Pain from osteoporotic fractures: rationale of therapeutic options

Hans G. Kress

Department of Special Anaesthesia and Pain Medicine, Medical University/AKH, Vienna, Austria

Address for correspondence:
Prof. Hans Georg Kress, MD, PhD, EDPM, FFPMCAI
Department Special Anaesthesia and Pain Medicine
Medical University/AKH
Waehringer Guertel 18-20
A-1090 Vienna, Austria
E-mail: hans-georg.kress@meduniwien.ac.at

Summary

Bone fractures are the most important cause of severe acute pain in osteoporosis, which is later often followed by chronic musculoskeletal pain due to dorsal kyphosis, exaggerated lordosis or compression of nerve roots or spinal cord. The functional stress on spinal muscles and ligaments results in the development of chronic back pain and impaired mobility. Injured structures in the lumber spine can also produce referred pain or a true radicular pain.
Drugs against osteoporosis may have some analgesic effects, as has been shown for denosumab or bisphosphonates like pamidronate. Similar results have been obtained with calcitonin, which is no longer available for the treatment of osteoporosis. Selective estrogen receptor modulators like raloxifene and the anabolic drug teriparatide can also reduce osteoporotic pain and augment fracture healing.
The vicious circle of osteoporotic pain, immobility, muscle atrophy and enhanced osteoporosis has to be interrupted by an effective multimodal pain management. Beside the treatment of osteoporosis and fractures, analgesic drugs play a major role in restoring physical functioning and mobility. The mainstay in pain management of osteoporotic fractures is the WHO 3-step analgesic ladder with the combined use of non-opioids (NSAIDs, paracetamol) with weak opioids like tramadol for mild to moderate pain, or strong opioids like morphine, hydromorphone, oxycodone, buprenorphine, fentanyl or tapentadol for moderate to severe pain. The combination of nonopioids with oral controlled release (CR) strong opioids or prolonged release (PR) tapentadol provides excellent analgesia even in severe pain from osteoporotic fractures. This is also true for transdermal therapeutic systems containing fentanyl or buprenorphine (skin patches).
There are differences in the relative fracture risk of opioids, which is highest with fentanyl and lowest with buprenorphine. Some opioids influence the endocrine system, particularly the sex hormones, and lowered testosterone and estrogen levels finally reduce bone density. Tapentadol is an exception, which acts simultaneously as a μ-opioid receptor agonist (MOR) and a noradrenalin reuptake inhibitor (NRI). It has minor effects on the endocrine system and sex hormones and should therefore be favored for long-term treatment of osteoporosis pain. The synergism between its two analgesic mechanisms improves analgesia and reduces adverse events.
In conclusion, the standard treatment of acute and chronic pain after osteoporotic fracture is a multimodal analgesic therapy including non-opioids, opioids, mobilization and rehabilitation. Opioids with minor effects on the endocrine system and bone density, such as buprenorphine or tapentadol, should be preferred for long-term pain management in these patients.

KEY WORDS: osteoporosis fracture; osteoporosis treatment; acute pain; chronic pain; multimodal pain management; non-opioids; opioids; sex hormones; tapentadol.

What is the challenge?

Up to 85% of patients with osteoporosis suffers from acute or chronic pain of different nociceptive and sometimes also neuropathic origins (1). The pathophysiology of pain in osteoporosis is complex, and so are the underlying mechanisms. Bone fractures are the most important cause of severe acute and consequent chronic nociceptive pain in osteoporosis. Anti-osteoporosis drugs can only marginally, if at all, control such type of acute pain, and additional analgesics are always necessary for pain due to bone fractures. After osteoporotic fracture there is always a typical and predominant nociceptive acute pain, which later often evolves into a chronic pain caused by the noxious stimulation of other parts of the musculoskeletal system due to dorsal kyphosis, exaggerated lordosis and/or compression of nerve roots or spinal cord (2-4).
As a consequence of these permanent structural changes, the functional stress on spinal muscles and ligaments causes chronic nociceptive back pain and impaired mobility (2, 3). The stimulation of structures in the lumbar spine can also produce a so-called referred pain into the lower limbs, which is perceived in distant regions that share the same segmental innervation as the original source of damage (3). This referred pain has to be distinguished from a true radicular neuropathic pain caused by a mechanically irritated dorsal root or ganglion.

The general dilemma of pain management following osteoporotic fracture

Up to 75% of osteoporosis patients with fractures believe in pain relief by rest, which may become deleterious in the long-term sequel (3)! Immobility will produce enhanced muscle atrophy that makes osteoporosis more likely to proceed, and finally muscle atrophy and immobility increase the risk of falls and fractures that will again enhance immobility, muscle atrophy as well as progression of osteoporosis (4). Therefore, besides bone stabilization and effective, immediate acute pain treatment, the long-term therapeutic goal following an osteoporotic fracture is to interrupt the vicious circle of fracture pain, immobility, muscle atrophy, progressing osteoporosis, risk of falls with resulting new fractures and further immobility, by an effective long-term strategy that should be based on an aggressive and efficient multimodal pain management and functional rehabilitation (4).

Nonsteroidal anti-inflammatory drugs (NSAIDs), selective COX-2 inhibitors (coxibs), paracetamol/acetaminophen or metamizol reduce only mild-to-moderate, but not severe nociceptive acute pain, and they have only poor effect on severe chronic or mainly neuropathic pain (5, 6). Moreover, the NSAID group of non-opioid analgesics is characterized by the relevant unwanted side effects that make them contraindicated in many – particularly elderly – patients (5). By contrast, opioid drugs can control the whole spectrum of moderate-to-severe, acute and chronic bone pain, but they differ with respect to their efficacy on neuropathic pain components, their endocrine side effects, tolerability and safety.

Multimodal pharmacological treatment of vertebral fracture has limitations, when fast mobilization and pain relief are needed or conservative multimodal treatment is impossible. Then interventional approaches such as percutaneous vertebroplasty or kyphoplasty are good and effective therapeutic alternatives (3, 4). At least during the first two weeks there is a significant and clinically important difference in pain relief after such interventional treatment compared to a multimodal conservative approach. In the long-term, however, there is not much difference, but many patients benefit from the first very fast improvements by such an intervention.

Multimodal pain management

After diagnosis, the major goal is of course to reduce pain either by treating the underlying condition itself, if possible, or by a symptomatic analgesic treatment. Pain relief will not only improve the overall health-related quality of life and emotional functioning, but above all avoid detrimental immobility by improving physical functioning of the osteoporotic patient (3, 4).

Pain management in osteoporosis should be multimodal for optimum effectiveness: besides causal treatment of the underlying osteoporotic processes and fractures (4), analgesics play a major and pivotal role in restoring physical functioning and mobility. If conservative multimodal treatment fails, interventional treatment such as vertebroplasty or kyphoplasty are promising options (3, 4), and all these measures have to be accompanied by a parallel consequent physical rehabilitation approach. Also social and psychological support is needed in many of these patients. Ideally the multimodal approach should always be used to treat subacute and particularly chronic pain in osteoporotic patients.

Pharmacological options

Drugs against osteoporosis

All drugs registered for the treatment of osteoporosis influence bone metabolism with a possible benefit for the patient's bone pain. After fracture, the anti-osteoporosis drugs can act on pain related to bone resorption and restoration of normal bone structure. Therefore, it makes sense to treat the underlying osteoporosis in accordance with established recent guidelines (4). Calcium and vitamin D, bisphosphonates, the new drug denosumab but also selective estrogen receptor modulators (SERM) like raloxifene, or the anabolic drug teriparatide are effective against osteoporosis (4).

Some of these causal treatments have also more or less analgesic effects, as has been shown for bisphosphonates like pamidronate already after the first week of therapy (7, 8). Aminobisphosphonates like alendronate, risedronate, ibandronate, and zoledronate have been used to relieve bone pain in patients with fragility vertebral fractures (4, 9). Antifracture agents like bisphosphonates decreased bone turnover, and showed an analgesic effect in postmenopausal women, without an immediate effect on pain due to osteoporotic fracture (4, 7-9). The pain relief seemed to result mainly from a prevention of new fragility vertebral fractures by the bisphosphonates.

Similar results have been observed with calcitonin (4, 10), but calcitonin is no longer available for osteoporosis treatment. Also selective estrogen receptor modulators like raloxifene were reported to alleviate pain in patients with osteoporosis, decrease analgesic consumption and improve quality of sleep (4, 11). In several randomized controlled trials, the anabolic drug teriparatide augmented fracture healing and reduced the risk of new vertebral fractures and back pain (4, 12).

The IgG_2 monoclonal antibody denosumab with its high affinity for human RANK-L acts as an antiresorptive drug able to prevent fractures in postmenopausal women with osteoporosis (4, 13). Denosumab also modified bone pain in different clinical settings (4). An observational, retrospective, single-centre study in 80 patients with recent osteoporotic vertebral fracture showed a better and faster pain relief in the denosumab-treated group compared to alendronate treatment (4, 13). In a prospective, observational second study denosumab significantly reduced bone pain in osteoporosis patients with or without prior bone fracture (14).

Combined use of opioid and non-opioid analgesic drugs

Beside the basic treatment of osteoporosis and fractures, analgesic drugs play a major role in restoring physical functioning and mobility (2). Non-opioids, such as metamizol or paracetamol, and NSAIDs including selective COX-2 inhibitors (so-called coxibs) are principally suitable for short-term treatment of patients with mild-to-moderate bone fracture pain, but in most cases non-opioid drugs alone cannot sufficiently control the acute and severe pain after a bone fracture. NSAIDs as a class are also associated with an increased risk of gastrointestinal adverse events mainly in elderly patients, and thromboembolic events in patients with heart or circulatory diseases or cerebrovascular risk factors, particularly if used at high doses (5). Therefore the product information for all NSAIDs and selective COX-2 inhibitors recommends their use only at the lowest effective dose and for the shortest period of time necessary (5, 6). Not many reports are found in the literature about acetaminophen in this

respect, and there is no robust clinical evidence for any relevant potential cardiovascular or cerebrovascular harm associated with paracetamol/acetaminophen (6). Finally, animal experiments suggested that ibuprofen or selective COX-2 inhibitors could slow down bone healing processes (15), but convincing confirmatory human data are still missing.

Therefore, other analgesic options, like weak or strong opioids will be needed for treatment of patients with moderate to severe bone fracture pain, especially for elderly patients with major gastrointestinal and cardiovascular risks that exclude the long-term use of NSAIDs (2, 3, 16). For acute pain management immediately after bone fracture, intravenous or fast acting oral non-opioids (NSAIDs, coxibs, metamizol 4 g/d, paracetamol 4 g/d) combined with intravenous or oral immediate release (IR) opioids (tramadol, morphine, hydromorphone, fentanyl, sufentanil) are necessary (2, 3).

For long-term pain management of osteoporotic fractures, however, the mainstay is the so-called WHO 3-step analgesic ladder (16) recommending the combined use of oral non-opioids (NSAIDs including coxibs, metamizol, paracetamol/acetaminophen) (5, 6,16) with enteral weak opioids like codeine, dihydrocodeine or tramadol for mild-to-moderate pain, or enteral or transdermal strong opioids like morphine, hydromorphone, oxycodone, buprenorphine, fentanyl or the new opioid tapentadol for moderate-to-severe pain (2, 3, 16). The secret of success in severe fracture pain is the combined use of strong opioids and non-opioids (Figure 1). The synergism between their two independent analgesic mechanisms improves analgesia, reduces adverse events and provides better safety and tolerability in elderly patients (16). The combination of non-opioid drugs with oral controlled release (CR) strong opioids or the new prolonged release (PR) tapentadol (17) provides sufficient analgesia of long duration even in severe pain from osteoporotic fractures. This is also true for transdermal therapeutic systems (TTS) containing fentanyl or buprenorphine (so-called opioid patches) (16) (Figure 1).

Are all opioid analgesics the same?

In terms of unwanted pathogenetic effects on osteoporosis, the different μ-opioid agonists are not simply interchangeable for the treatment of osteoporotic pain! There are significant differences in relative fracture risk associated with different opioid medications. Fentanyl has a rather high risk with an odds ratio of 2.23, the risk of tramadol or morphine is slightly lower, but buprenorphine, which is available as a transdermal patch or sublingual tablet, has an odds ratio even below one, i.e. the lowest relative fracture risk of all opioids tested in this study (18).

In fact, opioid drugs can negatively influence bone density during long-term treatment, as has been shown for male patients under methadone substitution therapy. Interestingly enough, females did not show comparable decreases under such an opioid substitution treatment (19).

The exact underlying processes are unclear (20-22). It has been demonstrated that opioids in general have a major in-

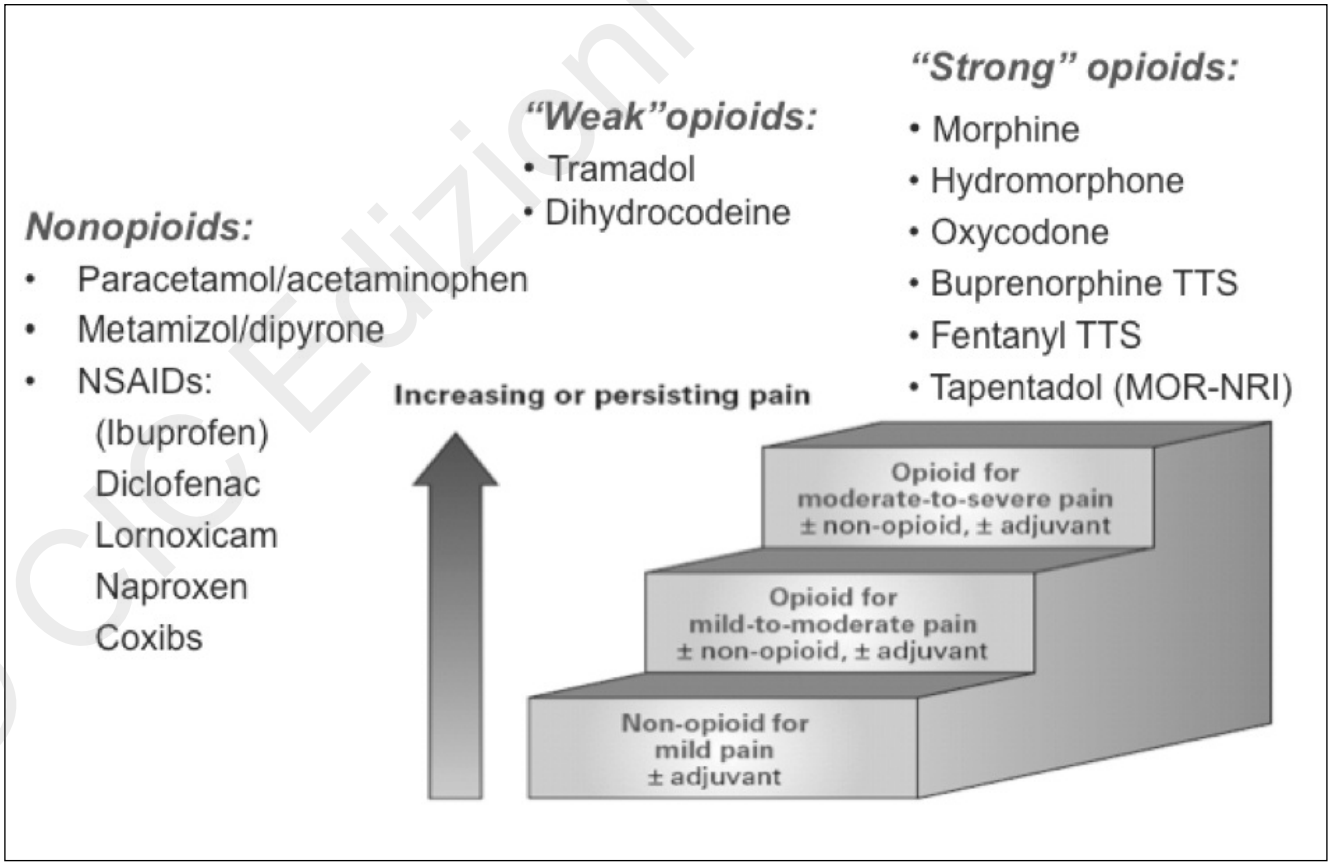

Figure 1 - WHO three-step analgesic ladder.

Coxibs = selective COX-2 inhibitors; NSAID = nonsteroidal anti-inflammatory drugs; MOR-NRI = μ-opioid-receptor agonist (MOR) and noradrenalin re-uptake inhibitor (NRI); TTS = Transdermal Therapeutic System.

fluence on the endocrine system, particularly on sex hormone levels in males and females. After the chronic use of several opioids hypogonadism has been observed, which was related to the central suppression of the hypothalamic secretion of gonadotropin-releasing hormone, decreased luteinizing hormone (LH), follicle-stimulating hormone (FSH), adrenal dehydroepiandrosterone, testosterone, progesterone and estradiol levels in women, as well as decreased testosterone in men (21). Also under short-term opioid medication the levels of testosterone, estrogen, cortisol, luteinizing hormone (LH) or gonadotropin releasing hormone significantly decreased (20, 21). Lowered testosterone and estrogen levels will finally result in a reduced bone mineral density and foster the development of osteoporosis. Thus, although opioids are the most potent analgesics, at least theoretically those opioids with stronger effects on sex hormones might not be the best choice for long-term pain management in osteoporotic patients. The new opioid drug tapentadol, which is available in USA, Australia and many European countries including Italy, seems to be an exception (21, 22).

Pharmacological advantages of tapentadol in osteoporotic patients

Tapentadol is a single enantiomer, which is the effective analgesic agent and has not to undergo any metabolism to be active. It is a unique centrally active analgesic drug because of its two simultaneous analgesic mechanisms in one molecule: μ-opioid-receptor agonist (MOR) and noradrenalin re-uptake inhibitor (NRI). Due to this specific pharmacological profile as MOR-NRI (17), tapentadol is effective in acute and chronic pain in osteoporosis. In addition, it has a very predictable and favorable pharmacokinetic profile for clinical use in elderly patients (17, 23, 24).

More important with respect to pain management after osteoporotic fractures, two single-dose studies in healthy male volunteers (a single-dose comparison study versus morphine and a second single-dose escalation study without an active comparator) revealed significantly smaller effects on blood concentrations of testosterone and luteinizing hormone (LH) when evaluated at 6 and 24 hours post-dose with tapentadol or placebo compared to an equi-analgesic dose of morphine (30 mg). The promising results from the volunteer studies have been confirmed by serum measurements of testosterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in male patients continuously treated during a 4-week period with multiple, equi-analgesic doses of tapentadol or oxycodone for their chronic osteoarthritic pain (21, 22). Mean changes from baseline of testosterone levels were significantly more pronounced for oxycodone 20 mg compared to the equi-analgesic dose of 100mg tapentadol. Even 200 mg tapentadol did not reach the same suppressive effect as compared with 20mg oxycodone during the 4-week treatment period. These data suggest that at least the long-term effects of tapentadol on testosterone and other sex hormone levels are smaller than those of equi-analgesic oxycodone or morphine doses (21, 22).

Together with its favorable pharmacokinetic profile, a low risk of drug-drug interactions, a broad efficacy in acute and severe chronic nociceptive and neuropathic pain, and a good tolerability and safety profile it could therefore be a preferential opioid for long-term treatment of osteoporotic patients with and without fractures (21-24).

Conclusion

The pharmacological standard treatment of acute and subsequent chronic pain in patients with osteoporotic fracture is a multimodal analgesic therapy including drugs against osteoporosis (e.g. bisphosphonates), non-opioids and opioids together with fast mobilization followed by intensive rehabilitation. If conservative therapy is impracticable or fails, vertebroplasty and kyphoplasty are good minimally invasive alternate options (3, 4).

Many opioid drugs are – at least theoretically – able to reduce bone density due to pharmacologically induced hormonal changes. The new centrally acting MOR-NRI analgesic tapentadol showed only minor effects on the endocrine system and sex hormone levels. Also buprenorphine seems to have minimal or even no negative effects on bone fracture risk. These opioids (transdermal buprenorphine or enteral tapentadol) with minor effects on endocrine system and fracture risk should thus be favored for long-term pain management after bone fracture in osteoporosis patients.

References

1. Hernlund E, Svedbom A, Ivergard M, Compston J, Cooper C, Stenmark J, McCloskey EV, Jonsson B, Kanis JA. Osteoporosis in the European Union: medical management, epidemiology and economic burden: a report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA) Arch Osteoporos. 2013;8:136.
2. Vellucci R, Mediati RD, Ballerini G. Use of opioids for treatment of osteoporotic pain. Clin Cases Miner Bone Metab. 2014;11:173-176.
3. Old JL, Calvert M. Vertebral compression fractures in the elderly. Am Fam Physician. 2004;69:111-115.
4. Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster JY. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2013;24:23-57.
5. Kress HG, Baltov A, Basiński A, Berghea F, Castellsague J, Codreanu C, Copaciu E, Giamberardino MA, et al. Acute pain: a multifaceted challenge - the role of nimesulide. Curr Med Res Opin. 2016;32:23-36.
6. Kress HG, Untersteiner G. Clinical update on benefit versus risks of oral paracetamol alone or with codeine: still a good option? Curr Med Res Opin. 2017;33:289-304.
7. Armingeat T, Brondino R, Pham T, Legré V, Lafforgue P. Intravenous pamidronate for pain relief in recent osteoporotic vertebral compression fracture: a randomized double-blind controlled study. Osteoporos Int. 2006;17:1659-1665.
8. Laroche M, Cantogrel S, Jamard B, Constantin A, Zabraniecki L, Cantagrel A, Mazières B. Comparison of the analgesic efficacy of pamidronate and synthetic human calcitonin in osteoporotic vertebral fractures: a double-blind controlled study. Clin Rheumatol. 2006;25:683-686.
9. Wells G, Cranney A, Shea B, Tugwell P. Responsiveness of endpoints in osteoporosis clinical trials. J Rheumatol. 1997;24:1230-1233.
10. Knopp-Sihota JA, Newburn-Cook CV, Homik J, Cummings GG, Voaklander D. Calcitonin for treating acute and chronic pain of recent and remote osteoporotic vertebral compression fractures: a systematic review and meta-analysis. Osteoporos Int. 2012;23:17-38.
11. Fujita T, Fujii Y, Munezane H, Ohue M, Takagi Y. Analgesic effect of raloxifene on back and knee pain in postmenopausal women with osteoporosis and/or osteoarthritis. J Bone Miner Metab. 2010;28:477-484.
12. Nevitt MC, Chen P, Dore RK, Reginster JY, Kiel DP, Zanchetta JR, Glass EV, Krege JH. Reduced risk of back pain following teriparatide treatment: a meta-analysis. Osteoporos Int. 2006;17:273-280.
13. Tetsunaga T, Tetsunaga T,Nishida K,Tanaka M,Sugimoto Y,Takigawa T, Takei Y,Ozaki T. Denosumab and alendronate treatment in patients

with back pain due to fresh osteoporotic vertebral fractures. J Orthop Sci. 2017;22:230-236.
14. Petranova T, Sheytanov I, Monov S, Nestorova R, Rashkov R. Denosumab improves bone mineral density and microarchitecture and reduces bone pain in women with osteoporosis with and without glucocorticoid treatment. Biotechnol Biotechnol Equip. 2014;28:1127-1137.
15. Su B, O'Connor JP. NSAID therapy effects on healing of bone, tendon, and the enthesis. J Appl Physiol (1985). 2013;115:892-899.
16. O'Brien T, Christrup LL, Drewes AM, Fallon MT, Kress HG, et al. European Pain Federation position paper on appropriate opioid use in chronic pain management. Eur J Pain. 2017;21:3-19.
17. Kress HG. Tapentadol and its two mechanisms of action: is there a new pharmacological class of centrally-acting analgesics on the horizon? Eur J Pain. 2010;14:781-783.
18. Dinges G. Osteoporosis pain management. Anasthesiol Intensivmed Notfallmed Schmerzther. 2009;44:568-577.
19. Grey A, Rix-Trott K, Horne A, Gamble G, Bolland M, Reid IR. Decreased bone density in men on methadone maintenance therapy. Addiction. 2011;106:349-354.
20. Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, Glaser SE, Vallejo R. Opioid complications and side effects. Pain Physician. 2008;11(2 Suppl):S105-120.
21. Eichenbaum G, Göhler K, Etropolski M, Steigerwald I, Pergolizzi J, Kim M, Vorsanger G. Does tapentadol affect sex hormone concentrations differently from morphine and oxycodone? An initial assessment and possible implications for opioid-induced androgen deficiency. J Opioid Manag. 2015;11:211-227.
22. Coluzzi F, Pergolizzi J, Raffa RB, Mattia C. The unsolved case of "bone-impairing analgesics": the endocrine effects of opioids on bone metabolism. Ther Clin Risk Manag. 2015;11:515-523.
23. Steigerwald I, Müller M, Davies A, Samper D, Sabatowski R, Baron R, Rozenberg S, Szczepanska-Szerej A, Gatti A, Kress HG. Effectiveness and safety of tapentadol prolonged release for severe, chronic low back pain with or without a neuropathic pain component: results of an open-label, phase 3b study. Curr Med Res Opin. 2012;28:911-936.
24. Pergolizzi J, Alon E, Baron R, Bonezzi C, Dobrogowski J, Gálvez R, Jensen T, Kress HG, Marcus MA, Morlion B, Perrot S, Treede RD. Tapentadol in the management of chronic low back pain: a novel approach to a complex condition? J Pain Res. 2011;4:203-210.