The Use of Opioids in Pain Management

One Complimentary CME/CE Credit

Reviewer

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Intended Audience

This activity is intended for physicians and other healthcare professionals that specialize in pain management for patients who suffer from acute or chronic pain.

Activity Purpose

This activity is designed to equip physicians with information to allow them to prescribe safe and efficacious therapies for the management of pain. A comprehensive discussion of pharmacological, clinical, and regulatory information in the field of pain management will promote beneficial outcomes for patients who suffer from acute or chronic pain conditions.

Learning Objectives

Upon completion of this activity, participants will

- Discuss current pain management strategies available to help treat patients with acute or chronic pain conditions
- Examine recent clinical data evaluating the safety and efficacy of immediate-release (short-acting) and extended-release (long-acting) opioid analgesic formulations for the treatment of moderate to severe acute and chronic pain
- Evaluate the effectiveness of extended-release opioid analgesics on improving patient outcomes, including quality of life and daily functioning

Method of Participation

It has been determined that this activity can be completed in 1 hour. The participant should review the learning objectives and faculty disclosure, read the abstract digest, reflect on the content, answer the posttest questions, and complete the enrollment and evaluation forms. To earn credit, a minimum score of 70% must be achieved on the posttest. A certificate of credit will be mailed to participants within 6 weeks of receipt of mailed or faxed forms. (Certificates will be immediately available if the completed posttest and forms are submitted online.) Complete information is located on the posttest. There is no fee to participate in the program or for the generation of the certificate.

Initial release date: **10/15/08** Expiration date: **10/14/09**

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Dr. Fine discloses that this activity discusses the unapproved/off-label use of analgesic medications for the treatment of acute and chronic pain conditions.

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The Use of Opioids in Pain Management

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Introduction

Pain is among the most frequent complaints presented to physicians, with moderately-severe pain the most common in terms of severity.[1,2] Approximately 75 million Americans suffer with pain. About 50 million of these people have chronic pain conditions, and 25 million experience acute pain as a result of injury or surgery.[3] Unrelieved or untreated pain can negatively affect a person's quality of life, including increasing functional impairment and disability, psychological distress (anxiety, depression), and sleep deprivation.[4]

The primary goal of any pain management treatment regimen is to provide rapid and effective analgesia. In many cases this can involve the use of pharmacologic treatments, such as acetaminophen (APAP), nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, antidepressants, or anticonvulsants, depending on the intensity and duration of the pain. For patients who do not obtain adequate analgesia from APAP or NSAIDs, opioids are an important treatment option to consider. Opioids are the most potent and efficacious analgesics available, and several medical societies recommend the use of opioids to treat various pain conditions.[5-8]

The continued widespread use of opioids as a pharmacologic treatment option for the management of pain is evidenced by the number of abstracts that were presented at the recent annual meetings of the American Academy of Pain Medicine (AAPM) and the American Pain Society (APS). Out of the combined 431 poster abstracts that were presented at these meetings on various topics related to pain, approximately 1/5 mentioned opioid use. The purpose of this continuing medical educational activity is to highlight studies focused on the use of opioid analgesics in pain management that were presented at the 2008 annual meetings of the AAPM and the APS. The majority of these studies were separated and summarized into 3 main sections: systems and policy, newer opioid analgesics and delivery systems, and tamper-resistant and abuse-deterrent opioid formulations.

Systems and Policy

Medication Costs for Chronic Pain

Pain is among the most frequent complaints presented to physicians, with moderately-severe pain the most common in terms of severity.[1,2] Pain is the most common cause of long-term disability, and lost work days due to pain are estimated at >50 million days per year.[9] The annual cost of untreated or undertreated pain to taxpayers and employers due to lost income, lost productivity, and medical expenses is over $60 billion dollars per year.[9] The substantial expenditures associated with pain, including medication costs, were assessed at the AAPM and APS meetings.

Cunningham et al evaluated whether pain rehabilitation programs helped reduce the use of pain medications, thereby reducing the costs to the patient.[10] A prospective cohort study concentrated on the costs of pain medications for 177 patients with chronic nonmalignant pain who were enrolled in a 3-week outpatient pain rehabilitation program, with 112 patients also completing a 6-month follow-up.[10] The patients were interviewed by pharmacists at admission, with completion of a 3-week program and a 6-month follow-up to determine daily medication use.[10] The results of the study revealed that significant medical cost savings (30% reduction) were observed after completion of the program and at the 6-month follow-up compared with costs at admission, cost-effective treatment options for patients with chronic pain conditions.[10] Thus, pain rehabilitation programs and other comprehensive pain programs may provide economic, as well as physiological and psychological benefits, to patients.

Unmet Needs in Pain Management

In the United States, undertreatment of pain is fairly common, with only 25% of patients suffering from pain receiving proper treatment.[11] Furthermore, an estimated 2/3 of ptients withmoderate to severe noncancer-related chronic pain have been living with untreated or undertreated pain for at least 5 years. Vo et al conducted a survey in 606 patients suffering from acute orchronic pain to determine the impact of pain on patients' health-related quality of life and work productivity that was presented at APS.[12] The results from this survey revealed that chronic pain had a significant impact on daily activities and quality of relationships with 79% of chronic pain patients reporting that pain disrupted their activities of daily living, and 67% of these patients indicating that pain negatively impacted their personal relationships.[12]

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There are several barriers to effective pain management that continue to contribute to this undertreatment of pain, and abstracts presented at AAPM and APS examined these barriers and unmet needs in pain management. In the same survey described previously, Vo et al also queried 491 physicians of various specialties (eg, PCPs, emergency room physicians, orthopedic surgeons, and pain medicine specialists) to identify what physicians feel are unmet needs of their patients among the current pain management treatment options that are available.[13]

The results revealed that 94% of physicians surveyed felt it was difficult to appropriately manage their patient's pain.[13] Furthermore, 79% of physicians felt that patient compliance with pain medication administration was less than optimal.[13] Finally, 96% of physicians indicated that their patients with chronic pain conditions frequently wake during the night due to breakthrough pain.[13]

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This study highlighted the challenges associated with appropriately managing pain patients.

A significant barrier to appropriate and effective pain management is the shortage of pain specialists to provide care for the millions of patients suffering from complex pain conditions, with only 6 board certified pain specialists available per 100 000 patients.[14] These numbers severely limit the options available to PCPs when attempting to consult and/or refer their pain patients to a specialist. Beck et al examined the workings of a pain medicine and primary care community rehabilitation model that recommends the collaboration between pain specialists and PCPs to address the needs of patients with persistent pain.[15] This study involved evaluating quality of life variables in 500 patients who received treatment from Pro-Care, a program that uses the rehabilitation model described previously.[15] The results from this study demonstrated that Pro-Care, which provided educational information for community PCPs, easy access for referrals to pain specialists, and a collaborative model of care, allowed for a significant improvement in quality of life variables, including general activity, walking, mood, and daily activities.[15] This suggests that a collaborative pain care model is an effective tool that should be replicated in larger prospective studies.

Another significant barrier to appropriate pain management is a lack of physician knowledge about current medical standards, research, and clinical guidelines for effective pain management. For instance, even though current guidelines recommend the use of around-the-clock opioids when opioid therapy is indicated for the treatment of chronic pain, it is unclear whether physicians adhere to these recommendations.[16] Alvarez et al analyzed pharmacy claims to examine the relative use of long-acting (ie, modified rlease formulations; LAOs) versus short-acting opioids (SAOsfor the treatment of chronic pain conditions.[17] A total of 3 993 011 opioid treatment episodes were analyzed over a 3-year period.[17] The results revealed that

79% of physicians felt that patient compliance with pain medication administration was less than optimal.[13]

85% of all chronic pain conditions were treated with SAOs.[17] Furthermore, although pain specialists were more likely to prescribe LAOs for chronic pain than nonspecialists, both pain specialists and nonspecialists prescribed SAOs >80% of the time for chronic pain.[17] It is unknown whether SAOs were prescribed to be used around the clock for persistent, continuous pain disorders, but these results should lead to further study to determine how to promote appropriate prescribing practices and adherence to published clinical guidelines.

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Finally, a series of studies were undertaken to identify patterns and gaps in physicians' and nurses' knowledge, attitudes, and practices related to appropriate pain management.[18,19] One hundred and ninety-five physicians affiliated with the Texas Medical Association completed a survey containing questions relating to pain assessment tools used in their practice, barriers to effective pain control, and attitudes about prescribing opioids to patients with a history of drug abuse.[18] The results from this study demonstrated that physicians felt that the barriers to providing effective pain management to their patients were insufficient time, problematic patient and family attitudes about the use of opioids, fear of regulatory scrutiny, lack of knowledge, and availability of resources.[18] Furthermore, 40% of these physicians felt that the use of opioids causes addiction, 13% would refuse to prescribe opioids to patients with a drug abuse history, and 4% would refuse to treat those patients at all.[18] Finally, the use of the numeric pain rating scale was used by the majority of the physicians surveyed (70%), although only 67% of these physicians believed that the scale was useful and accurate.[18]

A similar study assessed the beliefs about pain and analgesia held by 286 Texas nurses who were involved with the Nurse Oncology Education Program.[19] The nurses surveyed reported that the most important barriers to effective pain management were patient and family attitudes, physician attitude and practice, cultural differences, communication barriers, and time constraints.[19] Furthermore, 51% of nurses indicated that they had first-hand knowledge of physicians who refused to prescribe adequate pain medication to a patient.[19] Approximately 20% of nurses indicated that they would limit the number and frequency of opioid doses, 4% would refuse to prescribe opioids, and 1% would refuse to treat patients with a history of drug abuse.[19]

Taken together, these data highlight areas where healthcare delivery systems improvements are required, and physicians and other healthcare providers may need more education in order to provide appropriate pain management and to optimize positive treatment outcomes in their patients with acute or chronic pain conditions.

Abuse and Misuse of Prescription Analgesic Medications

In a recent report released by the Substance Abuse and Mental Health Services Administration (SAMSHA), pain relievers were the most common drugs of choice for first-time abusers. Over 500 000 people used controlled-release oxycodone for nonmedical uses.[20] However the majority of people 12 and older who obtained prescription pain relievers for nonmedical purposes received them from friends or relatives, not from "shopping around" at multiple doctors or pharmacies.[20] Furthermore, Katz et al[21] recently examined the epidemiology of abuse and diversion of prescription opioid products in the United States. From 2002–2003 over 190 million prescriptions for opioid products and 9.4 billion doses were dispensed in the United States. According to the National Survey on Drug Use and Health (NSDUH), over 11 million people in 2005 used opioids for nonmedical purposes, which means 1 in 5 doses of a dispensed opioid is being diverted and likely used inappropriately.

Because of the substantial increase in misuse, abuse, and diversion of prescription pain medications, several studies presented at AAPM and APS focused on the characteristics of patients who display aberrant drug-related behavior, as well as important programs that are currently available to assist physicians in managing chronic pain in their patients who have a history of medical misuse, abuse, or diversion of prescription medications. Webster performed a retrospective chart review in order to determine personal variables that were associated with self-reported motives for seeking drugs that were ultimately abused.[22] Forty patients who underwent treatment for opioid addiction were included in this study.[22] The results revealed that the most common initial purpose of opioid use was physician prescription for pain medication (70%).[22] Motives for seeking opioids were age dependent, with subjects <30 years old seeking opioids for recreational use and subjects >30 years old seeking opioids for the treatment of pain through prescriptions.[22] These results indicate that age may be a dependent factor in initial motivation for seeking opioids. Further research across various opioid abuse treatment centers focusing on motives for obtaining opioids to abuse should be performed.

PCPs are involved in the management of pain patients with a high-degree of comorbidities; and in many cases, these patients with psychiatric and addiction comorbidities were referred to a program, such as the Opioid Renewal Clinic, for assistance in managing opioid administration for chronic noncancer pain.

A series of studies presented at the AAPM meeting examined the characterstics and outcomes of patients erolled in a pharmacist-run program at a clinic (Opioid Renewal Clinic) supporting PCPs' management of patients who have chronic noncancer pain and displayed

aberrant drug behavior or substance misuse/abuse risk.[23-25] Wiedemer et al compared the characteristics of 401 patients receiving opioids who were referred to the clinic compared to those (n = 418) who were not referred.[24] In general, patients enrolled in the clinic were younger, more likely to be unemployed, and single compared with those not enrolled in the program.[24] These patients also had a higher prevalence of low back pain, OA, depression, and addiction disorder.[24]

Becker et al sought to determine the demographic and clinical characteristics of the patients who were enrolled but later discharged from the Opioid Renewal Clinic because of a failure to uphold the conditions set forth in the opioid treatment agreement.[23] The results indicated that the majority of patients discharged from the Opioid Renewal Clinic during a 2-year period (n = 86) had more than 1 pain condition (33%), history of substance abuse (59%), and an active mental health diagnosis (66%).[23] Furthermore, the most common reason for discharge of these patients were recurrent positive drug screens for illegal substances (47%).[23]

Wiedemer et al also performed a retrospective chart review of 196 patients referred to the Opioid Renewal Clinic to identify predictors of resolution of aberrant drug behavior over a 1-year period.[25] The results revealed that almost half (44%) of the patients admitted to the Opioid Renewal Clinic resolved their aberrant drug behavior within 1 year.[25] A history of cocaine dependence predicted a poor outcome for the patient and increased the chance of failure within the program.[25] In contrast, each additional pain diagnosis reduced the odds of failing the program by 14%.[25] These results suggest that patients with multiple pain conditions tended to resolve their aberrant drug behavior within the Opioid Renewal Clinic possibly due to the stronger motivation for pain relief. However, more research on this topic is warranted.

Taken together, this series of studies demonstrates that PCPs are involved in the management of pain patients with a high-degree of comorbidities; and in many cases, these patients with psychiatric and addiction comorbidities were referred to a program, such as the Opioid Renewal Clinic, for assistance in managing opioid administration for chronic noncancer pain. Because the main reason for referral and discharge from these clinics is the misuse and abuse of drugs, there is a clear need to provide education to both physicians and patients about interventions that are aimed at providing at-risk patients with the structure and guidance they require in order to be successful in a pain treatment and substance treatment programs. Furthermore, these data suggest that structured practices such as the Opioid Renewal Clinic approach, may be a very useful means to help PCPs manage patients who require opioid analgesics as a component of chronic pain management.

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Newer Opioid Analgesics and Delivery Systems

Extended-Release Hydrocodone/Acetaminophen (HC/APAP CR)

Extended-release opioid formulations, compared with immediate-release formulations, offer the opportunity to extend the dosing interval (8 to 24 hours for oral formulations), lengthen the duration of analgesia and reduce peak/trough effects, and improve patient convenience and compliance.[26] Combination opioid formulations, like hydrocodone/acetaminophen (HC/APAP), which combine drugs with different mechanisms of action (ie, an opioid and APAP), provide comparable or increased analgesia than the use of either agent alone, may reduce adverse events associated with higher doses of either of the individual analgesics, and possibly allow for lower doses of the individual components to be used.[27]

A 12-hour long-acting formulation of 15 mg HC/500 mg APAP (HC/APAP CR) is undergoing clinical trials to examine its safety and efficacy for the treatment of moderate to severe acute and chronic pain. A recent pharmacokinetic study demonstrated that HC/APAP CR produced a rapid rise in serum blood levels during the first hour, similar to immediate-release HC/APAP, with stable serum levels for up to 12 hours.[28]

The results from phase 3 clinical trials examining the safety and efficacy of HC/APAP CR for the treatment of moderate to severe pain were presented at AAPM and APS. The safety and efficacy of 1 and 2 tablets of HC/APAP CR administered twice daily (BID) in 163 patients with moderate to severe pain on the day following bunionectomy surgery was evaluated.[29] Extended-release HC/APAP (1 and 2 tablets) provided significantly greater pain relief compared with placebo ($P<.001$), and 2 tablets of HC/APAP CR provided consistently superior pain relief compared with 1 tablet ($P<.001$).[29]

A randomized, double-blind, placebo-controlled withdrawal trial examined the analgesic efficacy and safety of HC/APAP CR (1 or 2 tablets) administered BID in patients (enrolled patients: n = 773; patients in double-blind period: n = 511) with moderate to severe mechanicalchronic low back pain (CLBP).[30] Quality of life assessments, including disability level, sleep interference, and physician's and patient's global assessment of CLBP status after treatment were also evaluated.[31,32] Over the 12-week study period, 1 and 2 tablets of HC/APAP CR given BID significantly decreased CLBP intensity compared with placebo.[30] Additionally, disability levels and pain-related sleep interference were significantly lower in patients who received 1 or 2 tablets HC/APAP CR compared with placebo.[31] Finally, analysis of Subject's Global Assessment (SGA) and Physician's Global Assessment (PGA) of back pain status revealed that administration of 1 or 2 tablets of HC/APAP CR was associated with more favorable assements of CLBP from both patients and physicians compared with placebo administration.[32]

A phase 3 open-label clinical trial examined the effects of HC/APAP CR administered BID on a variety of quality of life variables, including pain-related physical function, work productivity, and sleep quality for 56 weeks in 431 patients with moderate to severe Chronic OA Pain or CLBP.[33] Long-term efficacy and safety were also assessed in these patients.[34] The results demonstrated that HC/APAP CR was associated with improvement in physical function and a reduction in work productivity impairments and pain-related sleep interference.[33] Furthermore, HC/APAP CR was efficacious for the treatment of OA and CLBP over the 56-week study period.[34] Finally, the incidence of adverse events associated with administration decreased over time, and the safety profile of HC/APAP CR was consistent with that of a mu-opioid receptor agonist.[34]

In summary, long-acting opioid formulations may provide a useful treatment alternative for patients experiencing moderate to severe pain. Recent data from clinical trials of a continuous-release formulation of HC/APAP demonstrate improvements in patients' quality of life and daily functioning, including sleep quality, physical functioning, and work productivity.

Immediate-Release and Extended-Release Tapentadol

Tapentadol is a novel, centrally acting analgesic with a dual mode of action: μ-receptor agonism and norepinephrine reuptake inhibition.[35-38] The safety and efficacy of immediate-release and extended-release formulations of tapentadol are currently being studied as treatment options for patients with moderate to severe acute or chronic pain, and results from these clinical studies were presented at AAPM and APS.[35-38]

Stegmann et al examined the tolerability and efficacy of immediate-release tapentadol for the treatment of moderate to severe pain in 268 patients who underwent bunionectomy surgery.[38] Patients were randomly assigned to 1 of 4 treatment groups (50 mg tapentadol IR, 100 mg tapentadol IR, 10 mg oxycodone IR, and placebo) and received an oral dose of the treatment drug every 4 to 6 hours over 3 days.[38] Both doses of tapentadol IR were effective in relieving moderate to severe pain following bunionectomy.[38] Furthermore, tapentadol IR (50 mg) had similar efficacy compared with oxycodone IR (10 mg), and a lower incidence of certain adverse events (eg, constipation).[38] Similar findings were observed in another bunionectomy study evaluating different doses of tapentadol IR (50, 75, or 100 mg) and oxycodone IR (15 mg), with all doses of tapentadol administered providing effective analgesia, and the incidence of gastrointestinal disorders was lower for the tapentadol IR groups compared with the oxycodone IR group.[36]

Another double-blind, randomized, placebo-controlled, multicenter study evaluated the efficacy of tapentadol IR to reduce pain in 659 patients who were primary candidates for joint replacement surgery for end-stage joint disease.[35] Patients were randomly assigned to receive oral doses of tapentadol IR (50 or 75 mg), oxycodone IR (10 mg), or placebo every 4 to 6 hours for 5 days.[35] The results from this study revealed that both doses of tapentadol IR and oxycodone IR provided significant pain relief compared with placebo.[35] Furthermore, tapentadol IR was associated with fewer gastrointestinal adverse effects compared with oxycodone IR.[35] These results are similar to findings observed with other studies discussed above evaluating the tolerability and analgesic efficacy of tapentadol IR in patients with moderate to severe acute pain.

A study examining the analgesic efficacy and safety profile of tapentadol ER was also presented at the AAPM meeting. Rauschkolb-Loeffler et al assessed the efficacy and tolerability of tapentadol ER in 670 patients with moderate to severe OA pain of the knee.[37] Patients were randomly assigned and titrated to a maintenance dose of 100 or 200 mg tapentadol ER, 20 mg oxycodone CR, or placebo administered twice daily for 4 weeks. The results from this study revealed that tapentadol ER was effective in the treatment of moderate to severe chronic OA pain, and 100 mg of tapentadol ER had similar analgesic efficacy compared with oxycodone CR.[37] Furthermore, patients receiving tapentadol ER experienced fewer gastrointestinal and central nervous system adverse events compared with oxycodone.[37]

Taken together, these studies demonstrate that IR and ER formulations of tapentadol have similar efficacy compared with short-acting and long-acting formulations of oxycodone, with a lower incidence of gastrointestinal adverse events. This evidence suggests that tapentadol may be a promising new treatment option for acute and chronic pain conditions. However, further research examining the safety profile, long-term tolerability, and long-term efficacy of tapentadol is essential to help determine the appropriate type of patient and pain conditions that would benefit from tapentadol treatment.

Fentanyl Buccal Tablets

Fentanyl buccal tablets (FBTs) are a relatively new formulation of fentanyl utilizing an effervescent drug delivery system in order to provide rapid absorption of fentanyl through the buccal mucosa.[39,40] Previous clinical studies have demonstrated that FBTs were efficacious and generally well-tolerated for the treatment of breakthrough pain in opioid-tolerant patients with chronic cancer- or noncancer-related pain.[41-43] However, these were short-term studies over a few weeks and it is unclear if the safety and efficacy of FBTs would be maintained long-term. Thus, several presentations at the annual meetings of the AAPM and the APS evaluated the long-term safety and efficacy of FBTs for the treatment of breakthrough pain in these patient types.

Weinstein et al examined the long-term safety and tolerability of FBT to adequately manage breakthrough pain in 197 opioid-tolerant patients with chronic cancer pain in an open-label, multicenter clinical study.[44] The mean duration of exposure to FBT was 122 days, with 36 (18%) of the total number of patients exposed to FBT for 12 months. There were 74 patients who discontinued the study for lack of efficacy (n = 3) or

adverse events (n = 71).[44] The adverse events reported were typical of a mu-opioid receptor agonist and were similar in occurrence and severity to those observed in previous short-term studies (eg, nausea, vomiting, and dizziness).[44] The authors concluded that FBT was a safe and generally well-tolerated treatment option for opioid-tolerant chronic cancer pain patients who experience breakthrough pain.

Because of the prevalence of medical misuse, abuse, and diversion of prescription opioids, there is a clear need for the development of opioid medications that deter abuse.[21]

Fine et al also analyzed data evaluating the tolerability and safety profile of FBTs in opioid-tolerant patients with cancer-related and breakthrough pain.[45] A pooled analysis of findings from 2 randomized, double-blind, placebo-controlled studies reported on the adverse events associated with administration of FBT for breakthrough pain in these patients. In both of these studies an open-label titration period was followed by 10 double-blind treatments with either FBT or placebo. Out of the 248 patients titrated with FBT, 164 progressed to the double-blind phase. Adverse events occurred in 72% of the patients, with 36% thought to be related to FBT administration.Treatment-related adverse events were similar to those that have been reported in previous studies (ie, dizziness, nausea, headache, fatigue, vomiting, and constipation).[45] These results indicate that adverse events associated with FBT therapy are similar to those observed with opioid treatment in general.

The efficacy of FBT has also been evaluated inopioid-tolerant patients with chronic noncancer pain.[46-48] Three studies presented at AAPM and APS evaluated the effects of FBT therapy on breakthrough pain in these patients with regard to efficacy and safety, response profile, and assessments of patient function.[46-48] Patients in these studies went through an initial dose titration period to determine an appropriate FBT dose, and then they received open-label FBT at the successful dose for 4 weeks, followed by a double-blind randomization period where they received 9 doses of either FBT or placebo (6 doses of FBT, 3 doses of placebo).[46-48] Compared with placebo, fentanyl buccal tablets were more efficacious and they were both safe and generally well-tolerated. Furthermore, the response profile of FBTs were consistent across various clinical measures, including pain intensity, any pain relief (APR), and meaningful pain relief (MPR) after 12 weeks of treatment.[46,47] Finally, clinician and patient ratings of function were consistently positive in these patients with improvements in mood, sleep, general activity, the ability to perform work, and participation in social interactions.[48]

Taken together, these studies demonstrate that FBTs can be an efficacious and relatively safe treatment option for breakthrough pain in opioid-tolerant patients withchronic cancer-related and noncancer-related pain.

Aerosolized Free and Liposome-Encapsulated Fentanyl

A noninvasive, nebulized mixture of free (rapid absorption) and liposome-encapsulated (sustained-release) fentanyl was developed to have both a rapid onset and extended duration of action and allows a patient to adjust dosing to match his or her analgesia needs.[49,50] Aerosolized free and liposome-encapsulated fentanyl is currently being examined as an innovative treatment for postsurgical acute pain. Clark et al examined the ability of aerolef to allow patient self-titration to obtain effective analgesia in postsurgical patients with acute pain.[50] The results from the study revealed that aerolef, at doses that were sufficient to produce analgesia, was generally well-tolerated and no serious adverse events were associated with administration.[50] Another study examined the efficacy, safety, and tolerability of aerolef following orthopedic surgery.[49] Ninety-nine patients were randomized to receive either aerolef or placebo.[49] Aerosolized free and liposome-encapsulated fentanyl was more efficacious compared with placebo, and time to effective pain relief was shorter with the drug. No patients in either treatment group required opioid antagonists or ventilatory support.[49] The results from this study suggest that patient-controlled inhalational analgesia can provide safe and effective pain relief.[49] Taken together, these studies demonstrate that aerosolized free and liposome-encapsulated fentanyl is an innovative, effective, and relatively safe approach for the treatment of postoperative pain.

Intranasal Hydromorphone

Intranasal hydromorphone is currently being studied for the management of moderate to severe trauma pain. Lacouture et al assessed the pharmacokinetic profile of intranasal hydromorphone in emergency trauma patients.[51] The results from the study demonstrated a rapid dose-related increase in plasma hydromorphone in these patients.[51] Furthermore, the concentrations of plasma hydromorphone were similar to those after intravenous administration.[51] These results indicate that in trauma patients presenting in the emergency room, intranasal hydromorphone is a novel approach to providing "needle-free" rapid and effective analgesia.

Intravenous Acetaminophen

Intravenous acetaminophen (IV-APAP) is currently undergoing clinical trials for the treatment of acute pain and fever. A multicenter, double-blind, randomized, placebo-controlled study examined the efficacy and safety of IV-APAP for the treatment of acute pain following vaginal hysterectomy.[52] The results from this study demonstrated significant improvements on measures of pain intensity, time to first rescue medication dose, and consumptionof rescue medications (eg, morphine) in patientstreated with IV-APAP compared with placebo.[52] Furthermore, IV-APAP was well-tolerated, and there were no clinically relevant differences between the 2 treatment groups on adverse

Findings from these meetings demonstrate the continuing need to educate physicians and other healthcare professionals on the appropriate use of opioids in the context of pain management and several novel approaches to increasing treatment options in order to provide patients with more effective therapy while reducing risk.

effects.[52] Thus, IV-APAP was more efficacious than placebo for the treatment of acute pain and fever following vaginal hysterectomy. More research should evaluate the safety and efficacy of IV-APAP for other acute pain conditions.

Tamper-Resistant and Abuse-Deterrent Opioid Formulations

Extended-Release Morphine Sulfate and Sequestered Naltrexone

Because of the prevalence of medical misuse, abuse, and diversion of prescription opioids, there is a clear need for the development of opioid medications that deter abuse.[21] An investigational extended-release opioid containing polymer-coated morphine sulfate pellets with a sequestered naltrexone core that is released by crushing, chewing, or dissolving the medication is currently undergoing clinical trials as an abuse-deterrent opioid formulation for the treatment of moderate to severe chronic pain.[53] Studies presented at AAPM and APS assessed the efficacy and safety of extended-release morphine sulfate and sequestered naltrexone combination (morphine ER/naltrexone) for the treatment of moderate to severe chronic pain.[53-55] The pharmacodynamics and abuse potential of this analgesic were also studied among recreational opioid users.[53,54] A multicenter, prospective, randomized, double-blind, crossover study compared the pharmacokinetics, efficacy, and safety of morphine ER/naltrexone with a currently available single-agent extended-release morphine sulfate analgesic (morphine ER) in 113 adults with moderate to severe osteoarthritis (OA) pain.[55] The morphine ER/naltrexone combination and morphine ER had similar effects on pain intensity ratings, physical function, anchange from baseline.[55] Furthermore, the level of naltrexone that was present in the plasma of those patients that received the morphine ER/naltrexone combination did not appear to affect pain scores.[55] Finally, there were no differences in the type, severity, or frequency of adverse effects for either treatment.[55]

Jones et al evaluated the abuse potential of morphine ER/naltrexone in recreational opioid users. A randomized, double-blind, triple-dummy, single-dose, 4-way–crossover study compared pharmacodynamics (eg, drug liking) and pharmacokinetics in 4 different treatment groups: 2 whole 60 mg morphine ER/naltrexone capsules, 2 crushed 60 mg morphine ER/naltrexone capsules, 120 mg morphine sulfate solution, and placebo.[53] Pharmacodynamic assessments evaluating drug liking/euphoria and abuse potential found that subjects who received the morphine solution had significantly higher scores compared with those subjects who received whole morphine ER/naltrexone capsules, crushed morphine ER/naltrexone capsules, or placebo.[53] Pharmacokinetic assessments (eg, mean Cmax and median Tmax) were similar between crushed morphine ER/naltrexone (80.6 ng/mL, 1.0 h) and the morphine solution (92.5 ng/mL, 1.0 h), but different from whole morphine ER/naltrexone (18.4 ng/mL, 8.0 h).[53]

In summary, these studies demonstrate that the morphine ER/naltrexone combination has similar efficacy and safety when compared with a single-agent morphine ER product. Furthermore, it appeared that when morphine ER/naltrexone is tampered with (ie, crushed), the release of sequestered naltrexone that is present in morphine ER/naltrexone capsules decreased drug liking/euphoria effects of the morphine, making the abuse potential of the crushed product similar to the intact product in recreational opioid users.

Abuse-Deterrent Sustained-Release Oxycodone

A novel formulation of oxycodone that is designed to be more resistant to tampering and misuse is currently being evaluated for its safety, pharmacokinetic properties, and abuse potential in various tampering simulations in 12 healthy volunteers.[56] Initial results from this single-dose, open-label, cross-over comparison study demonstrated that the abuse-deterrent sustained-release oxycodone formulation protected the drug from immediate-release in various tampering simulations.[56] Furthermore, the plasma profile for the chewed dosage form (controlled simulation for misuse of drug) was bioequivalent to the drug when administered whole, indicating that misuse of this compound by chewing would not result in a spike in plasma levels of the drug.[56]

Summary

The widespread use of opioids as part of pain management strategies for the treatment of acute and chronic pain conditions has spurred vigorous debate and new approaches to education about appropriate use of these drugs, their advantages and disadvantages as treatment options, how to optimize therapeutic outcomes and minimize risk and potential harms, and fostered number of guidelines to help physicians appropriately and safely manage their patients' pain. Physician interest in issues relating to opioid use in pain management is reflected in the number of presentations and variety of topics that focused on the use of opioid analgesics as treatment options at the 2008 annual meetings of AAPM and APS. Findings from these meetings demonstrate the continuing need to educate physicians and other healthcare professionals on the appropriate use of opioids in the context of pain management and several novel approaches to increasing treatment options in order to provide patients with more effective therapy while reducing risk.

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POSTTEST

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Posttest Questions

1. In a study by Vo et al examining the impact of pain on patients' health-related quality of life, _____of chronic pain patients reported that pain disrupted their activities of daily living.
a. 9%
b. 39%
c. 79%
d. 99%

2. In the same study by Vo et al, _____of physicians indicated that their patients with chronic pain conditions frequently wake during the night due to breakthrough pain.
a. 6%
b. 36%
c. 76%
d. 96%

3. A significant barrier to appropriate and effective pain management is the shortage of pain specialists to provide care for the millions of patients suffering from complex pain conditions, with only _____ board certified specialists available per 100 000 patients.
a. 6
b. 10
c. 15
d. 20

4. In the Webster study, what was the most frequent initial purpose of opioid use?
a. Recreational use/abuse
b. Physician prescription for pain medication
c. Decrease anxiety
d. Sleep aid

5. _____ is a novel, centrally acting analgesic with a dual mode of action (μ-receptor agonism and norepinephrine reuptake inhibition) for the treatment of moderate to severe acute and chronic pain.
a. Fentanyl buccal tablets
b. Substance P
c. Tapentadol
d. Extended-release morphine and sequestered naltrexone

6. Recent data presented at the 2008 AAPM and APS annual meetings from clinical trials of a continuous-release formulation of the combination opioid _____ demonstrated significant improvements in patients' quality of life and daily functioning.
a. Propoxyphene/acetaminophen
b. Hydrocodone/acetaminophen
c. Oxycodone/acetaminophen
d. All of the above

7. A study by Weinstein et al demonstrated that _____ was a safe and generally well-tolerated treatment option for opioid-tolerant chronic cancer pain patients who experience breakthrough pain.
a. Aerosolized free and liposome-encapsulated fentanyl
b. Intravenous acetaminophen
c. Intranasal hydromorphone
d. Fentanyl buccal tablets

8. According to Wiedemer et al, what percentage of patients admitted to the Opioid Renewal Clinic resolved their aberrant drug behavior within 1 year?
a. 4%
b. 34%
c. 74%
d. 94%

9. Coddings et al demonstrated that 1 or 2 tablets of _____ administered twice daily significantly decreased CLBP intensity compared with placebo.
a. Morphine
b. Tramadol
c. Extended-release hydrocodone/acetaminophen
d. Oxycodone CR

10. According to Strassels et al, physicians who were surveyed felt that the barriers to providing effective pain management to their patients were _____.
a. Insufficient time
b. Problematic patient and family attitudes about the use of opioids
c. Fear of regulatory scrutiny
d. All of the above

POSTTEST ANSWER SHEET

1._____ 2._____ 3._____ 4._____ 5._____ 6._____ 7._____ 8._____ 9._____ 10._____

Participant name:

Phone number: ___ – ___ – ____

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State: ZIP code:

Phone number: ○ Home ○ Work

Fax number:

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Quality of educational content	1	2	3	4	5	Level of instruction	1	2	3	4	5
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Scientifically rigorous	1	2	3	4	5	Appropriate teaching method used	1	2	3	4	5

Please indicate whether the following objectives were met:

LEARNING OBJECTIVES	Yes	No
Discuss current pain management strategies available to help treat patients with acute or chronic pain conditions	○	○
Examine recent clinical data evaluating the safety and efficacy of immediate-release (short-acting) and extended-release (long-acting) opioid analgesic formulations for the treatment of moderate to severe acute and chronic pain	○	○
Evaluate the effectiveness of extended-release opioid analgesics on improving patient outcomes, including quality of life and daily functioning	○	○

This activity was free of commercial bias. (If not, please explain below.)				○	○
This activity increased your knowledge in delivering patient care. (May comment below.)				○	○
This activity increased your knowledge in delivering patient care. (If so, how? May comment below.)				○	○
If yes, how soon will you implement a change?	○ Immediately	○ 1 month	○ 6 months	○ 12 months	
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How did you hear about this activity? (Please select all that apply	○ Brochure	○ E-mail	○ Colleague	○ Telephone
	○ Web site	○ Fax	○ Other_____	

EDUCATIONAL NEEDS – YOUR COMMENTS ARE APPRECIATED AND WILL HELP TO IMPROVE FUTURE ACTIVITIES

1) What topics would you like to see in future programs?

_____

2) How can we improve this activity?

_____

Comments: _____

_____

_____