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Rare and Serious Side Effects in Chronic Pain after Opioids

Sukhminder Jit Singh Bajwa*

Department of Anaesthesiology & Intensive Care Medicine, Gian Sagar Medical College & Hospital, India

Abstract

Opioids have been used since centuries for relief of both acute and chronic pain. The known and established side effects associated with usage of opioids such as nausea, vomiting, pruritis, respiratory depression, constipation, urinary retention, sedation and addiction constitute the main limitation while titration of the doses. Besides these established side effects, newer side effects of opioids are being reported with prolonged usage which has been rarely mentioned in the literature. These side effects are diverse in their presentation and have virtually involved every organ system ranging from cardio-vascular, pulmonary, immunologic, endocrine, musculo-skeletal, central nervous system, peripheral nervous system and so on. The present review elaborates in detail about these new serious side effects which have been reported rarely till now.

Keywords: Hypogonadism; Hyperalgesia; Opioids; Osteoporosis; Pulmonary haemorrhage; Sexual dysfunction

Introduction

Opioids have been the mainstay of treatment for centuries throughout the globe, both for acute and chronic pain. Relief of chronic pain has been the one of the main focus of research among anaesthesiologists for the last few decades and the role of opioids have been significant in alleviation of the symptomatology in approximately 90% of the patients [1-5]. Such a global use warrants careful titration of the various dosages so as to prevent any serious complications arising thereof.

The known and established side effects associated with usage of opioids such as nausea, vomiting, pruritis, respiratory depression, constipation, urinary retention, sedation and addiction constitute the main limitation while titration of the doses. The limitation and titration of doses becomes extremely difficult in situations where opioid administration is needed for a prolonged duration such as cancer and non cancer chronic pain syndromes. Besides these established side effects, newer side effects of opioids are being reported with prolonged usage which has been rarely mentioned in the literature. The emergence of these new side effects have heralded a new era which mandates closer look at reconsidering the therapeutic interventions involving the prolonged usage of opioids. The recognition of these side effects over the last few years has been made possible mainly due to practice of evidence based anaesthesia and pain relief practices. The various search engines for preparation of this manuscript were used which included Entrez (including Pubmed), NIH.gov, Medscape.com, WebMD.com, Scopus, Science Direct, MedHelp.org, yahoo.com and google.com. Manual search was carried out and various text books and journals of anesthesia, pharmacology and pain were also searched. The present communication elaborates in detail about these serious side effects which have been reported rarely till now (Table 1). Some of the newer side effects recently reported are:

Cardiac morbidity

The known cardiac side effects of opioids such as hypotension and bradycardia are mainly attributable to histamine release leading to vasodilatation [6]. Recently, some new cardiac side effects have come into recognition in patients on chronic opioid therapy [7]. The incidence of QTc prolongation and torsades de pointes arrhythmia is estimated at 16% and 36% respectively in patients receiving methadone for the treatment of de-addiction to heroin [8-10]. The most striking observation in patients with these side effects was the administration of a higher dose methadone (> 40mg). The most probable cause for these fatal side effects was use of (R) enantiomers and its possible interaction with CYP3A4 inhibitor such as valproate, fluoxetine and fluconazole [9,11]. It has also been observed that concomitant use of methadone and benzodiazepines such as diazepam can increase the risk of sudden cardiac death [12]. The predisposing risk factors for development of these side effects are difficult to enumerate in entirety but may include deranged hepatic function, electrolyte abnormalities, drug interactions of opioids with antidepressants, antipsychotics, antibiotics and so on. Therefore, it becomes highly prudent to monitor cardiac activity with serial ECG's in such high risk patients especially in the hospital setting during de-addiction interventions especially whenever a need is felt for increasing the dose of methadone or addition of other medications. The high risk group who should be screened for possible development of these cardiac side effects includes patients on CYP3A4 inhibitors, deranged hepatic functions and patients exhibiting hypokalemia [13].

Disturbed hormonal milieu

Chronic opioid therapy has been shown to cause deranged hormonal functions as is evident from decreased level of sex hormones leading to psychological and sexual dysfunctions [14]. A lower of testosterone and dihydro-epiandrosterone have been observed in patients taking opioids for prolonged duration. The resulting changes associated with lower androgens include decreased libido and sexual drive, depression, fatigue, emotionally labile state, erectile dysfunction and osteoporosis [15-17]. Similar mechanisms in females are associated with lower level of Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), dysmenorrhea and amenorrhea. The route and type of opioid also determine to some extent the severity of symptoms which are more prevalent in post-menopausal women. Few studies have established that a prolonged consumption of opioids over a long period in patients of both genders between the ages of 30-75 years have resulted in the manifestations of these hormonal symptoms. The percentage of population showing these symptoms may vary

***Corresponding author:** Sukhminder Jit Singh Bajwa, MD, Associate Professor, Department of Anaesthesiology & Intensive Care Medicine, Gian Sagar Medical College & Hospital, India, Tel: 09915025828/01752352182; E-mail: sukhminder_bajwa2001@yahoo.com

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Organ/organ system	Side effect with chronic opioid therapy
Cardio-Vascular system	QTc prolongation Torsades de pointes arrhythmia Sudden cardiac death
Endocrine system	Decreased libido, erectile dysfunction and sexual drive (Hypogonadism) Depression, fatigue and emotionally labile state Dysmenorrhea and amenorrhea
Respiratory system	Pulmonary haemorrhage Non-cardiogenic pulmonary oedema
Musculo-skeletal system	Decreased bone mineral density Osteoporosis and fractures
Immune system	Suppression of natural killer cells Impaired functions of macrophages, lymphocytes, and in-vivo antibodies
Psychological changes	Psychological and Cognitive impairment Anterograde and retrograde amnesia
Peripheral/Central Nervous System	Hyperalgesia, Disturbed sleep pattern

Table 1: Showing the organ system affected with new side effects of chronic opioid therapy.

from 15%-80% depending upon the various types of serum hormone estimated [15-18]. The basic mechanism involved in hypo secretion of these hormones is the disturbed hypothalamus pituitary and gonadal functions [19-21]. The strong evidence in relation to these hormonal changes is the significant improvement of pain with administration of opioids [22]. Though the duration and period of screening for these disturbed hormonal changes has not been established but results from a recent review suggests that patients on chronic opioid therapy should always be routinely screened for hypogonadism and sex hormonal changes whenever they present to hospital for one ailment or the other [23].

Pulmonary haemorrhage

Respiratory depression and bronchospasm are established side effects of opioids [21]. However, pulmonary haemorrhage due to opioid toxicity is very rarely mentioned in the literature and the most common opiate implicated is cocaine. The exact mechanism of alveolar haemorrhage is not clear but can be attributable to pulmonary vasoconstriction and endothelial injury [24]. There is also evidence that hypoxic alveolar damage resulting from bronchospasm induced by histamine release can cause pulmonary haemorrhage [25,26]. It is also prudent to exclude vasculitis, A-V malformations, pulmonary embolism, and hematological disorders and so on before labeling it as an opioid side effect [27]. Patients with chronic obstructive pulmonary disease are highly vulnerable to develop pulmonary haemorrhage [28]. The condition can be further aggravated by use of naloxone to reverse opioid toxicity which is known to cause pulmonary oedema by augmentation of increased catecholamine release and causing increased afterload. The screening for possible pulmonary haemorrhage should be carried out during any opioid intoxication or whenever there is history of chronic drug abuse. The adult population is the high risk group but the trend of opioid abuse has engulfed the teenagers also throughout the globe.

Skeletal manifestations

Few studies have successfully established that chronic opioid therapy is associated with increased incidence of osteoporosis and decreased bone mineral density [29,30]. Among the various opioids, morphine is largely held responsible for femur, hip and spine fracture which are possibly mediated through increased incidence of osteoporosis in this subset of patients [31]. Further, the possible role of opioids has also been demonstrated during chronic therapy in the inhibition of osteoblasts resulting in decreased osteocalcin production which is very essential for maintaining bone health [32,33]. The data is not substantial to establish screening guidelines for patients on chronic opioid therapy for detection of possible detrimental skeletal changes. However, one of the studies has arbitrarily concluded that more than 20% of patients on chronic opioid therapy for more than 10 years developed osteoporosis [31]. Post-menopausal women are at high risk of developing chronic opioid induced skeletal changes. Additionally, though not conclusive, hormonal changes induced by opioids such as hypogonadism may also contribute to the development of osteoporosis [16,34].

Diminished immunity

Majority of the patients requiring chronic opioid therapy belongs to oncologic group in whom the immunity is invariably on the lower side as compared to normal population. It has been proven that deleterious effects of pain lead to suppression of hypothalamic-pituitary-adrenal axis and possible suppression of natural killer cells hampering immunity to a large extent [35]. The opioids may relieve pain mediated depression of immune system but are themselves incriminated in impairing the functions of macrophages, lymphocytes, and in-vivo antibodies, the known essential components of immunity. Numerous studies have laid emphasis on the role of opioid receptors in the immunosuppressive effects of opioids as morphine was used as prototypical drug of opioid group. Besides mu receptor, the two other opioid receptor subclasses: delta and kappa, also have a significant role in immuno-regulation. The immune suppression by opioids is a complex mechanism mediated through the three opioid receptor subclasses depending on the classes of opioid ligands administered as has been studied in various animal models which is also responsible for variation in immune response with different class of opioids [36,37]. However, the most striking aspect is the high variability in immune suppression by different classes of opioids [38-40]. There have been no established protocols and guidelines so as to when and which patients to screen for possible development of immune depression. However, any patient on chronic opioid therapy developing infective or inflammatory changes should be investigated for possible immune depression. Whenever possible, in high risk patients such as elderly and immunocompromised, a multimodal approach to relieve pain will definitely be more beneficial as compared to use of opioids alone.

Psychological impact

The clinically available data suggests that chronic pain is highly associated with variable degree of psychological and cognitive impairment [41,42]. The primary aim is therefore to minimize these changes by abolition of pain. Opioids do provide relief from the various deleterious effects of pain but new researches are at variance regarding cognitive impairment induced by opioids themselves. As a matter of fact, the relationship between cognitive impairment and higher dosages of opioids is well established [42]. Administration of morphine for sudden breakthrough cancer pain is definitely associated with anterograde and retrograde amnesia [43]. The use of opioids should be

titrated carefully to prevent these psychological and cognitive changes thereby avoiding any compromise with the quality of life. In patients on higher dose of opioids for chronic pain relief, any new change in the cognitive functioning should warrant thorough screening for possible psychologic deterioration especially among elderly patients [44].

Hyperalgesia

In certain individuals, opioids can lower the nociceptive threshold on repeated administration of opioids. The resultant hyperalgesic state is possibly mediated by numerous central and peripheral cellular receptors as has been proven in various animal studies [45]. The tolerance to opioids as well as hyperalgesia involves an active role of protein kinase C mediated through neuromodulation [46,47]. These mechanisms get activated at various central sites such as brainstem nuclei, spinal nerve pathways and various afferent neurons [45]. The evidence is based on various animal studies which have proved that both tolerance and hyperalgesia are inter-related as both are produced by stimulation of opioid receptors. The other mechanisms for development of hyperalgesia involves the induction of neuroplastic adaptations leading to up regulation of excitatory neurotransmitters such as substance P, up regulation of dynorphin levels and release of excitatory neurotransmitters [48]. Literary evidence suggests that sudden increase of opioids dose administered by any route (oral, intravenous, transdermal and intrathecal) can result in development of paradoxical hyperalgesia [48,49]. The duration of opioid therapy causing development of hyperalgesia is not clearly established but results from one study on animal models have observed hyperalgesia after 8 days of intrathecal treatment with morphine. As such selection of patients who are highly vulnerable to development of hyperalgesia is not possible but patients developing tolerance are highly likely for developing hyperalgesia also during chronic opioid therapy.

Disturbed sleep pattern

A general presumption is that opioids induce sleep as they possess sedative properties. However, few experimental studies have come out with contradictory results. Administration of opioids can lead to disturbed sleep pattern in numerous ways such as decrease in total sleep time, disturbed arousal-sleep pattern and imbalance between deep sleep and Rapid Eye Movement (REM) sleep [50-52]. However, the most controversial fact in these studies was related to the general condition of the cancer patients as the different stages of oncologic process can interfere with normal sleep pattern. Few other studies have successfully established that administration of opioids can result in shortening of deep sleep duration whereas simultaneously increasing the light sleep pattern [53,54]. Normally sleep pattern is regulated by numerous neuro-endocrine mechanisms which include but is not limited to an interaction between serotonin, melatonin, nor-adrenaline, acetylcholine, gamma amino butyric acid, dopamine, histamine, hormones from hypothalamic pituitary axis and so on. It is postulated that opioids possibly interfere with either the secretion or actions of these neuro-endocrine substances to alter the normal sleep pattern. All these neuro-endocrine actions occur at the level of brainstem and reticular activating system of pons [55]. At molecular level, mu receptors are considered responsible for disturbed these sleep patterns while kappa and delta receptors have minimal role in regulation of sleep cycle [56]. Patients developing new onset insomnia should be screened for changes in REM pattern resulting from possible side effects of chronic opioid therapy.

Side Effects Related Specifically to Different Opioids

Fentanyl

Fentanyl has been used increasingly in modern day total intravenous anaesthesia and pain relief as well as through various routes like transdermal and oral transmucosal for acute and chronic pain relief [57]. Besides known opioid side effects, it has been associated with development of dysgeusia, dry mouth, gastro paresis in diabetics and loss of consciousness has been reported with accidental overdose [58].

Oxycodone

This opioid is used for relief of non-cancer pain and the adverse events associated with its use have been reported within the first three months. However, the long term use is associated with depression and chest pain [59]. A newer side effect of oxycodone has been reported with its use for alleviation of chronic pain. The cholestatic hepatitis associated with its use possibly results from the action of oxycodone on mu^{-1} and kappa receptors as has been established by the increased incidence of pruritis through increased central opioidergic tone [59].

Tramadol

Hypoglycaemia has been reported with use of tramadol which is a new side effect associated with its administration. The evidence is based on resolution of hypoglycaemia on discontinuation of tramadol [60].

Hydrocodone

There have been reports about the profound hearing loss with the use of hydrocodone and acetaminophen combination for relief of chronic pain and had to undergo for cochlear implantation surgery [61]. In another case series, sensori-neural deafness due to chronic use of hydrocodone has also been reported [62]. It is postulated that metabolic enzymatic reactions concerned with CYP2D6 and CYP3D4 and some associated co-morbidities such as hepatitis C are responsible for the development of these rare side effects.

Discussion

The emergence and incidence of these new and rare side effects warrants a deeper look into the various therapeutic strategies for relief of chronic pain. There is an increasing need felt for making the various physicians aware about these new emerging side effects with chronic use of opioids and to look for alternative therapies. The guidelines related to chronic use of opioid have to be formulated in near future considering the increasing incidence of these rare and new side effects. The guidelines formulated by American Society of Pain can serve as a good platform to formulate new measures to be adopted for prevention of these new side effects from chronic administration of opioids. However, these guidelines have to be formulated on the basis of evidence based approach and the possible alternative to chronic opioid therapy.

The data from various countries, especially developing countries should be collected and analyzed to assess the various benefits and risks parameters associated with chronic use of opioids. The titration of opioids should be highly individualized rather than going by the fixed dosage norms as there are increased chances of development of hyperalgesia and other side effects. Ideally, the dose of opioids should be on the lower side to start with and gradual escalation should be done on the basis of severity of pain [63].

The screening programs should be formulated and designed based on the individual patient profile and drug response in order to detect

early development of these rare but serious side effects. The need for regular follow-up cannot be under-emphasized for patients on chronic high dose opioid therapy and do require regular check-ups based on the type of disease process and the duration and dose of opioids [63]. The primary goal for the attending physician is the titration of the drugs and preferably lowering of the dose depending upon the individual patient profile and duration of the disease as well as the appearance of any new side effect related to opioid use. Other good alternative is to swap the opioids or switching over to some non-opioid drugs for the time being. However, the participation and education of the patients regarding the possible adverse drug effects is of primary importance and should be a good option to detect early appearance and treatment of any serious side effect.

Conclusions

The ever increasing incidence of such new and serious side effects mandates a more judicious use of opioids for relief of chronic pain. In spite of the discussed side effects, opioids will still be used for majority of patients suffering from chronic pain. A positive step in this direction has been taken up by American Pain society by publishing some newer guidelines related to chronic opioid therapy [63]. The proper prescribing practices, awareness among physician about these newer side effects, adoption of multimodal approaches and patient education are essential to deal with these newer threats of opioid analgesia. There is no such ideal opioid which can be presumed absolutely safe for the relief of chronic pain. However, the adoption of proper opioid administration practices can decrease the incidence of these side effects to a large extent. The formulation of new guidelines based on the possible prevention of these new and rare side effects can go a long way to search for an ideal combination of therapeutic regimens for the relief of chronic pain.

References

1. Trescot AM, Boswell MV, Atluri SL, Hansen HC, Deer TR, et al. (2006) Opioid guidelines in the management of chronic non-cancer pain. Pain Physician 9: 1-39.
2. Manchikanti L, Whitfield E, Pallone F (2005) Evolution of the National All Schedules Prescription Electronic Reporting Act (NASPER): A public law for balancing treatment of pain and drug abuse and diversion. Pain Physician 8: 335-347.
3. Manchikanti L (2006) Prescription drug abuse: What is being done to address this new drug epidemic? Testimony before the Subcommittee on Criminal Justice, Drug Policy, and Human Resources. Pain Physician 9: 287-321.
4. Manchikanti L (2007) National drug control policy and prescription drug abuse: Facts and fallacies. Pain Physician 10: 399-424.
5. Brunton LL, Lazo JS, Parker KL. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 11th Edition. Mc-Graw-Hill, New York: 2006. Pain Physician 2008: Opioid Special Issue: 11:S105-S120
6. Krantz MJ, Mehler PS (2003) Synthetic opioids and QT prolongation. Arch Intern Med 163: 1615.
7. Walker PW, Klein D, Kasza L (2003) High dose methadone and ventricular arrhythmias: A report of three cases. Pain 103: 321-324.
8. Roden DM (2004) Drug-induced prolongation of the QT interval. N Engl J Med 350: 1013-1022.
9. Ehret GB, Voide C, Gex-Fabry M, Chabert J, Shah D, et al. (2006) Drug-induced long QT syndrome in injection drug users receiving methadone: High frequency in hospitalized patients and risk factors. Arch Intern Med 166: 1280-1287.
10. Sagie A, Larson MG, Goldberg RJ, Bengtson JR, Levy D (1992) An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). Am J Cardiol 70: 797-801.
11. Pearson EC, Woosley RL (2005) QT prolongation and torsades de pointes among methadone users: Reports to the FDA spontaneous reporting system. Pharmacoepidemiol Drug Saf 14: 747-753.
12. Kuryshev YA, Bruening-Wright A, Brown AM, Kirsch GE (2010) Increased cardiac risk in concomitant methadone and diazepam treatment: pharmacodynamic interactions in cardiac ion channels. J Cardiovasc Pharmacol 56: 420-430.
13. Sticherling C, Schaer BA, Ammann P, Maeder M, Osswald S (2005) Methadone-induced Torsade de pointes tachycardias. Swiss Med Wkly 135: 282-285.
14. Rajagopal A, Vassilopoulou-Sellin R, Palmer JL, Kaur G, Bruera E (2004) Symptomatic hypogonadism in male survivors of cancer with chronic exposure to opioids. Cancer 100: 851-858.
15. Daniell HW (2002) Hypogonadism in men consuming sustained-action oral opioids. J Pain 3: 377-384.
16. Abs R, Verhelst J, Maeyaert J, Van Buyten JP, Opsomer F, et al. (2000) Endocrine consequences of long-term intrathecal administration of opioids. J Clin Endocrinol Metab 85: 2215-2222.
17. Daniell, Harry W (2006) Opioid-induced androgen deficiency. Curr Opin Endocrinol Diabetes 13: 262-266.
18. Raghavan S, Harvey AD, Humble SR (2011) New opioid side effects and implications for long-term therapy. Trends in Anaesth Crit Care 1: 18-21.
19. Giri M, Kaufman JM (1994) Opioidergic modulation of in vitro pulsatile gonadotropin-releasing hormone release from the isolated medial basal hypothalamus of the male guinea pig. Endocrinology 135: 2137-2143.
20. Blank MS, Fabbri A, Catt KJ, Dufau ML (1986) Inhibition of luteinizing hormone release by morphine and endogenous opiates in cultured pituitary cells. Endocrinology 118: 2097-2101.
21. Adams ML, Sewing B, Forman JB, Meyer ER, Cicero TJ (1993) Opioid-induced suppression of rat testicular function. J Pharmacol Exp Ther 266: 323-328.
22. Roantree E, Zylicz Z (2009) Opioid-induced hypogonadism in palliative care. Does it matter? Report on four patients treated with hormone substitution. Adv Pall Med 8: 69-74.
23. Katz N, Mazer NA (2009) The Impact of opioids on the endocrine system. Clin J Pain 25: 170-175.
24. Haim DY, Lippmann ML, Goldberg SK, Walkenstein MD (1995) The pulmonary complications of crack cocaine. A comprehensive review. Chest 107: 233-240.
25. Lao PN (1997) The effects of opiates on the lung. Clin Rev Allergy Immunol 15: 291-305.
26. Hoffman RS, Nelson KS, Howland MA, (2007) eds. Goldfrank's Manual of Toxicologic Emergencies. McGraw-Hill Professional Publishing 328.
27. Gossage JR, Kanj G (1998) Pulmonary arteriovenous malformations. A state of the art review. Am J Respir Crit Care Med 158: 643-661.
28. Porter R, O'Reilly H. (2011) Pulmonary Hemorrhage: A Rare Complication of Opioid Overdose. Pediatric Emerg Care 27: 742-744.
29. Ensrud KE, Blackwell T, Mangione CM, Bowman PJ, Bauer DC, et al. (2003) Central nervous system active medications and risk for fractures in older women. Arch Intern Med 163: 949-957.
30. Kinjo M, Setoguchi S, Schneeweiss S, Solomon DH (2005) Bone mineral density in subjects using central nervous system-active medications. Am J Med 118: 1414.
31. Tennant F (2009) A 10-year evaluation of chronic pain patients treated with opioids. Heroin Addict Relat Clin Probl 11: 31-34.
32. Perez-Castrillon JL, Olmos JM, Gomes JJ, Barrallo A, Riancho JA, et al. (2000) Expression of opioid receptors in osteoblast-like MG-63 cells, and effects of different opioid agonists on alkaline phosphatase and osteocalcin secretion by these cells. Neuroendocrinology 72: 187-194.
33. Rico H, Costales C, Cabranes JA, Escudero M (1990) Lower serum osteocalcin levels in pregnant drug users and their newborns at the time of delivery. Obstet Gynecol 75: 998-1000.
34. Daniell HW (2004) Opioid osteoporosis. Arch Intern Med 164: 338.

35. Wei G, Moss J, Yuan CS (2003) Opioid-induced immunosuppression: is it centrally mediated or peripherally mediated? Biochem Pharmacol 65: 1761-1766.

36. Bénard A, Cavaillès P, Boué J, Chapey E, Bayry J, et al. (2010) μ-opioid receptor is induced by il-13 within lymph nodes from patients with sézary syndrome. J Invest Dermatol 130: 1337-1344.

37. Welters ID (2003) Is immunomodulation by opioid drugs of clinical relevance? Curr Opin Anaesthesiol 16: 509-513.

38. Weber RJ, Gomez-Flores R, Sora I, Uhl GR (2006) Loss of morphine-induced suppression of NK cell activity and T-cell functions in m receptor knockout mice. Am J Immunol 2: 35-39.

39. Budd K (2006) Pain management: is opioid immunosuppression a clinical problem? Biomed Pharmacother 60: 310-317.

40. McCracken LM, Iverson GL (2001) Predicting complaints of impaired cognitive functioning in patients with chronic pain. J Pain Symptom Manage 21: 392-396.

41. Sjogren P, Christrup LL, Petersen MA, Hojsted J (2005) Neuropsychological assessment of chronic non-malignant pain patients treated in a multidisciplinary pain centre. Eur J Pain 9: 453-462.

42. Kamboj SK, Tookman A, Jones L, Curran HV (2005) The effects of immediate-release morphine on cognitive functioning in patients receiving chronic opioid therapy in palliative care. Pain 117: 388-395.

43. Bruera E, Macmillan K, Hanson J, MacDonald RN (1989) The cognitive effects of the administration of narcotic analgesics in patients with cancer pain. Pain 39: 13-16.

44. Angst MS, Clark JD (2006) Opioid induced hyperalgesia: A qualitative systematic review. Anesthesiology 104: 570-587.

45. Mao J, Price DD, Mayer DJ (1994) Thermal hyperalgesia in association with the development of morphine tolerance in rats: roles of excitatory amino acid receptors and protein kinase C. J Neurosci 14: 2301-2312.

46. Wu G, Fan SF, Lu ZH, Ledeen RW, Crain SM (1995) Chronic opioid treatment of neuroblastoma X dorsal root ganglion neuron hybrid F11 cells results in elevated GM1 ganglioside and cyclic adenosine monophosphate levels and onset of naloxone-evoked decreases in membrane K+ currents. J Neurosci Res 42: 493-503.

47. Ossipov MH, Lai J, King T, Vanderah TW, Porreca F (2005) Underlying mechanisms of pronociceptive consequences of prolonged morphine exposure. Biopolymers 80: 319-324.

48. Mercadante S, Ferrera P, Villari P, Arcuri E (2003) Hyperalgesia: an emerging iatrogenic syndrome. J Pain Symptom Manage 26: 769-775.

49. Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder SJ (2006) Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. Lancet 368: 704.

50. Kurz A, Sessler DI (2003) Opioid-induced bowel dysfunction: Pathophysiology and potential new therapies. Drugs 63: 649-671.

51. Pickworth WB, Neidert GL, Kay DC (1981) Morphine like arousal by methadone during sleep. Clin Pharmacol Ther 30: 796-804.

52. Shaw IR, Lavigne G, Mayer P, Choiniere M (2005) Acute intravenous administration of morphine perturbs sleep architecture in healthy pain-free young adults: A preliminary study. Sleep 28: 677-682.

53. Dimsdale JE, Norman D, DeJardin D, Wallace MS (2007) The effect of opioids on sleep architecture. J Clin Sleep Med 3: 33-36.

54. Vella-Brincat J, Macleod AD (2007) Adverse effects of opioids on the central nervous systems of palliative care patients. J Pain Palliat Care Pharmacother 21: 15-25.

55. Slatkin N, Rhiner M (2004) Treatment of opioid-induced delirium with acetylcholinesterase inhibitors: A case report. J Pain Symptom Manage 27: 268-273.

56. Singh Bajwa SJ, Bajwa SK, Kaur J (2010) Comparison of two drug combinations in total intravenous anesthesia: Propofol-ketamine and propofol-fentanyl. Saudi J Anaesth 4: 72-79.

57. Portenoy RK, Messina J, Xie F, Peppin J (2007) Fentanyl buccal tablet (FBT) for relief of breakthrough pain in opioid-treated patients with chronic low back pain: A randomized, placebo-controlled study. Curr Med Res Opin 23: 223-233.

58. Portenoy RK, Farrar JT, Backonja MM, Cleeland CS, Yang K, et al. (2007) Long-term use of controlled-release oxycodone for noncancer pain: Results of a 3-year registry study. Clin J Pain 23: 287-299.

59. Ho V, Stewart M, Boyd P (2008) Cholestatic hepatitis as a possible new side-effect of oxycodone: a case report. J Med Case Rep 2: 140.

60. Grandvuillemin A, Jolimoy G, Authier F, Dautriche A, Duhoux F, et al. (2006) [Tramadol-induced hypoglycemia. 2 cases]. Presse Med 35: 1842-1844.

61. Friedman RA, House JW, Luxford WM, Gherini S, Mills D (2000) Profound hearing loss associated with hydrocodone/acetaminophen abuse. Am J Otol 21: 188-191.

62. Ho T, Vrabec JT, Burton AW (2007) Hydrocodone use and sensorineural hearing loss. Pain Physician 10: 467-472.

63. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, et al. (2009) Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain 10: 113-130.