Breakthrough Pain and Pain Management

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Objectives

- Discuss alternative treatments of breakthrough pain in cancer pain patients receiving spinal analgesics.
- Review the use of oral transmucosal fentanyl citrate for the treatment of breakthrough pain in patients with cancer.
- Determine the incidence and possible treatment modalities of breakthrough pain in opioid-treated patients with non-malignant pain.
- Report on a placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer.
- Review the pharmacological and clinical characteristics of oral transmucosal fentanyl citrate for the treatment of breakthrough pain in patients with cancer.
- Discuss reasons buprenorphine has failed to gain popularity in the treatment of cancer-related pain.
- Review the prevalence, characteristics, and treatments of breakthrough pain in patients receiving opioid therapy for chronic noncancer pain.
- Assess the efficacy and safety of a radioisotope to reduce incident pain in patients with bone metastases following prostate cancer.
- Report the use of a computer-integrated infusion system to provide patient-controlled continuous epidural analgesia during labor.

- State the advantage of precision diffusion kinetics in the administration of potent opioid analgesics.

Alternative treatments of breakthrough pain in patients receiving spinal analgesics for cancer pain.

Mercadante S et al

Journal: J Pain Symptom Manage, 30(5):485-491, 2005. 18 References
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Faculty Disclosure: Abstracted by J. Joyce, who has nothing to disclose.

Oral analgesics for cancer pain management have been demonstrated as successful in the majority of patients. Nevertheless, some patients fail to respond to pharmacological therapy or suffer from unacceptable adverse effects. As a result, more complex and individualized treatments requiring multiple analgesic regimens and alternate administration routes are required to effectively address the shortcomings thus far experienced. For patients who do not effectively respond to systemic opioid administration, including drug and/or route switching, spinal treatment may be indicated. This treatment is complex and requires expertise to accomplish.

Breakthrough pain is defined as a transitory increase in pain intensity on a baseline pain of moderate intensity in patients receiving regularly administrated analgesic treatment. These fluctuations are challenging to treat successfully because of the unpredictability and need for rapid intervention. Traditional treatment is based on the use of short-onset opioids administered via fast routes such as oral, transmucosal, or intravenous. The strategies of treatment are based on individual solutions.

This study investigated intrathecal analgesics for cancer pain management. The authors prospectively treated 84 episodes of breakthrough pain in 12 patients admitted to a pain center. The patients were selected for intrathecal

treatment after receiving different trials with systemic opioids. They presented with breakthrough pain that required alternative methods, including sublingual ketamine or intrathecal boluses of local anesthetics.

Patients receiving spinal treatment pose important clinical problems. Regardless of the difficulties in finding the best treatment balance between local anesthetic and morphine doses, another problem is presented by the treatment of pain flares. A drug delivery system for on-demand delivery of intrathecal morphine has been developed. Intrathecal morphine has a slow onset, while local anesthetics have the shortest onset time. Local anesthetics also have an individualized dose-effect relationship with narrow therapeutic windows, whether administered chronically or as a bolus. *Levo*-bupivacaine (LB) seems to have convenient properties and is nearly equipotent to bupivacaine. Proper dose titration under an initial strict surveillance may find the dose effective to control pain in a short period of time without producing significant adverse effects.

Intranasal administration of ketamine or opioids can produce significant breakthrough pain relief within 10 minutes, but the development of tolerance to ketamine over time cannot be excluded. Mean volumes of 0.6 mL of a local anesthetic were effective within minutes and well tolerated in patients receiving a continuous intrathecal infusion of a combination of morphine and LB in different doses. Similarly, ketamine in doses of 25 mg sublingually was effective and relatively well tolerated.

Although the availability of transmucosal drugs remains variable, significant effects are demonstrable using mucosal absorption methods. Using drugs other than opioids, the problem of highly tolerant patients, who are poorly responsive to systemic opioids, can often be overcome.

Oral transmucosal fentanyl citrate for cancer breakthrough pain: a review.

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Journal: Oncol Nurse Forum 33(2):257-264, 2006. 60 References
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Breakthrough pain (BP) is defined as a transitory exacerbation of pain that occurs in a background of otherwise stable pain in patients receiving chronic opioid therapy. BP is generally of rapid and paroxysmal onset with a brief duration (peak intensity 3-52 min). The prevalence is reported at 51-86% in patients with cancer. Subtypes of BP include: incident, predictable (consistent temporal causal relationship with predictable motor activity, such as movement, defecation, micturition, breathing, or coughing); incident, unpredictable (inconsistent temporal causal relationship with motor activity, such as sneezing, bladder spasm, or coughing); idiopathic (not associated with a known cause; generally of longer duration that incident pain); and end of dose (occurring before a scheduled dose of an around-the-clock analgesic, more gradual onset, and longer duration than incident or idiopathic). BP is associated with increased pain-related functional impairment, psychological distress and use of medical resources.

Oral morphine has not been adequate to treat BP due to its relatively low potency for an opiate as 90% is ionized at the mouth pH, and it is the least lipid-soluble opioid. Relative potency of oral transmucosal fentanyl citrate (OTFC) to morphine (IV) is about 10:1; 20 g of IV fentanyl (FEN) is approximately equivalent to 200 g of OTFC and 2-4 mg of IV morphine, or 6-12 mg of oral morphine.

FDA approval is only for BP in patients with malignancies who are receiving and are tolerant to opioid therapy because life-threatening hypoventilation can occur at any dose in patients not tolerant to opioids. When compared to oral FEN, OTFC produces higher maximum plasma concentration (3.0 vs. 1.2 ng/mL) with faster time to peak concentration (22 vs. 101 min) and greater bioavailability (52% vs. 32%). About 25% of OTFC goes directly into the blood stream via mucosal absorption; 75% is swallowed and more slowly

absorbed from the gut (50% goes through first pass effect metabolism in the liver and 25% becomes bioavailable).

The onset of analgesia with OTFC is as quickly as 6 min with peak effects 20-30 min later and duration of 2-5 hrs. The recommended time for consumption of an OTFC is 15 min to achieve the desired onset and peak effects; permeability is lowest in the gingiva and tongue. Ideally, the matrix should be swabbed across the inside of the cheek and not placed on the tongue. Patients should avoid drinking coffee, cola, or citrus fruit juices before drug administration. It appears that no change of dosing is indicated for older adults but they may be twice as sensitive to the effects of FEN given IV. Another advantage to OTFC is the amount absorbed remains stable over multiple administrations as the peak concentration of drug is dependent on the total dose delivered. Dose-related side effects include somnolence, nausea, dizziness, and dental cavities.

OTFC is relatively easy to titrate to a successful dose level and is highly rated by patients. Patients have reported significantly lower pain intensity, greater pain intensity difference, and pain relief with OTFC compared to immediate-release morphine. In repeated studies, few patients withdrew and the vast majority chose to continue with OTFC after the study was completed. To evaluate long-term safety, 167 patients who had participated in 3 previous studies were invited; 155 (93%) chose to enroll. They were instructed not to use more than 2 OTFC units to treat a single episode of BP and no more than 6 OTFC units/day. The duration of the study period was 1-423 days; average number of breakthrough episodes/day was 2.9 with 2.4 treated successfully; 61% of patients remained on the same OTFC does throughout the study period, indicating that patients do not appear to develop tolerance.

The average cost per unit of OTFC is about $8 with average consumption of 4 units/day; the yearly cost would be approximately $10,000 compared to about $3000/yr for comparative doses of other oral opioids. But the use of OTFC has been shown to decrease the need for emergency center visits, parenteral opioids, and hospital admissions.

In conclusion, OTFC is relatively easy to use, noninvasive, effective, safe, and acceptable to patients. Patients must be instructed on proper OTFC use, handling, storage, and disposal.

Breakthrough pain in opioid-treated chronic non-malignant pain patients referred to a multidisciplinary centre: a preliminary study.

Hojsted J et al:

Journal: Acta Anaesthesiol Scand 50(10):1290-1296, 2006. 40 References
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This study investigated the prevalence, characteristics, and mechanisms of breakthrough pain (BTP) in patients with chronic, non-malignant pain who were referred to a pain center and assessed the short-term effects of pain treatment. BTP is defined as a transient increase in pain to greater than moderate intensity, which occurred on a baseline pain level of moderate intensity or less. All patients referred to a multidisciplinary pain center from November 2002 to May 2004 were enrolled. Inclusion criteria were: at least 18 yrs of age, duration of pain > 3 months, and on oral opioids > 1 month. Exclusion criteria were: psychiatric disease and/or history of current substance abuse.

Patients were assessed at the initial visit (T_o) and after a 3-month treatment period (T_3). The pain intensity was assessed using a visual analog scale (VAS) of the brief pain inventory (BPI), which measures pain at its worst, least, and average during the previous 24 hours and current pain intensity. The BTP was evaluated as spontaneous or precipitated by some event: voluntary actions/position change and/or involuntary actions (micturition, defecation, cough). The mini-mental state examination (MMSE) was used to assess cognitive functioning; possible scores were 0-30; scores >23 were generally considered normal. Anxiety and depression were evaluated using

the hospital anxiety and depression scale (HADS), which is a self-assessment questionnaire. The treatment goal was to convert short-acting oral opioids to long-acting oral opioids and discontinuing on-demand and parenteral opioids.

A total of 33 consecutive patients (20 females, 13 males); 27 were included in the final results. Median age was 55 years (range 26-74 years) and median pain duration was 6 years (5 months-32 years). The pain pathophysiology was disc prolapse (9), lower back (5), unspecified musculoskeletal (4), neurogenic after surgery (3), para- and tetraplegia (2), spinal fracture (2), ulcerative colitis (2), spinal stenosis (1), whiplash (1), post-traumatic headache (1), spondylolisthesis (1), postherpetic neuralgia (1), and refractory angina pectoris (1). One pain area was reported by 8 patients, 16 had 2 pain areas, and 9 patients had 3 or more areas. BTP was reported at T_o by 30 of 33 (prevalence 90%) and at T_3 by 19 of 27 (70%). The worst, least, average, and current pain intensity and duration of BTP were statistically reduced from T_0 to T_3; only the number of BTPs did not change. Most BTPs were exacerbation of background pain assumed to be the same pain mechanisms. At T0, 85% of somatic nociceptive and 82% of neuropathic pain came from background pains of the same pain mechanisms.

The median oral morphine dose at T0 was 55 mg (range 3.75-540 mg) and at T_3, 60 mg (0-180). At T_0, 15 patients were receiving short-acting opioids, 6 were taking long-acting opioids, and 6 received a combination. By T_3, all opioids were converted to long-acting opioids except 1 patient who stopped opioid treatment. At T_0/T_3 (n=33/n=27), the reported side effects were: cognitive complaints, 33/22; dryness of mouth, 21/10; sweating, 13/9; sleep disturbances, 12/9; mood changes, 12/8; nausea, 8/0; hyperalgesia/allodynia, 8/0; sedation, 6/8; myoclonus, 4/5; constipation, 1/11; hallucinations, 1/0; itching, 1/0; and restless legs, 1/0, respectively. Use of gabapentin and tricyclic antidepressants did not change significantly from T_0 to T_3.

Median MMSE scores at T0 were 29 (24-30) and at T_3, 29 (22-30). No statistically significant differences were seen between anxiety or depression

scores at either assessment; but consistent and statistically significant associations were found at T_0 and T_3 between high average pain intensity for the past 24 hours and high scores on HADS for both anxiety and depression.

In conclusion, BTP is frequent and severe in patients with chronic, non-malignant pain. Opioid stabilization appeared to reduce pain intensity and duration of BTP.

A randomized, placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer.

Portenoy RK et al:

Journal: Clin J Pain, 22(9):805-811, 2006. 28 References
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The prevalence of cancer-related breakthrough pain (BTP), a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain, is 50% to 90%. Consensus is supported that BTP should be independently assessed and treated. The most common approach involves access to a "rescue," or supplemental, medication--a short-acting opioid provided in combination with the fixed-schedule opioid regimen. The effectiveness of oral rescue drugs in the management of BTP in opioid-treated patients with chronic pain has not been adequately evaluated.

The typical characteristics of BTP, particularly the fact that the pain peaks within minutes, suggests that responsiveness to an oral drug may be less than optimal because the onset of analgesia may follow the peak of the target pain. The potential usefulness of a nonparenteral drug for BTP with a faster onset of effect was the rationale for the development of oral transmucosal fentanyl citrate (OTFC) as a treatment for BTP. Controlled studies to show that this formulation could provide analgesia at 15 minutes.

The fentanyl buccal tablet (FBT) incorporates a novel drug delivery platform, OraVescent technology, which employs an effervescent reaction to enhance the fentanyl absorption through the buccal mucosa and facilitate rapid system exposure to the analgesic. The present article concerns the first controlled clinical study designed to evaluate the efficacy, safety, and tolerability of FBT in opioid-treated patients with chronic pain associated with cancer.

After initial screening, opioid-treated adult patients with a chronic cancer pain who experience 1-4 BTP episodes per day were potentially eligible for participation in the study. Eligible patients entered an open-label titration phase to establish an effective dose of FBT for use in the double-blind phase. Patients were subjected to FBT tablets by batch available in 100, 200, 400, 600, and 800 μg doses.

Once a dose provided the satisfactory relief within 30 minutes, without unacceptable adverse effects, during 2 consecutive BTP episodes, this dose was used throughout the double-blind period. Patients discontinued the study if titration to the highest dose (800 μg) did not yield satisfactory pain relief or FBT produced unacceptable adverse effects.

In the double-blind phase, patients were randomly assigned to 1 of 18 prespecified dose sequences of 10 tablets (7 FBT and 3 placebo). All 10 doses were to be taken within a 21-day period, with a maximum of 4 episodes treated per day. Patients were instructed to obtain a baseline pain intensity (PI) measurement when a BTP episode began. FBT or placebo was then administered in a blinded fashion. PI and pain relief (PR) were recorded 15, 30, 45, and 60 minutes thereafter. Patients also recorded adverse events (AEs) after each dose.

Analgesic effects of FBT separated from placebo as early as 15 minutes after administration and the extent of separation increased up to and including the 60-minute time points. A ≤33% reduction in PI, considered a clinically relevant effect, occurred by 15 minutes in 13% of episodes treated with FBT;

by 30 minutes, this level of response was observed in 48% of episodes. PI decreased from a mean of 6.9 at baseline to 4.6 at 30 minutes. Although patients with all types of pain responded, those with neuropathic pain responded better than those with nociceptive pain.

Treatment-related AEs were largely limited to adverse effects typical of opioids. Twelve and 3 of the 123 enrolled patients withdrew from the titration and double-blind period, respectively, as a result of AEs. Only 2 patients could not tolerate the drug as a result of its effects on the oral mucosa. Overall, 65% of patients were able to find an effective dose of FBT during the titration phase. Twenty of the 123 enrolled patients (16%) did not report satisfactory relief at the highest dose allowed during titration.

Oral transmucosal fentanyl citrate for the treatment of breakthrough pain in cancer patients: an overview of its pharmacological and clinical characteristics.

Mystakidou K et al:

Journal: Am J Hosp Palliat Med 22(3):228-232, 2005. 21 References
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As many as two-thirds of cancer patients experience transient exacerbations of severe pain that occur against a background of otherwise controlled, tolerable pain, which is known as breakthrough pain (BTP). BTP is characterized by rapid onset (median interval 3 minutes from onset to peak; range 1 sec to 30 minutes), moderate to severe intensity, and a relatively short duration (30 minutes). Oral transmucosal fentanyl citrate (OTFC) has been developed specifically to treat BTP. OTFC is a potent, short-acting, rapid-onset, lipophilic, synthetic opioid with specificity for μ-receptors in the brain, spinal cord, and other tissues. It is formulated as a solid drug matrix

on a handle that allows the unit to rotate in the mouth and is available in 6 strengths (200, 400, 600, 800, 1200, or 1600 µg).

The effects of fentanyl are related to blood levels with 1-2 ng/mL providing analgesia and 10-20 ng/mL providing surgical anesthesia and profound respiratory depression in those who are not opioid-tolerant. OTFC administration results in an initial rapid absorption form the buccal mucosa and a more prolonged absorption of swallowed fentanyl from the gastrointestinal tract. Blood levels will depend on how much of the drug is absorbed orally. Usually, about 25% of the total OTFC is absorbed orally; about 25% of the total dose escapes hepatic and intestinal first-pass elimination. Absorption curves for each dose level are similar in shape, indicating that increasing dose levels produce predictable increasing serum fentanyl levels. More than 90% of fentanyl is metabolized into norfentanyl and other inactive metabolites in the liver and intestinal mucosa by cytochrome P450 3A4 isoenzyme system and oxidative µ-dealkylation and excreted in the urine. Total plasma clearance is 0.5 L/hr/kg (range 0.3-0.7 L/hr/kg) with a terminal elimination half-life of about 7 hours.

OTFC is a sweetened lozenge with an integral oromucosal applicator that is administered by sucking. A successful dose is identified under closely supervised titration. It is noted that chronic, persistent background pain should be controlled with opioid therapy and patients should not be having more than 4 episodes of BTP. The initial dose should be 200 µg with upward titration as needed if adequate analgesia is not obtained within 15 minutes after the lozenge is finished. A maximum of 2 lozenges is used to treat each pain episode. If more than 1 lozenge is required in several consecutive episodes, the next available strength should be considered. A maximum of 4 unit doses per day is recommended; if more than 4 are needed, the fixed-schedule analgesic dose should be increased or the overall pain management strategy reevaluated.

OTFC adverse events are opioid-related, including somnolence, dizziness, nausea, constipation, asthenia, and confusion. Hypoventilation and possible

respiratory failure result from an overdose so all patients must be followed closely for symptoms of respiratory symptoms. Concomitant use of other depressants may produce additive sedative effects and OTFC should not be administered to patients who have received monoamine oxidase inhibitors within the previous 14 days.

Several small, short-term studies in adult patients have evaluated the efficacy of OTFC for the management of BTP. The vast majority of patients achieved adequate analgesia once the appropriate dose was identified; satisfaction scores were very high, and emergency room visits, parenteral opioids, and hospital admissions were reduced.

It is concluded that OTFC has a safety profile and pharmacokinetic characteristics to make it the ideal agent for the management of BTP in cancer patients already receiving around-the-clock opioid medication.

Safety and effectiveness of intravenous morphine for episodic breakthrough pain in patients receiving transdermal buprenorphine.

Mercadante S et al:

Journal: J Pain Symptom Manage, 32(2):175-179, 2006. 11 References
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Faculty Disclosure: Abstracted by J. Joyce, who has nothing to disclose.

Buprenorphine (BUP) is a partial mu-receptor agonist that has been used for at least 30 years in the treatment of cancer-related pain. It has never gained popularity. The reasons for the reluctance to use BUP include the adverse event profile of the parenteral and sublingual formulations, the presumed ceiling effect for analgesia, and possible problems if used with other opioids due to its potential antagonist activity when administered to a patient receiving a full agonist drug. As a result, BUP has been labeled an atypical opioid, difficult to place on the “analgesic ladder,” and less easy to use

clinically than other strong opioids.

BUP has recently been formulated into a transdermal patch. The aim of this open-label study was to evaluate the safety and effectiveness of IV-morphine (IV-MO) in advanced cancer patients who are receiving transdermal BUP (transdermal therapeutic system; TTS-BUP). In cancer patients, breakthrough pain is a transient flare of pain, severe in intensity, which is superimposed on an otherwise stable pain pattern in patients treated with opioids. The availability of supplemental doses of short-acting opioid in addition to the continuous analgesic medication is the main treatment suggested to manage these pain flares. The use of BUP in association with other opioids has been a concern because of a possible antagonistic effect, which might reduce analgesia or induce withdrawal symptoms.

Clinically, the combination of BUP with morphine in the analgesic dose range results in a magnitude of effect compatible with an additive type of interaction. In the current study, IV-MO provided a strong and rapid analgesic effect in patients presenting with severe pain flares and having basal pain responsive to the TTS-BUP regimen. Acute adverse effects occurring after IV-MO were those commonly observed with opioid therapy. The occurrence of such adverse effect was independent of the basal TTS-BUP regimen and, as a consequence, of the IV-MO dose administered as needed.

There are obvious limitations of this study, principally the lack of blinding and a control group. These results must be interpreted with caution. In contrast to a previous experience, timing for evaluation in this study was fixed at 15 minutes, which seemed to be more objective and reasonably acceptable for judging the effect of a treatment for breakthrough pain on the basis of data reported in the literature.

In conclusion, IV-MO at a dose equivalent to 20% of the oral morphine equivalent of TTS-BUP is safe and effective in most patients experiencing pain exacerbation.

Prevalence and characteristics of breakthrough pain in opioid-treated patients with chronic noncancer pain.

Portenoy RK:

Journal: J Pain 7(8):583-591, 2006. 16 References
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A transitory exacerbation of pain occurring on a background of otherwise controlled chronic pain is termed breakthrough pain (BTP); 50-90% of patients with chronic pain experience BTP. This study aimed to identify the phenomenon of BTP in opioid-treated patients with chronic noncancer pain and compare that to BTP reported by cancer patients. Nine pain treatment programs were included between February-April 2004 to enroll patients who had controlled baseline pain. Inclusion criteria were age 18-75 yrs, presence of constant or almost constant pain if not for treatment, and taking opioids for management.

The questionnaire consisted of items that assessed the pain named by the patient as the controlled baseline pain (location, time since onset, quality); the incidence of additional, temporary flares of severe or excruciating pain of < 12hrs duration; time to maximal intensity, whether pain increased gradually or abruptly, number of episodes per day, typical duration, location, predictability, precipitating factors, and specific interventions that reduced the pain.

A total of 228 patients, 21-81 years of age, were included in the study, with the most common pain identified as chronic back (51%), chronic cervical neck (8%), and fibromyalgia (5%). Among those with BTP, the most common syndrome was low back pain (52%), and the underlying pathophysiology was somatic (38%), neuropathic (18%), visceral (4%), or mixed (40%). A total of 189 distinct types of BTP were reported. The mean number of episodes per day was 2, with mean minutes to maximum severity

26.5 min (SD 36.5), and median minutes to maximum severity 10 min (range 0-180); mean duration was 107.4 min with median duration 60 min (range 1-720 min). Pains peaked within 5 min of onset in 46%, within 30 min in 78%, and within 60 min in 89%; 33% had durations of 30 min or less; 50% were described as excruciating, 50% as severe. Patients reported a precipitating factor for 69% of patients, and 92% of these were activity-related; 45% of pains could never be predicted; 31% could sometimes be predicted

Patients were already taking opioid analgesics for their chronic pain as well as nonsteroidal anti-inflammatories, antidepressants, anticonvulsants, muscle relaxants, clonidine, and local/topical anesthetics. Medication aborted or reduced the frequency of the pain for 81% of the incidences. Nonpharmacologic approaches were reported, including rest, lying down, sitting (57%); heat (27%); movement, stretching, or physical therapy (12%), cold (12%), relaxation, distraction, or meditation (9%), massage (4%), or transcutaneous electrical nerve stimulation (4%). Patients reported that only 35% of BTP responded consistently to the interventions.

It is concluded that BTP is highly prevalent and varied for patients with chronic noncancer pain; further research is needed to determine whether these findings are comparable to the cancer population.

Incident pain and analgesic consumption decrease after samarium infusion: a pilot study.

Ripamonti C et al:

Journal: Support Care Cancer Sep 12, 2006 [online print]. 22 References
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Faculty Disclosure: Abstracted by T. Tilton, who has nothing to disclose.

In a pilot study, the authors' aim was to observe the variations of pain intensity on movement and at rest and the variation of analgesic drug

consumption in patients with prostate cancer and painful bone metastases who received a single dose of 1.0 mCi/kg of 153-Sm lexidronam (LEX; Quadramet® Schering SpA, Segrate, Milano). Radioisotopes such as strontium-89, samarium-153, rhenium-186, and rhenium-188 are used in clinical practice to emit b particles which are deposited and concentrated in areas of active bone turnover so that all metastases are treated at the same time. Not understood is the mechanism responsible for pain relief but perhaps the radiation-induced tumor necrosis decreases the number of cells in the inflammatory and immunological reactions, thus reducing chemical mediators (prostaglandins, substance P, bradykinins, interleukins, and tumor necrosis factors) that increase pain perception.

Patients with hormone refractory prostate cancer and painful bone metastases were prospectively evaluated. Parameters assessed before lexidronam and once a week for 4 weeks after the infusion, included: pain intensity at rest and on movement (incident pain) rated by the patient using a six-point Verbal Rating Scale (VRS); analgesic drug consumption as administered on a regular basis and as rescue medication; and the absence of severe bone marrow toxicity defined as hemoglobin count < 7.5 g/dL, white blood cell count < 22,500/μL, and platelet count <100,000/μL.

A total of 13 patients, mean age 64.5 (range 54-78), with positive 99mTc-MDP bone scan were treated. Twenty-three percent of patients were not taking analgesics at baseline; 61.5% of patients reported improvement of pain intensity on movement of at least 2 points on the VRS; 15.4% reported no pain at baseline and continued to be pain free; 23% did not report any significant reduction; 53.8% had improvement in pain at rest; 77% had a reduction of at least 2 points for pain on movement or pain at rest. Nine of 10 patients who were on analgesics before lexidronam reported a reduction in analgesic consumption, both regular and rescue medications: 2 changed from weak opioids to none; 1 from codeine to non-steroidal anti-inflammatories (NSAID); 2 decreased the dose of fentanyl patch; 1 reduced the dose of oral morphine; 2 reduced rescue medications (1 from NSAIDs to nothing and 1 from short-release oral rescue therapy to nothing); and 1

reduced the dose of regular oral morphine from 270 to 200 mg/day and rescue medication from short release oral morphine to NSAID. No patients reported any side effects immediately after lexidronam infusion. No one had to be catheterized due to incontinence. Bone marrow toxicity was mild and rapidly reversible in 3 patients and blood cell counts gradually returned to normal, indicating reversibility of the myelotoxicity.

In conclusion, 1.0 mCi/kg dose of 153-Sm lexidronam is safe and effective for the palliation of painful bone metastases in patients with prostate cancer particularly in the management of incident movement-related pain. Further research is indicated to identify the risks and benefits of radioisotopes as part of a multi-modality regimen, in combination with bisphosphonates (to reduce skeletal complications) and that of lexidronam for palliative purposes.

Computed-integrated patient-controlled epidural analgesia: a preliminary study on a novel approach of providing pain relief in labour.

Sia AT et al

Journal: Singapore Med J 47(11):951-956, 2006. 12 References
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Epidural analgesia (EA) maintained with a continuous infusion for patients in labor has been used for many parturients. The authors devised a clinical algorithm that converts an ordinary continuous infusion pump into patient-controlled epidural analgesia (PCEA) which was computer integrated to assess the need for a basal infusion dependent on the patient’s analgesic use over the previous hour. Basal infusion magnitude would be automatically and proportionally increased for a patient who made more demands than one who did not. The aim of this study was achievement of labor analgesia without breakthrough pain after the placement of combined spinal-epidural

analgesia (CSE).

Forty healthy patients with cephalic presentation at ≥ 36 weeks gestation presenting in early spontaneous labor and requesting EA were enrolled. Exclusion criteria were patients who had received parenteral opioids in the previous 4 hours, any contraindication to neuraxial block, multiple pregnancies, non-cephalic presentation, premature labor, or obstetrical complications.

CSE was placed at L3-4; 2 mg of ropivacaine (ROP) and 15 mg fentanyl (FEN) were injected intrathecally (T_o) followed by insertion of the epidural catheter. Patients were then assigned 1 of 2 regimens of 0.1% ROP with FEN 2 mg/mL: a continuous epidural infusion (CEI; n=20) of 10 mL/hr initiated 15 minutes after To; or PCEA (n=20) that altered the infusion rate based on demand (no demand in 1 hour caused cessation of the infusion and maximum demand (5 doses in 1 hour) led to a 5 mL/hr increase in the infusion rate).

Demographics were similar between the groups. All patients had effective blocks. Breakthrough pain was reported in 2 in the PCEA group and 8 in the CEI group. Mean duration of analgesia was 591 min and 399 min, respectively. No differences in the characteristics of labor analgesia, side effects, obstetrical outcome, total hourly consumption of epidural ROP (median 12.2 mg/hr vs. 10 mg/hr, respectively) were seen.

In conclusion, the use of computed-integrated PCEA reduced the incidence of breakthrough pain, which could ultimately reduce the need for anesthesia provider intervention. The authors were able to convert an ordinary infusion pump to one that could analyze patient need and automatically adjust the infusion rate.

Applied nanotechnology for the management of breakthrough cancer pain.

et Sprintz M al:

Journal: Minerva Anestesiol 71(7-8):419-423, 2005. 39 References
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An important yet unmet need in the treatment of cancer pain is symptom management. As technology advances and cancer shifts from terminal disease to a chronic, treatable condition, the issue of symptom management will begin to take a leading role. The most prominent under-treated symptom in cancer is pain. Breakthrough pain is a term that describes acute episodes of severe pain superimposed upon a background of otherwise well-controlled chronic pain. It may be caused by the cancer itself, cancer treatment, or certain activities like walking or dressing.

Nanotechnology offers new and revolutionary answers to this problem. Nanotechnology refers to the manipulation of objects with dimensions not exceeding 100 nm in magnitude. The objective of nanotechnology is to form functioning devices, which may themselves be of dimensions much larger than the component building blocks. Currently, the mainstay pharmacological management of severe cancer pain consists of opioid analgesics. New drug delivery systems have been developed to address pain management needs, including novel solutions utilizing nanotechnology, implantable drug delivery devices, transdermal and transmucosal patches.

The advantage of such precise diffusion kinetics with the use of potent opioids for analgesia is accurate and predictable controlled release dosing of the drug, thereby minimizing risk of overdose and increased side effects. The clinical advantage of accurate diffusion kinetics is the very precise and controlled release of drugs, which is vitally important when using potent opioid analgesics. The transbuccal patch system of analgesic delivery offers many advantages over traditional delivery forms, including: improved patient compliance, decreased need for multiple dose regimens, avoidance of needle injection, very rapid onset of action, avoidance of hepatic first-pass

metabolism, ease of administration, and self-administration.

Nanotechnology is the foundation on which many disruptive technologies will appear to dramatically alter the way medicine is practiced in the 21st century.