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General Pharmacology of Long-Acting, Extended-Release, and Sustained-Release Opioids for the Treatment of Chronic Nonmalignant Pain

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LONG–ACTING OPIOIDS: PROMISE VERSUS REALITY

Both short-acting (SA) opioids and long-acting (LA) opioids have been used for chronic pain (defined as pain lasting >3 months). SA opioids have a duration of action ranging between 2 and 4 hours, result in rapidly fluctuating drug levels and are suitable for acute, unstable, intermittent, breakthrough, and procedure-related pain.[1] End-of-dose failure pain is not considered a breakthrough pain by some investigators, but suboptimal around-the-clock (ATC) dosing, and is managed by increasing the ATC dose.[2,3] LA products are sustained-release/extended-release (SR/ER) potent opioid formulations which slowly release opioid over 8-24 hours or are particular opioids which have a long half-life and duration of action of >8 hours (buprenorphine, levorphanol, and methadone).[1,4,5] There are several potential reasons to prefer LA over SA opioids. Analgesia is associated with maintaining plasma opioid levels; each individual has a minimally effective plasma opioid concentration.[5-7] LA opioids theoretically maintain analgesic opioid levels better compared with SA opioids, depending on how SA opioids are dosed.[8] If patients take their SA opioid ATC, there appears to be no particular benefit to LA opioids.[9-11] Another proposed advantage to LA opioids is reduced side effects. Side effects are also related to plasma levels of opioids and SA opioids produce wider peak to trough levels leading to a greater risk of side effects at peak times. The transient high levels with SA opioids may increase side effects relative to LA opioids.[11-14]

Other proposed benefits to LA relative to SA opioids are improved sleep, less end-of-dose failure, less risk of addiction, and improved health-related quality of life.[4] However, in reality, there is insufficient evidence to substantiate claims of benefits to LA over SA opioids.[15,16] None of the comparison trials have demonstrated a reduced need for rescue analgesics with LA opioids. Sleep improved to a greater extent in only one of three studies with LA opioids. Function as an outcome, measured in only a minority of studies, was not different between opioid formulations. Side effects in general did not differ between formulations. One study demonstrated reduced nausea with LA opioids and another reduced depression and confusion with SA opioids.[15-17] These findings have not changed to date. No study to date has compared the risk of addiction with SA relative to LA opioids.[15,16,18] A study was done on the risk of aberrant behavior based on opioid formulation. "Drug-liking" effects were greater with SA than the LA opioids; however, this study was done in recreational drug users and not in individuals with chronic noncancer pain (CNCP) and so in reality is not applicable.[4] Trial heterogeneity in design and patient population prevent meta-analysis, but taking this into account, pain intensity outcomes between SA and LA opioids do not appear to differ.[15] Although some guidelines recommend LA opioids for CNCP, this is not based on analgesia, side effects, improved function, quality of life, or reduced risk of aberrant opioid behaviors.[19-21] Most comparison studies are of moderate to poor quality by present standards. While most focused on analgesia, none have systematically collected adverse events using a validated questionnaire but rather depended on patient spontaneous reports or diaries. It is estimated that opioid-related side effects are eight times more frequent when side effects are collected systematically rather than by patient volunteered reporting or diaries.[22,23] As a result, true differences in side effects between SA and LA opioids are largely unknown.

There are several drawbacks to using LA opioids. Pharmaceutical limitations of LA opioids are such that the lowest dose available with some LA opioids formulations may be too high for opioid-naïve individuals, the elderly, those with comorbidities, or those with organ failure.[14] In this setting, starting with an SA opioid then converting to an LA opioid once pain is controlled is a better strategy. For example, transdermal fentanyl 25 μg/h patch is contraindicated in opioid-naïve individuals and in the

postoperative setting. This dose of fentanyl is equivalent to 60 mg of morphine a day.[14] Another advantage of SA opioids is that these products can be more rapidly titrated to an effective dose more rapidly than LA opioids. The ATC dose should not be adjusted until steady state and steady state is reached more quickly with SA opioids due to the short half-life.[14] LA opioids have been used for initial dosing and titration but require close observation for adverse effects.[24] In at least one study, there was greater risk of side effects when initially using an LA opioid with titration than an SA opioid.[25] While individuals are on an LA opioid, many will require an SA opioid as rescue for breakthrough pain. This is relatively well established for cancer pain, more so than in CNCP. Two different opioids for pain management increase the risk for dosing errors. Methadone is particularly problematic when used in the opioid naïve. Methadone should not be increased for 4-5 days and has several disadvantages including the risk for corrected electrocardiographic QT (QTc) interval prolongation and Torsade de Pointe.[26-28] Buprenorphine has a long half-life and requires coupling with a SA opioid for breakthrough pain.[29]

ADDICTION AND ABUSE OF LA ANALGESIC PRODUCTS

LA opioid products are scheduled under the Controlled Substances Act and can be misused and abused. Misuse and addiction have paralleled the increase of prescriptions for LA opioids over recent years.[30] Evidence from observational studies suggest that long-term opioid analgesics for chronic pain increase the risk for opioid abuse.[31] No study to date has assessed the risk of abuse, addiction or related outcomes with long-term opioid therapy versus placebo or nonopioid analgesics. In uncontrolled studies, rates of abuse vary substantially based on strict inclusion criteria, even when controlling for care setting (primary care vs pain clinic).[32-39] Some of the variability in prevalence may be due to differences in ascertaining opioid addiction. Family and personal history of addiction and a psychiatric disorder increase the risk for opioid addiction. Certain genes involving dopamine neurotransmission, opioid receptors, and neurotrophic factors may increase the risk for addiction.[40] Risk mitigation strategies which include prediction questionnaires and urine drug screens are associated with reduced opioid misuse behaviors.[41,42]

Two studies have demonstrated a relationship between the total daily opioid dose measured as morphine equivalent doses (MED) and opioid overdose and mortality. In two studies, the hazard ratio (HR) was as high as 11 for individuals on >100 mg MED per day.[43,44] Another study demonstrated that overdose deaths were related to the maximum daily opioid dose. The adjusted HR was 4.5 for those on a MED >100 mg per day and was even higher for those with chronic pain and opioid doses >100 mg MED per day (HR 7.2).[45] Causes of opioid-related deaths are multifactorial. Root causes are physician error due to opioid knowledge deficits, patient nonadherence, unanticipated medical and mental health comorbidities, and payer policies that mandate methadone as first-line therapy without taking into account prescriber expertise or experience with methadone.[46] There are different patient demographics associated with opioid deaths depending on the location of overdose or death. Patient characteristics described in the emergency room include middle-aged male, public insurance, lower income, comorbid chronic pulmonary disease or neurologic disease, and history of sleep apnea. Overdoses which occur at home are associated with a college degree, female gender, and combined opioid and benzodiazepines.[47,48]

Methadone is a particular risk factor. Although methadone accounts for 4.5-18.5 percent of opioids distributed by state, it accounts for nearly 40 percent of single opioid-related deaths.[49] Also, deaths from fentanyl have doubled between 2013 and 2014 in certain states. Most deaths are from injections of illegally produced acetyl fentanyl.[50]

At least two methods have successfully reduced opioid-related deaths. Reformulation of oxycodone ER to an abuse-deterrent pharmaceutical which has reduced deaths from oxycodone by 82 percent.[51] Second, state supported overdose education and nasal naloxone distribution programs have reduced opioid deaths in communities.[52,53]

RESPIRATORY DEPRESSION

Respiratory depression is the most important and feared serious opioid adverse effect which is immediately life threatening. The type of opioid and patient characteristic associated with respiratory depression has changed over the decade. In a systematic review of opioid-related respiratory depression in patients with chronic pain, morphine and cancer pain were most commonly associated with respiratory depression prior to the year 2000. After the year 2000, methadone or fentanyl and patients with noncancer pain where the most often associated respiratory depression.[54] Specific root causes contributing to respiratory depression prior to 2000 were increased plasma morphine levels, renal failure, and sensory deafferentiation. In the years following 2000, elevated opioid plasma levels and drug interactions with

cytochrome P450 enzymes were factors associated with respiratory depression. Other factors are pharmacodynamic interactions between opioids and benzodiazepines which lead to synergistic respiratory depression.[55] Long-term maintenance methadone decreases hypoxemic as well as hypercapnic ventilatory responses.[56] This may place patients with sleep apnea at risk for respiratory depression.[57,58] All phases of the respiratory cycle are influenced by opioids. At low doses, there is decreased tidal volume and at high doses decreased respiratory rate.[59] As a result, rapid dose titration in an opioid-naïve individual who has not developed tolerance is a strong risk factor for respiratory depression.[60] The degree to which opioids suppress peripheral and central chemoreceptors depends on the characteristics of the particular opioid.[61] In animal models, single opioid doses produce variable durations of respiratory depression. Respiratory depressive effects were short lived for fentanyl and oxycodone as single doses whereas morphine, morphine-6-glucuronide, and buprenorphine produced prolonged respiratory depression.[62] The route of administration also plays a role. Oral opioids have less effect on hypoxic and hypercapnic ventilatory drive than parenteral opioids.[63] There also may be a genetic predisposition to opioid-related respiratory depression.[64]

Part of the difficulty of defining respiratory depression with opioids is that there are different definitions of respiratory depression which involve sensorium, respiratory rate, hypoxemia, and hypercapnea. Oxygen desaturation has been used in the past as the hallmark of respiratory depression.[65,66] Not infrequently, respiratory rate has been used on hospital wards. However, the respiratory rate may decrease while the tidal volume compensates thus maintaining oxygen saturation.[67,68] This compensatory mechanism may fail during an acute illness leading to reduced respiratory rate, tidal volume, and oxygen desaturation.[69]

Naloxone is an allyl derivative of noroxymorphone, first synthesized in 1960. It is a nonselective competitive opioid antagonist for all three major opioid receptors (mu, delta, and kappa).[70] It has a high first past hepatic clearance (>95 percent) and thus low oral bioavailability. Metabolism is primarily through glucuronidation to naloxone-3 glucuronide, 70 percent is excreted in urine as the conjugate metabolite, and 30 percent unchanged.[70-73] The extent and duration of naloxone-induced reversal of opioid-associated respiratory depression is variable and related to the opioid dose, the mode of administration, coadministered medications, underlying disease, pain, state of arousal, genetic makeup of the patient, and exogenous stimulating factors.[74,75] Naloxone rapidly gains access to the central nervous system (CNS). Its' elimination half-life from plasma is quite short, 33 minutes, such redosing of naloxone may be needed, particularly for LA opioids.[76] The onset to effect is <2 minutes. Naloxone should be given at a rate of 20-100 μg (intravenous) IV every 2 minutes to reverse respiratory depression but not analgesia. An IV infusion may be needed for individuals on LA opioids.[69,77] Buprenorphine will require large doses of naloxone, 2-4 mg IV, and an infusion to reverse respiratory depression.[75,76] Intranasal (recently approved by the Food and Drug Administration for use in opioid overdose) and subcutaneous naloxone are also effective and as effective as parenteral naloxone in reversing respiratory depression. This is particularly important if patients do not have IV access.[78]

CONSTIPATION AND NARCOTIC BOWEL SYNDROME

Constipation is the most common long-term side effect with opioids and should be anticipated. Unfortunately, very little tolerance develops to opioid effects on bowel function. Adverse effects are due to μ-receptors on enteric neurons but also arise from activation of the CNS μ-receptors.[79,80] Constipation can occur with spinal opioids. Opioids reduce peristalsis by inhibiting longitudinal smooth muscle, increasing segmentation by disinhibiting circular muscle, reduce bowel secretions, and increase water absorption. Sphincter function is also adversely affected.[81-83] Opioid-induced constipation can be accompanied by straining at stool, colic, nausea, abdominal distention, bloating, anorexia, and vomiting.[83]

The narcotic bowel syndrome is the paradoxical development of abdominal pain while on opioids and is frequently under recognized as an opioid side effect.[82,84] The narcotic bowel syndrome is estimated to occur in 6 percent of individuals on long-term opioid.[85] Pain is described as burning or colicky. There can be an overlap of symptoms of opioid-induced constipation; both include bloating, distention, nausea, and constipation as well as anorexia.[86] The syndrome bears a remarkable similarity to the irritable bowel syndrome and functional abdominal pain syndrome.[87] A common differential diagnosis includes pain from chronic pancreatitis, partial bowel obstruction, peptic ulcer disease, abdominal angina, renal calculi, uterine fibroids, and ovarian cysts.

Management of constipation associated with opioids is primarily preventative with the use of stimulating and osmotic laxatives, stool softeners, and suppositories. Osmotic laxatives include lactulose, sorbitol, polyethylene glycol, and magnesium

hydroxide. Stimulating laxatives include bisacodyl or senna derivatives.[88-92] There does not appear to be an advantage of one laxative over another.[93-95] Laxatives should be initiated at the time opioids are prescribed to prevent constipation and titrated to effect which is highly variable. A minority will require suppositories or enemas to treat constipation and/or fecal impaction. Oral naloxone has been used in the past; presently in certain countries (not the United States), there is a combination formulation of SR oxycodone and naloxone which is reported to reduce constipation relative to oxycodone alone.[96,97] Methylnaltrexone, which does not cross the blood-brain barrier, has been used for refractory constipation unresponsive to laxatives.[98-100] Lubiprostone has recently been approved to treat opioid-induced constipation.[101-103]

Management of the narcotic bowel syndrome requires first an "index of clinical suspicion" and a careful history.[104] Patients may not understand the reasoning behind opioid reduction or withdrawal in the face of increasing abdominal pain; an empathetic discussion and patient education is a necessity. Patient concerns and fears about opioid withdrawal should be addressed.[82] Abdominal radiographs can be misleading as they may show evidence of a "partial intestinal obstruction," secondary pseudo-obstruction or ileus.[82,86,105,106] Clonidine and parenteral continuous infusion metoclopramide have also been used to treat the narcotic bowel syndrome.[85,107,108]

DRUG–DRUG INTERACTIONS

Drug-drug interactions vary among different products and opioids. Knowledge of particular opioid-drug interactions and underlying pharmacokinetic and pharmacodynamic mechanisms is important before initiating opioids or switching opioids and allows safer administration. Approximately 6 percent of patients with CNCP on LA opioids are exposed to potential major drug-drug interactions.[109]

Pharmacodynamic interactions between CNS depressants (alcohol, sedatives, hypnotics, tranquilizers, and tricyclic antidepressants) and opioids potentiate sedation and respiratory depression of both drug classes. Benzodiazepines are involved in 31 percent of opioid deaths.[110] There is an increased risk for motor vehicle accidents when individuals drive while on both a benzodiazepine and an opioid.[111] Although in healthy individuals, the combinations of benzodiazepines and opioids do not increase the abuse liability of an opioid, the combination does enhance behavioral toxicity of either drug class.[112]

Alcohol increases the positive "liking" effects of opioids while adversely affecting physical function and cognition.[113] The prevalence of alcohol-related disorders in individuals on oral potent opioids is 5.5 percent and is twice that of the general population which is 2.2 percent.[114] There are major pharmacokinetic interactions between LA opioids and alcohol. Alcohol is linked to dose-dumping of certain SR/ER opioids.[115-118] Therefore, clinicians who prescribe LA opioids to patients need to warn them about the danger of using alcohol while on opioids.

Monoamine oxidase (MAO) inhibitors can increase respiratory depression of certain opioids. Using certain opioids with antidepressants and MAO inhibitors may also cause the serotonin syndrome.[119,120] Phenylpiperidine opioids (meperidine, tramadol, methadone, and dextromethorphan) are weak serotonin reuptake inhibitors and have been most often associated with the serotonin syndrome when combined with MAO inhibitors. Morphine, codeine, oxycodone, and buprenorphine appear to have little serotonin reuptake inhibition and are less likely to precipitate a serotonin syndrome.[120] Tramadol has been reported to increase the risk for the serotonin syndrome when combined with selective serotonin reuptake inhibitors (SSRIs). The risk is particularly greater in older individuals, those on high doses of tramadol, and those using medications which inhibit cytochrome CYP2D6.[121]

Opioids reduce the efficacy of diuretics by increasing the release of antidiuretic hormone (ADH).[122] As a result, morphine used in acute decompensated heart failure worsens outcomes of acute heart failure and doubles mortality (11 percent vs 5 percent) as well as doubles the odds for in-hospital death.[123] Opioids reduce the clearance of acidosis related to severe cardiogenic pulmonary edema.[124] In addition to systemic opioids, spinal opioids are also associated with increased ADH levels and impaired diuresis.[125] Therefore, morphine should not be used as a symptom treatment for acute cardiogenic pulmonary edema.[126]

Methadone and buprenorphine are associated with prolongation of the QTc interval. Since 2002, methadone-associated arrhythmias have been disproportionately represented in the US Food and Drug Administration Adverse Event Reporting System (FAERS).[127] Prolongation of the QTc interval with methadone correlates with respiratory arrest and the need for intubation.[128] Female gender, those with cardiac channel congenital abnormalities, and those with low magnesium or potassium are at increased risk for prolonged QTc intervals with methadone.[129-134] Genetic polymorphisms of the cytochrome CYP2C19 have been associated with QTc prolongation. Extensive

metabolizers require higher methadone doses; have altered methadone enantiomer clearance (defined as the R-methadone/methadone ratio) and greater QTc changes.[135] Also individuals with congenital long QTc syndrome mutations are at risk for methadone-induced arrhythmias.[136]

Buprenorphine effects on the QTc interval are 100 times less than methadone when adjusted for therapeutic plasma concentrations.[137] Within the opioid maintenance population, QTc interval prolongation is much less frequent with buprenorphine than with methadone.[138] Individuals on methadone with a dangerously prolonged QTc interval (>500 ms) can be switched to buprenorphine with resolution of the prolonged QTc interval.[139-141] Nevertheless, buprenorphine has been associated with QTc prolongation if combined with a CYP3A4 inhibitor.[142]

Recommendations have been recently published on the safe use of methadone for pain by the American Pain Society and College of Problems on Drug Dependency which should be read by clinicians prescribing methadone for pain.[27,28] Specific recommendations include patient education, counseling patients on methadone safety, use of electrocardiograms to identify individuals at risk for complications related to methadone, use of alternative opioids in patients at high risk for methadone-induced arrhythmias, careful dose initiation, titration and diligent monitoring with follow-up.[28]

DRUG INTERACTIONS AND CYTOCHROME P450

Drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can cause higher or lower than expected blood levels of certain opioids, leading to either opioid toxicity or withdrawal. Inhibitors of certain cytochromes delay clearance leading to opioid toxicity or prevent activation of an opioid prodrug leading to poor analgesia.

Cytochrome CYP2D6 metabolizes a large number of medication classes (antidepressants, antipsychotics, beta blockers, and opioids) and is responsible for metabolizing 25 percent of current drugs.[143,144] CYP2D6 is not inducible but the gene allele can be amplified leading to ultra-rapid metabolism. Poor metabolizers have two alleles with reduced function or are nonfunctional. Individuals are classified as ultra-rapid metabolizers with allele amplification, extensive metabolizers with both alleles functional, intermediate metabolizers with one functional allele, and poor metabolizers with two nonfunctional alleles.[143,144] CYP2D6 metabolizes codeine, tramadol, oxycodone, and hydrocodone. Poor metabolizers have reduced analgesia with tramadol (which requires o-demethylation to o-desmethyl-tramadol) and codeine (which requires o-demethylation to morphine).[143,144] Ultra-rapid metabolizers can have life-threatening toxicity with codeine or tramadol.[145,146] An updated version of Clinical Pharmacogenetics Implementation Consortium guidelines recommend that codeine be used based on CYP2D6 gene type for reasons of safety and efficacy.[147] Drugs which block CYP2D6 interfere with codeine and tramadol analgesia and delay clearance of hydrocodone and oxycodone.[148-152]

Both hydrocodone and oxycodone metabolism is also dependent on CYP3A4.[148-153] Hydrocodone is metabolized to hydromorphone through CYP2D6 and norhydrocodone, a weak but active metabolite, through CYP3A4. The clearance of hydrocodone is determined by both enzymes.[154] Oxycodone metabolized through CYP2D6 to oxymorphone and through CYP3A4, the weak active metabolite noroxycodone. Drug interactions at both enzymes have an effect on oxycodone analgesia and safety.[150,153,155]

Transdermal fentanyl is commonly used for chronic pain. There are large patient-to-patient variations in transdermal fentanyl pharmacokinetic parameters.[156,157] Fentanyl clearance at steady state is dependent on CYP3A4. CYP3A4 levels are influenced by liver disease, drug inhibitors such as ketoconazole and inducers such as rifampin.[158,159]

Methadone is extensively metabolized through multiple cytochromes (CYP2B6, CYP3A4, CYP1A2, CYP2D6, CYP2C9, and CYP2C19).[160] Methadone is subject to multiple drug interactions. Methadone induces its own metabolism through induction of CYP2B6 and CYP3A4.[161] Induction of both enzymes may result in "analgesic tolerance" over time due to increased clearance of methadone. Estradiol during pregnancy increases methadone clearance through induction of CYP2B6.[162] More than 50 drug-drug interactions are reported with methadone.[160] Methadone prescribers should inquire about any new medications including complementary and over-the-counter medications periodically and particularly if patients on stable doses of methadone develop withdrawal or opioid toxicity.[160]

DRUG INTERACTIONS AND EFFLUX PUMPS

Cerebral endothelial cells contain energy-dependent efflux transporters which function as a blood-brain barrier. These efflux pumps are also located in the brain parenchyma, astrocytes, and microglia.[163] P-glycoprotein, the major efflux pump, functions to prevent harmful compounds from entering the CNS. Multiple opioids are P-glycoprotein substrates (morphine, oxycodone, methadone,

and fentanyl).[164] Polymorphisms of the P-glycoprotein pump gene (ABCB1) influence analgesia and opioid side effects.[165-170] The ABCB1 gene can be upregulated by chronic morphine exposure causing analgesic tolerance.[171] Drugs which inhibit P-glycoprotein (verapamil) increase opioid toxicity and drugs which introduce P-glycoprotein (rifampin) diminish opioid responses or cause withdrawal symptoms.[172-174] P-glycoprotein is also found along the gastrointestinal tract, induction of P-glycoprotein in the gastrointestinal tract will reduce drug absorption.[175] This leads to opioid toxicity when rotating from a P-glycoprotein substrate opioid to an opioid which is not subject to P-glycoprotein efflux if one only relies on opioid equivalent tables.[175]

The risk of drug-drug interactions increases with age, the number of prescribed drugs, and comorbidities. A large observational study found that >70 percent of individuals on long-term opioids had drug-drug interactions.[176] Very few involved serious contraindicated drug combinations. Interactions were usually drugs with additive CNS depressant effects, inducers and inhibitors of CYP3A4, inhibitors of CYP2D6 and combinations of tramadol with SSRIs, tricyclic antidepressants, and antipsychotics.[176]

OPIOID TOLERANCE

Tolerance to sedation and respiratory depression is critical to the safe use of certain opioid products, certain dosing units, and strengths. For example, patients must be opioid tolerant before using transdermal fentanyl 25 μg/h or rapidly acting fentanyl products for breakthrough pain. Patients are considered opioid tolerant if on morphine 60 mg/d, oxycodone 30 mg/d, hydromorphone 8 mg/d, fentanyl 25 μg/h, or oxymorphone 25 mg/d for a minimum of 1 week. Starting maximal daily doses for those who are opioid naïve are morphine 30 mg, fentanyl 12 μg/h, methadone 2.5-7.5 mg, oxycodone 20 mg, and oxymorphone 10 mg. The same starting dose should be used regardless of the initial pain severity; high pain severity does not warrant starting individuals who are opioid naïve on greater than recommended initial opioid doses.

OTHER ISSUES

ER/LA opioids should be swallowed whole. ER/LA opioids in capsules should be swallowed intact or when necessary the pellets from the capsule can be sprinkled on applesauce and swallowed without chewing. Transdermal products should not be exposed to external heat. Fever or exertion increases fentanyl absorption leading to opioid toxicity or fatal overdose.[177]

When converting patients from one opioid to another, one should use instructions for conversion written in the Dosage and Administration instructions of individual product information pamphlets. Incomplete cross-tolerance and great interindividual variability in opioid responses requires conservative dosing when switching from one opioid to another. It is recommended that dosing start with half the calculated equianalgesic dose and titrate the new opioid to effect. Doses may also need to be tailored based on comorbidity, organ failure, and coadministered medications that have potential for drug interactions.[178]

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REFERENCES

1. Rauck RL: What is the case for prescribing long-acting opioids over short-acting opioids for patients with chronic pain? A critical review. *Pain Pract.* 2009; 9(6): 468-479.
2. Davies AN: Breakthrough cancer pain. *Curr Pain Headache Rep.* 2014; 18(6): 420.
3. Davies AN, Dickman A, Reid C, et al.: The management of cancer-related breakthrough pain: Recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. *Eur J Pain.* 2009; 13(4): 331-338.
4. McCarberg BH, Barkin RL: Long-acting opioids for chronic pain: Pharmacotherapeutic opportunities to enhance compliance, quality of life, and analgesia. *Am J Ther.* 2001; 8(3): 181-186.
5. Gourlay GK: Sustained relief of chronic pain. Pharmacokinetics of sustained release morphine. *Clin Pharmacokinet.* 1998; 35(3): 173-190.
6. Hill HF, Chapman CR, Saeger LS, et al.: Steady-state infusions of opioids in human. II. Concentration-effect relationships and therapeutic margins. *Pain.* 1990; 43(1): 69-79.
7. Hill HF, Saeger L, Bjurstrom R, et al.: Steady-state infusions of opioids in human volunteers. I. Pharmacokinetic tailoring. *Pain.* 1990; 43(1): 57-67.
8. Ferrell B, Wisdom C, Wenzl C, et al.: Effects of controlled-released morphine on quality of life for cancer pain. *Oncol Nurs Forum.* 1989; 16(4): 521-526.
9. Chary S, Goughnour BR, Moulin DE, et al.: The dose-response relationship of controlled-release codeine (Codeine Contin) in chronic cancer pain. *J Pain Symptom Manage.* 1994; 9(6): 363-371.
10. Arkinstall WW, Goughnour BR, White JA, et al.: Control of severe pain with sustained-release morphine tablets v. oral morphine solution. *CMAJ.* 1989; 140(6): 653-657, 661.
11. Caldwell JR, Hale ME, Boyd RE, et al.: Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal antiinflammatory drugs: A double blind, randomized, multicenter, placebo controlled trial. *J Rheumatol.* 1999; 26(4): 862-869.
12. Klepstad P, Dale O, Kaasa S, et al.: Influences on serum concentrations of morphine, M6G and M3G during routine clinical drug monitoring: A prospective survey in 300 adult cancer patients. *Acta Anaesthesiol Scand.* 2003; 47(6): 725-731.
13. Amabile CM, Bowman BJ: Overview of oral modified-release opioid

products for the management of chronic pain. *Ann Pharmacother.* 2006; 40(7-8): 1327-1335.
14. Fine PG, Mahajan G, McPherson ML: Long-acting opioids and short-acting opioids: Appropriate use in chronic pain management. *Pain Med.* 2009; 10(suppl 2): S79-S88.
15. Chou R, Clark E, Helfand M: Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: A systematic review. *J Pain Symptom Manage.* 2003; 26(5): 1026-1048.
16. Carson S, Thakurta S, Low A, et al.: *Drug Class Review: Long-Acting Opioid Analgesics: Final Update 6 Report.* Portland (OR): Oregon Health & Science University, 2011.
17. Chou R, Carson S: *Drug Class Review on Long-Acting Opioid Analgesics: Final Report Update 5.* Portland (OR): Oregon Health & Science University, 2008.
18. Nuckols TK, Anderson L, Popescu I, et al.: Opioid prescribing: A systematic review and critical appraisal of guidelines for chronic pain. *Ann Intern Med.* 2014; 160(1): 38-47.
19. Pedersen L, Borchgrevink PC, Riphagen, II, et al.: Long- or short-acting opioids for chronic non-malignant pain? A qualitative systematic review. *Acta Anaesthesiol Scand.* 2014; 58(4): 390-401.
20. Kalso E, Allan L, Dellemijn PL, et al.: Recommendations for using opioids in chronic non-cancer pain. *Eur J Pain.* 2003; 7(5): 381-386.
21. Webster LR, Bath B, Medve RA, et al.: Randomized, double-blind, placebo-controlled study of the abuse potential of different formulations of oral oxycodone. *Pain Med.* 2012; 13(6): 790-801.
22. Jonsson T, Christrup LL, Hojsted J, et al.: Symptoms and side effects in chronic non-cancer pain: Patient report vs. systematic assessment. *Acta Anaesthesiol Scand.* 2011; 55(1): 69-74.
23. Ioannidis JP, Evans SJ, Gotzsche PC, et al.: Better reporting of harms in randomized trials: An extension of the CONSORT statement. *Ann Intern Med.* 2004; 141(10): 781-788.
24. Klepstad P, Kaasa S, Jystad A, et al.: Immediate- or sustained-release morphine for dose finding during start of morphine to cancer patients: A randomized, double-blind trial. *Pain.* 2003; 101(1-2): 193-198.
25. Salzman RT, Roberts MS, Wild J, et al.: Can a controlled-release oral dose form of oxycodone be used as readily as an immediate-release form for the purpose of titrating to stable pain control? *J Pain Symptom Manage.* 1999; 18(4): 271-279.
26. Weimer MB, Chou R: Research gaps on methadone harms and comparative harms: Findings from a review of the evidence for an American Pain Society and College on Problems of Drug Dependence clinical practice guideline. *J Pain.* 2014; 15(4): 366-376.
27. Chou R, Weimer MB, Dana T: Methadone overdose and cardiac arrhythmia potential: Findings from a review of the evidence for an American Pain Society and College on Problems of Drug Dependence clinical practice guideline. *J Pain.* 2014; 15(4): 338-365.
28. Chou R, Cruciani RA, Fiellin DA, et al.: Methadone safety: A clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. *J Pain.* 2014; 15(4): 321-337.
29. Mercadante S, Villari P, Ferrera P, et al.: Safety and effectiveness of intravenous morphine for episodic breakthrough pain in patients receiving transdermal buprenorphine. *J Pain Symptom Manage.* 2006; 32(2): 175-179.
30. Dasgupta N, Kramer ED, Zalman MA, et al.: Association between non-medical and prescriptive usage of opioids. *Drug Alcohol Depend.* 2006; 82(2): 135-142.
31. Edlund MJ, Martin BC, Russo JE, et al.: The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain: The role of opioid prescription. *Clin J Pain.* 2014; 30(7): 557-564.
32. Martell BA, O'Connor PG, Kerns RD, et al.: Systematic review: Opioid treatment for chronic back pain: Prevalence, efficacy, and association with addiction. *Ann Intern Med.* 2007; 146(2): 116-127.
33. Banta-Green CJ, Merrill JO, Doyle SR, et al.: Measurement of opioid problems among chronic pain patients in a general medical population. *Drug Alcohol Depend.* 2009; 104(1-2): 43-49.
34. Boscarino JA, Rukstalis M, Hoffman SN, et al.: Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system. *Addiction.* 2010; 105(10): 1776-1782.
35. Compton PA, Wu SM, Schieffer B, et al.: Introduction of a self-report version of the Prescription Drug Use Questionnaire and relationship to medication agreement noncompliance. *J Pain Symptom Manage.* 2008; 36(4): 383-395.
36. Saffier K, Colombo C, Brown D, et al.: Addiction Severity Index in a chronic pain sample receiving opioid therapy. *J Subst Abuse Treat.* 2007; 33(3): 303-311.
37. Cowan DT, Wilson-Barnett J, Griffiths P, et al.: A survey of chronic noncancer pain patients prescribed opioid analgesics. *Pain Med.* 2003; 4(4): 340-351.
38. Hojsted J, Nielsen PR, Guldstrand SK, et al.: Classification and identification of opioid addiction in chronic pain patients. *Eur J Pain.* 2010; 14(10): 1014-1020.
39. Fleming MF, Balousek SL, Klessig CL, et al.: Substance use disorders in a primary care sample receiving daily opioid therapy. *J Pain.* 2007; 8(7): 573-582.
40. Mistry CJ, Bawor M, Desai D, et al.: Genetics of opioid dependence: A review of the genetic contribution to opioid dependence. *Curr Psychiatry Rev.* 2014; 10(2): 156-167.
41. Starrels JL, Becker WC, Alford DP, et al.: Systematic review: Treatment agreements and urine drug testing to reduce opioid misuse in patients with chronic pain. *Ann Intern Med.* 2010; 152(11): 712-720.
42. Turk DC, Swanson KS, Gatchel RJ: Predicting opioid misuse by chronic pain patients: A systematic review and literature synthesis. *Clin J Pain.* 2008; 24(6): 497-508.
43. Dunn KM, Saunders KW, Rutter CM, et al.: Opioid prescriptions for chronic pain and overdose: A cohort study. *Ann Intern Med.* 2010; 152(2): 85-92.
44. Gomes T, Mamdani MM, Dhalla IA, et al.: Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med.* 2011; 171(7): 686-691.
45. Bohnert AS, Ilgen MA, Ignacio RV, et al.: Risk of death from accidental overdose associated with psychiatric and substance use disorders. *Am J Psychiatry.* 2012; 169(1): 64-70.
46. Webster LR, Cochella S, Dasgupta N, et al.: An analysis of the root causes for opioid-related overdose deaths in the United States. *Pain Med.* 2011;12(suppl 2): S26-S35.
47. Siegler A, Tuazon E, Bradley O'Brien D, et al.: Unintentional opioid overdose deaths in New York City, 2005-2010: A place-based approach to reduce risk. *Int J Drug Policy.* 2014; 25(3): 569-574.
48. Hasegawa K, Brown DF, Tsugawa Y, et al.: Epidemiology of emergency department visits for opioid overdose: A population-based study. *Mayo Clinic Proc.* 2014; 89(4): 462-471.
49. Kuehn BM: Methadone overdose deaths rise with increased prescribing for pain. *JAMA.* 2012; 308(8): 749-750.
50. Mercado-Crespo MC, Sumner SA, Spelke MB, et al.: Notes from the field: Increase in fentanyl-related overdose deaths—Rhode Island, November 2013-March 2014. *MMWR Morb Mortal Wkly Rep.* 2014; 63(24): 531.
51. Sessler NE, Downing JM, Kale H, et al.: Reductions in reported deaths following the introduction of extended-release oxycodone (OxyContin) with an abuse-deterrent formulation. *Pharmacoepidemiol Drug Saf.* 2014 (in press).
52. Walley AY, Xuan Z, Hackman HH, et al.: Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: Interrupted time series analysis. *BMJ.* 2013; 346: f174.
53. Walley AY, Doe-Simkins M, Quinn E, et al.: Opioid overdose prevention with intranasal naloxone among people who take methadone. *J Subst Abuse Treat.* 2013; 44(2): 241-247.
54. Dahan A, Overdyk F, Smith T, et al.: Pharmacovigilance: A review of opioid-induced respiratory depression in chronic pain patients. *Pain Physician.* 2013; 16(2): E85-E94.
55. Jann M, Kennedy WK, Lopez G: Benzodiazepines: A major component in unintentional prescription drug overdoses with opioid analgesics. *J Pharm Pract.* 2014; 27(1): 5-16.
56. Panagiotou I, Mystakidou K: Non-analgesic effects of opioids: Opioids' effects on sleep (including sleep apnea). *Curr Pharm Des.* 2012; 18(37): 6025-6033.
57. Rose AR, Catcheside PG, McEvoy RD, et al.: Sleep disordered breathing and chronic respiratory failure in patients with chronic pain on long term opioid therapy. *J Clin Sleep Med.* 2014; 10(8): 847-852.
58. Walker JM, Farney RJ, Rhondeau SM, et al.: Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. *J Clin Sleep Med.* 2007; 3(5): 455-461.
59. Weil JV, McCullough RE, Kline JS, et al.: Diminished ventilatory

response to hypoxia and hypercapnia after morphine in normal man. *N Engl J Med.* 1975; 292(21): 1103-1106.
60. Bouillon T, Bruhn J, Radu-Radulescu L, et al.: A model of the ventilatory depressant potency of remifentanil in the non-steady state. *Anesthesiology.* 2003; 99(4): 779-787.
61. Santiago TV, Edelman NH: Opioids and breathing. *J Appl Physiol.* 1985; 59(6): 1675-1685.
62. Kuo A, Wyse BD, Meutermans W, et al.: In vivo profiling of seven common opioids for antinociception, constipation and respiratory depression: No two opioids have the same profile. *Br J Pharmacol.* 2014 (in press).
63. Robinson RW, Zwillich CW, Bixler EO, et al.: Effects of oral narcotics on sleep-disordered breathing in healthy adults. *Chest.* 1987; 91(2): 197-203.
64. Chidambaran V, Mavi J, Esslinger H, et al.: Association of OPRM1 A118G variant with risk of morphine-induced respiratory depression following spine fusion in adolescents. *Pharmacogenomics J.* 2014 (in press).
65. Wheatley RG, Somerville ID, Sapsford DJ, et al.: Postoperative hypoxaemia: Comparison of extradural, i.m. and patient-controlled opioid analgesia. *Br J Anaesth.* 1990; 64(3): 267-275.
66. Madej TH, Wheatley RG, Jackson IJ, et al.: Hypoxaemia and pain relief after lower abdominal surgery: Comparison of extradural and patient-controlled analgesia. *Br J Anaesth.* 1992; 69(6): 554-557.
67. Barbour SJ, Vandebeek CA, Ansermino JM: Increased tidal volume variability in children is a better marker of opioid-induced respiratory depression than decreased respiratory rate. *J Clin Monit Comput.* 2004; 18(3): 171-178.
68. Bouillon T, Bruhn J, Roepcke H, et al.: Opioid-induced respiratory depression is associated with increased tidal volume variability. *Eur J Anaesthesiol.* 2003; 20(2): 127-133.
69. Boland J, Boland E, Brooks D: Importance of the correct diagnosis of opioid-induced respiratory depression in adult cancer patients and titration of naloxone. *Clin Med.* 2013; 13(2): 149-151.
70. Martin WR: Naloxone. *Ann Intern Med.* 1976; 85(6): 765-768.
71. Ngai SH, Berkowitz BA, Yang JC, et al.: Pharmacokinetics of naloxone in rats and in man: Basis for its potency and short duration of action. *Anesthesiology.* 1976; 44(5): 398-401.
72. Vizi ES, Foldes FF, Rich J, et al.: The structure-action relationship and kinetics of some naloxone and naltrexone derivatives. *Pharmacology.* 1976; 14(1): 76-85.
73. Berkowitz BA: The relationship of pharmacokinetics to pharmacological activity: Morphine, methadone and naloxone. *Clin Pharmacokinet.* 1976; 1(3): 219-230.
74. Olofsen E, van Dorp E, Teppema L, et al.: Naloxone reversal of morphine- and morphine-6-glucuronide-induced respiratory depression in healthy volunteers: A mechanism-based pharmacokinetic-pharmacodynamic modeling study. *Anesthesiology.* 2010; 112(6): 1417-1427.
75. van Dorp E, Yassen A, Sarton E, et al.: Naloxone reversal of buprenorphine-induced respiratory depression. *Anesthesiology.* 2006; 105(1): 51-57.
76. Yassen A, Olofsen E, van Dorp E, et al.: Mechanism-based pharmacokinetic-pharmacodynamic modelling of the reversal of buprenorphine-induced respiratory depression by naloxone: A study in healthy volunteers. *Clin Pharmacokinet.* 2007; 46(11): 965-980.
77. Goldfrank L, Weisman RS, Errick JK, et al.: A dosing nomogram for continuous infusion intravenous naloxone. *Ann Emerg Med.* 1986; 15(5): 566-570.
78. Sabzghabaee AM, Eizadi-Mood N, Yaraghi A, et al.: Naloxone therapy in opioid overdose patients: Intranasal or intravenous? A randomized clinical trial. *Arch Med Sci.* 2014; 10(2): 309-314.
79. De Schepper HU, Cremonini F, Park MI, et al.: Opioids and the gut: Pharmacology and current clinical experience. *Neurogastroenterol Motil.* 2004; 16(4): 383-394.
80. Mori T, Shibasaki Y, Matsumoto K, et al.: Mechanisms that underlie mu-opioid receptor agonist-induced constipation: Differential involvement of mu-opioid receptor sites and responsible regions. *J Pharmacol Exp Ther.* 2013; 347(1): 91-99.
81. Szigethy E, Schwartz M, Drossman D: Narcotic bowel syndrome and opioid-induced constipation. *Curr Gastroenterol Rep.* 2014; 16(10): 410.
82. Drossman D, Szigethy E: The narcotic bowel syndrome: A recent update. *Am J Gastroenterol.* 2014; 2(1): 22-30.
83. Davis MP: The opioid bowel syndrome: A review of pathophysiology and treatment. *J Opioid Manag.* 2005; 1(3): 153-161.
84. Kurlander JE, Drossman DA: Diagnosis and treatment of narcotic bowel syndrome. *Nat Rev Gastroenterol Hepatol.* 2014; 11(7): 410-418.
85. Tuteja AK, Biskupiak J, Stoddard GJ, et al.: Opioid-induced bowel disorders and narcotic bowel syndrome in patients with chronic noncancer pain. *Neurogastroenterol Motil.* 2010; 22(4): 424-430, e496.
86. Farmer AD, Ferdinand E, Aziz Q: Opioids and the gastrointestinal tract—A case of narcotic bowel syndrome and literature review. *J Neurogastroenterol Motil.* 2013; 19(1): 94-98.
87. Grover CA, Wiele ED, Close RJ: Narcotic bowel syndrome. *J Emerg Med.* 2012; 43(6): 992-995.
88. Wirz S, Nadstawek J, Elsen C, et al.: Laxative management in ambulatory cancer patients on opioid therapy: A prospective, open-label investigation of polyethylene glycol, sodium picosulphate and lactulose. *Eur J Cancer Care.* 2012; 21(1): 131-140.
89. Bouvy ML, Buurma H, Egberts TC: Laxative prescribing in relation to opioid use and the influence of pharmacy-based intervention. *J Clin Pharm Ther.* 2002; 27(2): 107-110.
90. Sykes N: Emerging evidence on docusate: Commentary on Tarumi et al. *J Pain Symptom Manage.* 2013; 45(1): 1.
91. Twycross R, Sykes N, Mihalyo M, et al.: Stimulant laxatives and opioid-induced constipation. *J Pain Symptom Manage.* 2012; 43(2): 306-313.
92. Larkin PJ, Sykes NP, Centeno C, et al.: The management of constipation in palliative care: Clinical practice recommendations. *Palliat Med.* 2008; 22(7): 796-807.
93. Cass LJ, Frederik WS: A clinical comparison of bulk and stimulant laxatives. *J Lancet.* 1955; 75(3): 105-108.
94. Connolly P, Hughes IW, Ryan G: Comparison of "Duphalac" and "irritant" laxatives during and after treatment of chronic constipation: A preliminary study. *Curr Med Res Opin.* 1974; 2(10): 620-625.
95. Dettmar PW, Sykes J: A multi-centre, general practice comparison of ispaghula husk with lactulose and other laxatives in the treatment of simple constipation. *Curr Med Res Opin.* 1998; 14(4): 227-233.
96. Simpson K, Leyendecker P, Hopp M, et al.: Fixed-ratio combination oxycodone/naloxone compared with oxycodone alone for the relief of opioid-induced constipation in moderate-to-severe noncancer pain. *Curr Med Res Opin.* 2008; 24(12): 3503-3512.
97. Sykes NP: Oral naloxone in opioid-associated constipation. *Lancet.* 1991; 337(8755): 1475.
98. Hellwig TR, Pottebaum AA: The role of methylnaltrexone in opioid-induced constipation. *S D Med.* 2013; 66(10): 425, 427.
99. Rauck RL: Treatment of opioid-induced constipation: Focus on the peripheral mu-opioid receptor antagonist methylnaltrexone. *Drugs.* 2013; 73(12): 1297-1306.
100. Bader S, Durk T, Becker G: Methylnaltrexone for the treatment of opioid-induced constipation. *Expert Rev Gastroenterol Hepatol.* 2013; 7(1): 13-26.
101. Cryer B, Katz S, Vallejo R, et al.: A randomized study of lubiprostone for opioid-induced constipation in patients with chronic noncancer pain. *Pain Med.* 2014 (in press).
102. Lubiprostone (Amitiza) for opioid-induced constipation. *Med Lett Drugs Ther.* 2013; 55(1418): 47-48.
103. Wong BS, Camilleri M: Lubiprostone for the treatment of opioid-induced bowel dysfunction. *Expert Opin Pharmacother.* 2011; 12(6): 983-990.
104. Sharma A, Jamal MM: Opioid induced bowel disease: A twenty-first century physicians' dilemma. Considering pathophysiology and treatment strategies. *Curr Gastroenterol Rep.* 2013; 15(7): 334.
105. Azizi Z, Javid Anbardan S, Ebrahimi Daryani N: A review of the clinical manifestations, pathophysiology and management of opioid bowel dysfunction and narcotic bowel syndrome. *Middle East J Dig Dis.* 2014; 6(1): 5-12.
106. Sandgren JE, McPhee MS, Greenberger NJ: Narcotic bowel syndrome treated with clonidine. Resolution of abdominal pain and intestinal pseudo-obstruction. *Ann Intern Med.* 1984; 101(3): 331-334.
107. Bruera E, Brenneis C, Michaud M, et al.: Continuous Sc infusion of metoclopramide for treatment of narcotic bowel syndrome. *Cancer Treat Rep.* 1987; 71(11): 1121-1122.
108. Wong V, Sobala G, Losowsky M: A case of narcotic bowel syndrome successfully treated with clonidine. *Postgrad Med J.* 1994; 70(820): 138-140.
109. Pergolizzi JV Jr, Ma L, Foster DR, et al.: The prevalence of opioid-related major potential drug-drug interactions and their impact on health care costs in chronic pain patients. *J Manag Care Pharm.* 2014; 20(5): 467-476.

110. Chen LH, Hedegaard H, Warner M: Drug-poisoning deaths involving opioid analgesics: United States, 1999-2011. *NCHS Data Brief.* 2014; (166): 1-8.
111. Leung SY: Benzodiazepines, opioids and driving: An overview of the experimental research. *Drug Alcohol Rev.* 2011; 30(3): 281-286.
112. Zacny JP, Paice JA, Coalson DW: Separate and combined psychopharmacological effects of alprazolam and oxycodone in healthy volunteers. *Drug Alcohol Depend.* 2012; 124(3): 274-282.
113. Gudin JA, Mogali S, Jones JD, et al.: Risks, management, and monitoring of combination opioid, benzodiazepines, and/or alcohol use. *Postgrad Med.* 2013; 125(4): 115-130.
114. Jobski K, Schmid U, Behr S, et al.: 3-Year prevalence of alcohol-related disorders in German patients treated with high-potency opioids. *Pharmacoepidemiol Drug Saf.* 2012; 21(10): 1125-1129.
115. Krajacic A, Tucker IG: Matrix formation in sustained release tablets: Possible mechanism of dose dumping. *Int J Pharm.* 2003; 251(1-2): 67-78.
116. Fiske WD, Jobes J, Xiang Q, et al.: The effects of ethanol on the bioavailability of oxymorphone extended-release tablets and oxymorphone crush-resistant extended-release tablets. *J Pain.* 2012; 13(1): 90-99.
117. Lennernas H: Ethanol-drug absorption interaction: Potential for a significant effect on the plasma pharmacokinetics of ethanol vulnerable formulations. *Mol Pharm.* 2009; 6(5): 1429-1440.
118. Sathyan G, Sivakumar K, Thipphawong J: Pharmacokinetic profile of a 24-hour controlled-release OROS formulation of hydromorphone in the presence of alcohol. *Curr Med Res Opin.* 2008; 24(1): 297-305.
119. Browne B, Linter S: Monoamine oxidase inhibitors and narcotic analgesics. A critical review of the implications for treatment. *Br J Psychiatry.* 1987; 151: 210-212.
120. Gillman PK: Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity. *Br J Anaesth.* 2005; 95(4): 434-441.
121. Park SH, Wackernah RC, Stimmel GL: Serotonin syndrome: Is it a reason to avoid the use of tramadol with antidepressants? *J Pharm Pract.* 2014; 27(1): 71-78.
122. Van Vugt DA, Meites J: Influence of endogenous opiates on anterior pituitary function. *Fed Proc.* 1980; 39(8): 2533-2538.
123. Iakobishvili Z, Cohen E, Garty M, et al.: Use of intravenous morphine for acute decompensated heart failure in patients with and without acute coronary syndromes. *Acute Card Care.* 2011; 13(2): 76-80.
124. Gray A, Goodacre S, Seah M, et al.: Diuretic, opiate and nitrate use in severe acidotic acute cardiogenic pulmonary oedema: Analysis from the 3CPO trial. *QJM.* 2010; 103(8): 573-581.
125. Korinek AM, Languille M, Bonnet F, et al.: Effect of postoperative extradural morphine on ADH secretion. *Br J Anaesth.* 1985; 57(4): 407-411.
126. Graham CA, Cattermole GN: Morphine should be abandoned as a treatment for acute cardiogenic pulmonary oedema. *Emerg Med Australas.* 2009; 21(2): 160.
127. Kao D, Bucher Bartelson B, Khatri V, et al.: Trends in reporting methadone-associated cardiac arrhythmia, 1997-2011: An analysis of registry data. *Ann Intern Med.* 2013; 158(10): 735-740.
128. Farsi D, Mirafzal A, Hassanian-Moghaddam H, et al.: The correlation between prolonged corrected QT interval with the frequency of respiratory arrest, endotracheal intubation, and mortality in acute methadone overdose. *Cardiovasc Toxicol.* 2014; 14(4): 358-367.
129. Wolbrette D: Gender differences in the proarrhythmic potential of QT-prolonging drugs. *Curr Womens Health Rep.* 2002; 2(2): 105-109.
130. Byrne A, Stimmel B: Methadone and QTc prolongation. *Lancet.* 2007; 369(9559): 366; author reply 366-367.
131. Abramson DW, Quinn DK, Stern TA: Methadone-associated QTc prolongation: A case report and review of the literature. *Primary Care Companion J Clin Psychiatry.* 2008; 10(6): 470-476.
132. Krantz MJ, Martin J, Stimmel B, et al.: QTc interval screening in methadone treatment. *Ann Intern Med.* 2009; 150(6): 387-395.
133. Chang KC, Huang CL, Liang HY, et al.: Gender-specific differences in susceptibility to low-dose methadone-associated QTc prolongation in patients with heroin dependence. *J Cardiovasc Electrophysiol.* 2012; 23(5): 527-533.
134. Mujtaba S, Romero J, Taub CC: Methadone, QTc prolongation and torsades de pointes: Current concepts, management and a hidden twist in the tale? *J Cardiovasc Dis Res.* 2013; 4(4): 229-235.
135. Wang SC, Ho IK, Tsou HH, et al.: Functional genetic polymorphisms in CYP2C19 gene in relation to cardiac side effects and treatment dose in a methadone maintenance cohort. *OMICS.* 2013; 17(10): 519-526.
136. Anchersen K, Hansteen V, Gossop M, et al.: Opioid maintenance patients with QTc prolongation: Congenital long QT syndrome mutation may be a contributing risk factor. *Drug Alcohol Depend.* 2010; 112(3): 216-219.
137. Katchman AN, McGroary KA, Kilborn MJ, et al.: Influence of opioid agonists on cardiac human ether-a-go-go-related gene K(+) currents. *J Pharmacol Exp Ther.* 2002; 303(2): 688-694.
138. Wedam EF, Bigelow GE, Johnson RE, et al.: QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. *Arch Intern Med.* 2007; 167(22): 2469-2475.
139. Fareed A, Patil D, Scheinberg K, et al.: Comparison of QTc interval prolongation for patients in methadone versus buprenorphine maintenance treatment: A 5-year follow-up. *J Addict Dis.* 2013; 32(3): 244-251.
140. Krantz MJ, Garcia JA, Mehler PS: Effects of buprenorphine on cardiac repolarization in a patient with methadone-related torsade de pointes. *Pharmacotherapy.* 2005; 25(4): 611-614.
141. Esses JL, Rosman J, Do LT, et al.: Successful transition to buprenorphine in a patient with methadone-induced torsades de pointes. *J Interv Card Electrophysiol.* 2008; 23(2): 117-119.
142. Baker JR, Best AM, Pade PA, et al.: Effect of buprenorphine and antiretroviral agents on the QT interval in opioid-dependent patients. *Ann Pharmacother.* 2006; 40(3): 392-396.
143. Zhou SF: Polymorphism of human cytochrome P450 2D6 and its clinical significance: Part I. *Clin Pharmacokinet.* 2009; 48(11): 689-723.
144. Zhou SF: Polymorphism of human cytochrome P450 2D6 and its clinical significance: Part II. *Clin Pharmacokinet.* 2009; 48(12): 761-804.
145. Zahari Z, Ismail R: Influence of cytochrome P450, family 2, subfamily D, polypeptide 6 (CYP2D6) polymorphisms on pain sensitivity and clinical response to weak opioid analgesics. *Drug Metab Pharmacokinet.* 2014; 29(1): 29-43.
146. Kirchheiner J, Schmidt H, Tzvetkov M, et al.: Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. *Pharmacogenomics J.* 2007; 7(4): 257-265.
147. Crews KR, Gaedigk A, Dunnenberger HM, et al.: Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clin Pharmacol Ther.* 2014; 95(4): 376-382.
148. Stamer UM, Zhang L, Book M, et al.: CYP2D6 genotype dependent oxycodone metabolism in postoperative patients. *PLoS One.* 2013; 8(3): e60239.
149. Kummer O, Hammann F, Moser C, et al.: Effect of the inhibition of CYP3A4 or CYP2D6 on the pharmacokinetics and pharmacodynamics of oxycodone. *Eur J Clin Pharmacol.* 2011; 67(1): 63-71.
150. Samer CF, Daali Y, Wagner M, et al.: Genetic polymorphisms and drug interactions modulating CYP2D6 and CYP3A activities have a major effect on oxycodone analgesic efficacy and safety. *Br J Pharmacol.* 2010; 160(4): 919-930.
151. Susce MT, Murray-Carmichael E, de Leon J: Response to hydrocodone, codeine and oxycodone in a CYP2D6 poor metabolizer. *Prog Neuropsychopharmacol Biol Psychiatry.* 2006; 30(7): 1356-1358.
152. Lurcott G: The effects of the genetic absence and inhibition of CYP2D6 on the metabolism of codeine and its derivatives, hydrocodone and oxycodone. *Anesth Prog.* 1998; 45(4): 154-156.
153. Samer CF, Daali Y, Wagner M, et al.: The effects of CYP2D6 and CYP3A activities on the pharmacokinetics of immediate release oxycodone. *Br J Pharmacol.* 2010; 160(4): 907-918.
154. Hutchinson MR, Menelaou A, Foster DJ, et al.: CYP2D6 and CYP3A4 involvement in the primary oxidative metabolism of hydrocodone by human liver microsomes. *Br J Clin Pharmacol.* 2004; 57(3): 287-297.
155. Soderberg Lofdal KC, Andersson ML, Gustafsson LL: Cytochrome P450-mediated changes in oxycodone pharmacokinetics/pharmacodynamics and their clinical implications. *Drugs.* 2013; 73(6): 533-543.
156. Solassol I, Caumette L, Bressolle F, et al.: Inter- and intra-individual variability in transdermal fentanyl absorption in cancer pain patients. *Oncol Rep.* 2005; 14(4): 1029-1036.
157. Solassol I, Bressolle F, Caumette L, et al.: Inter- and intraindividual variabilities in pharmacokinetics of fentanyl after repeated 72-hour transdermal applications in cancer pain patients. *Ther Drug Monit.* 2005; 27(4): 491-498.
158. Feierman DE, Lasker JM: Metabolism of fentanyl, a synthetic opioid

analgesic, by human liver microsomes. Role of CYP3A4. *Drug Metab Dispos.* 1996; 24(9): 932-939.
159. Kokubun H, Ebinuma K, Matoba M, et al.: Population pharmacokinetics of transdermal fentanyl in patients with cancer-related pain. *J Pain Palliat Care Pharmacother.* 2012; 26(2): 98-104.
160. Kapur BM, Hutson JR, Chibber T, et al.: Methadone: A review of drug-drug and pathophysiological interactions. *Crit Rev Clin Lab Sci.* 2011; 48(4): 171-195.
161. Campbell SD, Crafford A, Williamson BL, et al.: Mechanism of autoinduction of methadone N-demethylation in human hepatocytes. *Anesth Anal.* 2013; 117(1): 52-60.
162. Dickmann LJ, Isoherranen N: Quantitative prediction of CYP2B6 induction by estradiol during pregnancy: Potential explanation for increased methadone clearance during pregnancy. *Drug Metab Dispos.* 2013; 41(2): 270-274.
163. Bendayan R, Lee G, Bendayan M: Functional expression and localization of P-glycoprotein at the blood brain barrier. *Microsc Res Tech.* 2002; 57(5): 365-380.
164. Mercer SL, Coop A: Opioid analgesics and P-glycoprotein efflux transporters: A potential systems-level contribution to analgesic tolerance. *Curr Top Med Chem.* 2011; 11(9): 1157-1164.
165. Takashina Y, Naito T, Mino Y, et al.: Impact of CYP3A5 and ABCB1 gene polymorphisms on fentanyl pharmacokinetics and clinical responses in cancer patients undergoing conversion to a transdermal system. *Drug Metab Pharmacokinet.* 2012; 27(4): 414-421.
166. Hamabe W, Maeda T, Kiguchi N, et al.: Negative relationship between morphine analgesia and P-glycoprotein expression levels in the brain. *J Pharmacol Sci.* 2007; 105(4): 353-360.
167. Hassan HE, Mercer SL, Cunningham CW, et al.: Evaluation of the P-glycoprotein (Abcb1) affinity status of a series of morphine analogs: Comparative study with meperidine analogs to identify opioids with minimal P-glycoprotein interactions. *Int J Pharm.* 2009; 375(1-2): 48-54.
168. Mercer SL, Cunningham CW, Eddington ND, et al.: Opioids and efflux transporters. Part 3: P-glycoprotein substrate activity of 3-hydroxyl addition to meperidine analogs. *Bioorg Med Chem Lett.* 2008; 18(12): 3638-3640.
169. Cunningham CW, Mercer SL, Hassan HE, et al.: Opioids and efflux transporters. Part 2: P-glycoprotein substrate activity of 3- and 6-substituted morphine analogs. *J Med Chem.* 2008; 51(7): 2316-2320.
170. Kalvass JC, Olson ER, Cassidy MP, et al.: Pharmacokinetics and pharmacodynamics of seven opioids in P-glycoprotein-competent mice: Assessment of unbound brain EC50,u and correlation of in vitro, preclinical, and clinical data. *J Pharmacol Exp Ther.* 2007; 323(1): 346-355.
171. Yousif S, Saubamea B, Cisternino S, et al.: Effect of chronic exposure to morphine on the rat blood-brain barrier: Focus on the P-glycoprotein. *J Neurochem.* 2008; 107(3): 647-657.
172. Letrent SP, Polli JW, Humphreys JE, et al.: P-glycoprotein-mediated transport of morphine in brain capillary endothelial cells. *Biochem Pharmacol.* 1999; 58(6): 951-957.
173. Letrent SP, Pollack GM, Brouwer KR, et al.: Effects of a potent and specific P-glycoprotein inhibitor on the blood-brain barrier distribution and antinociceptive effect of morphine in the rat. *Drug Metab Dispos.* 1999; 27(7): 827-834.
174. Henthorn TK, Liu Y, Mahapatro M, et al.: Active transport of fentanyl by the blood-brain barrier. *J Pharmacol Exp Ther.* 1999; 289(2): 1084-1089.
175. Fudin J, Fontenelle DV, Payne A: Rifampin reduces oral morphine absorption: A case of transdermal buprenorphine selection based on morphine pharmacokinetics. *J Pain Palliat Care Pharmacother.* 2012; 26(4): 362-367.
176. Richarz U, Jacobs A, Spina E: How frequently are contraindicated or warned against combinations of drugs prescribed to patients receiving long-term opioid therapy for chronic pain? *Pharmacoepidemiol Drug Saf.* 2012; 21(5): 453-462.
177. Ashburn MA, Ogden LL, Zhang J, et al.: The pharmacokinetics of transdermal fentanyl delivered with and without controlled heat. *J Pain.* 2003; 4(6): 291-297.
178. Knotkova H, Fine PG, Portenoy RK: Opioid rotation: The science and the limitations of the equianalgesic dose table. *J Pain Symptom Manage.* 2009; 38(3): 426-439.