Osteoporosis and Sarcopenia 8 (2022) 93–97

Contents lists available at ScienceDirect

Osteoporosis and Sarcopenia

journal homepage: http://www.elsevier.com/locate/afos

Review article

Pharmacological options for pain control in patients with vertebral fragility fractures

Nuttan Kantilal Tanna [a, *], Terence Ong [b, c]

[a] Northwick Park Hospital, London North West University Healthcare NHS Trust, London, United Kingdom
[b] Department of Medicine, Faculty of Medicine, University Malaya, 50603, Kuala Lumpur, Malaysia
[c] School of Medicine, Taylor's University, 47100 Selangor, Malaysia

ARTICLE INFO

Article history:
Received 25 April 2022
Received in revised form
10 September 2022
Accepted 11 September 2022
Available online 3 October 2022

Keywords:
Vertebral fracture
Osteoporosis
Pain
Analgesia
Opioid

ABSTRACT

This review considers the evidence base and current knowledge for pharmacological treatment options that are available for pain control in patients with vertebral fractures sustained after a low trauma incident. Due care needs to be taken when considering prescribed options for pain control. The decision should be based on first establishing whether the presentation is one of acute severe pain at the time of a new vertebral fragility fracture incident or whether the complaint is one of the debilitating, longer term chronic back pain syndrome, accompanied by a clinical suspicion of a possible new fracture. The article also presents currently debated questions in this important area of clinical and patient care and will be of interest to the readership worldwide.

1. Introduction

Osteoporosis is a silent metabolic bone condition. It is associated with natural loss of bone density with ageing [1,2], although with other underlying clinical risk factors this can be a presentation seen in younger age groups [3]. Both men and women start to lose bone density from around age 40 [1,4]. The pathological consequence of osteoporosis is often first identified only when a patient presents with a low trauma fragility fracture accompanied by pain. Pain can be contextualized as physiological feedback that raises a person's awareness to discomfort, attributable to the activation of mechanisms for homeostatic recovery and messaging from and via the brain's complex neural network [5,6].

Vertebral fractures represent 16% of all fractures due to osteoporosis, second only to hip fractures [7]. As many as a third of low trauma vertebral fractures are not identified [8], but painful vertebral body compression fractures are prevalent in older patients. Large population studies have described a link between low back pain and osteoporosis in older people [9–12], with vertebral fracture a differential diagnosis that should be considered in clinical practice.

Vertebral fragility fractures are usually stable without involvement of the posterior vertebral arch and injury to the spinal cord is uncommon [13]. Two-thirds of patients will have spontaneous resolution of pain in 3–6 weeks and initial management is non-operative with pain management and bracing [2,14].

Clark et al [15] have reported on independent predictors of vertebral fracture causing back pain compared to other causes. These include older age, history of previous fracture, shorter duration of back pain which is often described as crushing pain, and pain that improved on lying down and which did not radiate down the legs [15]. Vertebral fragility fractures can cause severe pain as well as disability in the longer term [16], with an increased, more than 4-fold risk of secondary fractures [17,18]. Additionally, women with these fractures have been shown to have a higher mortality and rate of hospitalisation compared to those without a fracture, even after adjustment for age, bone mineral density and comorbid conditions [19]. Kado et al. [20] demonstrated further that hyperkyphosis is associated with higher morbidity with a prediction of an increased risk for death, which was independent of factors such as underlying spinal osteoporosis or the extent and severity of vertebral fractures.

* Corresponding author. Northwick Park Hospital, London North West University Healthcare NHS Trust, Watford Road, Harrow, HA1 3UJ, United Kingdom.
E-mail address: nuttantanna@nhs.net (N.K. Tanna).
Peer review under responsibility of The Korean Society of Osteoporosis.

https://doi.org/10.1016/j.afos.2022.09.003

2. Pain and disability associated with vertebral fragility fractures

Patients with low trauma vertebral fractures will need advice on pharmacological options to help with pain control. There are few good quality trials of pain medication and effectiveness in management of vertebral fragility fractures. The management strategy will be different in the acute phase versus that of treatment over the longer term. In the acute fracture phase, the pain experienced will be more severe and many fracture patients also complain of chronic pain and physical disability over the longer term [2,13,16,21]. Chronic pain is a multidimensional syndrome, comprising of sensory, affective, and cognitive aspects [21,22]. Age can affect each of these aspects and thereby impact on the level of pain experienced by the patient. Osteoporotic fracture induced spinal instability, joint imbalance and tension in muscular structures also contribute to chronic pain [2,8]. The sensation of chronic pain can be altered by the patient's memory, perception, expectations, and emotions [23,24].

3. Pharmacology approach in vertebral fragility fractures

The optimal management strategy will therefore combine appropriate analgesia, with or without adjuvant therapies, and include supportive non-pharmacological options. The choice of the appropriate analgesic should be based on the intensity of pain felt by the patient and can be objectively assessed using a numeric rating scale [25,26] (see Table 1). For optimized medicines use, polypharmacy and drug burden issues, deprescribing, possible drug interactions, side effects and any patient compliance or adherence challenges will need to be addressed [27,28].

Non-opioid and opioid analgesics used for pain management remain the first line of treatment. Analgesia requirements are usually adjusted according to the World Health Organization (WHO) analgesic ladder (Fig. 1). The ladder was initially designed to address cancer-related pain management but has now been applied to other non-malignant conditions. Recommendations are to start at the bottom of the ladder using milder analgesia (paracetamol and non-steroidal anti-inflammatory medicines) and up-titrating as appropriate towards the stronger pain control option of opioids. However, pain associated with fracture is usually most intense at the time of onset of fracture before subsiding over time [29]. Adopting the upward unidirectional approach of the WHO ladder is unlikely to meet the patient's fracture management requirements especially when pain is severe. Therefore, an effective pain management strategy should begin with assessment of pain severity using one of numerous pain rating scales, such as the Numeric Rating Scale [25,26], Visual Analogue Scale or Abbey Pain Scale [30,31] (Table 1), and is appropriate for both an acute presentation or for one with chronic pain syndrome with a clinical suspicion of a new vertebral fracture. If pain is deemed to be severe, then starting at the top of the ladder with strong opioids and down-titrating as pain improves, that is a reverse analgesia WHO ladder approach, would be more appropriate.

Other pain control-oriented options could include bone-targeted therapies, which are primarily designed to help maintain bone mineral density (for example osteoclast inhibitors, such as the bisphosphonates and denosumab, or the osteo-anabolic agents such as Teriparatide) and adjuvants (antidepressants, anticonvulsants, neuropathic medicines). All interventions should be individualized and directed at relieving pain, improving quality of life, and increasing the functioning of patients [32,33]. Nerve growth factor inhibitors are biologic medicines currently under investigation for use for pain relief in osteoarthritis pain management [33] and may offer another option in the future for management of ongoing chronic pain in patients with vertebral fractures.

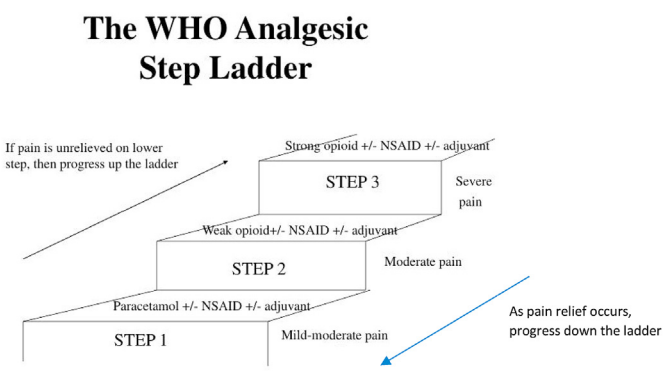

Fig. 1. The Analgesic Step Ladder (Adapted with acknowledgment [[57,72]).

There is some evidence that bone targeted therapies help with pain control. Bisphosphonates are the recommended first line treatment for osteoporosis and fracture risk reduction in most situations [34,35]. With an osteoclast mediated, antiresorptive mechanism of action, bisphosphonates help moderate the loss of skeletal bone mineral density. Stabilization of the vertebrae and prevention of further bone loss may be how they help the patient with ongoing pain reduction. Bisphosphonates are often used for treatment of pain in bone malignancy and Paget's disease, but the exact analgesic pathway for the bisphosphonates is unclear. Their anti IL-1, IL-6 and anti-TNF properties which dampen the inflammatory process has been hypothesized as the pathway resulting in pain relief [29]. In addition, intracerebroventricular injection of clodronate in animal models resulted in an analgesic response, pointing towards a central nociceptive effect [36]. The degree of pain control varies with the different bisphosphonates [36,37].

This analgesic effect of bisphosphonates has been reported with intravenous and oral bisphosphonates. Intravenous pamidronate has been most studied [38–40]. In an observational study of 26 patients with vertebral fragility fractures and back pain who were treated with 30 mg pamidronate over 2 consecutive days, with this dose then repeated every 3 months for 1 year, the patients reported pain relief and improved mobility within 48 hours of the first treatment [39]. A randomized double blind controlled clinical trial of 32 patients comparing 30 mg pamidronate given daily for 3 consecutive days and a placebo infusion, reported around 50% reduction in pain at day 7 and day 30 [40]. Fever and transient myalgia were the side effects reported by some of these patients. A recent study has reported the positive effect of 1 preoperative administered zoledronate infusion on pain intensity after patients

Table 1
Analgesia for the pain syndrome [NRS: Numeric Rating Scale [25,26,30,31]].

Mild pain [NRS less than or equal to 3]	NSAIDs[b] or Paracetamol, with adjuvant therapy[a]	Place for bone-targeted therapies?
Moderate pain [NRS 4–6]	Weak opioids±NSAIDs[b] or paracetamol, with adjuvant therapy[a]	Place for bone-targeted therapies?
Strong pain [NRS greater than 6]	Opioids[b] and NSAIDs[b] or paracetamol, with possible adjuvant therapy[a].	Place for bone-targeted therapies?

[a] Adjuvant therapies contribute to mitigating pain, increasing the effect of analgesics.
[b] Cautions: polypharmacy risks, adverse effects, abuse, addiction potential especially with opioids (Adapted from Refs. [21,25,29,32,33,60]).

had percutaneous vertebroplasty for osteoporotic vertebral compression fractures [41]. Zoledronate caused mild side effects but reduced bone loss and increased bone density with a reduction of risk for a further fracture as compared with the group of patients who only had the vertebroplasty procedure.

Denosumab prescribed as a 6 monthly subcutaneous injectable therapy, specifically inhibits the receptor activator for nuclear factor-kappa B ligand (RANKL) and prevents osteoporotic fractures. Studies have reported on effects of denosumab compared with alendronate alone on bone mineral density (BMD) or reduction of fracture risk. Tetsunaga et al [42] studied the impact of both these antiresorptive osteoporosis pharmacotherapies on pain relief in patients (mean age 77 years, range 55–92) with fresh vertebral fractures. This retrospective single center study [42] found that denosumab enabled earlier pain relief than alendronate and helped avoid pain catastrophizing in patients with osteoporotic vertebral fractures assessed after 6 months of treatment. Moretti et al [43] evaluated denosumab with the aims of studying the effects on osteoporosis related disability and health related quality of life. Their study population [43] included post-menopausal women with vertebral fractures with mean age 70.6 (SD 8.81) years, given denosumab 60 mg every 6 months with calcium carbonate and vitamin D supplements for a year. They found that denosumab was effective in reducing back pain related disability (Spine Pain Index $P < 0.001$).

Teriparatide is an osteo-anabolic agent usually reserved for use for secondary prevention of vertebral fragility fractures. Teriparatide treatment was associated with less back pain in a pivotal randomized controlled trial [44] and within a meta-analysis, teriparatide-treated patients reported less back pain against the comparator in multiple active and placebo-controlled trials [45]. Chen et al [46] studied 112 postmenopausal women with vertebral compression fractures, and reported that back pain and health related quality of life outcomes were improved in the treated group over 12 months, as compared with calcium and vitamin D supplements only. In osteoporotic women with percutaneous kyphoplasty, subsequent treatment with teriparatide over 12 months had a significant effect, with reduction in incidence of new vertebral compression risk, less back pain and with improved quality of life [47]. The improvement in back pain was sustained for at least 12 months after the teriparatide treatment was discontinued [47]. Further studies have reported better fracture site pain in teriparatide treated patients in comparison to bisphosphonates [48–50]. Akhter et al's systematic review and meta-analysis found high quality evidence to support the use of teriparatide 20 mcg daily injected dose to improve pain severity relative to all comparators [50].

4. Currently debated pain medication questions

4.1. Is there a risk for fracture non-union and poor healing with non-steroidal anti-inflammatory drugs (NSAIDs) if used with acute fragility fractures?

Dodwell et al [51] identified studies that signalled a possible association between NSAIDs and fracture non-union, suggestive of a need for caution with use of NSAIDs in patients with acute fractures. The meta-analysis [51] pooled analysis of the few available higher quality studies, finding that these had not reported on the risk of non-union and concluded that there was a need for more research to address this uncertainty. Furthermore, as different rates of non-union have been reported in long bones and vertebral bones, more research is needed to understand how relevant the issue of non-union may be to the rate of vertebral fracture healing. Cautions with NSAIDs use include gastrointestinal bleeding, kidney injury and cardiovascular risks, particularly in the elderly population. Any planned use needs to be for the shortest possible duration.

4.2. What is the suggested duration of use of paracetamol?

Paracetamol is used in both acute and chronic pain presentations [52]. For chronic pain where long term use may be needed, Paracetamol has generally been considered the safer option. Concerns with long term use in osteoarthritis and low back pain [52,53] have been identified. These include an increase in gastrointestinal bleeding and systolic blood pressure, with liver injury, and possible respiratory, kidney function and in utero exposure effects.

4.3. When should opioids be considered?

Prescription narcotics such as the opioids are used to treat pain and may be required for their stronger analgesic affect (Table 1, Fig. 1). Use in acute stages of a fracture helps with pain control, with improved mobilization and quality of life [54,55]. Doses can be titrated based on the patient's perceived pain score, bearing in mind the potential for overuse and addiction with higher doses and long-term use. The effectiveness of opioids in improving pain and disability in chronic low back pain due to vertebral fractures is weak [56]. Chen et al [46] studied a cohort of chronic pain patients, finding a lack of correlation between opioid dose adjustment and pain score change. This is because chronic pain has an unpredictable nonlinear trajectory complicated by the patient's mood, perception of pain, experience, circumstances, and fear [57]. Significant side effects, associated with opioid use, include cardiorespiratory depression, gastrointestinal disturbance, cognitive impairment and increase in risk of falls [58–60]. Tanna et al [59] highlighted polypharmacy and falls risks with combined use of opioids and sedative drugs, antidepressants, muscle relaxants, and anticholinergics, with the recommendation that these patients would benefit from regular medicines deprescribing and optimization reviews [28].

4.4. How should vertebral fracture patients with a complaint of pain due to muscle spasms or compression of a nerve root be treated?

Paravertebral muscle spasms can cause pain. Muscle relaxants used as an adjuvant therapy may help break the cycle of pain and muscle spasm. Side effects include drowsiness and long-term dependency, and every patient should have an individualized risk benefit evaluation. Radicular pain as a result of nerve root compression may need other specific pharmacologic adjuvant treatments, and tricyclic anti-depressants, and anticonvulsants or neuropathic pain medicines such as gabapentin or pregabalin may be considered in these patients [22,61].

4.5. What is the role of calcitonin for pain control in patients with vertebral fractures?

Acute vertebral fractures are often accompanied by bone pain and muscle spasm and disabling pain can persist for several months [62]. General measures include short-term bed rest and pain relief with paracetamol, NSAIDs, and opioids with treatments titrated in line with patient needs, and as appropriate (Table 1, Fig. 1). Where pain is not controlled by these general measures, calcitonin with its antiresorptive action mediated via the osteoclast pathway, has been used as an analgesic, with discontinuation after 6–12 weeks [63–65]. A recent systematic review synthesized the findings of 11 randomized-controls trials with the aim of assessing the efficacy of

calcitonin for treating acute pain associated with vertebral compression fractures [66]. High quality evidence was found supporting the efficacy of salmon calcitonin with reduction in compression fracture pain after 1 week of treatment; this has also been reported by previous studies [63,67]. Boucher et al. [66] also suggested that salmon calcitonin may reduce pain at later time points; they were unable to pool the data to confirm this due to the substantial heterogeneity between studies. Licensed indications for calcitonin include hypercalcaemia of malignancy, Paget's disease of the bone, and the prevention of acute bone loss due to sudden immobility [63]. With a possible risk of malignancy, avoiding prolonged use has been advised [68]; this is despite the review undertaken by Wells et al. [69] who considered the biological rationale and an additional analysis of historical data with respect to the possibility, with conclusion that although an association cannot be excluded, the relationship was weak, and causality was unlikely. Pending further research, calcitonin is not recommended as a long-term therapy for osteoporosis, and in addition, has not been shown to help with chronic pain conditions [8,64,65].

4.6. Management of chronic pain with old vertebral fractures?

Patients with a vertebral fracture may experience chronic back pain related to degenerative changes adjacent to the vertebral fracture [13,18,70]. Additionally, the biomechanics of the spine are disrupted post-fracture resulting in spinal misalignment. This potentially leads to chronic soft-tissue or arthritic pain. Patients with mild to moderate pain symptoms can be managed conservatively. However, complex pain syndromes can be difficult to manage and may require an integrated approach [21]. Rarely, spine surgeons may be called upon to restore sagittal alignment with spine fusion procedures [13,71]. Pain specialists may provide multifaceted interventions including pharmacotherapy, transcutaneous electrical nerve stimulation, and acupuncture [8].

5. Conclusions

In summary, low trauma vertebral fractures are common and often may not come to clinical attention. Vertebral fractures are accompanied by pain with debilitating effect on patients. With a poor evidence base, there is need for more research on how vertebral fracture pain can be managed. This review lists the various options that can be considered based on current knowledge.

CRediT author statement

Nuttan Kantilal Tanna: Conceptualization, Formal analysis, Data curation, Writing – original draft.

Terence Ong: Analysis, Data curation, Writing - review and editing.

Conflicts of interest

The authors declare no competing interests.

Acknowledgments

With thanks to Dr Emma C Alexander for assisting with the referencing. **ORCID** Nuttan Tanna: 0000-0003-1637-283X. Terence Ong: 0000-0001-7473-446X.

References

[1] Compston JE. Osteoporosis. Clin Endocrinol 1990;33:653–82.
[2] Nuti R, Brandi ML, Checchia G, Di Munno O, Dominguez L, Falaschi P, et al. Guidelines for the management of osteoporosis and fragility fractures. Intern Emerg Med 2019;14:85–102.
[3] Unnanuntana A, Gladnick BP, Donnelly E, Lane JM. The assessment of fracture risk. J Bone Joint Surg Am 2010;92:743–53.
[4] Adams MA, Dolan P. Biomechanics of vertebral compression fractures and clinical application. Arch Orthop Trauma Surg 2011;131:1703–10.
[5] Melzack R. Pain and the neuromatrix in the brain. J Dent Educ 2001;65:1378–82.
[6] Craig AD. Pain mechanisms: labeled lines versus convergence in central processing. Annu Rev Neurosci 2003;26:1–30.
[7] Kanis JA, Norton N, Harvey NC, Jacobson T, Johansson H, Lorentzon M, et al. Scope 2021: a new scorecard for osteoporosis in Europe. Arch Osteoporos 2021;16:82. 82.
[8] Kendler DL, Bauer DC, Davison KS, Dian L, Hanley DA, Harris ST, et al. Vertebral Fractures: clinical importance and management. Am J Med 2016;129:221.e1.10.
[9] Nagae M, Hiraga T, Wakabayashi H, Wang L, Iwata K, Yoneda T. Osteoclasts play a part in pain due to the inflammation adjacent to bone. Bone 2006;39:1107–15.
[10] Sinaki M, Pfeifer M, Preisinger E, Itoi E, Rizzoli R, Boonen S, et al. The role of exercise in the treatment of osteoporosis. Curr Osteoporos Rep 2010;8:138–44.
[11] Fernández-de-las-Peñas C, Hernández-Barrera V, Alonso-Blanco C, Palacios-Ceña D, Carrasco-Garrido P, Jiménez-Sánchez S, Jiménez-García R. Prevalence of neck and low back pain in community-dwelling adults in Spain: a population-based national study. Spine 2011;36:213–9.
[12] Chou YC, Shih CC, Lin JG, Chen TL, Liao CC. Low back pain associated with sociodemographic factors, lifestyle and osteoporosis: a population-based study. J Rehabil Med 2012;45:76–80.
[13] Sahota O, Ong T, Salem K. Vertebral fragility fractures (VFF): who, when and how to operate. Injury 2018;49:1430–5.
[14] Madassery S. Vertebral compression fractures: evaluation and management. Semin Intervent Radiol 2020;37:214–9.
[15] Clark EM, Gooberman-Hill R, Peters TJ. Using self-reports of pain and other variables to distinguish between older women with back pain due to vertebral fractures and those with back pain due to degenerative changes. Osteoporos Int 2016;27:1459–67.
[16] Johansson L, Sundh D, Nilsson M, Mellström D, Lorentzon M. Vertebral fractures and their association with health-related quality of life, back pain and physical function in older women. Osteoporos Int 2018;29:89–99.
[17] Jin YZ, Lee JH, Xu B, Cho M. Effect of medications on prevention of secondary osteoporotic vertebral compression fracture, non-vertebral fracture, and discontinuation due to adverse events: a meta-analysis of randomized controlled trials. BMC Muscoskel Disord 2019;20:399.
[18] Shigenobu K, Hashimoto T, Kanayama M, Ohha H, Yamane S. The efficacy of osteoporotic treatment in patients with new spinal vertebral compression fracture pain, ADL, QOL, bone metabolism and fracture-healing - in comparison with weekly teriparatide with bisphosphonate. BoneKEy Rep 2019;11:100217.
[19] Kado DM, Browner WS, Palermo L, Nevitt MC, Genant HK, Cummings SR. Vertebral fractures and mortality in older women: a prospective study. Arch Intern Med 1999;159:1215–20.
[20] Kado DM, Lui LY, Ensrud KE, Fink HA, Karlamangla AS, Cummings SR. Hyperkyphosis predicts mortality independent of vertebral osteoporosis in older women. Ann Intern Med 2009;150:681–7.
[21] Paolucci T, Saraceni VM, Piccinini G. Management of chronic pain in osteoporosis: challenges and solutions. J Pain Res 2016;9:177–86.
[22] National Institute for Health and Care Excellence. Neuropathic pain in adults: pharmacological management in non-specialist settings. CG173 [Internet]. London: NICE; cited 14 January 2022. Available from: https://www.nice.org.uk/guidance/cg173/chapter/Introduction.
[23] Craig AD. How do you feel — now? The anterior insula and human awareness. Nat Rev Neurosci 2009;10:59–70.
[24] Iannetti GD, Mouraux A. From the neuromatrix to the pain matrix (and back). Exp Brain Res 2010;205:1–12.
[25] National Institute for Health and Care Excellence. Fractures (non-complex): assessment and management. NG38 [Internet]. London: NICE; cited 14 January 2022. Available from: https://www.nice.org.uk/guidance/NG38/chapter/Recommendations#initial-pain-management-and-immobilisation.
[26] Vannucci L, Fossi C, Gronchi G, Brandi ML. Low-dose diclofenac in patients with fragility fractures. Clin Cases Miner Bone Metab 2017;14:15–7.
[27] National Institute for Health and Care Excellence. Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. CG76 [Internet]. London: NICE; cited 14 January 2022. Available from: https://www.nice.org.uk/guidance/cg76.
[28] National Institute for Health and Care Excellence. Shared decision-making about medicines. London: NICE; cited 14 January 2022. Available from: https://pathways.nice.org.uk/pathways/medicines-optimisation#path=view%3A/pathways/medicines-optimisation/shared-decision-making-about-

medicines.xml&content=view-index.
[29] Ong T, Sahota O, Gladman JRF. The Nottingham Spinal Health (NoSH) Study: a cohort study of patients hospitalised with vertebral fragility fractures. Osteoporos Int 2020;31:363–70.
[30] Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Breivik Hals EK, et al. Assessment of pain. Br J Anaesth 2008;101:17–24.
[31] Brown D. Pain assessment with cognitively impaired older people in the acute hospital setting. Rev Pain 2011;5:18–22.
[32] Enthoven WTM, Roelofs PDDM, Deyo RA, van Tulder MW, Koes BW. Non-steroidal anti-inflammatory drugs for chronic low back pain. Cochrane Database Syst Rev 2016;2:CD012087. CD012087.
[33] Zajączkowska R, Kocot-Kępska M, Leppert W, Wordliczek J. Bone pain in cancer patients: mechanisms and current treatment. Int J Mol Sci 2019;20:6047.
[34] National Institute for Health and Care Excellence. Osteoporosis. Quality standard:QS149 [Internet]. London: NICE; cited 14 January 2022. Available from: https://www.nice.org.uk/guidance/qs149.
[35] National Institute for Health and Care Excellence. Osteoporosis: assessing the risk of fragility fracture. Clinical guideline:CG146 [Internet]. London: NICE; cited 14 January 2022. Available from:https://www.nice.org.uk/guidance/cg146.
[36] Bonabello A, Galmozzi MR, Bruzzese T, Zara GP. Analgesic effect of bisphosphonates in mice. Pain 2001;91:269–75.
[37] Kim S, Seiryu M, Okada S, Kuroishi T, Takano-Yamamoto T, Sugawara S, Endo Y. Analgesic effects of the non-nitrogen-containing bisphosphonates etidronate and clodronate, independent of anti-resorptive effects on bone. Eur J Pharmacol 2012;699:14–22.
[38] Abdulla AJJ. Use of pamidronate for acute pain relief following osteoporotic vertebral fractures. Rheumatology 2000;39:567–8.
[39] Gangji V, Appelboom T. Analgesic effect of intravenous pamidronate on chronic back pain due to osteoporotic vertebral fractures. Clin Rheumatol 1999;18:266–7.
[40] 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;17:1659–65.
[41] Hu W, Wang H, Shi X, Song Y, Zhang G, Xing S, et al. Effect of preoperative zoledronic acid administration on pain intensity after percutaneous vertebroplasty for osteoporotic vertebral compression fractures. Pain Res Manag 2020:8039671.
[42] Tetsunaga T, Tetsunaga T, Nishida K, Tanaka M, Sugimoto Y, Takigawa T, et al. Denosumab and alendronate treatment in patients with back pain due to fresh osteoporotic vertebral fractures. J Orthop Sci 2017;22:230–6.
[43] Moretti A, de Sire A, Curci C, Toro G, Gimigliano F, Iolascon G. Effectiveness of denosumab on back pain-related disability and quality-of-life in patients with vertebral fragility fractures. Curr Med Res Opin 2019;35:151–5.
[44] Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344:1434–41.
[45] Nevitt MC, Chen P, Kiel DP, Reginster JY, Dore RK, Zanchetta JR, et al. Reduction in the risk of developing back pain persists at least 30 months after discontinuation of teriparatide treatment: a meta-analysis. Osteoporos Int 2006;17:1630–7.
[46] Chen L, Vo T, Seefeld L, Malarick C, Houghton M, Ahmed S, et al. Lack of correlation between opioid dose adjustment and pain score change in a group of chronic pain patients. J Pain 2013;14:384–1392.
[47] Kong M, Zhou C, Zhu K, Zhang Y, Song M, Zhang H, et al. 12-Month teriparatide treatment reduces new vertebral compression fractures incidence and back pain and improves quality of life after percutaneous kyphoplasty in osteoporotic women. Clin Interv Aging 2019;14:1693–703.
[48] Shin YH, Shin WC, Kim JW. Effect of osteoporosis medication on fracture healing: an evidence based review. J Bone Metab 2020;27:15–26.
[49] Ikeda S, Nakamura E, Narusawa K, Fukuda F, Matsumoto H, Nakai K, et al. Comparison of once-weekly teriparatide and alendronate against new osteoporotic vertebral fractures at week 12. J Bone Miner Metabol 2020;38:44–53.
[50] Akhter S, Qureshi AR, El-Khechen HA, Bozzo A, Khan M, Patel R, et al. The efficacy of teriparatide on lumbar spine bone mineral density, vertebral fracture incidence and pain in post-menopausal osteoporotic patients: a systematic review and meta-analysis. BoneKEy Rep 2020;13:100728.
[51] Dodwell ER, Latorre JG, Parisini E, Zwettler E, Chandra D, Mulpuri K, Snyder B. NSAID exposure and risk of nonunion: a meta-analysis of case–control and cohort studies. Calcif Tissue Int 2010;87:193–202.
[52] McCrae JC, Morrison EE, MacIntyre IM, Dear JW, Webb DJ. Long-term adverse effects of paracetamol - a review. Br J Clin Pharmacol 2018;84:2218–30.
[53] National Institute for Health and Care Excellence. Osteoarthritis: care and management: CG177 [Internet]. London: NICE; cited 14 January 2022. Available from: https://www.nice.org.uk/guidance/cg177/chapter/1-Recommendations.
[54] Ringe J, Faber H, Bock O, Valentine S, Felsenberg D, Pfeifer M, et al. Transdermal fentanyl for the treatment of back pain caused by vertebral osteoporosis. Rheumatol Int 2002;22:199–203.
[55] Vorsanger GJ, Farrell J, Xiang J, Chow W, Moskovitz BL, Rosenthal NR. Tapentadol, oxycodone or placebo for acute pain of vertebral compression fractures: a randomized Phase IIIb study. Pain Manag 2013;3:109–18.
[56] Deyo RA, Von Korff M, Duhrkoop D. Opioids for low back pain. BMJ 2015;350:g6380.
[57] Ballantyne JC, Kalso E, Stannard C. WHO analgesic ladder: a good concept gone astray. BMJ 2016;352:i20.
[58] Longo UG, Loppini M, Denaro L, Maffulli N, Denaro V. Osteoporotic vertebral fractures: current concepts of conservative care. Br Med Bull 2012;102:171–89.
[59] Tanna N, Tatla T, Winn T, Chita S, Ramdoo K, Batten C, Pitkin J. Clinical medication review and falls in older people—what is the evidence base? Pharmacol Pharm 2016:89–96. 07.
[60] Spiegl UJ, Fischer K, Schmidt J, Schnoor J, Delank S, Josten C, et al. The conservative treatment of traumatic thoracolumbar vertebral fractures. Dtsch Arztebl Int 2018;115:697–704.
[61] Prather H, Hunt D, Watson JO, Gilula LA. Conservative care for patients with osteoporotic vertebral compression fractures. Phys Med Rehabil Clin 2007;18:577–91.
[62] Fink HA, Ensrud KE, Nelson DB, Kerani RP, Schreiner PJ, Zhao Y, et al. Disability after clinical fracture in postmenopausal women with low bone density: the fracture intervention trial (FIT). Osteoporos Int 2003;14:69–76.
[63] Knopp JA, Diner BM, Blitz M, Lyritis GP, Rowe BH. Calcitonin for treating acute pain of osteoporotic vertebral compression fractures: a systematic review of randomized, controlled trials. Osteoporos Int 2005;16:1281–90.
[64] Endo N, Fujino K, Doi T, Akai M, Hoshino Y, Nakano T, Iwaya T. Effect of elcatonin versus nonsteroidal anti-inflammatory medications for acute back pain in patients with osteoporotic vertebral fracture: a multiclinic randomized controlled trial. J Bone Miner Metabol 2017;35:375–84.
[65] Ameis A, Randhawa K, Yu H, Côté P, Haldeman S, Chou R, et al. The Global Spine Care Initiative: a review of reviews and recommendations for the non-invasive management of acute osteoporotic vertebral compression fracture pain in low- and middle-income communities. Eur Spine J 2018;27:861–9.
[66] Boucher E, Rosgen B, Lang E. Efficacy of calcitonin for treating acute pain associated with osteoporotic vertebral compression fracture: an updated systematic review. CJEM 2020;22:359–67.
[67] 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.
[68] Medicines and Healthcare products Regulatory Agency. Calcitonin (Miacalcic): increased risk of cancer with long-term use [Internet]. London: MHRA [cited 14 January 2022]. Available from: https://www.gov.uk/drug-safety-update/calcitonin-miacalcic-increased-risk-of-cancer-with-long-term-use.
[69] Wells G, Chernoff J, Gilligan JP, Krause DS. Does salmon calcitonin cause cancer? A review and meta-analysis. Osteoporos Int 2016;27:13–9.
[70] Francis RM, Aspray TJ, Hide G, Sutcliffe AM, Wilkinson P. Back pain in osteoporotic vertebral fractures. Osteoporos Int 2008;19:895–903.
[71] Hoyt D, Urits I, Orhurhu V, Orhurhu MS, Callan J, Powell J, et al. Current concepts in the management of vertebral compression fractures. Curr Pain Headache Rep 2020;24:16.
[72] Reid C, Davies A. The World Health Organization three-step analgesic ladder comes of age. Paliat Med 2004;18:175–6.