Quantifying the Impact of Drug-Drug Interactions Associated With Opioids

Joseph V. Pergolizzi, MD

Abstract

Opioids have long been the mainstay of pain control for patients with cancer; however, their use in patients with chronic, moderate to severe pain has increased greatly in the past decade. The risk of drug-drug interactions (DDIs) is a concern with all medications, but is of particular concern in patients using opioids. Most opioids are metabolized via the cytochrome P450 enzyme system, the same system that metabolizes more than half of all prescription medications. Pharmacokinetic (PK) DDIs are those in which a drug causes a change in the absorption, distribution, metabolism, and/or elimination of another drug. PK DDIs involving opioids may result in reduced analgesic efficacy or toxicity of the opioid. Pharmacodynamic DDIs result when 2 drugs are coadministered and the concentration-response curve of 1 or both drugs is altered without a change in PK. The risk of DDIs in patients receiving opioids is particularly worrisome in those with comorbidities and those taking numerous medications. Given the high rates of polypharmacy in the elderly population, clinicians should use caution when prescribing opioids, and perhaps avoid certain opioids. DDIs can result in significant morbidity and mortality, primarily through overdosing or undertreatment, and are associated with increased healthcare utilization and costs. Clinicians often underestimate the risk of DDIs in patients using opioids. Comprehensive studies of real-world opioid utilization patterns are needed to determine the quantitative impact of opioid DDIs.

(Am J Manag Care. 2011;17:S288-S292)

For author information and disclosures, see end of text.

There is increasing concern about the risks of drug-drug interactions (DDIs), in which patients experience an interaction affecting the efficacy and/or toxicity of 1 or more drugs, and potential drug-drug interactions (PDDIs), in which patients are exposed to the potential for a DDI, in the general population. The risks of DDIs and PDDIs are of particular concern in individuals using opioids, the majority of which are metabolized via the cytochrome P450 (CYP450) enzyme system.[1] More than half of all prescription medications rely on this same pathway for metabolism, and many affect how this system metabolizes other drugs, thus elevating the potential for DDIs in the increasing numbers of individuals who use opioids for chronic noncancer pain, as well as those who take opioids for nonmedical reasons.[2] Of particular concern are pharmacokinetic (PK) DDIs, in which a drug causes a change in the absorption, distribution, metabolism, and/or elimination of another drug. PK DDIs involving opioids may result in reduced analgesic efficacy or toxicity of the opioid.[1] Pharmacodynamic (PD) interactions result when 2 drugs are coadministered and the concentration-response curve of 1 or both drugs is altered without a change in pharmacokinetics. For example, additional sedation may result if an opioid is administered to a patient currently taking a benzodiazepine. Clinicians should monitor patients for both PK and PD DDIs.

Such interactions can result in significant morbidity and mortality, primarily through overdosing or undertreatment, as well as the potential for increased healthcare utilization and costs.[3-6]

Prevalence

The epidemiologic evidence surrounding DDIs overall varies widely, with estimates of PDDIs ranging from 5.4% to 63%.[5-8]

In 1 study evaluating DDIs in 2779 Veterans Administration (VA) patients who had been prescribed an antidepressant and had a current prescription for at least 1 systemically active drug, Preskorn et al found that 60% were taking at least 1 drug that was predominantly a substrate for 1 CYP enzyme, while one-third were taking at least 1 drug that was a substantial inhibitor of 1 or more of those same CYP enzymes. A total of 300 patients (11%) received concurrent drugs that could cause CYP-enzyme mediated adverse DDIs, yet the VA's drug alert system identified only 9% (26) of these cases, and only 11% (6) of the 55 different

potentially harmful combinations.[9] Although patients were not receiving opioids, and currently available drug alert systems may be more sophisticated, this study demonstrates the potential risks even in a healthcare system utilizing a computerized drug alert system.[10] Given the increasing number of young veterans receiving opioid medication, there is the potential for future problems within the VA system.[11]

In a study of medical records and prescription data from a public hospital in Brazil, Moura et al reported that 1282 PDDIs were identified in 816 prescriptions.[12] They also found that 37% of patients had been exposed to at least 1 potential DDI during their hospital stay, 62% of prescriptions (504 of 816) contained at least 1 potential drug interaction, and 38% of prescriptions contained more than 1 potential interaction. Hospitalized patients who experienced a DDI had a mean stay of 15 days compared with 8 days for those who did not have a DDI, with a 2-fold higher cost of hospitalization (odds ratio: 3.10; 95% confidence interval: 2.19-4.42).[12] While causality between a DDI and length of stay cannot be expressly implied, the data do suggest a relationship. The most frequently interacting drug pairs were digoxin + furosemide, amitriptyline + phenytoin, amikacin + ketoprofen, captopril + spironolactone, and phenytoin + dexamethasone.[12]

In my own research involving opioid-related PDDIs in outpatients, my colleagues and I reported a PDDI prevalence of approximately 26% in patients with noncancer chronic pain who were taking opioids.[13,14] Lafata et al had similar results in their study estimating the frequency of PDDIs involving warfarin, digoxin, cyclosporine, and lovastatin/simvastatin in prescriptions dispensed to patients from 10 organizations comprising the HMO Research Network's Center for Education and Research on Therapeutics. They found that 17.8% to 28% of patients were dispensed a PDDI using a "days supply" definition and 7.1% to 17.1% of patients were dispensed a PDDI using a "same day" definition. Extrapolated to the general insured US population, this translates to anywhere from 1.29 to 2.67 adults dispensed warfarin, digoxin, cyclosporine, or lovastatin/simvastatin along with a potentially interacting drug annually.[15]

Clinicians often underestimate the risk of DDIs in patients using opioids, even as they admit that they are quite concerned about the potential for such interactions.[16] Unfortunately, the extent of the problem with opioids is poorly understood, due to a lack of comprehensive studies of real-world opioid utilization patterns.[12-14,17-19]

Increasing Opioid Use in the General Population

Although opioids have long been the mainstay of pain control for cancer patients, with an estimated 60% of cancer patients benefitting from their analgesic properties, their use for chronic noncancer pain has increased greatly in the past decade.[20,21] Today, long-acting opioids are prescribed for patients with chronic, moderate to severe pain.[22-26] Methadone is commonly used to treat patients with opioid dependency.[27,28]

Brixner et al found that opioid use nearly doubled in Medicaid patients between 1998 and 2003.[21] Meanwhile, Israeli researchers reported that use of morphine, oxycodone, pethidine, methadone, and fentanyl increased nearly 50% from 2.46 daily defined doses (DDDs)/1000 inhabitants per day in 2000 to 3.61 DDDs/1000 inhabitants per day in 2008, with the majority of the increase related to fentanyl consumption.[29]

Thielke et al reported a 35% to 50% increase in long-term opioid prescribing between 2000 and 2005 in commercial and Medicaid populations in Arkansas.[30] An analysis of national prescriptions in Norway found a 9% increase in the number of individuals receiving opioids between 2004 and 2007, and that nearly 10% of the population received opioids in 2001, just 3% for cancer pain.[31]

These drugs are often used outside of official labeling, typically in too-large or too-frequent dosing, and are frequently used even in the treatment of mild pain.[32-34]

Prevalence and Potential Clinical Consequences of Opioid PK DDIs

As noted earlier, there are few data regarding the prevalence of opioid-related PK DDIs. My colleagues and I conducted a retrospective evaluation of a large commercial claims database and Medicare claims data in patients with chronic low back pain who were taking opioids. We identified an overall PDDI prevalence rate of 27%. Patients younger than 65 years had the highest prevalence of PDDIs (approximately 30%), with a prevalence rate of 23.1% in those older than 65 years.[13]

My colleagues and I also analyzed medical claims from 102,016 patients with osteoarthritis who had received at least 1 prescription for a CYP450-metabolized opioid for at least 12 months, and evaluated PDDIs that put patients at risk of DDIs during a 30-day period after the opioid was prescribed. Half of the patients were older than 65 years. One-fourth of patients experienced a PDDI with similar rates seen in the younger than 65 cohort (28.8%) and 65 and older cohort (22.8%).[14]

Interestingly, we found no association between advanced age and PDDI risk, with patients aged 35 to 44 years having the highest risk (46%) of a PDDI. Polypharmacy was not required for a PDDI; even taking 1 other prescription in the 3 months prior to the index date increased the risk of PDDI

3-fold compared with patients who had not taken any other medication. Each additional prescription increased the risk by 138%.[14] Yet an estimated 32% of patients taking opioids receive more than 5 concurrent medications; 21%, more than 10.[35]

Increased Healthcare Utilization and Costs Related to Opioid PDDIs

Opioid PDDIs may potentially result in increased healthcare utilization and costs. Summers et al conducted a retrospective analysis of paid claims from a large, commercially insured population to evaluate overall costs in patients receiving CYP450-metabolized opioids and found that total costs 6 months after a PDDI were substantially higher ($8165 vs $7498, P <.01) than in matched patients who did not experience a PDDI.[4] This study did not establish a causal relationship between PDDIs and increased cost; this relationship merits further research.

To examine the economic impact of potential CYP450 pharmacokinetic DDIs among patients with osteoarthritis and patients with low back pain taking opioids, my colleagues and I performed retrospective database analyses. We examined associated clinical events, health services utilization, and payments during the 6 months post PDDI. Overall, mean total costs at 6 months for patients with osteoarthritis younger than 65 years who experienced a PDDI were $9469, compared with $8382 for a similar group without a PDDI (P = .004). For patients with osteoarthritis who were 65 years or older and experienced a PDDI, mean total costs at 6 months were $9829 compared with $8622 for those without a PDDI (P = .001). For patients with low back pain, the mean overall costs for those younger than 65 years who experienced a PDDI were $7086 compared with $6353 for those without a PDDI (P <.001); and $7806 versus $7043 ($P$ = .013), respectively, for patients 65 years and older. Patients with PDDIs, regardless of age, also had significantly higher prescription payments, claims for office visits, and associated payments than similar patients without PDDIs.[17,20] As with the study by Summers et al, this study did not establish a causal relationship between PDDIs and increased cost. The relationship between PDDIs and cost merits further research.

Opioid DDIs and the Elderly

The risk of DDIs in patients receiving opioids is particularly worrisome in medically complicated patients, primarily the elderly.[36] Patients in this population have significant rates of polypharmacy, have several physicians involved in their care, and often do not tell their doctors about all medications they take.[37-39] Thus, exposure to potential drug interactions is common. A European study of 1601 elderly outpatients found that nearly half (46%) had at least 1 potential clinically significant DDI, 10% of which were very severe.[40] Yet there is evidence that many DDIs in elderly patients could be avoided.[41]

Many drugs commonly used in elderly populations, including antiarrhythmics, antipsychotics, azole antifungals, benzodiazepines, beta blockers, calcium channel blockers, oncologic therapies, celecoxib, histamine H_2-receptor antagonists, hormonal therapies, selective serotonin/norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), sildenafil, insomnia medications, statins, tamoxifen, tricyclic antidepressants, and warfarin, can contribute to clinically relevant DDIs (both PK and PD) when given with most opioids.[36]

Given the high rates of polypharmacy in the elderly population relative to other age groups, as well as the relatively high incidence of renal, hepatic, and/or cardio-respiratory impairment, cerebrovascular disease, dementia, and brain injury, clinicians should use significant caution when prescribing opioids in the elderly, and perhaps even avoid certain opioids altogether.[36] The issue of opioid-related PK DDIs is explored in greater detail in another article in this supplement.

Comorbidities Present an Additional Risk Factor for Opioid DDIs

Individuals infected with HIV often have comorbid opioid dependence. For example, ritonavir and lopinavir/ritonavir increase plasma concentrations of oral oxycodone to the extent that dose reductions may be required to prevent adverse events; co-administering a buprenorphine/naloxone combination with a tipranavir/ritonavir combination can reduce the efficacy of tipranavir; and ritonavir, efavirenz, and nevirapine administered in conjunction with methadone can reduce therapeutic levels of the drug so significantly that patients experience withdrawal symptoms.[42-46] In addition, efavirenz coadministered with buprenorphine also demonstrates significant reduction in the bioavailability of the drug, although with no withdrawal symptoms.[42]

Psychiatric comorbidities are more common in patients with chronic pain than in those without, with a lifetime prevalence rate ranging from 44% to 54% for depressive disorders and of approximately 20% for anxiety disorders.[22] Manchikanti et al found that approximately 75% of 533 patients receiving chronic opioid therapy were also taking benzodiazepines and/or antidepressants, with approximately 25% taking all 3 simultaneously.[47]

The potential for a PK DDI in these patients is considerable given that several SSRIs (fluoxetine, fluvoxamine, and paroxetine) can significantly inhibit 1 or more CYP enzymes at effective doses. Fluoxetine and paroxetine substantially inhibit CYP 2D6, which is responsible for metabolizing codeine and tramadol.[1,36,48] Gnanadesigan et al recently described 4 cases of serotonin syndrome in elderly residents of a California long-term care facility who were also taking an opioid; DDIs may have played a role.[49]

It is important that clinicians be aware of this potential interaction and of the fact that not all SSRIs have the same pharmacokinetic properties; thus, they should not be used interchangeably in patients receiving opioid therapy, particularly chronic opioid therapy.

Minimizing PK DDIs in Chronic Pain Patients

Given the increasing reliance on opioids to manage chronic noncancer pain, clinicians should be aware of opportunities to minimize potential opioid-associated PK DDIs. Physicians and pharmacists can also educate patients regarding potential interactions and recommend analgesic alternatives.[50]

Careful selection of opioids, particularly in an elderly and/or polypharmacy population, is also important. For instance, in patients taking 1 or more additional drugs that are metabolized through the CYP450 pathway, morphine, hydromorphone, oxymorphone, and tapentadol are potential options. The first 3 bypass the CYP-mediated metabolism, reducing the risk of DDIs, while tapentadol's inhibiting activity on CYP2D6 activity is not considered clinically relevant.[36] Careful drug titration and close attention to any side effects experienced by the patient can also limit the potential for PK DDIs.[51]

One challenge for physicians and pharmacists has been the lack of agreement on PK DDI perpetrators within reference sources such as drug monographs and automated drug interaction software. Thus, as the authors of a recent review on the topic noted, "Interpreting the clinical relevance of a given perpetrator is often difficult, particularly for healthcare providers subject to 'information overload' and 'alert fatigue.'" However, the authors were able to narrow a list of 349 candidate CYP-perpetrator pairs down to 39 inhibitors and 10 inducers, a "manageable list."[52]

Clinicians must also take extra steps to identify all drugs, herbs, and supplements patients take, given that nearly 40% of patients take medications their physicians are not aware of. This often occurs in patients under the care of several physicians, with the risk of DDIs directly related to the number of physicians patients see.[45,46]

In conclusion, additional research is needed to determine the quantitative impact of PK DDIs associated with opioid use. PD DDIs are also important and should not be neglected within the broader scope of continuous monitoring for DDIs and individualized patient care.

Author Affiliation: Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD; Department of Anesthesiology, Georgetown University School of Medicine, Washington, DC; and the Association of Chronic Pain Patients, Tyler, TX.

Funding Source: This supplement has been supported by funding from Endo Pharmaceuticals.

Author Disclosure: Dr Pergolizzi reports serving as a consultant/advisory board member/lecturer for and receiving honoraria from Endo Pharmaceuticals, Grünenthal, Johnson & Johnson, and Purdue Pharma.

Authorship Information: Concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; provision of study materials.

Address correspondence to: 840 111th Ave North, Ste 7, Naples, FL 34108. Attn: Dr Pergolizzi. E-mail: jpjmd@msn.com.

REFERENCES

1. Armstrong SC, Wynn GH, Sandson NB. Pharmacokinetic drug interactions of synthetic opiate analgesics. *Psychosomatics.* 2009;50(2):169-176.

2. Zhou SF, Xue CC, Yu XQ, Li C, Wang G. Clinically important drug interactions potentially involving mechanism-based inhibition of cytochrome P450 3A4 and the role of therapeutic drug monitoring. *Ther Drug Monit.* 2007;29(6):687-710.

3. Lemesle F, Lemesle F, Nicola W, et al. First case of stress cardiomyopathy as a result of methadone withdrawal secondary to drug-drug interaction. *Am J Emerg Med.* 2010;28(3):387.e385-e386.

4. Summers KH, Puenpatom R, Rajan N, et al. Economic impact of potential drug-drug interactions in opioid analgesics. *J Med Econ.* 2011;14(4):390-396.

5. Glintborg B, Andersen SE, Dalhoff K. Drug-drug interactions among recently hospitalised patients—frequent but mostly clinically insignificant. *Eur J Clin Pharmacol.* 2005;61(9):675-681.

6. Riechelmann RP, Zimmermann C, Chin SN, et al. Potential drug interactions in cancer patients receiving supportive care exclusively. *J Pain Symptom Manage.* 2008;35(5):535-543.

7. Cruciol-Souza JM, Thomson JC. Prevalence of potential drug-drug interactions and its associated factors in a Brazilian teaching hospital. *J Pharm Pharm Sci.* 2006;9(3):427-433.

8. Janchawee B, Wongpoowarak W, Owatranporn T, et al. Pharmacoepidemiologic study of potential drug interactions in outpatients of a university hospital in Thailand. *J Clin Pharm Ther.* 2005;30(1):13-20.

9. Preskorn S, Shah R, Neff M, et al. The potential for clinically significant drug-drug interactions involving the CYP 2D6 system: effects with fluoxetine and paroxetine versus sertraline. *J Psychiatr Pract.* 2007;13(1):5-12.

10. Johnson CL, Carlson RA, Tucker CL, et al. Using BCMA software to improve patient safety in veterans administration medical centers. *J Healthcare Infor Manag.*16(1):46-51.

11. Wu PC, Lang C, Hasson NK, et al. Opioid use in young veterans. *J Opioid Manag.* 2010;6(2):133-139.

12. Moura C, Acurcio F, Belo N. Drug-drug interactions associated with length of stay and cost of hospitalization. *J Pharm Pharm Sci.* 2009;12(3):266-272.

13. Pergolizzi JV Jr, Labhsetwar S, Puenpatom R, et al. Prevalence of exposure to potential CYP450 pharmacokinetic drug-drug interactions among patients with chronic low back pain taking opioids. *Pain Pract.* 2011;11(3):230-239.

14. Pergolizzi JV Jr, Labhsetwar S, Puenpatom R, et al. Exposure to potential CYP450 pharmacokinetic drug-drug interactions among osteoarthritis patients: incremental risk of multiple prescriptions. *Pain Pract.* 2011;11(4):325-336.

15. Lafata JE, Schultz L, Simpkins J, et al. Potential drug-drug interactions in the outpatient setting. *Med Care.* 2006;44(6): 534-541.

16. Bhamb B, Brown D, Hariharan J, et al. Survey of select practice behaviors by primary care physicians on the use of opioids for chronic pain. *Curr Med Res Opin.* 2006;22(9):1859-1865.

17. Pergolizzi J Jr et al. Economic impact of potential CYP450 pharmacokinetic drug-drug interactions among osteoarthritis patients taking opioids. *Pain Practice.* In press.

18. Chou R, Ballantyne J, Fanciullo G, et al. Research gaps on use of opioids for chronic noncancer pain: findings from a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *J Pain.* 2009;10(2):147-159.

19. Chapman CR, Lipschitz DL, Angst MS, et al. Opioid pharmacotherapy for chronic non-cancer pain in the United States: a research guideline for developing an evidence-base. *J Pain.* 2010;11(9):807-829.

20. Pergolizzi J Jr et al. Economic impact of potential CYP450 pharmacokinetic drug-drug interactions among chronic low back pain patients taking opioids. *Pain Practice.* In press.

21. Brixner D, Oderda G, Roland C, et al. Opioid expenditures and utilization in the Medicaid system. *J Pain Palliat Care Pharmacother.* 2006;20(1):5-13.

22. Reid M, Engles-Horton L, Weber M, et al. Use of opioid medications for chronic noncancer pain syndromes in primary care. *J Gen Intern Med.* 2002;17(3):173-179.

23. Palacio A, Uribe C, Li H, et al. Financial and clinical characteristics of fibromyalgia: a case-control comparison. *Am J Manag Care.* 2010;16(5 suppl):S118-S125.

24. Altman R, Smith H. Opioid therapy for osteoarthritis and chronic low back pain. *Postgrad Med.* 2010;122(6):87-97.

25. Cifuentes M, Webster B, Genevay S, et al. The course of opioid prescribing for a new episode of disabling low back pain: opioid features and dose escalation. *Pain.* 2010;151(1):22-29.

26. Chen H, Lamer TJ, Rho RH, et al. Contemporary management of neuropathic pain for the primary care physician. *Mayo Clin Proc.* 2004;79(12):1533-1545.

27. McCarty D, Perrin N, Green C, et al. Methadone maintenance and the cost and utilization of health care among individuals dependent on opioids in a commercial health plan. *Drug Alcohol Depend.* 2010;111(3):235-240.

28. Rosenblum A, Joseph H, Fong C, et al. Prevalence and characteristics of chronic pain among chemically dependent patients in methadone maintenance and residential treatment facilities. *JAMA.* 2003;289(18):2370-2378.

29. Ponizovsky A, Marom E, Zeldin A, et al. Trends in opioid analgesics consumption, Israel, 2000-2008. *Eur J Clin Pharmacol.* 2011;67(2):165-168.

30. Thielke S, Simoni-Wastila L, Edlund M, et al. Age and sex trends in long-term opioid use in two large American health systems between 2000 and 2005. *Pain Med.* 2010;11(2):248-256.

31. Fredheim O, Skurtveit S, Breivik H, et al. Increasing use of opioids from 2004 to 2007 - pharmacoepidemiological data from a complete national prescription database in Norway. *Eur J Pain.* 2010;14(3):289-294.

32. Ackerman S, Mordin M, Reblando J, et al. Patient-reported utilization patterns of fentanyl transdermal system and oxycodone hydrochloride controlled-release among patients with chronic nonmalignant pain. *J Manag Care Pharm.* 2003;9(3):223-231.

33. Malkin JD, Ackerman SJ, Schein J, et al. Cost and utilization patterns of fentanyl transdermal system and oxycodone hydrochloride controlled-release in a California Medicaid population. *J Manag Care Pharm.* 2002;8(2):132-140.

34. Toblin R, Mack K, Perveen G, Paulozzi LJ. A population-based survey of chronic pain and its treatment with prescription drugs. *Pain.* 2011;152(6):1249-1255.

35. Parsells KJ, Cook SF, Kaufman DW, et al. Prevalence and characteristics of opioid use in the US adult population. *Pain.* 2008;138(3):507-513.

36. Smith H, Bruckenthal P. Implications of opioid analgesia for medically complicated patients. *Drugs Aging.* 2010;27(5):417-433.

37. Frank C, Godwin M, Verma S, et al. What drugs are our frail elderly patients taking? do drugs they take or fail to take put them at increased risk of interactions and inappropriate medication use? *Can Fam Physician.* 2001;47:1198-1204.

38. Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. *Lancet.* 2007;370(9582): 185-191.

39. Tamblyn RM, McLeod PJ, Abrahamowicz M, et al. Do too many cooks spoil the broth? multiple physician involvement in medical management of elderly patients and potentially inappropriate drug combinations. *Cmaj.* 1996;154(8):1177-1184.

40. Bjorkman IK, Fastbom J, Schmidt IK, et al. Drug-drug interactions in the elderly. *Ann Pharmacother.* 2002;36(11):1675-1681.

41. Juurlink DN, Mamdani M, Kopp A, et al. Drug-drug interactions among elderly patients hospitalized for drug toxicity. *JAMA.* 2003;289(13):1652-1658.

42. Sustiva [product information]. Princeton, NJ: Bristol-Myers Squibb; 2011.

43. Viramune [product information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2011.

44. Norvir [prescribing information]. North Chicago, IL: Abbott Laboratories; 2010.

45. Bruce R, Altice F, Moody D, et al. Pharmacokinetic interactions between buprenorphine/naloxone and tipranavir/ritonavir in HIV-negative subjects chronically receiving buprenorphine/naloxone. *Drug Alcohol Depend.* 2009;105(3):234-239.

46. Nieminen TH, Hagelberg NM, Saari TI, et al. Oxycodone concentrations are greatly increased by the concomitant use of ritonavir or lopinavir/ritonavir. *Eur J Clin Pharmacol.* 2010;66(10):977-985.

47. Manchikanti L, Manchikanti K, Pampati V, et al. Prevalence of side effects of prolonged low or moderate dose opioid therapy with concomitant benzodiazepine and/or antidepressant therapy in chronic non-cancer pain. *Pain Physician.* 2009;12(1):259-267.

48. Bernard S, Bruera E. Drug interactions in palliative care. *J Clin Oncol.* 2000;18(8):1780-1799.

49. Gnanadesigan N, Espinoza R, Smith R, et al. Interaction of serotonergic antidepressants and opioid analgesics: is serotonin syndrome going undetected? *J Am Med Dir Assoc.* 2005;6(4):265-269.

50. Gagnon L, Fairchild A, Pituskin E, et al. Optimizing pain relief in a specialized outpatient palliative radiotherapy clinic: contributions of a clinical pharmacist [published online ahead of print April 13, 2011]. *J Oncol Pharm Pract.*

51. Geppetti P, Benemei S. Pain treatment with opioids: achieving the minimal effective and the minimal interacting dose. *Clin Drug Investig.* 2009;29(suppl 1):3-16.

52. Polasek T, Lin F, Miners J, et al. Perpetrators of pharmacokinetic drug-drug interactions arising from altered cytochrome P450 activity: a criteria-based assessment. *Br J Clin Pharmacol.* 2011;71(5):727-736.