Guidelines on the Management of Paget’s Disease of Bone*

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Introduction

Paget’s disease is a chronic focal abnormality of bone turnover. Although there remains considerable controversy regarding its etiology, several different methods of treatment have now become available. In this review, a working party derived from members of the Bone and Tooth Society and the National Association for the Relief of Paget’s Disease, has examined the evidence currently available regarding the diagnosis and treatment of Paget’s disease in order to develop guidelines to assist in the management of this condition.

In assessing the evidence available we have adopted the guidelines prepared by the U.S. Agency for Health Care Policy and Research128, including:

Ia. Evidence from meta-analyses of randomized controlled trials (RCTs).
Ib. Evidence from at least one RCT.
IIa. Evidence from a controlled study without randomization.
IIb. Evidence from another type of well-designed experimental study.
III. Evidence from well-designed nonexperimental descriptive studies (these would include comparative studies, cohort studies, and case-control studies).
IV. Expert opinions or clinical experience.

The recommendations that we made on the basis of this evidence have been graded according to the level of the evidence that supports them. These were:

A. Based on evidence level I.
B. Based on evidence levels II or III.
C. Based on evidence level IV.

Background

Paget’s disease is a disorder in which there is a marked increase in bone turnover in localized parts of the skeleton. This results in an abnormal bone leading to expansion, structural weakness resulting in deformity and an increased risk of fracture, and pain. The alterations in bone shape result in mechanical changes but also can lead to pressure effects causing pain in adjacent joints and nerve compression syndromes. Perhaps the most important nerve compression problem is involvement of the skull base leading to deafness. The abnormal bone has increased metabolic activity and blood flow, which in itself contributes to the pain and can also increase neurological complications as part of a vascular steal syndrome.

Epidemiology

Paget’s disease appears to be particularly prevalent in populations of northern European ancestry. A radiological study in the UK undertaken in the 1970s suggested that the prevalence at that time might be of the order of 5.4% of the population over the age of 55 years (grade III35). There is a marked age dependency such that the prevalence in patients over the age of 85 years was nearly five times greater than that seen in those aged 60 years. A similar survey undertaken at the same time in the USA suggested that the prevalence there was lower, at 2.3% of the population between the ages of 65 and 74 years (grade III30). Like the British study, this survey also demonstrated a marked age dependency. A more recent study conducted using the same methodology and in some of the same towns within the UK suggested that the prevalence of Paget’s disease has decreased over the intervening 20 years (grade III58). The estimate for the prevalence of Paget’s disease in patients over the age of 55 has decreased to 2%, but the increasing incidence with age was maintained. Based on this study, the investigators estimated that 118,000 women and 144,000 men in England and Wales have Paget’s disease.

There is no information regarding the changes in prevalence of Paget’s disease within North America, but a study from New Zealand suggested a similar decline in prevalence in that country. In this study, clinical data from 1041 patients attending a Paget’s disease clinic were studied. Over the period from 1973 to 1993, there was a reduction in the proportion of patients with severe disease as judged by plasma alkaline phosphatase activity and severity of involvement on isotope bone scan (level III36).

Clinical Burden

Although it is generally accepted that most patients with Paget’s disease are asymptomatic, there is no robust evidence of the prevalence of symptoms in patients with radiological Paget’s disease. It is commonly accepted that around 5% of patients have symptoms (level IV72), but estimates vary considerably. Accordingly, it is difficult to assess the true burden of Paget’s disease in the general population. A questionnaire survey of the Paget
Table 1. Clinical features of Paget’s disease (from refs. 68 and 73, level IV)

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<tr>
<th>Feature</th>
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<tr>
<td>Pain</td>
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<td>Bone pain</td>
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<td>Joint pain</td>
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<td>Deformity</td>
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<tr>
<td>Bowing of long bones</td>
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<td>Skull deformities</td>
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<td>Fracture</td>
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<tr>
<td>Complete</td>
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<td>Fissure fracture</td>
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<td>Neurological</td>
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<td>Deafness</td>
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<tr>
<td>Other cranial nerve palsies</td>
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<td>Spinal cord compression</td>
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<td>Neoplastic transformation</td>
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Foundation in the USA reported depression in nearly half the responders, with less 25% reporting that their health was very good or excellent (level III58). However, a follow-up study indicated that much of the perceived ill-health was related to age and comorbid conditions, although the patient’s perception of Paget’s disease impact was an important determinant of health status (level III59). There is no reliable information available regarding the costs of Paget’s disease and its treatment.

Diagnosis

Clinical

Paget’s disease may present with obvious signs or symptoms or be an incidental finding during investigation of other conditions. Typical clinical features are listed in Table 1.

Radiological

Plain radiographs. The diagnosis of Paget’s disease is primarily radiological. A number of different radiological features have been described by a variety of investigators (Table 2, level III79,124,136). Although a large number of differential diagnoses must be considered,73 radiological diagnosis is usually not a problem. Where plain radiology is equivocal, computed tomography may be helpful, particularly if a high-resolution technique is used to demonstrate internal skeletal structure.

Plain radiographs are less sensitive than scintigraphy in the diagnosis of Paget’s disease (see later). Therefore, there is no benefit to be obtained from using a skeletal survey of plain radiographs to assess the extent of skeletal involvement when isotope scanning would be more sensitive and involve less radiation.

Plain radiographs also are valuable in the diagnosis of secondary complications of Paget’s disease such as arthritis or fracture.

- We recommend that the diagnosis of Paget’s disease be confirmed with plain radiology of at least one skeletal site in all patients with the condition (grade C).
- Full skeletal survey is not usually appropriate to establish the extent of skeletal involvement.
- Any painful areas in Paget’s disease should be examined by plain radiographs to determine whether there is an underlying cause.

Scintigraphy. Isotope bone scanning using 99mTc-labeled bisphosphonate tracer is more sensitive than plain radiography in the identification of pagetic lesions. One study has suggested that such isotope scanning will detect up to 50% more lesions than are visible on plain films (level III135). The technique also has the advantage of being able to visualize the whole skeleton and thus assess the extent of disease.

As knowledge of disease distribution is useful in planning treatment (especially to determine whether or not the base of the skull is involved) isotope scintigraphy should be considered in all patients at presentation to assess disease extent and activity.

In contrast, scintigraphy is less specific than plain radiography and changes detected by isotope bone scanning may need to be confirmed by conventional radiography of at least one site.

Conventional isotope scintigraphy delivers a radiation dose of 3–5 mSv. Although this is equivalent to the background radiation received over a period of 2–3 years, it is comparable to the dose delivered by other tests that may be used in patients with Paget’s disease. Thus, a pelvic radiograph is associated with a radiation exposure of 0.7–1.4 mSv, and lumbar spine films deliver 1.3–2.7 mSv. The dose is less than with some other measurements; for instance, CT scanning of the trunk can deliver from 5 to 15 mSv.

Attempts have been made to quantify the results of scintigraphy, but these are best considered research techniques and do not have an accepted place in clinical practice.

- We recommend that, although isotope scintigraphy is not the method of choice for the diagnosis of Paget’s disease, all patients with Paget’s disease should have scintigraphy performed to assess the extent of skeletal involvement (grade C).

Biochemical

Paget’s disease is associated with increased bone turnover. It is therefore expected that markers of bone turnover will be increased in active disease. Total plasma alkaline phosphatase activity is elevated in 85% of patients with untreated Paget’s disease (level IV45). In many of the patients with “normal” alkaline phosphatase activity the disease is monostotic or confined to a small number of bones (level IV38). There is a strong relationship between the extent of disease activity measured by scintigraphy and the degree of the elevation of alkaline phosphatase in untreated Paget’s disease (level IIb74,89). In patients with monostotic disease, bone specific alkaline phosphatase may still be elevated. In patients with abnormal liver function, or other causes of elevated alkaline phosphatase activity not due to bone, bone specific alkaline phosphatase might be a reasonable means of assessing disease activity.

In a comparative study of different markers of bone turnover in patients with Paget’s disease, the highest diagnostic sensitivity was 84%, obtained with bone specific alkaline phosphatase. The next most sensitive marker was total alkaline phosphatase, with a sensitivity of 74% (level IIb53). Although Paget’s disease is primarily the result of disordered osteoclastic bone resorption the markers of bone resorption performed less well with lower sensitivity (level IIb53).

- Bone specific alkaline phosphatase is less readily available than total alkaline phosphatase and does not exhibit major benefits over the more readily available total alkaline phosphatase. We recommend that plasma total alkaline phosphatase activity be used as the standard marker of bone turnover in patients with Paget’s disease (grade B).
- In patients with Paget’s disease, but without an elevation of plasma total alkaline phosphatase activity, we recommend the use of bone specific alkaline phosphatase as a marker of bone turnover (grade B).
• In patients with liver disease we recommend the use of bone specific alkaline phosphatase to monitor the activity of Paget’s disease.

Histological

Bone biopsy is rarely required to establish the diagnosis of Paget’s disease. Occasionally, it may be useful in differentiation from osteoblastic metastases or osteosarcoma (grade C).

Treatments for Paget’s Disease

Symptomatic

The main symptom of Paget’s disease is pain. In some cases this seems to arise in association with elevated bone turnover, but may also be due to nerve compression as the result of bone deformity or coexisting arthritis. All patients need careful clinical assessment to determine the likely cause of the pain so that appropriate treatment can be given.

Paget’s bone pain resulting from increased bone turnover responds well to osteoclast inhibitors, whereas that arising from nerve compression and osteoarthritis does not. These causes of pain should be treated with standard measures, such as simple analgesics, nonsteroidal anti-inflammatory agents, or opioid analgesia, either individually or in combination. Some patients will also benefit from the addition of low-dose tricyclic antidepressant therapy to an analgesic regimen. Physical methods of pain control may also be helpful. These include acupuncture, transcutaneous electrical nerve stimulation, physiotherapy, and hydrotherapy. Some patients may also derive considerable benefit from different aids and appliances such as walking sticks and frames, and also shoe raises. Joint replacement should be considered in patients with advanced osteoarthritis whose symptoms are resistant to medical therapy. Surgery may also be required in nerve compression syndromes that have not responded to medical treatment.

Specific

Specific therapy for Paget’s disease is aimed at decreasing the abnormal bone turnover. Because the primary defect appears to be in the osteoclast, most treatments are aimed at decreasing osteoclastic bone resorption.

Different therapies have been used over the years. However, since the introduction of the bisphosphonates, these have increasingly assumed the prime role in the management of Paget’s disease. We therefore consider the use of these agents in some detail, but spend less time discussing the use of other agents more likely to be considered only when bisphosphonate therapy has failed. Because of this, their use is likely to be confined to specialist centers.

Comparison of different treatment regimens is made difficult by the lack of any generally agreed-upon standard for therapeutic response. Many of the earliest reports have described the response in terms of percentage fall in alkaline phosphatase activity. This perspective is seriously flawed because it does not take account of the absolute level of alkaline phosphatase in the patients, and it is not informative as to the number who obtain biochemical remission with normal alkaline phosphatase activity.

Bisphosphonates. Bisphosphonates are a class of drugs related to the naturally occurring mineralization inhibitor, pyrophosphate. They were initially developed for use in the detergent industry where they prevent the formation of lime scale within pipes. However, in biological systems their basic chemical structure causes them to become bound to the surface of hydroxyapatite crystals within bone, especially on those surfaces undergoing active osteoclastic resorption.

The bisphosphonates work by two main mechanisms of action, depending on the chemical nature of the side-chain attached to the basic bisphosphonate core. Nitrogen-containing bisphosphonates, such as pamidronate, alendronate, and risedronate, inhibit enzymes of the mevalonate pathway. Among other actions, this pathway is responsible for attaching lipid moieties to small GTP-binding proteins present in the osteoclast, which are essential for cell survival and activity. Inhibition of this pathway by bisphosphonates inhibits resorptive function and triggers programmed cell death (apoptosis). Non-nitrogen-containing bisphosphonates, such as etidronate, clodronate, and tiludronate, become incorporated within stable ATP analogs, which interfere with cellular metabolic pathways, and again trigger cell death by apoptosis.

Four bisphosphonates are licensed in the UK for use in Paget’s disease. These include etidronate, pamidronate, tiludronate, and risedronate. In addition, several other bisphosphonates are available in the UK for other indications and have been shown to be of use in the management of Paget’s disease. These include clodronate, alendronate, and ibandronate. Other bisphosphonates, including olpadronate and zoledronate, are currently under investigation for use in Paget’s disease.

All bisphosphonates have poor absorption from the gastrointestinal tract. This is compounded by the fact that they will also combine with any calcium in the stomach, further inhibiting absorption. Thus, if a bisphosphonate is given orally, it is imperative that it is not given together with food or drink containing calcium. Each bisphosphonate available on the market has different instructions for use that require adherence to ensure proper absorption.

Etidronate. Etidronate was the first bisphosphonate used in the management of Paget’s disease. When given orally in doses of between 5 and 20 mg/kg per day, there was improvement in the biochemical indices of Paget’s disease, as indicated by a reduction in alkaline phosphatase activity of between 40% and 70% and a similar reduction in urinary hydroxyproline excretion (level Ib10,30,108). Pagetic pain was also improved. Although biochemical control was better with higher doses of etidronate, these doses were associated with more adverse effects including; increased gastrointestinal side-effects (level III77) and increased rates of fracture (level III80). This latter phenomenon has subsequently been shown to be due to focal osteomalacia (level III84). This can occur within 2 weeks after the institution of high-dose etidronate therapy (20 mg/kg per day) for Paget’s disease (level IIB1).

Use of lower doses of etidronate has been associated with lower rates of gastrointestinal side-effects (level III77) and fracture, similar to that seen in the general population (level III86). Although such regimens may be of clinical benefit (level III77,73,126), they have been associated with higher rates of biochemical treatment failure than the high-dose regimen. Treatment with low-dose etidronate has also been associated with long-term resistance to treatment (level III11).

To avoid mineralization defects, it is now recommended that etidronate be given in a dose of 400 mg/day for no longer than 6 months. After a treatment-free period of 6 months it is possible to repeat this course of therapy.

Pamidronate. Pamidronate was originally given orally in the management of Paget’s disease (level I105,9,52,87,126). However, the high incidence of gastrointestinal side-effects led to its universal use as an intravenous infusion. A variety of different therapeutic regimens have been investigated (level
alkaline phosphatase activity. There was also an improvement in tiludronate treatment is associated with a 40%–70% suppression of bone turnover (level III110,113). This appears to be dependent on the administered dose of pamidronate and may reflect the extent to which the treatment has suppressed disease activity (level II95,116).

In addition to improvement in bone turnover, pamidronate therapy has also been associated with a reduction in bone pain (level II/III11,33,31,52,86,87,126,138). There are a few case reports of patients with neurological complications of Paget’s disease improving following pamidronate therapy (level III44,98,132).

Although pamidronate is generally well tolerated, it has been associated with a substantial number of febrile reactions following intravenous therapy (level III131,132). These appear to be most common after the first infusion. In addition, some patients have experienced an increase in bone pain following pamidronate infusion (level III131). More serious adverse reactions are rare, but include uveitis (level III56,85,94), which is usually self-limiting.

The early reports of pamidronate use in management of Paget’s disease found no evidence of abnormal bone mineralization (level III132). However, some patients receiving high-dose pamidronate treatment for Paget’s disease have evidence suggestive of a mineralization defect on bone biopsy (level III132). The clinical significance of this is uncertain, and some have suggested that the changes were not attributable to inhibition of mineralization but merely a predictable response to the rapid changes in bone turnover rate (level IV132).

Tiludronate. Tiludronate is a sulfur-containing bisphosphonate that has been available for the management of Paget’s disease for some years. It is normally given as a 3 month course of 400 mg as a single daily oral dose.

Early studies with tiludronate have demonstrated a 60% reduction in bone turnover (level II132). Subsequently, double-blind controlled studies have demonstrated that bone turnover markers are better suppressed by tiludronate than placebo (level Ib110) or etidronate (level III106). These studies suggested that tiludronate treatment is associated with a 40%–70% reduction in alkaline phosphatase activity. There was also an improvement in patients’ symptoms of pagetic bone pain.

Tiludronate is usually well tolerated but is sometimes associated with looseness of the stools.

Risedronate. Risedronate is the most recent bisphosphonate to be introduced for the management of Paget’s disease in the UK. Although it is a nitrogen-containing bisphosphonate, the nitrogen atom is part of a pyridinyl ring. Animal studies have suggested that risedronate may have up to 1000 times the ability of etidronate to inhibit bone resorption. In the management of Paget’s disease, it is given as a single daily dose of 30 mg for a period of 2 months.

An initial uncontrolled study of 162 patients with Paget’s disease indicated that the aforementioned dose of risedronate was associated with a 60%–70% reduction in alkaline phosphatase activity and improvement in bone pain in a significant number of patients (level II22). These results were dependent on the dose of risedronate applied (level II27).

A subsequent randomized, double-blind comparison of risedronate with etidronate showed that alkaline phosphatase levels were normalized in nearly 75% of patients receiving risedronate, whereas only about one in seven patients receiving etidronate achieved normal alkaline phosphatase activity (level Ib90).

The improvement in bone turnover is associated with an improvement in radiological changes of the disease (level III26).

In the clinical trials to date, risedronate has been well tolerated without significant adverse reaction.

Clodronate. Clodronate is a first generation bisphosphonate, which has been licensed in the UK for use in malignant hypercalcemia. It has been used for the management of Paget’s disease in a variety of different clinical trials but is not licensed for this indication in the UK. It is about ten times as potent as etidronate at inhibiting bone resorption but avoids the risk of inhibition of mineralization. In Paget’s disease, when given either orally or intravenously, it is capable of reducing bone turnover and improving pagetic symptoms (level III53,63,139).

Alendronate. Alendronate is a third generation bisphosphonate that has been licensed in the UK for use in osteoporosis. In other countries it also has a license for use in the management of Paget’s disease. In the latter indication the usual dose is 40 mg/day for 6 months. The 40 mg tablet is not available in the UK.

In Paget’s disease, when given by either intravenous infusion or orally, alendronate has been associated with a marked reduction in bone turnover, accompanied by an improvement in bone pain (level Ib104 and level II4,5,50,80,93). A single comparative study showed alendronate to be more potent at suppressing Paget’s disease activity than etidronate (level Ib116). In addition, examination of radiographs showed that alendronate treatment leads to a cessation of radiological progression of Paget’s disease (level III133) and healing of radiological lesions (level Ib116).

Ibandronate. Ibandronate is a potent new bisphosphonate. It is not currently available in the UK. Preliminary studies have shown that a single injection of 2 mg ibandronate is capable of suppressing disease activity in patients with Paget’s disease. In patients in whom this had been insufficient to suppress disease activity, application of a higher dose was sometimes more effective (level II135).

Olpadronate. Olpadronate is chemically similar to pamidronate with the nitrogen atom being converted to a tertiary amine by the addition of two methyl groups. Preliminary studies in Europe and South America have suggested that the compound may be beneficial in the management of Paget’s disease, but larger scale studies are awaited (level III69,96,115,130).

Zoledronate. Zoledronate is a potent new bisphosphonate presently under development. Preliminary studies have suggested that it may be a potent agent for the treatment of Paget’s disease (level II15,54 and level Ib28). It is not yet available for routine clinical use.

Comparison between bisphosphonates. Three double-blind studies have been performed in which bisphosphonates were compared with one another: Roux’s study of tiludronate vs. etidronate (level Ib106); Siris’s study of alendronate vs. etidronate (level Ib110); and Miller’s study of risedronate vs. etidronate (level Ib107). In each study, etidronate was less effective than the other bisphosphonate in suppressing biochemical markers of disease activity. None of these studies showed a significant difference between the bisphosphonates in response of bone pain, but trends were observed in favor of the more potent bisphosphonate (level Ib90,115).

• The primary treatment for Paget’s disease is inhibition of bone turnover using bisphosphonate. Oral tiludronate (400 mg/day for 12 weeks), oral risedronate (30 mg/day for 2 months), or intravenous pamidronate (three infusions of 60 mg at fortnightly intervals or six infusions of 30 mg at weekly intervals) have all been shown to be effective (grade A).
• As other oral bisphosphonates have greater activity and fewer adverse effects, etidronate is not recommended in the management of Paget’s disease (grade B).

Calcitonins. Calcitonin is a 32-amino-acid peptide secreted by the C cells of the thyroid. Its primary physiological action appears to be the suppression of plasma calcium concentration by a combination of reduced bone resorption and increased urinary calcium losses. Its physiological significance in land-living mammals is unclear, although it is clearly of major homeostatic importance in fish. It inhibits bone resorption by a direct action on osteoclasts, which is mediated by calcitonin receptors that are found on those cells. Prior to the introduction of bisphosphonates, calcitonin was the treatment of choice for the management of Paget’s disease. Studies have shown that it is capable of inhibiting the activity of pagetic bone (level II\(^{20,71,117}\)), reducing the symptoms of Paget’s disease (level II\(^{20,71,117}\)), and improving the radiological appearance of Paget’s lesions (level II\(^{20}\)).

As a polypeptide, calcitonin is rapidly degraded in the gastrointestinal tract and therefore needs to be given parenterally. Initially, this was done using either subcutaneous or intramuscular injections. Both these routes of administration have been associated with significant side-effects, including flushing and nausea and vomiting (level II\(^{58,82}\)). More recently, it has been possible to administer calcitonin via a nasal spray with similar benefit, but with fewer side-effects (level II\(^{39,99,157}\)).

In view of the weaker activity, shorter duration of action, and adverse side-effect profile compared with bisphosphonates, we do not recommend the use of calcitonin for the first line management of Paget’s disease. It may have a role in those patients in whom bisphosphonates are not tolerated or have proven to be ineffective (grade B).

Plicamycin. Plicamycin (formerly mitramycin) is a cytotoxic antibiotic capable of inhibiting osteoclast activity. Although it is capable of reducing bone turnover and bone pain in patients with Paget’s disease (level III\(^{47,48,67,107,111,112}\)), these effects are limited by severe systemic toxicity. In particular, there are problems with both marrow and hepatic toxicity. The drug is no longer routinely available in the UK and we cannot recommend its use outside specialist centers and, even then, only in extreme circumstances (grade B).

Other agents. A variety of other agents have been used for the management of Paget’s disease. These include gallium nitrate, glucagon, corticosteroids, and a variety of cytotoxic agents. None of these can be recommended in the routine management of Paget’s disease (grade B).

Surgery

Within the management of Paget’s disease, surgery is generally confined to the management of fracture, deformity, or arthritis. Although it has been suggested that, because pagetic bone is more vascular, there is increased risk of blood loss during surgery (level III\(^{101}\)), this has not been reported by all investigators (level III\(^{84,122}\)). Nonetheless, it would appear reasonable to administer antipagetic therapy before surgery, if only to make sure that treatment of the underlying disease has not removed the need for surgery.

Fracture. An increased rate of malunion has been reported for fractures through pagetic bone. This appears to be particularly the case for proximal femur fractures (level III\(^{22,28}\)). The investigators recommend medical treatment for such patients prior to surgery (level IV), although, given the mode of presentation of such fractures, an approach of this type is often impractical. At other sites, conventional surgical techniques appear to be successful.

Deformity. Osteotomy has been used to correct deformity of Paget’s disease, particularly if it causes pain or is associated with fissure fractures. More recently, some of the newer surgical techniques using Ilizarov fixators have been reported to be successful in this situation (level III\(^{34}\)). No randomized studies of surgical correction of pagetic deformity have been undertaken.

• Patients with painful pagetic deformities, particularly if these are associated with fissure fracture, should be considered for surgical treatment (grade B).

Arthritis. There is considerable experience with regard to arthroplasty for the management of osteoarthritis in patients with Paget’s disease. Most recent series have reported results similar to those achieved in nonpagetic patients, although there is a slight increase in the risk of heterotopic ossification and nonunion of the trochanter in hip arthroplasty (level III\(^{84,122}\)).

• Patients with osteoarthritis related to Paget’s disease, whose symptoms do not settle with medical therapy, should be considered for surgery (grade B).

Indications for Treatment of Paget’s Disease

A number of different criteria for the treatment of Paget’s disease have been put forward (level IV\(^{38,69,119}\)). We examine the evidence for each of these indications in turn.

Bone Pain

Bone pain is the only complication of Paget’s disease for which there is firm evidence that specific antipagetic therapy is associated with clinical benefit. There have been five placebo-controlled, double-blind studies of bisphosphonate treatment in Paget’s disease in which pain was assessed as one of the end-points, and four of these showed that bisphosphonate was superior to placebo (level I\(^{10,102,104,78,101}\)). Other comparative studies of bisphosphonates have shown that pain relief tends to be better with more powerful bisphosphonates, although the differences between treatments were not statistically significant (level III\(^{90,110,118}\)).

Pain relief has also been reported with calcitonin (level II\(^{34,71}\)) and plicamycin (level II\(^{57,113}\)), but this has not been demonstrated within the context of a randomized, controlled clinical trial.

• Pain in pagetic bone is a definite indication for antipagetic treatment (grade A).

Fracture

Fracture is a common complication of Paget’s disease, but the effects of antipagetic therapy on fracture have not been systematically studied. Indeed, one early study of etidronate suggested that fracture risk was increased with high-dose treatment\(^{10}\); this was probably the result of impaired mineralization.

It might be expected that agents that reduce bone turnover in Paget’s disease would improve fracture risk. However, only two placebo-controlled studies with detailed information on fractures have been performed. One study found that 1 of 9 placebo-treated patients suffered a fracture during a 6 month follow-up period compared with 2 of 41 etidronate-treated patients (level I\(^{10}\)). In another short-term study with oral tiludronate, one fracture occurred in the 400 mg dose group and none in the placebo group (level I\(^{11}\)). These differences were not significant in either study. However, both these studies had very low power to detect change in fracture risk, and thus it would be inappro-
priate to conclude that bisphosphonates do not reduce fracture risk. Further research is indicated.

The effect of medical treatment on fissure fractures has not been studied.

There is no evidence that treatment of Paget’s disease improves healing of fractures.

- Treatment of Paget’s disease solely to reduce fracture risk is not indicated (grade C).
- Treatment of Paget’s disease following fracture to improve healing is not justified. (grade C).

Prevention of Bone Deformity

Bone deformity, particularly affecting weight-bearing long bones, is a common complication of Paget’s disease. Suppression of bone turnover might be expected to help prevent bone deformity on a theoretical basis, but the effects of antipagetic therapy on bone deformity have not been assessed in controlled clinical trials.

Clinical observations in a small number of patients have indicated that bisphosphonate therapy might reduce facial deformities in patients with Paget’s disease (level III 21, 209).

- The effects of antipagetic therapy on bone deformity are unclear (grade C).
- Bisphosphonate therapy may be justified in the management of facial deformities due to Paget’s disease (grade B).
- Therapy of Paget’s disease cannot be justified solely for the prevention of deformity elsewhere (grade C).

Osteolytic Lesions

There is evidence from a controlled trial to suggest that alendronate promotes radiological healing of osteolytic lesions in Paget’s disease (level I 104). Uncontrolled studies have shown healing of osteolytic lesions with other bisphosphonates (level II 26, 41, 209), suggesting that this may be a class effect of all potent bisphosphonates. The clinical significance of this is unclear and we do not make specific recommendations about the treatment of osteolytic disease in the absence of other indications for treatment.

Prevention of Osteoarthritis

The risk of osteoarthritis is increased in Paget’s disease, but there is no evidence that antipagetic therapy affects the development or progression of osteoarthritis:

- Because there is often diagnostic difficulty in distinguishing between pagetic bone pain and the pain of osteoarthritis in an adjacent joint, it is not unreasonable to treat patients in whom there is uncertainty as to the cause of pain (grade C).

Deafness

Deafness is a common complication of Paget’s disease, but the effects of antipagetic treatment on development or progression of deafness are poorly understood. No controlled studies have been undertaken; however, several small clinical series have suggested that treatment of Paget’s disease (mainly with calcitonin) can reduce the rate of progression of hearing loss, although no improvement in hearing has been seen (level III 26, 81, 88, 125). In view of this, and the irreversibility of hearing loss if it does occur, many investigators have recommended treating Paget’s disease of the skull base to minimize the risk of developing deafness.

- In patients with Paget’s disease of the skull base, treatment should be considered to minimize the risk of hearing loss (grade B).

Quality of Life

Two studies have examined the short-term effects of bisphosphonates on functional status in Paget’s. Both of these studies examined the effects of bisphosphonate therapies and neither demonstrated any significant difference following treatment (level III 80, 118). It must be remembered that quality of life was not the primary end-point in either of these studies and that neither study was designed with the appropriate power to detect small changes in quality of life.

Spinal Cord Compression

Several case reports have demonstrated the ability of calcitonin (level III 33, 43, 64, 68, 114, 134) and bisphosphonates (level III 243, 98, 132) to improve neurological function in patients with Paget’s disease and spinal cord dysfunction. This is in contrast to surgery, which has been associated with problems in a significant number of patients (level III 142 and level IV 78). As these are relatively rare complications, it is unlikely that it will be possible to undertake a randomized comparison of surgery and medical intervention.

In such patients it is important to consider causes of spinal compression other than Paget’s disease.

- Patients who develop neurological symptoms as a result of spinal Paget’s disease should initially be treated medically. If this fails to relieve symptoms then surgical decompression should be considered (grade B).

Blood Loss

It has also been suggested that antipagetic therapy given preoperatively may reduce intraoperative blood loss (level IV 22), although this has been disputed by others (level III 84). The effect of antipagetic therapy on operative blood loss has never been studied in a randomized trial.

Hypercalcemia

Hypercalcemia is a rare complication of Paget’s disease due to a combination of increased bone turnover and either immobilization (level III 18, 53, 91) or hyperparathyroidism (level III 95, 100). Clinical observations have suggested that treatment of the underlying Paget’s disease might be helpful in these circumstances (level III 7). Given the benefit of bisphosphonates in hypercalcemia due to other causes it is reasonable to offer such treatment to hypercalcemic patients with Paget’s disease.

- Patients with Paget’s disease and hypercalcemia should be treated with bisphosphonate (grade B).

Sarcoma

There is no evidence that treatment affects either the development or progression of Paget’s sarcomata.

Young Age

Some experts have advised that patients presenting with Paget’s disease at a young age should be given treatment regardless of other indications. There is no evidence to support this contention.
Monitoring Treatment

The ultimate aim of treatment is to relieve the symptoms and prevent the complications of Paget’s disease. In general terms, this is only measurable in a practical way for pain and radiological improvement of osteolytic lesions. In certain very specific situations, outlined in what follows, other clinical changes can be useful.

Improvement in the biochemical markers of excess bone turnover is easily measured and provides the most rapid indication of treatment effect. Although the optimum levels of reduction in bone turnover are not fully established, the consensus view is that biochemical markers ideally should be suppressed into the population reference (normal) range.

Biochemical Response to Treatment

Total serum alkaline phosphatase activity is the most commonly used biochemical marker of disease activity (see earlier). It has good reproducibility (coefficient of variation 10%) and is sensitive to clinically important changes in disease activity. It has generally been accepted that a fall of 25% in total alkaline phosphatase activity represents a significant treatment response (grade C).

Bone specific alkaline phosphatase is more sensitive and specific that total alkaline phosphatase (level IIb112), although this difference is unlikely to be of clinical importance for the majority of patients. The situations where this benefit may be of importance include patients with liver disease, patients with monostotic disease, and those with total alkaline phosphatase within the normal range. In these patients, consideration should be given to using bone specific alkaline phosphatase to monitor disease progress.

In all studies of bisphosphonate therapy the nadir alkaline phosphatase level occurred 3–6 months after commencement of therapy, followed by a gradual offset of treatment effect (level Ib). We therefore recommend that bone turnover be measured every 3 months for the first 6 months of therapy, and thereafter at intervals of 6 months (grade C).

Urinary markers of bone resorption such as deoxypyridinoline or hydroxyproline respond more quickly to treatment (nadir within 1 month posttreatment) and may also indicate relapse before changes in alkaline phosphatase occur. The reproducibility of these markers is not as good, however, and 50% changes are required at the individual level to be significant. There is therefore little clinical benefit to be obtained from the routine clinical use of resorption markers.

Isotope Bone Scans

Isotope bone scans are a rather insensitive method of response measurement and there is considerable delay between biochemical response and improvement in bone scan (about 6 months). It also exposes patients to extra doses of radiation. However, in monostotic disease and situations wherein there is persistent pain despite normal bone biochemistry, repeat scans may be useful (grade C).

When Should Patients Be Retreated?

If patients do relapse they can be re-treated effectively, especially with potent bisphosphonates (level II105,121).

There have been no clinical trials specifically evaluating re-treatment of Paget’s disease following relapse, but a consensus exists that re-treatment is indicated when there is (all grade C):

1. Symptom relapse or persistence This is particularly the case for pain but should be confirmed by objective evidence of continuing disease activity. In the absence of evidence of continuing disease activity other causes of pain should be sought.

2. Biochemical relapse In those instances where treatment has been based on the presence of asymptomatic disease in a critical site, it is necessary to base re-treatment on biochemical criteria. There is no clinical trial evidence on which to base criteria for this. However, it is generally accepted that an increase of alkaline phosphatase of 25% above nadir (even if the total is still within the normal range) indicates significant relapse.

As the effects of treatment are generally apparent by 3 months after introduction of therapy, and maximal by 6 months, it is appropriate to offer re-treatment if a patient has failed to respond 6 months after treatment. There is some anecdotal experience to suggest that such patients may respond to administration of a bisphosphonate that is more potent than that given originally (grade C). (Table 2;42,92)

Table 2. Radiological features of Paget’s disease

| ● Early disease—primarily lytic |
| V-shaped “cutting cone” in long bones |
| Osteoporosis circumscripta in skull |
| ● Combined phase (mixed lytic and sclerotic) |
| Cortical thickening |
| Loss of corticomedullary distinction |
| Accentuated trabecular markings |
| ● Late phase—primarily sclerotic |
| Thickening of long bones |
| Increase in bone size |
| Sclerosis |

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