Pharmacological options for pain control in patients with vertebral fragility fractures

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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.
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 also contribute to chronic pain [2,8]. The sensation of chronic pain experienced by the patient. Osteoporotic fracture induced can affect each of these aspects and thereby impact on the level of pain severity at the time of onset of fracture before subsiding over time [29].

Therefore, an effective pain management strategy should begin with assessment of pain severity especially when pain is severe. Therefore, an effective pain 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.

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 vertebral 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

![The WHO Analgesic Step Ladder](image)

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

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

| Pain Level       | Treatment Options                                                                 |
|------------------|-----------------------------------------------------------------------------------|
| Mild [NRS less than or equal to 3] | NSAIDs* or Paracetamol, with adjuvant therapy*                                    |
| Moderate pain [NRS 4–6] | Weak opioids* or NSAIDs* or paracetamol, with adjuvant therapy*                   |
| Strong pain [NRS greater than 6] | Opioids* and NSAIDs* or paracetamol, with possible adjuvant therapy*             |

* Adjuvant therapies contribute to mitigating pain, increasing the effect of analgesics.

* 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.

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