Introduction
Spinal fusion is one of the most commonly performed procedures for treating conditions of the spine, with a reported increase of 113% in the number of procedures between 1998 and 2011 in the United States. In the same period, the average age of patients undergoing spinal fusion increased from 49 years to just under 56 years, and re-fusion rates rose by 171%. It is reasonable to expect a continuing increase in the average age of patients undergoing spinal fusion based on unprecedented rates of population aging. Alongside the exponential growth of the aging population, osteopenia and osteoporosis have also become increasingly common conditions. As a result, the number of elderly osteoporotic patients needing instrumented spinal fusion has increased dramatically.

Spinal instrumentation and fusion in elderly osteoporotic patients with diminished bone density and quality can be a significant challenge for spine surgeons. Despite advances in hardware manufacturing and fixation techniques, adverse outcomes such as proximal junctional kyphosis (PJK), pseudarthrosis, instrumentation failure, graft subsidence, and compression fractures of the adjacent cranial vertebral body are frequently seen in osteoporotic patients after instrumented spinal fusion. In a retrospective analysis of 140 patients who underwent primary posterior thoracolumbar or lumbar spinal fusion, Bjerke et al. demonstrated that osteoporosis related complications such as PJK, pseudarthrosis, and instrumentation failure were significantly higher in patients with osteopenia and osteoporosis than those with normal bone density.

Tempel et al. showed that patients with DEXA T scores under -1.0 (i.e. with osteopenia or osteoporosis; T-score between -1.0 and -2.5, or less than -2.5 respectively) who undergo stand-alone lateral lumbar interbody fusion are at a much higher risk of developing graft subsidence and are at an increased risk of requiring additional surgery. Toyone et al. studied the long-term prevalence of vertebral fractures after lumbar spinal fusion with instrumentation. These authors suggested that “postmenopausal female patients who underwent lumbar spinal instrumentation surgery were susceptible to develop subsequent vertebral fractures within 2 years after surgery.”

Since the success of spinal fusion can depend on the quality and quantity of bone, effective pharmacologic treatment strategies to improve bone mineral density and facilitate new bone formation must be pursued in elderly osteoporotic patients before spinal fusion. These pharmacotherapeutic strategies can be divided into three main categories based on their mechanism of action: inhibition of bone resorption using bisphosphonates, stimulation of bone formation with parathyroid hormone (PTH) analogs, or combination therapies with simultaneous or sequential use of bisphosphonates and PTH analogs.

Bisphosphonates
Bisphosphonates (BPs) are the standard antiresorptive agents and the most commonly prescribed drugs for the treatment of osteoporosis. To better understand the
clinical outcomes of bisphosphonate use, it is important to elucidate the chemistry that underlies their effect on bone physiology.

Chemical structure and mechanism of action

These pharmacotherapeutics are called bisphosphonates because they contain two phosphonate groups in their chemical structure. This molecular structure is very similar to that of naturally occurring pyrophosphates thereby inhibits activation of the enzymes that utilize pyrophosphates. Once absorbed into the circulation, bisphosphonates are quickly retained in the skeleton with the highest concentrations found at sites of active bone resorption. A high concentration of BPs at resorption sites interrupts osteoclast function and induces osteoclast apoptosis, which results in decreased resorption and bone loss.

Commonly used BPs and current evidence

There are several bisphosphonates available for the treatment of osteoporosis including, but not limited to alendronate, risedronate, ibandronate, and zoledronic acid. While alendronate, risedronate, and ibandronate are available in oral formulations, zoledronic acid is only available in an intravenously delivered form. Ibandronate also has an intravenous formulation. Once a patient is deemed appropriate for pharmacologic osteoporosis therapy, the treatment is chosen based on multiple different clinical factors, including renal function and tolerance of oral medications. Due to the mechanism of bisphosphonate excretion via the kidney, and the lack of clinical trial data in patients with osteoporosis and severe renal impairment, BPs should not be used in patients with CrCl <30–35 mL/min.

The efficacy of bisphosphonates in reducing the risk of fractures in postmenopausal women has been demonstrated in multiple large scale, randomized controlled trials. The incidence of vertebral fracture has been shown to be reduced with any of the most common bisphosphonates: alendronate, risedronate, ibandronate, or zoledronic acid (Table 1). There is convincing evidence to support the positive impact of BPs on bone quality and outcomes in osteoporotic patients undergoing spinal fusion. In a retrospective comparative study of 64 osteoporotic patients undergoing lumbar spinal fusion, post-operative administration of 5mg of zoledronic acid infusion was shown to increase the speed of fusion. Patients treated with IV zoledronic acid, the fusion rates at three and six months were found to be 90%, compared with 70% and 75% in the control group, respectively (P<0.05). Despite the increased speed of fusion, there was no significant difference between the two groups at 12 months post-operatively. Additionally, there was a significant decrease in vertebral compression fractures in the group treated with zoledronic acid (P<0.05). In another retrospective comparative study, Tu et al. compared 32 osteoporotic patients who underwent lumbar interbody fusion surgery (LIFS) and received 5 mg of zoledronic acid infusions at three days and one year after the surgery, with 32 patients with osteoporosis who underwent LIFS but did not receive zoledronic acid postoperatively. At the two-year follow up, 75% of the patients treated with zoledronic acid achieved fusion, compared with 56% in the control group. Control group patients were noted to have developed significantly more vertebral compression fractures, loosened pedicle screws, and cage subsidence. Chen et al. performed a prospective randomized, placebo controlled, and triple-blind trial including 69 osteoporotic patients treated with either zoledronic acid infusion (5 mg) or placebo (the same volume of saline) after single-level posterior lumbar interbody fusion (PLIF). The zoledronic acid group was associated with significantly higher rates of fusion at three, six, and nine months postoperatively (P<0.05). However, there was no statistically significant difference between the histomorphometric and control groups at the 12-month follow up. No patients in zoledronic acid group developed adjacent vertebral compression fractures, whereas six patients (17 %) in the control group did (P<0.05). Furthermore, the mean Oswestry disability index (ODI) score in the zoledronic acid group was significantly lower compared with the control group at nine months and 12 months after the surgery (P<0.05). In another prospective randomized controlled study, Nagahama et al. evaluated the effects of postoperative weekly alendronate (35 mg) administration on spinal fusion in patients undergoing single-level PLIF. The alendronate-treated group achieved significantly higher rates of fusion, with 95% fusion at the one-year follow up compared with only 65% in the control group treated daily with 1 µg vitamin D (P=0.025). Additionally, the use of alendronate protected against the subsequent development of vertebral compression fracture: it occurred in 24% of patients in the control group versus 0% in the alendronate treated group (P=0.027). Interestingly, the results of this study showed that bone formation markers in the alendronate group was elevated at one and three months after surgery but decreased below preoperative levels six months postoperatively. However, bone formation markers in the control group remained above the preoperative levels at one, three, six, and 12 months after surgery. Bone resorption markers in the control group were above the preoperative levels at one and three months postoperatively, while the levels were below the preoperative baseline throughout the postoperative period for the alendronate group.

Based on existing evidence, it can be suggested that the use of bisphosphonates in osteoporotic patients promotes lumbar intervertebral fusion and reduces subsequent vertebral compression fractures.

Parathyroid Hormone (PTH) Analogs

PTH analogs are a relatively new class of osteoporosis treatment, having been used effectively for the past decade and a half in North America. In contrast to bisphosphonates, which prevent osteoporosis via an anti-resorptive mechanism, PTH analogs are anabolic agents that increase bone formation.

Table 1. Level I studies showing the decrease in vertebral fracture risk with the use of BPs in postmenopausal woman.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Study</th>
<th>Evidence Level</th>
<th>Follow Up Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>Kushida et al.</td>
<td>Level I</td>
<td>3 years</td>
<td>Risk Reduction 58% (P &lt; 0.05)</td>
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<tr>
<td></td>
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<td>Relative Risk = 0.41, 95% CI (0.18-0.97)</td>
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<tr>
<td>Risedronate</td>
<td>Reginster et al.</td>
<td>Level I</td>
<td>≥3 years</td>
<td>Risk Reduction 49% (P = 0.001)</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Chesnut et al.</td>
<td>Level I</td>
<td>≥3 years</td>
<td>*Risk Reduction 62% (P = 0.0001)</td>
</tr>
<tr>
<td>Zoledronic Acid</td>
<td>Black et al.</td>
<td>Level I</td>
<td>3 years</td>
<td>Risk Reduction 70% (P &lt; 0.0001)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Relative Risk = 0.30, 95% CI (0.24-0.38)</td>
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*The results of the study from Chesnut et al.21 showed 62% risk reduction for daily regimen and 50% risk reduction for intermittent regimen. Abbreviations: CI (confidence interval).
Chemical structure and mechanism of action

PTH is an 84-amino-acid polypeptide that plays a central role in the maintenance of calcium homeostasis by directly increasing calcium resorption in kidneys and indirectly enhancing calcium absorption in intestines by stimulating calcitriol. Although persistently high PTH levels, as occur in primary hyperparathyroidism, result in the predominance of osteoclast-mediated bone resorption and consequent net bone loss, intermittent administration of synthetic PTH analogs leads to a predominance of osteoblast-mediated bone formation. PTH promotes osteoblast growth and decreases osteoblast apoptosis. Activation of the PTH receptor in osteoblasts induces signaling pathways essential for osteoblast proliferation and differentiation. Through the same signaling pathway, sclerostin (a bone formation inhibitor) production is also reduced (Figure 1).

Commonly used PTH analogs and current evidence

Teriparatide and Abaloparatide are the two recombinant PTH analogs approved by the Food and Drug Administration (FDA) for the treatment of osteoporosis in postmenopausal women. It is assumed that the biological activity of intact PTH resides in the N-terminal of its amino-acid sequence. Teriparatide has a sequence identical to that of the 34 N-terminal amino acids (the biologically active region) of the 84-amino-acid human parathyroid hormone. It is administered as a subcutaneous injection into the thigh or abdominal wall and the recommended dosage is 20 mcg once a day. Teriparatide is extensively absorbed after subcutaneous injection with a bioavailability of 95%. Peripheral metabolism of PTH is believed to occur by non-specific enzymatic mechanisms in the liver followed by excretion via the kidneys. Since the safety and efficacy of teriparatide have not been evaluated beyond two years of treatment, use of this drug for more than two years is not recommended. Animal research showed an unequivocal increase in bone tumor incidence only after an extended duration of treatment (20 or 24 months) at the highest dose level of teriparatide (30 mcg/kg). Fortunately, seven-year results from an ongoing 15-year post-marketing surveillance study have not detected a pattern indicative of a causal relationship between teriparatide treatment and adult osteosarcoma in humans.

Neer et al studied the effects of teriparatide treatment in a prospective randomized placebo controlled trial including 1637 postmenopausal women with prior vertebral fractures. Their results showed that treatment of postmenopausal osteoporosis with teriparatide decreases the risk of vertebral and nonvertebral fractures; increases vertebral, femoral, and total-body bone mineral density; and is well tolerated. The respective relative risks of new vertebral fractures in the 20-µg and 40-µg teriparatide treatment groups, as compared with the placebo group, were 0.35 and 0.31 respectively (95% confidence intervals, 0.22 to 0.55 and 0.19 to 0.50). Although the two dose regimens had similar effects on the risk of fracture, the 40-µg dose increased bone mineral density more than the 20-µg dose and was more likely to cause side effects.

Literature includes high-level evidence supporting the use of teriparatide treatment to enhance osseous union in osteoporotic patients undergoing instrumented spinal fusion. In a prospective randomized study, Ebata et al. assessed the role of once-weekly teriparatide administration on patient outcomes following posterior lumbar interbody fusion (PLIF) or transferal lumbar interbody fusion (TLIF). Seventy-five osteoporotic patients were randomly selected to receive either weekly teriparatide administered subcutaneously from week one, for six months postoperatively (the teriparatide arm), or no teriparatide (the control arm). Six months postoperatively, complete fusion occurred in 69.0% of the patients in the teriparatide arm and in 35.1% of the patients in the control arm (P=0.013).

Inoue et al studied the efficacy of preoperative teriparatide in affecting insertion torque of pedicle screws during fusion surgery in postmenopausal women with osteoporosis. Twenty-nine patients who had thoracic and/or lumbar spine fusion were divided into two groups based on whether they were treated with teriparatide (N=13) or not (N=16) before the surgery. In the teriparatide-treated group, patients received preoperative teriparatide therapy as either a daily (20 mcg/day, N=7) or a weekly (56.5 mcg/week, N=6) injection for a mean of 61.4 days and a minimum of 31 days. During surgery, the insertional torque was measured in 212 screws inserted from T-7 to L-5 and compared between the two groups. The mean insertional torque value in the teriparatide group was significantly higher than in the control group (P<0.01). There was no significant difference between the daily and weekly teriparatide groups with respect to mean insertional torque value. The authors suggested that teriparatide injections beginning at least one month prior to surgery can be effective in increasing the insertional torque of pedicle screws during surgery in patients with postmenopausal osteoporosis.

Abaloparatide is also a 34-amino-acid analog of the amino-terminal (1-34) fragment of human PTH. Abaloparatide is con-
considered to be more selective in stimulating bone formation without increasing bone resorption. The minimal effects of abaloparatide on bone resorption may relate in part to lesser increases in the pro-resorptive cytokine RANKL (receptor activator of nuclear factor kappa B ligand) compared with the effect of teriparatide. The recommended dosage of abaloparatide is 80 mcg subcutaneously once daily. Similar to teriparatide, cumulative use of abaloparatide for more than 2 years during a patient’s lifetime is not recommended. The metabolism of abaloparatide is consistent with non-specific proteolytic degradation into smaller peptide fragments, followed by elimination by renal clearance.

In a double-blind randomized clinical trial including 2463 postmenopausal women with osteoporosis (Abaloparatide Comparator Trial in Vertebral Endpoints—ACTIVE), Miller et al demonstrated that the use of subcutaneous abaloparatide, compared with placebo, reduced the risk of new vertebral and nonvertebral fractures over 18 months. New morphometric vertebral fractures occurred in 0.58% (N=4) of the participants in the abaloparatide group and in 4.22% (N=30) of those in the placebo group (risk difference [RD] versus placebo, −3.64 [95% CI, −5.42 to −2.10]; relative risk, 0.14 [95% CI, 0.05 to 0.39]; P<0.001). The abaloparatide-treated group demonstrated significant increases in bone mineral density (BMD) from baseline at the total hip, femoral neck, and lumbar spine (P<0.001).

Miller et al further studied the results from 2463 postmenopausal women with osteoporosis in the ACTIVE to compare the response to treatment with daily injections of abaloparatide 80 µg with matching placebo or open-label daily injections of teriparatide 20 µg for 18 months. The proportions of patients experiencing BMD gains from a baseline of >0%, >3%, and >6% at the total hip, femoral neck, and lumbar spine at six, 12, and 18 months of treatment were compared among the placebo, abaloparatide, and teriparatide groups. Responders were defined prospectively as patients experiencing BMD gains at all three anatomic sites. At months six, 12, and 18, there were significantly more >3% BMD responders in the abaloparatide group compared with the placebo and teriparatide groups: month six, 19.1% versus 0.9% for placebo and 6.5% for teriparatide; month 12, 33.2% versus 1.5% and 19.8%; month 18, 44.5% versus 1.9% and 32.0% (P<0.001 for all comparisons of abaloparatide to placebo and to teriparatide). The authors concluded that, “In postmenopausal women with osteoporosis, a significantly greater proportion of patients treated with abaloparatide experienced increases in BMD than did those treated with placebo or teriparatide.”

Although available evidence indicates that abaloparatide has the potential to increase bone formation and improve BMD, no clinical studies to date have reported on the effects of abaloparatide treatment on bony union in osteoporotic patients undergoing instrumented spinal fusion.

### Bisphosphonates versus PTH Analogs

After the introduction of PTH analogs, researchers performed studies comparing bisphosphonates with PTH analogs to develop better treatment algorithms for enhancing osseous union after spinal fusion in osteoporotic patients. Overall, there is supportive evidence that teriparatide use alone is associated with higher osseous fusion rates compared with the use of bisphosphonates alone.

### Combined Use of Bisphosphonates and PTH Analogs

To obtain superior effects on the skeleton, combined use of an antiresorptive bisphosphonate with a bone-forming PTH analog was put forward as an appealing hypothesis. Although evidence suggests potential advantages of using simultaneous combination therapies on hip BMD over monotherapy alone, the effect of combination therapies on spine BMD, osteoporotic fracture incidence, and postoperative spinal fusion needs to be further studied (Table 3).

### Sequential Use of Bisphosphonates and PTH Analogs

PTH analogs are not recommended to be used for more than two years, due to concerns over neoplasms raised by animal stud-
Summary and Authors' Suggestions

Osteoporosis presents a unique challenge for spine surgeons as it relates to achieving osseous union following instrumented spinal fusion. Antiresorptive bisphosphonates and bone forming PTH analogs are two commonly used pharmacotherapeutics to minimize the risk of postoperative complications due to reduced bone quality in elderly osteoporotic patients. The use of bisphosphonates or PTH analogs alone has been shown to improve bone quality in osteoporosis. There is evidence that using PTH analogs alone is associated with higher osseous-union rates than the use of bisphosphonates alone after instrumented spinal fusion. Although simultaneously inhibiting osteoclasts and stimulating osteoblasts may sound sensible, concurrent use of bisphosphonates and PTH analogs has not been proven to be more efficacious for treatment of osteoporosis than using either therapy alone. However, there may be potential benefits in sequential use of PTH analogs and bisphosphonates. We suggest that, unless there is any contraindication, every elderly osteoporotic patient should start PTH analogs at least four to six weeks before instrumented spinal fusion and continue for a minimum of five months after surgery. It is advisable to switch to an antiresorptive bisphosphonate after discontinuation of PTH analogs to preserve the gain in BMD. Decisions on the extension of PTH analog treatment at six months after operation, the type of bisphosphonate to be initiated, and duration of treatment, must be taken on a case-by-case basis.

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