lien Vo[1], Kate Lapane[2], Kathy Annunziata[3]
[1]*Janssen Scientific Affairs, Raritan, New Jersey, USA,* [2]*University of Massachusetts Medical School, Worcester, MA, USA,* [3]*Kantar Health, New York, NY, USA*

Purpose

Undertreated pain is an important public health problem. Inadequate pain treatment in the older adult population may stem from a reluctance of patients, caregivers, and clinicians to use analgesics owing to concerns about adverse side effects such as constipation, nausea/vomiting, sedation, and dizziness/falls, or fear of addiction. The purpose of this study was to describe pain management among older adults and to evaluate the extent to which potentially inadequate pain management is associated with indices of quality of life.

Method

Data from the 2011 US National Health and Wellness Survey, a syndicated, internet-based, cross-sectional study of the healthcare attitudes, behaviors, and characteristics of the adult population were used. Participants were recruited through an existing Web-based consumer panel and completed a self-administered, internet-based questionnaire. Participants reported medications used for pain. For each prescription medication, participants indicated type of pain for which medication was used, duration of use, days used in past month, and satisfaction with medication. Participants were stratified by age (<65 years, younger vs ≥65 years, older. Analyses were appropriately weighted for the complex survey designed.

Results

We identified 16,500 participants ≥65 years of age and 58,500 participants <65 years of age. Overall, 36% of adults ≥65 years of age and 32% of adults <65 years of age reported pain in the past 12 months. The most commonly reported sources of pain were: arthritis pain (older 58%; younger 28%), back problems (older 52%; younger 53%), joint pain (older 49%; younger 39%), shoulder pain/stiffness (older 29%; younger 29%), headache (older 18%; younger 39%) and neck pain (older 22%; younger 27%). Pain severity was similar by age group, but frequency was greater in older adults. Pain severity in the past week was moderate for 34% and severe for 35% for older adults and 33% moderate and 33% severe for younger adults. Daily pain was reported in 60% of older adults and 42% of younger adults. Fifty-six percent of older adults in pain received no prescription pain medication. Among older adults in pain receiving no prescription pain medication, 51% experienced daily pain and 23% noted severe pain in the past week. Among older adults receiving pain medications, 57% received short acting opioids, 32% received NSAIDS, 8% muscle relaxants, 3% received long acting opioids and 3% serotonin norepinephrine inhibitors. Among older adults, 57% reported that pain interfered at least moderately with daily living in the past 4 weeks whereas only 45% of younger adults reported at least moderate interference.

Conclusions

Pain is common among older adults, is often moderate to severe, and for the majority, occurs daily. Despite this profile, pain management appears to be suboptimal as pain is reported to moderately interfere with the lives of older adults. Understanding factors that contribute to suboptimal implementation of evidence-based guidelines for pain management in older adults is needed.

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Costs of care for back and neck pain in a predominantly rural insured employee population

William H. Rogers[1], Aarti Patel[2], Lien Vo[2], Carmela Benson[2], Victor G. Villagra[3], Debra Lerner[1]
[1]Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, MA, USA, [2]Janssen Scientific Affairs, LLC, Raritan, NJ, USA, [3]National Rural Electric Cooperative Association, Arlington, VA, USA

Purpose

Musculoskeletal pain, particularly back and neck pain, is a major burden for employers as well as the employees themselves, their families, and the nation. Using data from employees of predominantly rural electrical cooperatives, this study determined the economic burden of pain measuring both the frequency of among episodes of back and neck pain, with or without neuropathic features, and their associated medical and pharmacy claims costs.

Method

An employee benefits trust provided HIPAA-compliant, de-identified medical and pharmacy claims data covering January 2007 to September 2011. According to zip code, 48% of employees resided in rural areas vs 21% nationally. Using the relevant back and neck pain diagnosis codes, claims were organized into episodes and classified as: back and/or neck pain with neurologic or radiating pain (b/n neuro); or back and/or neck pain with no neurologic or radiating pain (b/n). A new treatment episode began the date on which a person had one or more qualifying pain-related claim (the "index claim") before and after ≥6 months without a qualifying pain claim. For comparison purposes, a group of random index claims was sampled (one per employee). Analyses excluded claims for cancer diagnoses. Claims costs (allowed amounts adjusted for inflation) for each group were aggregated for the 1 year interval starting with index claim. To assess the relative magnitude of back and/or neck pain costs, the costs expected for similar employees without back and/or neck pain were modeled and compared to actual incurred claims costs. The modeling procedure used the RAND Health Insurance Experiment methodology, which accounts for the cost of large, low probability claims. For each claim type (b/n neuro, b/n, and random) we estimated the medical and pharmacy costs based on 2 different models: (a) age and gender alone, and (b) age/gender, prior claims costs, and AHRQ CCS comorbidities from the year preceding the index date.

Results

Among 51,125 employees, with an average of 3.35 years of claims eligibility, the average annual medical expenditure was $6,882 and the average annual pharmacy expenditure was $1,248. Among claimants, 4920 b/n neuro new treatment episodes occurred among 4032 employees (mean age 46.7; 69% male; incidence rate 1.6%/yr) and 12,318 b/n episodes occurred among 9051 employees (mean age 45.9; 70% male; incidence rate 5.8%/yr). The random treatment episode group included 37,171 treatment dates for the same number of employees (mean age 45.9; 73% male). In the year following the index claim, average medical claims costs were $17,538 for b/n neuro, $15,042 for b/n and $9,522 for the random treatment claims. Average pharmacy costs were, respectively, $1,792 for b/n neuro, $1,904 for b/n and $1,586 for the random treatment episode group. For models based on age/gender alone, the estimated medical costs were $7,908 for b/n neuro, $7,677 for the b/n and $7,985 for the random treatment episode group. Estimated pharmaceutical costs were, respectively, $1,452 for the b/n neuro, $1,396 for b/n and $1,405 for the random group. Based on the more comprehensive models, the estimated medical claims costs were $9,828 for the b/n neuro, $9,567 for the b/n, and $8,112 for the random group. Estimated pharmaceutical costs were $1,662 for b/n neuro, $1,786 for the b/n, and $1,510 for the random group.

Conclusions

Compared to the costs of care for employees without back and/or neck pain-related diagnoses, the first-year medical claims costs associated with neuropathic back and neck pain or non-neuropathic back pain were much higher. Their claims costs also exceeded estimated costs based on demographic and/or comorbidity characteristics. First-year pharmacy costs were only modestly higher than predicted. This study affirms that, in a rural population, care for pain-related conditions, especially with neuropathic involvement, imposes a relatively large economic burden.

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Effects of tapentadol on levels of sexual hormones associated with opioid-induced androgen deficiency

Joseph Pergolizzi[1], Karin Goehler[2], Ilona Steigerwald[3], Mila Etropolski[4], Myoung Kim[5], Gary Vorsanger[5]
[1]Naples Anesthesia and Pain Associates, Naples, Florida, USA, [2]Global Clinical Pharmacology, Grünenthal GmbH, Aachen, Germany, [3]Medical Affairs Europe & Australia, Grünenthal GmbH, Aachen, Germany, [4]Janssen Research & Development, L.L.C., Raritan, New Jersey, USA, [5]Janssen Scientific Affairs, LLC, Raritan, New Jersey, USA

Purpose

It has been known for decades that heroin abuse is associated with low levels of serum testosterone. More recently, this association has been defined as opioid-induced androgen deficiency (OPIAD), which results from suppression of adrenal, pituitary, hypothalamic, and gonadal (eg, luteinizing hormone [LH], testosterone) hormone production. OPIAD affects roughly 5 million men in the United States who are taking μ-opioid analgesics for the management of chronic noncancer pain. Symptoms of OPIAD include reduced libido, erectile dysfunction, fatigue, hot flashes, depression, anemia, decreased muscle mass, weight gain, and osteoporosis. Despite its prevalence, OPIAD is often unrecognized or untreated, possibly because some of its symptoms (eg, depression, reduced libido) are also associated with the underlying pain conditions. Tapentadol is a centrally acting analgesic with 2 mechanisms of action, μ-opioid receptor agonism and norepinephrine reuptake inhibition. Because tapentadol has an 18-fold lower affinity for the μ-opioid receptor in humans than morphine, treatment with tapentadol may be associated with less OPIAD than that observed with other μ-opioid analgesics. The effects of tapentadol immediate release (IR) and tapentadol extended release (ER) on gonadotropin (LH and/or follicle-stimulating hormone [FSH]) and testosterone levels were evaluated as secondary objectives in 3 randomized, double-blind, placebo and/or active-controlled studies in healthy subjects or patients with moderate to severe, chronic osteoarthritis knee pain.

Method

The first study in healthy subjects was a 4-way crossover, single-administration study in which adult males were randomized to receive a single dose of placebo, tapentadol IR (50 mg or 100 mg), or morphine IR 30 mg in each of four 2-day periods. The second study in healthy subjects was a 4-period dose-escalation study in which adult male and female subjects received placebo during one 3-day treatment period and a different escalating dose of tapentadol IR during each of the other three 3-day treatment periods (doses ranged from 75 to 250 mg every 6 hours). The third study (NCT00745069) was a parallel-group, forced-titration study in which adult male and female patients with moderate to severe, chronic osteoarthritis knee pain received placebo, 1 of 2 titration regimens of tapentadol ER (25-50-100 mg or 100-150-200 mg), or oxycodone controlled release (CR; 10-10-20 mg) twice daily during a 14-day titration period, followed by a 14-day fixed-dose maintenance period. Levels of testosterone and LH were evaluated in males in the studies in healthy subjects, and levels of testosterone, LH, and FSH were evaluated for all patients in the study in patients with osteoarthritis knee pain.

Results

In the crossover study in healthy subjects, median serum testosterone levels at 6 hours after dosing were comparable for placebo (2.79 ng/mL) and tapentadol IR (50 mg, 2.84 ng/mL; 100 mg, 3.11 ng/mL), but were lower in subjects randomized to receive morphine 30 mg (1.62 ng/mL). At 6 hours after dosing, median serum LH levels were also similar for subjects who received placebo (3.9 mIU/mL) and tapentadol IR treatment (50 mg, 3.6 mIU/mL; 100 mg, 3.7 mIU/mL), but were lower for those who received morphine 30 mg (1.7 mIU/mL). In the dose-escalation study in healthy subjects, mean testosterone levels increased slightly from baseline to 24 hours with placebo (mean [standard error (SE)] change, 0.86 [0.470] nmol/L) and decreased with tapentadol IR in a dose-related trend (decreases ranged from -0.22 [1.684] nmol/L for the 75-mg dose to -7.37 [2.739] nmol/L for the 150-mg dose). In that study, mean

changes from baseline to 24 hours in LH levels were comparable for placebo and all doses of tapentadol IR. In the study in patients with osteoarthritis knee pain, no clinically important changes were observed in testosterone, LH, or FSH serum concentrations during the double-blind treatment period. In the placebo, tapentadol ER 100-mg, tapentadol ER 200-mg, and oxycodone CR 20-mg groups, respectively, mean (SE) changes in testosterone concentration from baseline to endpoint were -0.1 (0.58) nmol/L, -1.3 (0.46) nmol/L, -1.3 (0.59) nmol/L, and -1.1 (0.47) nmol/L; mean (SE) changes in LH concentration were 0.6 (1.04) U/L, 1 (1.95) U/L, -2.4 (2.12) U/L, and -3.1 (1.40) U/L; and mean (SE) changes in FSH concentration were -1.4 (3.02) U/L, 0.5 (1.86) U/L, 2.3 (2.35) U/L, and 0.5 (1.73) U/L.

Conclusions

Results of these studies indicate that tapentadol treatment had small effects on LH and testosterone levels that were not considered to be of clinical relevance. The minimal effects of tapentadol on sexual hormone levels relative to morphine may be related to tapentadol's 2 mechanisms of action (μ-opioid receptor agonism and norepinephrine reuptake inhibition). While further study is warranted, given what is known about androgen deficiency and opioid use, these results suggest that tapentadol may provide a better analgesic option than other μ-opioid agonists for patients taking long-term opioid therapy.

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Using PhotoVOICE to chronicle the daily experiences of primary care patients living with chronic pain

Lorraine Wallace[1], Randy Wexler[1], W. Fred Miser[1], Leon McDougle[1], J. David Haddox[2]
[1]*The Ohio State University, Columbus, OH, USA,* [2]*Purdue Pharma, L.P., Stamford, CT, USA*

Purpose

The photoVOICE methodology, developed by Wang and colleagues, was first used to explore the perspectives of village women living in Yunnan, China. Through photography individuals are able to act as recorders of real-life experiences. PhotoVOICE turns the camera lens toward the eyes and experiences of people that may not otherwise be heard. By enlisting individuals to take photographs, the researcher is provided with a new lens in which to view patients' everyday health experiences. While psychometrically sound pain assessment tools are available (eg, McGill Pain Questionnaire), there is a paucity of research that comprehensively defines chronic pain from the perspective of patients. To our knowledge, the photoVOICE methodology has been used in just one small, pilot study to explore the chronic pain experience of older adults receiving care at a university-based multidisciplinary pain center. The purpose of this study was to examine the utility of photoVOICE as a unique and innovative method in exploring the daily experiences of primary care patients living with chronic pain.

Method

The electronic medical record at The Ohio State University Wexner Medical Center (OSUWMC) was queried to identify a random sample of English-speaking patients meeting all of these criteria: (1) seen within the past 6 months at a clinic within the OSUWMC primary care ne2rk, (2) aged 30-65 years, and (3) receiving an opioid medication for long-term, noncancer pain management. Using a computer-generated sequence, patients were randomly selected and recruited to participate in this study. Patients agreeing to participate were scheduled for a one-on-one baseline interview with a trained research assistant (RA). During the baseline interview, the RA provided the patient with an overview of study procedures and administered a battery of sociodemographic questionnaires. Each patient received a single-use digital camera to take photographs. Next, over a 7-10 day period, each patient took photographs that best reflected (1) his/her experiences with chronic pain and (2) what he/she would like his/her life to be without chronic pain. Patients received a postage-paid, insured envelope to return the camera to the research team. Once a patient's photographs were developed and printed, he/she participated in a one-on-one follow-up interview with a RA. Patients were asked to look through his/her respective photographs and select 4-6 that best represented his/her experiences with chronic pain. For each of the selected photographs, the patient (1) provided a title, (2) composed a brief narrative describing how the photograph depicted his/her experience with chronic pain, and (3) discussed why he/she shared this photograph. The RA recorded all responses verbatim.

Results

Twenty-seven (n=27) patients (women [n=21]; men [n=6]) submitted photographs and completed both one-on-one interviews. Patients averaged 53.3±6.5 years of age (range=33-73 years) with most reporting their general health to be either fair or poor (n=21; 77.8%). Slightly more than half of patients were African-American (n=15; 55.6%), while the remainder were Caucasian (n=12; 44.4%). Most patients were insured through either Medicaid or Medicare (n=21; 77.8%). Thirteen (48.1%) patients were high school graduates, 10 (37%) had completed some college, while 4 (14.8%) were college graduates. Patients submitted an average of 20.2±3.1 photographs (range=8-27). Analysis of the data illuminated 5 dominant themes: (1) daily need for multiple medications, including opioids; (2) difficulties climbing a flight of stairs; (3) struggling to get out of bed in the morning; (4) extreme challenges with participating in day-to-day life activities; and (5) experiencing feelings of hopelessness and helplessness on a regular basis.

Conclusions

Patients in this study were able to record photographs to help tell their chronic disease narrative. Common themes included difficulty in day-to-day activities, the need for multiple medications including opioids, and feelings of despair. The photoVOICE methodology enabled patients to capture meaningful images to depict their daily experiences of living with chronic pain. Given differing communication preferences among patients, the photoVOICE method may enable some people to more effectively relate their chronic suffering to healthcare professionals caring for them.

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Fentanyl buccal tablet compared with immediate-release oxycodone for the management of breakthrough pain in opioid-tolerant patients with chronic pain

Mark Wallace[1], Lynn Webster[2], Arvind Narayana[3], Lindsay Janka[3]
[1]*UC San Diego Thornton Hospital, San Diego, CA, USA,* [2]*Lifetree Clinical Research and Pain Clinic, Salt Lake City, UT, USA,* [3]*Teva Pharmaceuticals, Frazer, PA, USA*

Purpose

In a pooled analysis of 2 head-to-head studies of patients with chronic pain being treated for breakthrough pain (BTP [N=536]), fentanyl buccal tablet was associated with a more rapid onset of analgesia vs immediate-release oxycodone (OxyIR), with significantly greater pain intensity (PI) differences (PIDs) observed as early as 5 minutes and significant differences in pain relief (PR) observed as early as 10 minutes. This subanalysis focuses on the efficacy and safety of fentanyl buccal tablet in patients with back pain as the primary chronic pain condition (62%).

Method

Opioid-tolerant adults with a ≥3-month history of chronic pain experiencing 1 to 4 BTP episodes per day were eligible. Each study consisted of 2 randomized, open-label, dose titration periods and 2 randomized, double-blind, double-dummy treatment periods. After titrating fentanyl buccal tablet and OxyIR to a successful dose (the single dose providing adequate analgesia without unacceptable adverse events [AEs]), patients treated 10 BTP episodes with 1 study drug and 10 with the other. During the double-blind periods, patients rated PI on an 11-point scale (0=no pain; 10=worst pain imaginable) predose and 5 to 60 minutes postdose. The primary measure was mean PID at 15 minutes postdose. Secondary measures included PID 5, 10, 30, 45, and 60 minutes postdose; PR, rated on a 5-point scale (0=none; 4=complete PR), 5 to 60 minutes postdose; time to meaningful PR; and proportion of episodes with ≥33% or ≥50% reduction in PI at 5 to 60 minutes postdose. A medication preference questionnaire was administered after the completion of the second double-blind period.

Results

A total of 331 patients with back pain (mean age 50.5 years, 43% male, 94% white) were enrolled and 196 entered the double-blind periods, received treatment, and were evaluable for efficacy. The PID per episode was significantly greater after fentanyl buccal tablet than after OxyIR at 15 minutes (0.90 vs 0.74; $P<.0001$), with significant ($P<.01$) differences observed as early as 10 minutes (0.36 vs 0.30) through 45 minutes. PR was significantly ($P<.01$) greater after fentanyl buccal tablet than after OxyIR at 15 minutes (0.71 vs 0.59) and at 30 and 45 minutes. Time to meaningful PR was more rapid with fentanyl buccal tablet than with OxyIR, with significant differences observed at ≤30 minutes ($P<.01$). The proportion of episodes with ≥33% improvement in PI was greater with fentanyl buccal tablet than with OxyIR, with significantly greater reductions observed at 30 minutes ($P<.01$), as was the proportion of episodes with ≥50% improvement in PI, with significantly greater reductions observed at 5, 10, 30, and 45 minutes ($P<.05$). On the medication preference questionnaire, 48% preferred fentanyl buccal tablet, 38% preferred OxyIR, and 14% had no preference. Overall, 168 of 327 (51%) patients reported ≥1 AEs (fentanyl buccal tablet, 36%; OxyIR, 36%) and 34 of 327 (10%) patients discontinued from the studies because of ≥1 AEs. Rates of AEs and discontinuation because of AEs were similar between treatments. One treatment-related serious AE of unresponsiveness was reported after a patient consumed 2 doses of fentanyl buccal tablet 800 µg and alcohol. The patient recovered but was discontinued from the study.

Conclusions

In this pooled analysis of patients with back pain, treatment with fentanyl buccal tablet for BTP was associated with a more rapid onset of analgesia compared with OxyIR, with statistically significant PIDs as early as 10 minutes post-treatment. The incidence of AEs reported with each treatment was similar, and fentanyl buccal tablet was well tolerated.

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Fentanyl buccal tablets for the relief of breakthrough pain in opioid-tolerant patients with chronic noncancer-related pain: a subanalysis of a 12-week, randomized, double-blind, placebo-controlled study in patients with back pain

Lynn Webster[1], Mark Wallace[2], Arvind Narayana[3], Lindsay Janka[3]
[1]*Lifetree Clinical Research and Pain Clinic, Salt Lake City, UT, USA,* [2]*UC San Diego Thornton Hospital, San Diego, CA, USA,* [3]*Teva Pharmaceuticals, Frazer, PA, USA*

Purpose

A randomized, double-blind, placebo-controlled study in patients with noncancer-related chronic pain (N=148) showed the effectiveness of fentanyl buccal tablet vs placebo for treatment of breakthrough pain (BTP) across a range of efficacy measures over 12 weeks, with statistically significant differences in pain relief (PR) observed as early as 5 minutes. This subanalysis focuses on the efficacy and safety of fentanyl buccal tablet in patients with back pain as the primary chronic pain condition (47%).

Method

Opioid-tolerant adults with a ≥3-month history of chronic pain and 1 to 4 BTP episodes per day were eligible. After titrating to a successful fentanyl buccal tablet dose (the single dose providing adequate analgesia without unacceptable adverse events [AEs]), patients received open-label fentanyl buccal tablet at the successful dose for 4 weeks followed by double-blind, randomized treatment for 9 BTP episodes (6 fentanyl buccal tablet, 3 placebo). The open-label/double-blind sequence was repeated twice. Patients rated pain intensity (PI; 0-10 scale) predose and 5 to 120 minutes postdose during double-blind treatment. The sum of PI differences (PIDs) 5 to 60 minutes postdose ($SPID_{60}$) after week 12 was the primary measure. Secondary measures were PR (0-4 scale, 5-120 minutes), time to any PR, time to patient-assessed meaningful PR, and percentage of episodes with ≥33% and ≥50% improvement in PI (5-120 minutes).

Results

In total, 70 patients with back pain were titrated (mean age 52.6 years, 43% male, 93% white), 50 (71%) achieved a successful dose, and 38 (54%) completed the study. In the final double-blind period, results favored fentanyl buccal tablet vs placebo for $SPID_{60}$ per episode (least-squares mean [SEM], 7.21 [0.93] vs 5.05 [1.07]; P=.006); PID per episode with fentanyl buccal tablet was significantly greater than with placebo (P<.05) at all time points assessed from 30 to 120 minutes in all 3 double-blind periods. PR was significantly (P<.05) greater after fentanyl buccal tablet than after placebo beginning at 15 through 120 minutes in the first 2 double-blind periods and at 45 through 120 minutes in the final double-blind period. Time to any PR was more rapid with fentanyl buccal tablet than with placebo, with significant (P<.01) differences observed at ≤15 minutes in the first 2 double-blind periods and at ≤30 minutes in the final double-blind period, as was time to meaningful PR, with significant (P<.05) differences observed at ≤30 minutes in the first double-blind period, at ≤15 minutes in the second double-blind period, and at ≤45 minutes in the final double-blind period. The proportion of episodes with ≥33% improvement in PI was significantly greater with fentanyl buccal tablet than with placebo at 30 minutes in all double-blind periods (34%-38% vs 18%-26%; P<.05). The proportion of episodes with ≥50% improvement in PI was significantly (P<.05) greater beginning at 30 minutes in the first double-blind period (20% vs 10%) and at 45 minutes in the second and third periods (30%-33% vs 19%-21%). The most common AEs were nausea (14%), dizziness (13%), and somnolence (10%). Three serious treatment-related AEs were reported in 2 patients receiving fentanyl buccal tablet (drug dependence, accidental multiple drug overdose, and pneumonia); all 3 resolved with no residual effects.

Conclusions

In patients with chronic back pain experiencing BTP, fentanyl buccal tablet was associated with a more rapid onset of analgesia vs placebo after 12 weeks of treatment. Fentanyl buccal tablet was generally well tolerated, and the safety profile was consistent with the profile observed in previous studies.

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Abuse liability of oral formulations of hydromorphone in opioid-experienced, recreational drug users: importance of onset of effect

Lynn Webster, Michael Smith, Matt Iverson
Lifetree Clinical Research and Pain Clinic, Salt Lake City, UT, USA

Purpose

Rate of onset is an important determinant of the abuse liability of opioid formulations. The purpose of this study was to compare the abuse-related effects of various formulations of hydromorphone, with particular emphasis on early time intervals after drug administration. Included in the study was hydromorphone ER, a once-daily opioid formulation that releases hydromorphone at a controlled rate.

Method

This was a double-blind, placebo-controlled, randomized study in subjects (N=28) with a history of recreational opioid use. In phase A, subjects received immediate-release (IR) hydromorphone 8 mg, intact hydromorphone ER 16 and 32 mg, a milled preparation of hydromorphone ER 8 mg, and placebo in a crossover design. In phase B, subjects who tolerated all treatments in Phase A received single doses of IR hydromorphone (8 mg) and hydromorphone ER (64 mg). Time to maximum effect (TE_{max}) and area under the effect curve at 2 hours (AUE_{0-2}) were assessed for subject-rated outcomes of "high", "drug liking", and "euphoria".

Results

All formulations produced effects significantly different than placebo ($P<.05$). For all subject-rated outcomes, the TE_{max} for all intact doses of hydromorphone ER (range: 7.8-13.3 hours) was greater than the TE_{max} for 8 mg IR hydromorphone (range: 2.4-3.5 hours) ($P<.05$). For AUE_{0-2}, all intact doses of hydromorphone ER produced significantly lower levels of "high" and "euphoria" compared with 8 mg hydromorphone IR ($P<.05$). The effects of milled hydromorphone ER were similar to those of IR hydromorphone.

Conclusions

The slower onset of effect and decreased reports of "high" and "euphoria" suggest that this formulation of hydromorphone ER may have less abuse liability than IR hydromorphone when intact tablets are taken whole.

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Bridging from conventional marketed extended release formulations to new tamper resistant alternatives

H. J. Stahlberg, M. Brett, E. Galia, J. Ossig, B. Wenge
Grünenthal GmbH, Aachen, Germany

Purpose

Tamper resistant formulations (TRF) may enhance patient safety by eg maintaining the intended release properties of oral dosage forms and preventing misuse eg by crushing. TRF may also raise the hurdle for intentional abuse by different tampering methods. Grünenthal (GRT) has developed a TRF technology with increased tablet hardness using a high molecular weight polymer. A switch from a conventional extended release (ER) formulation to these safer drug product alternatives requires bridging studies. Currently, clear guidance is not available. The aim was to provide an acceptable program of bioequivalence trials.

Method

Following scientific advice the bioequivalence of 6 dose strengths of the GRT-TRF against reference marketed ER formulations of an analgesic product was investigated in a study program with healthy subjects in 8 randomized, 2-way cross-over trials. Oral doses were administered as fasted and fed single doses as well as under multiple dose conditions. Serum drug concentrations were determined by a validated LC-MS/MS method. Non-compartmental PK analysis was performed and the usual 80%-125% confidence interval acceptance criteria for bioequivalence were applied for the key pharmacokinetic parameters.

Results

The results reflect the minimum and maximum values observed for the whole set of 6 single (fasted and fed) and 2 multiple dose bridging trials. The 90% confidence intervals [%] for PK parameter Cmax or Cmin/max,ss and AUC0-t or AUC,ss were 91%-119% and 92%-109%, respectively. Thus bioequivalence of the GRT-TRF to the reference formulations could be shown in all 8 trials.

Conclusions

Although GRT-TRF tablets are extremely hard, their in-vivo performance is comparable to the standard extended release formulations. Bioequivalent TRF tablets enable physicians to simply switch patients from conventional to reformulated TRF products.

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Influence of anatomic location of lidocaine 5% patch on effectiveness and tolerability for postherpetic neuralgia

Matthew Wieman, Leah Bednarek, Surya Chitra
Endo Pharmaceuticals Inc., Chadds Ford, PA, USA

Purpose

Lidocaine 5% patch is approved only to relieve postherpetic neuralgia (PHN) pain and is recommended as a first-line therapy in PHN guidelines. Lidocaine 5% patch has a low risk of adverse events and drug-drug interactions compared with systemic therapies and may be preferred for medically complicated patients. PHN can occur anywhere on the body, but often follows acute herpes zoster occurring in trigeminal and brachial plexus dermatomes. An analysis was conducted to determine whether the anatomic location of PHN pain influences the effectiveness or tolerability of lidocaine 5% patch.

Method

This was a posthoc analysis by anatomic site (face [including neck], trunk [chest, abdomen, back, hips], and extremities [arm, leg]) of a 4-week, multicenter, open-label study that enrolled patients of all ages with PHN persisting ≥1 month after herpes zoster onset. Effectiveness was measured by Brief Pain Inventory (BPI) average pain intensity (0 [no pain] to 10 [worst imaginable pain]).

Results

Of 332 enrolled patients (59.6% women [n=198]; 92.5% white [n=307]; mean [SD] age, 71.2 [13.9] y), those (n=203) who applied lidocaine 5% patch to a single anatomic site only and had baseline and postbaseline pain score data were analyzed (trunk, n=130; face, n=41; extremities, n=32). BPI average pain improved significantly from baseline in each of the 3 anatomic areas (mean score decrease, 1.50-2.04; $P \leq .002$). There was no significant difference in effectiveness between the 3 groups ($P \geq .45$). Tolerability was similar for each anatomic location.

Conclusions

Lidocaine 5% patch was effective and well tolerated for each anatomic area compared.

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Safety of combination therapies for postherpetic neuralgia

Matthew Wieman[1], Ingrid Tacken[1]
[1]*Endo Pharmaceuticals Inc., Chadds Ford, PA, USA,* [2]*Grünenthal GmbH, Aachen, Germany*

Purpose

Lidocaine 5% patch and calcium channel α2-δ ligands pregabalin and gabapentin are approved for the relief of postherpetic neuralgia (PHN) pain and are recommended individually as first-line therapies in PHN guidelines.[1,2] Clinical trials in small populations have demonstrated that in patients with inadequate pain relief receiving either lidocaine 5% patch or an α2-δ ligand as monotherapy, the combination of lidocaine 5% patch with an α2-δ ligand provided additional clinically relevant pain relief and was well tolerated. [3-5] This posthoc analysis of pooled data from 2 studies (study 1, lidocaine 5% patch with gabapentin in the United States[5]; study 2, lidocaine 5% patch with pregabalin in the European Union[3]) examines the safety and tolerability of lidocaine 5% patch combined with a calcium channel α2-δ ligand for PHN pain.

Method

Study 1 was a nonrandomized, open-label, multicenter study in which patients with PHN who had a partial response (defined as pain >4 on a scale of 0-10) to gabapentin monotherapy received add-on lidocaine 5% patch (≤4 patches every 24 h) plus gabapentin for 2 weeks.[4] Study 2 was a phase III, randomized, open-label, multicenter, noninferiority study in which patients with PHN and an insufficient response (defined as pain >4 on a scale of 0-10) to either lidocaine 5% patch or pregabalin monotherapy received lidocaine 5% patch plus pregabalin for 8 weeks.[2]

Results

In study 1 (n=11), 4 (36.4%) patients receiving lidocaine 5% patch plus gabapentin experienced ≥1 adverse event (AE). 1 treatment-related AE (ecchymosis) was observed and led to discontinuation. In study 2 (n=35), 11 (31.4%) patients receiving lidocaine 5% patch plus pregabalin reported AEs, 6 (17%) reported treatment-related AEs, and 5 (14.3%) discontinued owing to AEs. No serious AEs were reported for either study. In study 2, most treatment-related AEs were attributed to pregabalin.

Conclusions

Conclusions: This posthoc analysis suggests that for PHN, lidocaine 5% patch in combination with calcium channel α2-δ ligands is generally well tolerated for up to 8 weeks of follow-up with pregabalin and for up to 2 weeks of follow-up with gabapentin..

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Extended-release oxymorphone for the treatment of patients with chronic pain: a pooled Safety analysis at morphine-equivalent doses ≥180 mg/d

Errol Gould[1], Matthew Wieman[2]
[1]*Employee of Endo Pharmaceuticals Inc. at the time of the analysis, Chadds Ford, PA, USA,* [2]*Endo Pharmaceuticals Inc., Chadds Ford, PA, USA*

Purpose

Since the safety of high-dose opioids for patients with chronic pain has not been well studied, a posthoc analysis was conducted to review the safety profile of oxymorphone extended-release (ER) at doses equivalent to oral morphine ≥180 mg/d.

Method

Patients with chronic pain (n=422) who participated in 10 clinical trials of oxymorphone ER were included in a pooled safety analysis. The frequency of observed adverse events (AEs) was categorized under 3 oxymorphone ER dose ranges: 60-<80 mg/d, 80-<120 mg/d, and ≥120 mg/d (respectively equivalent to oral morphine 180-<240 mg/d, 240-<360 mg/d, and ≥360 mg/d).

Results

Patients received oxymorphone ER at doses of 60-<80 mg/d (n=140), 80-<120 mg/d (n=239), or ≥120 mg/d (n=180); dose titration resulted in some patients being counted in >1 dose range. With increasing dose, there were small increases (<10%), no change, or small decreases in the frequency of AEs commonly associated with opioids (eg, constipation, sedation, dizziness, and falls). The frequency of some AEs not typically associated with opioids increased with dose (eg, upper respiratory tract infection, urinary tract infection, muscle spasms, and anemia).

Conclusions

Higher doses of oxymorphone ER (60-≥120 mg/d; equivalent to 180-≥360 mg/d oral morphine) did not appear associated with a marked increase in AEs that are typically considered opioid-related. These results are valid only for oxymorphone ER and should not be used to draw conclusions regarding the safety and tolerability of other opioid analgesics.

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Effects of age, race, and sex on the pharmacokinetics of oxymorphone extended-release tablets: a posthoc analysis of 2 studies

Matthew Wieman, Janet Jobes, Qinfang Xiang
Endo Pharmaceuticals Inc., Chadds Ford, PA, USA

Purpose

The effects of age, race, and sex on the pharmacokinetics of oxymorphone extended-release (ER) tablets have not been investigated. This posthoc analysis considered the pharmacokinetics of oxymorphone ER in male and female volunteers subcategorized by age in study 1 (young [18-40 y] vs older [≥65 y]) and by race in study 2 (white vs black).

Method

Subjects in study 1 received oxymorphone ER 20 mg once daily for 6 days. Subjects in study 2 received 2 single doses of oxymorphone ER 40 mg on 2 occasions separated by 7 days. Plasma concentrations for oxymorphone and its 6-OH-oxymorphone and oxymorphone-3-glucuronide metabolites were analyzed. In both studies, naltrexone was administered to minimize opioid effects.

Results

Study 1 included 24 men, 24 women, 24 young, and 24 older subjects; study 2 included 13 men, 18 women, 24 white, and 7 black subjects. Pharmacokinetic analyses in both studies indicated that only age-based differences were significant after controlling for body weight. Geometric least squares (LS) mean steady-state area under the concentration vs time curve in older (27.6) vs younger (19.7) subjects was significantly higher (ratio: 1.40 [90% CI: 1.2-1.6]), and geometric LS mean maximum concentration in older (3.5) vs younger (2.6) subjects was significantly higher (ratio: 1.33 [90% CI: 1.2-1.5]). Data were similar for oxymorphone metabolites.

Conclusions

No gender or race differences were evident in this analysis of oxymorphone ER pharmacokinetics; however, small sample sizes limit the sensitivity of this analysis. Mean and maximum concentrations of oxymorphone ER and its metabolites were significantly higher in older subjects. Therefore, dose reduction in elderly subjects is advisable to minimize adverse events.

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Observations of venlafaxine metabolism in urine specimens from patients treated for chronic pain

EiThandar Win[1], Candis Morello[1,2], Joseph Ma[1,3], Brookie Best[1,4], Rabia Atayee[1,3], Amadeo Pesce[5,6]
[1]*University of California, San Diego (UCSD), Skaggs School of Pharmacy & Pharmaceutical Sciences, La Jolla, CA, USA,* [2]*Diabetes Intense Medical Management Clinic, Veterans Affairs San Diego Healthcare System, La Jolla, CA, USA,* [3]*Doris A. Howell Palliative Care Service, San Diego, CA, USA,* [4]*UCSD Department of Pediatrics, Rady Children's Hospital, San Diego, CA, USA,* [5]*Millennium Research Institute, San Diego, CA, USA,* [6]*Department of Pathology and Laboratory Medicine, UCSD School of Medicine, La Jolla, CA, USA*

Purpose

Venlafaxine is a novel antidepressant which works by inhibiting the reuptake of both serotonin and norepinephrine. Venlafaxine is also used to treat neuropathic pain, such as peripheral diabetic neuropathy. Venlafaxine is primarily metabolized by cytochrome P450 (CYP) 2D6 into its primary active metabolite, O-desmethylvenlafaxine. Studies have shown that CYP2D6 genotyped and/or phenotyped poor metabolizers may experience more adverse effects on standard doses of venlafaxine. Monitoring the metabolic ratio (MR) of O-desmethylvenlafaxine to venlafaxine may be an important tool for clinicians trying to improve efficacy and minimize toxicity in patients taking venlafaxine. However, little to no data is available on the urinary metabolic ratio of O-desmethylvenlafaxine to venlafaxine in patients with chronic pain. The primary objective was to determine metabolic ratio inter- and intrapatient variability in urine specimens from patients being treated for pain. Secondary objectives included investigation into whether factors such as age, gender, urinary pH and CYP2D6 mediated drug-drug interactions affect the metabolism of venlafaxine.

Method

In this retrospective data analysis, urine specimens from clinician practices throughout the United States were tested at Millennium Laboratories from November 2011 to April 2012 using Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS). The test results were de-identified and the concentrations of venlafaxine and O-desmethylvenlafaxine concentrations were analyzed. All specimens with venlafaxine and O-desmethylvenlafaxine concentrations less than 100 ng/mL were excluded from analysis. In addition, specimens with creatinine concentrations less than 20 mg/dL were also excluded to prevent analysis of diluted specimens. The urinary metabolic ratio (MR) was calculated as O-desmethylvenlafaxine divided by venlafaxine and log-transformed to approximate Gaussian distribution. Regarding the interpatient variability analysis and analyses of effect of age, gender, urinary pH and CYP2D6 drug interactions on MR, only first visit data were used. For the intrapatient variability analysis, patients with at least 2 visits were included. Statistical analyses were performed using OriginPro 8.6 and Microsoft Excel®.

Results

Out of over 24,000 de-identified urine specimens tested for venlafaxine, 530 specimens from unique patients (single or first-visit) were positive for both venlafaxine and O-desmethylvenlafaxine. Geometric mean MR of O-desmethylvenlafaxine to venlafaxine was 2.88. However, the MR ranged from 0.02 to 98.43 showing over 4000-fold difference. Percent coefficient of variation (%CV) of MR between these 530 patients was calculated as 159%. In addition, data from 85 patients with more than one visit were examined for intra- patient variability analysis. Mean %CV in each patient's MRs was calculated as 43% (range: 1%-120%).

Average age of the patients in the analysis population was 49 years (range: 19-84). 381 subjects (72%) were females and 146 (28%) were males. Age and gender did not affect MR. Urinary pH ranged from 4-8.8. A positive correlation was found between urinary pH and MR ($P<.001$, $r^2=.05$, $y=0.14x-0.43$).

Upon analyzing the effects of CYP2D6 inhibitors on urinary MR, a subpopulation of 21 patients with reported prescriptions for bupropion, a known potent CYP2D6 inhibitor, showed a 77% decrease in median MR compared to the whole test population (Mann-Whitney test: *P*=<.001, median MR 0.69 vs 3.02). Similarly, another subpopulation of 23 patients with reported prescriptions for methadone, a weak or moderate CYP2D6 inhibitor, showed a 65% decrease in median MR (Mann-Whitney test: *P*=<.001, median MR 1.05 vs 3.02). Assessment of the effect of the CYP2D6 substrate oxycodone, which may compete for enzyme binding, did not show any significant difference in MR (n=113 with concomitantly detected oxycodone).

Conclusions

High interpatient variability in the urine O-desmethylvenlafaxine/venlafaxine metabolic ratio was observed. Intra-patient variability of MR was lower than interpatient variability. Age, gender and urinary pH did not significantly influence the urinary metabolic ratio. Bupropion and methadone substantially decreased the O-desmethylvenlafaxine/venlafaxine ratio, but the CYP2D6 substrate oxycodone did not affect the MR. Determining which patient-specific variables influence the urinary venlafaxine metabolic ratio may provide insight for healthcare professionals in optimizing venlafaxine monitoring and in understanding venlafaxine metabolism.

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The efficacy and tolerability of tapentadol immediate release (IR) vs oxycodone IR for moderate to severe, acute low back pain with radicular leg pain

Charles Oh[1], David Biondi[1], Jim Xiang[2], Mila Etropolski[2]
[1]*Janssen Scientific Affairs, L.L.C., Raritan, NJ, USA,* [2]*Janssen Research & Development, L.L.C., Raritan, NJ, USA*

Purpose

This phase III study (NCT00986180) evaluated efficacy and tolerability of tapentadol IR vs oxycodone IR for moderate-to-severe, acute low back pain (LBP) with radicular leg pain.

Method

Patients (≥18 years) with acute LBP (intensity ≥5; 11-point NRS) with radicular leg pain were randomized to flexible dosing with tapentadol IR (50 mg, 75 mg, or 100 mg) or oxycodone HCl IR (5 mg, 10 mg, or 15 mg) every 4-6 hours as needed for 10 days. Patients recorded pain intensity twice-daily. The primary efficacy endpoint was sum of pain intensity differences (SPID) over 120 hours ($SPID_{120}$; starting at first study dose); tapentadol IR was considered noninferior to oxycodone IR when the upper bound of the 95% CI for the least-squares mean difference was <120. SPID over 2, 3, and 10 days and 30% and 50% responder rates were evaluated. Treatment-emergent adverse events (TEAEs) were recorded. Patients were recruited from clinical practices; IRB approvals and patient written consents were obtained.

Results

Least-squares mean of $SPID_{120}$ was 264.6 for tapentadol IR (n=287) and 264 for oxycodone IR (n=298; 95% CI: -32.1, 30.9). SPID at 2, 3, and 10 days, and 30% and 50% responder rates at 3, 5, and 10 days were similar between treatment groups. TEAEs (≥10%) with tapentadol IR (n=321) vs oxycodone IR (n=324) included vomiting (15.9% vs 24.7%), nausea (15.9% vs 20.7%), and dizziness (11.8% vs 10.5%).

Conclusions

Using a flexible-dosing regimen, tapentadol IR was noninferior to oxycodone IR for relief of acute LBP, with a more favorable gastrointestinal tolerability profile.

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The impact on sleep quality of Butrans® (buprenorphine) Transdermal System in patients with moderate-to-severe chronic low back pain

Aaron Yarlas[1], Kate Miller[1], Warren Wen[2], Rupa Shah[2], Shau Yu Lynch[2], Bradley Dain[2], Steven Ripa[2]
[1]QualityMetric, Inc., Lincoln, RI, USA, [2]Purdue Pharma LP, Stamford, CT, USA

Purpose

Previous research on CLBP patients has established that pain frequency and intensity are associated with a greater likelihood of sleep disturbance and lower sleep quality. A recent trial (Steiner et al, 2011) comparing CLBP patients receiving one of 2 doses with Butrans® (buprenorphine) Transdermal System (BTDS) - 5 mcg/hour (BTDS 5) or 20 mcg/hour (BTDS 20) - in a 12-week randomized controlled trial found statistically greater pain relief for BTDS 20 than for those receiving the control treatment (ie, BTDS 5). The current posthoc analysis of data from this trial was conducted to examine changes in the burden of CLBP on sleep with 12 weeks of BTDS 20 compared with BTDS 5, and to describe sleep outcomes over 12 months of continued BTDS 20 treatment. In addition, comparison of sleep burden between trial patients and an age- and gender-matched U.S. general population sample was made.

Method

Data were from a multicenter, enriched-enrollment, randomized, double-blind trial which tested the efficacy and safety of treatment with BTDS 5 and BTDS 20 for opioid-experienced CLBP patients. The trial consisted of a pre-randomization run-in period - used to establish tolerability and responsiveness to BTDS 20 - followed by a 12-week double-blind phase and a voluntary-enrollment 52-week open-label extension phase. BTDS 5, rather than placebo, was chosen as a control to minimize potential opioid withdrawal effects following the run-in period.

Patients' sleep problems and quality were assessed using the Medical Outcomes Study Sleep Scale (MOS-SS), a 12-item survey measure of several aspects of sleep outcomes. The MOS-SS yields scores on several domains, including Disturbance (sleep initiation and maintenance problems), and a Sleep Problem Index (SPI) capturing overall sleep quality. This survey was administered before and after the run-in period, at 4, 8, and 12 weeks of the double-blind phase, and several times during the extension phase.

The burden of CLBP on sleep outcomes and treatment impact on burden was examined by comparing trial patients with an age- and gender-matched U.S. general population sample at baseline and week 12. The impact of treatment on sleep outcomes at week 12 was conducted using analysis of covariance (ANCOVA) models. Differences in the rate of change in Disturbance and SPI scores across treatment arms and double-blind phase visits were assessed using repeated-measures mixed-models. Repeated-measures mixed-models also tested for changes in Disturbance and SPI scores during the 52-week extension for patients treated consistently with BTDS 20.

Results

At baseline, patients' Disturbance and SPI scores were significantly worse than those of the matched U.S. general population sample; by week 12 of the double-blind phase, BTDS 20 patients' average scores improved to become better than those in the U.S. general population sample, while BTDS 5 patients' scores did not. ANCOVA models found that, when controlling for pre-treatment scores, BTDS 20 patients showed significantly less Disturbance and better overall sleep quality (ie, higher SPI scores) than BTDS 5 patients at week 12 double-blind (both *Ps*<.05), with no statistical treatment differences for other sleep domains (including snoring, somnolence, or awakening due to headache/shortness of breath). Repeated-measures mixed-models yielded that treatment arm differences for both Disturbance and SPI scores emerged at week 4 double-blind and were consistently maintained through week 12, as

evidenced by statistically significant effects for treatment ($P<.05$ in both models), but not for visit or their interaction ($Ps>.05$ in both models). Repeated-measures mixed-models found no reductions in Disturbance and Quality scores from the double-blind endpoint through 12 months of consistent BTDS 20 treatment in the maintenance phase ($P>.05$ for visit in both models).

Conclusions

Patients with moderate-to-severe CLBP experience impaired sleep outcomes. Untreated, this patient population experiences more frequent sleep disturbance and lower sleep quality than the general population. Treatment with BTDS 20 offers these patients sleep quality improvement that leads to less frequent sleep disturbance and higher sleep quality than the general population. The advantage of BTDS 20 over BTDS 5 for reducing sleep disturbance and improving sleep quality appears within 4 weeks of treatment, and this advantage is maintained for at least 12 weeks. Further, the gains in sleep outcomes may be sustained for one full year of BTDS 20 use.

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Butrans® (buprenorphine) Transdermal System (BTDS) treatment reduces impairment in activities of daily living in moderate-to-severe chronic low back pain

Kate Miller[1], Aaron Yarlas[1], Warren Wen[2], Rupa Shah[2], Shau Yu Lynch[2], Bradley Dain[2], Steven Ripa[2]
[1]QualityMetric, Inc., Lincoln, RI, USA, [2]Purdue Pharma LP, Stamford, CT, USA

Purpose

The symptoms of chronic lower back pain (CLBP), particularly pain, can interfere with the ability to perform basic and instrumental activities of daily living (ADLs) such as sleeping, sitting, bending, lifting, walking, and working. A recent randomized, double-blind, placebo-controlled trial (Steiner et al, 2011) found that treatment with Butrans® (buprenorphine) Transdermal System (BTDS) at doses of 10 mcg/hr (BTDS 10) and 20 mcg/hr (BTDS 20) were efficacious for decreasing pain in patients with moderate-to-severe CLBP. The current posthoc analysis of data from this trial assesses the initial burden of CLBP on patients' ability to engage in these ADLs, as well as the impact of 12 weeks' BTDS treatment, relative to placebo, on changes in the likelihood of their ability to perform ADLs.

Method

Data were from a multicenter, enriched-enrollment, double-blind, randomized trial of opioid-naive patients with moderate-to-severe CLBP. The trial consisted of a screening period, a 21-day run-in period to establish responsiveness and tolerability to BTDS 10/20, and a 12-week double-blind phase in which patients were randomly assigned to treatment with BTDS 10, BTDS 20, or placebo. At screening, before and after run-in, and at weeks 4, 8, and 12 of the double-blind phase all patients were administered 3 questionnaires: the 36-item Short Form Health Survey (SF-36v2) to measure health-related quality of life, the Oswestry Disability Index (ODI) to assess condition-specific activity limitations, and the Medical Outcomes Study Sleep Scale (MOS-SS) to assess sleep quality. Following a taxonomy of roughly 15,000 ADLs that was developed by the World Health Organization, researchers have previously linked content from each of these measures to a "Core Set" of daily functions relevant for LBP patients. In the current posthoc analysis, we identified 23 items from these instruments that reflect this linked content and identified patients as able/unable to perform the ADL. Each item selected falls under one of the following categories: Sleeping, Sitting/Standing/Lifting/Bending, Walking, and Working. Baseline and endpoint frequencies and percentages of patients in each treatment group who were able to perform the ADL were assessed. Independent logistic regression models for each item, with family-wise alpha of .05 preserved across the 23 significance tests, assessed treatment arm differences in patients' ability to perform ADLs by estimating odds ratios at the double-blind phase endpoint.

Results

Data from patients in BTDS 10 and BTDS 20 treatment arms were combined into a single BTDS treatment group for all analyses. Across both treatment arms at baseline, an average of 26% of patients were classified as able to perform the ADL; following 12 weeks of treatment in the DB phase, this percentage rose to 46% in the placebo group and 58% in the BTDS group. At endpoint, the average percentages of able patients in the BTDS group were 59% for the Sleeping ADLs (22% at baseline), 55% for the Sitting/Standing/Lifting/Bending group (23% at baseline), 43% for the Walking group (24% at baseline) and 66% in the Working group (31% at baseline). This compares to lower mean percentages of able patients among the placebo group: 46% for Sleeping, 42% for Sitting/Standing/Lifting/Bending, 36% for Walking and 52% for Working.

Results from logistic regression models indicated that compared to placebo, BTDS users were roughly twice as likely to have no physical-health-related restrictions in amount of time spent in work or activities, types of activities undertaken, or amount of work accomplished. They were more than twice as likely to be able to sleep without being disturbed by

pain, fall back asleep after waking, lift and carry groceries, lift objects without extra pain, bend, kneel, or stoop without restriction, and experience no emotionally-based restrictions in amount of work accomplished and degree of care given to work. Unlike for the above items, where statistically significant differences between placebo and BTDS arms were observed (all posthoc multiplicity-adjusted Ps<0.05), treatment arm differences in improvement of walking abilities did not reach statistical significance (posthoc multiplicity-adjusted *Ps*>.05).

Conclusions

Twelve weeks of treatment with BTDS 10/20 led to statistical increases, relative to placebo, in the ability of patients with moderate-to-severe CLBP to perform several key ADLs. Specifically, treatment with BTDS conferred a roughly 2-fold statistically significant increase over placebo in the likelihood of being able to perform daily functions related to sleeping, lifting, bending, and working.

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Use of the urinary morphine to codeine ratio analyzed using LC-MS/MS in the detection of heroin use in patients with pain

David Yee[1], Brookie Best[1,2], Joseph Ma[1,3], Rabia Atayee[1,3], Amadeo Pesce[4,5]
[1]University of California, San Diego (UCSD), Skaggs School of Pharmacy & Pharmaceutical Sciences, La Jolla, CA, USA, [2]UCSD Department of Pediatrics, Rady Children's Hospital, San Diego, CA, USA, [3]Doris A. Howell Palliative Care Service, San Diego, CA, USA, [4]Millennium Research Institute, San Diego, CA, USA, [5]Department of Pathology and Laboratory Medicine, UCSD School of Medicine, La Jolla, CA, USA

Purpose

Heroin use in patients being treated for pain presents a significant risk for morbidity and mortality. It is important to develop methods to detect this abuse. However, the use of 6-monoacetylmorphine (6-MAM) as the definitive marker for heroin use may lead to a high proportion of false negatives as a result of its rapid conversion to morphine. Further, codeine can be an impurity in both heroin and morphine preparations. Codeine itself is metabolized to morphine by CYP2D6. Sources of specimens with the combined presence of codeine and morphine include codeine medications, impure heroin, and codeine impurities present in morphine medications. Methods of differentiation between heroin use, codeine use, and morphine use when 6-MAM is not present have not been fully established. Previous studies have indicated that a morphine to codeine ratio of greater than 1 may be an indication of heroin use. This analysis uses a large population of urinary specimens from pain clinics analyzed by LC-MS/MS to determine how the ratio of morphine to codeine differs with heroin use compared to medicinal codeine or morphine. Better established reference ranges may assist in the detection of heroin use.

Method

This was a retrospective data analysis of urine specimens collected between January 2012 and May 2012 and analyzed at Millennium Laboratories by Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) to determine concentrations of codeine, morphine, and 6-MAM. Specimens were excluded if the creatinine concentrations were <20 mg/dL. 7594 de-identified specimens with concentrations of codeine and morphine above 50 ng/mL (lower limit of quantitation, LLOQ) were used to represent populations of patients being treated for pain which included codeine use, morphine use, and heroin use. This population was further separated into those with reported prescriptions for codeine without morphine or 6-MAM (n=1077), those reporting prescriptions of medicinal morphine without codeine or 6-MAM (n=717), and those positive for 6-MAM (>10 ng/mL, LLOQ) without reported prescriptions of codeine or morphine (n=2014). In this analysis these populations represent codeine use, morphine use, and heroin use, respectively. Distributions and geometric mean morphine/codeine ratios were determined to see if the morphine/codeine ratio differs in these populations.

Results

Using the ratio of morphine to codeine in all specimens testing positive for codeine and morphine, 3 distinct populations were observed. These populations can be identified through separation of specimens based on current medications and the presence or absence of 6-MAM. Specimens with concentrations of 6-MAM >10 ng/mL without reported prescriptions for codeine or morphine showed a geometric mean morphine/codeine ratio of 87.5 (95% confidence interval from 90.3-84.7). This population had 95th and 5th percentile ratios of 227 and 35, respectively. 1077 specimens with reported use of codeine, no reported use of morphine and no detected levels of 6-MAM, showed a geometric mean morphine to codeine ratio of 0.25 (95% CI: 0.27-0.22) with 95th and 5th percentiles of 2.35 and 0.02 respectively. Approximately 15% of specimens with reported prescriptions for codeine had a morphine to codeine ratio above one. A 2 sample t-test showed that morphine to codeine ratios in codeine and heroin use

populations are significantly different (*P*<.001). 717 specimens reporting use of morphine and not codeine with 6-MAM below 10 ng/mL showed a geometric mean of 224.1 (95% CI: 292.2-171.8). This population showed a negative skew of -0.78 with 95th and 5th percentiles of 7381 and 0.26 respectively.

Conclusions

Urinary morphine/codeine ratio showed 3 distributions that represent codeine, morphine and heroin use. Distributions of the morphine to codeine ratio in specimens representing codeine use showed that 15% of subjects may have ratios greater than one leading to a high proportion of false positives using this previously reported cutoff value. Patients with morphine to codeine ratios within the range consistent with heroin use should be more closely monitored as this may indicate possible heroin use. This retrospective analysis indicates that high morphine/codeine ratios may be helpful in the detection of heroin abuse when 6-MAM is not detected.

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A randomized clinical trial of a web-based intervention to improve patient self-efficacy and coping with neuropathic pain

Jonas Bromberg, Pronabesh DasMahapatra, Synne Venuti, Kevin Zacharoff
Inflexxion, Inc., Newton, MA, USA

Purpose

This study tested a Web-based intervention (www.painACTION.com) designed to: (1) increase self-efficacy to perform pain self-management activities, (2) reduce pain-related psychological distress, and (3) reduce pain frequency and severity. A key component of comprehensive pain treatment is facilitating active engagement in self-management activities. However, many people with chronic pain lack the skills and confidence to play an active role in managing their condition. Poor self-management can contribute to negative outcomes, including increased pain, pain-related disability, depression, and diminished quality of life. Although they have been shown effective, behavioral interventions that reinforce self-management skills are not routinely included in the medical management of neuropathic pain. To address this gap, Web-based interventions may expand existing approaches to the medical management of neuropathic pain by effectively addressing the behavioral factors known to impact the psychological adjustment and quality of life for patients living with chronic pain.

Method

The study was a parallel group design with 2 conditions: 1) an experimental group that completed eight 20-minute web sessions over a 4-week intervention period (2 site visits per week), and five 20-minute "booster" sessions during the follow-up period; and 2) a control group that viewed a website containing a series of articles about neuropathic pain and pain self-management. These articles were representative of the patient education materials provided at pain clinics or available on NIH websites. Assessments for both groups were conducted at baseline, 1 month, 3 months, and 6 months.

Results

Relative to the control group, at 6-month follow-up the experimental group showed significantly greater mean decreases in: worst pain, pain severity, pain interference, overall work impairment, and depression. The experimental group also showed a significantly greater mean increase in resting as a coping strategy.

Conclusions

Since many people with neuropathic pain have limited access to expert behavioral support to improve their self-management and coping skills, Web-based interventions may be an effective adjunct to current standard medical approaches to pain treatment, and an effective component of a comprehensive disease management approach.

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Healthcare providers' perceptions about opioid REMS education

Kevin Zacharoff, Pravin Pant, Synne Venuti
Inflexxion, Inc., Newton, MA, USA

Purpose

Opioid misuse and abuse, resulting in injury and death, has emerged as a major public health problem in the United States. The White House policy statement, *"Epidemic: Responding to America's Prescription Drug Abuse Crisis"*, released in April 2011 underscored the role of prescriber education as part of the solution to this important national problem. Following the White House position, education has been identified as a core component of the Food and Drug Administration's (FDA) recently approved (July 2012) shared opioid Risk Evaluation and Mitigation Strategy (REMS) for extended-release and long-acting opioids. In the outline for prescriber education, FDA underscored the idea that healthcare professionals who prescribe these analgesics "are in a key position to balance the benefits of prescribing against the risks of serious adverse outcomes including addiction, unintentional overdose, and death."

A survey of healthcare providers was conducted with 3 aims: to ascertain prescribing clinicians' familiarity with proposed REMS for extended-release and long-acting opioid medications, to gauge their prescribing habits of these medications for the management of moderate to severe chronic pain, and to assess their likelihood in participating in a proposed, voluntary opioid REMS continuing education course, including identifying some of their perceived barriers to participation.

Method

A survey of 130 healthcare providers was conducted electronically via the pain education website *PainEDU.org*.

Results

A majority of survey participants were familiar to some degree with the REMS for extended-release and long-acting opioids. The majority of healthcare providers surveyed also expressed that they were likely to some degree, to prescribe extended-release or long-acting opioids as part of the management for moderate to severe chronic pain. The majority of survey participants expressed a high likelihood of participating in an opioid REMS educational program when it is available.

Conclusions

Participation will be a critical metric of success for an opioid REMS education program. This survey of PainEDU.org registrants indicates a high likelihood of awareness of the opioid REMS and intent to participate in an educational program once it is available.

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Development of a goal attainment measure for patients with osteoarthritis of the hip and/or knee or chronic low back pain

Susan D Mathias[5], Sarah Zander[1], Susan Vallow[1], Carmela Benson[2], Anisha M. Patel[3], M.Soledad Cepeda[4], Byron D. Jones[6]
[1]Janssen Global Services, Titusville , NJ, USA, [2]Janssen Scientific Affairs, LLC, Titusville, NJ, USA, [3]Janssen Scientific Affairs, LLC, Raritan, NJ, USA, [4]Janssen Research and Development, Titusville, NJ, USA, [5]Health Outcomes Solutions, Winter Park, FL, USA, [6]Pain Matters, LLC, Lakewood, CO, USA

Purpose

Goal attainment measures (GAM) have previously been developed for a few chronic diseases. However, challenges with these measures include the need for a trained professional to administer and tailor patient goals, and the lack of a mechanism for scoring these GAMs. We developed a self-administered GAM that could efficiently assist patients to identify patient-centric goals related to osteoarthritis of hip and/or knee (OA) or chronic low back pain (cLBP), while adhering to current standards for questionnaire development. OA and cLBP represent 2 of the most chronic painful and disabling conditions in healthcare, with enormous associated costs, both direct and indirect.

Method

A comprehensive literature review was conducted to explore published research and existing measures related to goal-attainment. Standardized interview guides were developed to conduct in-depth telephone interviews with OA and cLBP subjects to inform questionnaire development. A GAM questionnaire with 3 versions was drafted: a Baseline version that guided respondents through the goal setting process; a Follow-up version as an interim assessment of progress made on the original goal, and a Final follow-up version to assess success on the original goal. Cognitive debriefing telephone interviews were then conducted with OA and cLBP subjects focusing on content, clarity, and appropriateness of the draft GAM questionnaire in order to finalize these measures.

Results

A total of 23 subjects with OA (mean age=56 years, 73% women, 73% Caucasian, 54% with college education or higher, 55% with annual income of <$50,000) and 55 subjects with cLBP, 53% of which had neuropathic pain (mean age=52 years, 55% women, 78% Caucasian, 82% with some college education and 53% with annual income of <$50,000) were interviewed. In the OA group, respondents reported an impact in their ability to perform daily activities including walking, riding a bike, climbing stairs, hiking, bending, squatting, and performing household chores. Those with cLBP reported that pain affects their ability to perform daily activities including household chores, exercising/working out, bending, standing, walking, sitting, lifting, driving, and laying down/sleeping for long periods of time. When asked about their previous experience setting goals, 78% of OA patients reported selecting a goal themselves or after discussion with a healthcare professional. About 50% of cLBP subjects selected the goal after consultation with their healthcare provider, 35% selected the goal themselves and 15% were assigned the goal. These results informed the questionnaire development. During cognitive debriefing interviews, participants (9 with OA and 10 with cLBP) were asked to either select a goal from a list of sample goals provided or to develop their own goal. The most commonly cited goals were walking (37%), cleaning the house (16%), and stretching (16%). Fifty-three percent selected a specific goal on their own, while 47% used or modified the sample goals. 84% of respondents described the questionnaire as easy to complete. Average time to complete the baseline, follow-up and final follow-up versions of the questionnaire was 21 minutes, 11 minutes and 10.5 minutes, respectively. Overall, subjects were able to self-administer the GAM questionnaire and did not find the process of goal-setting difficult. Final revisions were made based on patient feedback.

Conclusions

Goal-setting is a way to personalize treatment to allow patients to set meaningful goals that may help them adhere to treatment regimens. This self-administered GAM measure was developed using rigorous accepted standards, and contain an easily interpretable approach to scoring. Subjects were comfortable self-administering the GAM and found it easy to complete. The GAM can be used in a clinical setting as an outcome measure of treatment effectiveness and could potentially improve patient outcomes.