Adverse Skeletal Effects of Drugs – Beyond Glucocorticoids

Susannah O'Sullivan, Andrew Grey


Abstract and Introduction

Abstract

Osteoporotic fractures are an important public health problem with significant individual and societal costs. In addition to the major risk factors for osteoporotic fracture, low bone mineral density (BMD), age, low body weight and history of fracture or falls, some drugs are now considered to be important secondary risk factor for bone loss and fracture, particularly amongst predisposed individuals. Currently available data are often generated from small observational clinical studies, making risk assessment and development of management guidelines difficult. In many cases, the exposed population has a low baseline risk for fracture and additional assessment and treatment may not be necessary. In this review, we focus on drugs other than glucocorticoids identified as potentially causing adverse skeletal effects, summarizing the existing evidence from preclinical and clinical studies, and suggest recommendations for patient management.

Introduction

Osteoporosis and resultant fractures of the spine, hip and other sites are important public health problems with significant individual and societal costs. The risk for osteoporotic fracture is based upon low bone density and the presence of one or more clinical risk factors (see ). A history of fracture during adulthood or falls are important clinical factors in determining the risk of future fracture; however, age is the most influential risk factor, such that middle-aged adults with other risk factors are likely to be at low absolute fracture risk in the medium term. Using these clinical risk factors and BMD when available, fracture risk assessment tools (based upon data collected from large prospective observational studies) have been developed to estimate the 5–10 year probability of hip fracture and other fractures in untreated patients. Clinicians should be aware that fracture risk can also be estimated using the FRAX or Garvan tools without BMD data. Chronic glucocorticoid use is an established risk factor for osteoporosis, with studies showing that use of glucocorticoids leads to accelerated bone loss and an increased risk of fracture. Other drugs are increasingly recognized as potential causes of bone loss and fracture, particularly amongst predisposed individuals. In this review, we focus on the drugs other than glucocorticoids identified or suspected to cause adverse skeletal effects. In the majority of cases, these concerns are based upon observational clinical data. For many drugs with established adverse skeletal effects, the clinical significance is frequently limited or
uncertain, and concern for skeletal health is likely to be relevant only for those receiving long-term therapy and with other risk factors for bone loss and fracture.

Table 1. Clinical risk factors for fracture

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advancing age</td>
</tr>
<tr>
<td>Previous fracture during adulthood</td>
</tr>
<tr>
<td>History of a fall or falls in the past 12 months</td>
</tr>
<tr>
<td>Glucocorticoid therapy</td>
</tr>
<tr>
<td>Parental history of hip fracture</td>
</tr>
<tr>
<td>Low body weight</td>
</tr>
<tr>
<td>Current cigarette smoking</td>
</tr>
<tr>
<td>Excessive alcohol consumption</td>
</tr>
<tr>
<td>Medical diseases (e.g. rheumatoid arthritis, hyperparathyroidism, coeliac disease, hypogonadism)</td>
</tr>
</tbody>
</table>

Hormonal Treatments

Aromatase Inhibitors

Aromatase inhibitors (AIs) are a class of drugs used as adjuvant endocrine therapy in postmenopausal women with oestrogen receptor (ER)-positive breast cancer. They reversibly (anastrozole and letrozole) or irreversibly (exemestane) bind the aromatase enzyme, which is responsible for the peripheral conversion of androgens to oestrogens, thus inhibiting the main source of endogenous oestrogens in postmenopausal women.\[^5\] In large randomized controlled adjuvant therapy trials in breast cancer, AIs have shown significant advantages in terms of progression-free survival and distant recurrences compared with tamoxifen.\[^6\] Although they are generally administered for 5 years, more prolonged use is under investigation. Preclinical studies of the effects of AIs suggest a positive or neutral effect on bone metabolism.\[^7-9\] In small, short-term studies in postmenopausal women, the effects of AIs on bone turnover were inconsistent.\[^10,11\]

In postmenopausal women receiving AIs, bone loss is increased from a rate of 1–2% per year\[^12\] to an average of 2–2.5% per year throughout the duration of therapy.\[^13\] Despite this evidence of accelerated bone loss, in a 5-year prospective trial, no patients with normal BMD at baseline became osteoporotic.\[^14\] In the only trial comparing AI treatment to placebo, exemestane increased bone resorption and decreased BMD in the femoral neck but not the lumbar spine.\[^15\] The majority of randomized clinical studies compare the effects of AIs to tamoxifen rather than to placebo. All three AIs increase bone turnover and decrease BMD when compared with tamoxifen.\[^14,16\] Trials of AIs were not designed to explore fracture outcomes as primary events, but were reported as adverse events of oncology trials. Allowing for this, there is evidence for an increased fracture risk in women taking AIs as
compared to those taking tamoxifen [odds ratio (OR) 1.47, 95% confidence interval (CI) 1.34–1.61]. However, as tamoxifen is a weak antiresorptive agent in postmenopausal women and probably reduces fracture risk,[18,19] the risk estimate for AIs from this study is likely to be inflated. AI-related fracture rates may decrease upon cessation of the drug.[20] In a small placebo-controlled trial, there was no significant increase in fracture risk in patients treated with exemestane.[15]

Opinions and guidelines vary regarding the appropriate management of women receiving AIs. In a recent publication, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) group acknowledges this difficulty[21] and comments that this is reflected in the diversity of recommendations.[22–24] Important factors that should influence management are patient age and the knowledge that a standard duration of exposure to AI therapy is only 5 years. An assessment of fracture risk based upon clinical risk factors, coupled with dual-energy X-ray absorptiometry (DXA) of the hip and lumbar spine is reasonable in older patients (>60 years) initiating AIs.[21] Bisphosphonate therapy[25] or denosumab[26] could be considered in those assessed as being at high baseline fracture risk (e.g. women with established osteoporosis or FRAX-determined 10-year probability of major osteoporotic fracture >20%).[27] Ongoing monitoring might be considered for those with intermediate risk of fracture, but there are no data to guide the frequency of monitoring in this population. In younger postmenopausal women (age <60 years) treated with AIs, decisions to investigate with BMD and to treat or monitor should take into account their low baseline risk for fracture.

Gonadotrophin Hormone-releasing Hormone Agonists

Gonadotrophin hormone-releasing hormone (GnRH) agonists are synthetic peptides used to down-regulate the GnRH receptor, leading to pituitary desensitization and suppressed gonadal function. In women, GnRH agonists are used to treat a variety of conditions in which it is desirable to suppress ovarian function and lower oestradiol levels, including endometriosis, uterine leiomyomas and ER-positive breast cancer.[28] A consistent finding in premenopausal women treated with GnRH is accelerated bone loss, which is partially reversed with cessation of treatment.[29,30] In children and adolescents, GnRH agonists are used for treating central precocious puberty (CPP)[31] and endometriosis.[32] In children with CPP treated with a GnRH agonist, BMD was in the normal range for age and sex.[33] This compares to adolescents with endometriosis, where an observational study found that 1/3 of patients receiving a GnRH agonist and norethindrone acetate had BMD below the age- and gender-matched normal range.[34] There are no data regarding the risk of fragility fractures in premenopausal women, adolescents or children receiving GnRH agonists.

GnRH agonists are used in men as androgen deprivation therapy (ADT) for treatment of locally advanced or metastatic prostate cancer, but indications for their use are being expanded to include localized prostate cancer and men in whom the level of prostate-specific antigen (PSA) rises after prostatectomy.[35] ADT reduces testosterone and oestradiol levels, leading to increased bone resorption.[36] Prospective studies show a 2–3% decrease in BMD per year during initial therapy[37] and a steady decline during long-term treatment.[38] Observational studies in older men provide evidence that GnRH agonists increase the risk of clinical fractures.[39] If this effect applied to premenopausal women,
adolescents and children, it is unlikely to be associated with a clinically important increase in absolute risk of fracture due to their low baseline risk for fracture. Despite the low baseline risk for fracture, many clinicians use "add-back therapy" for women and adolescents receiving a GnRH agonist for more than 6 months to ameliorate oestrogen deficiency symptoms and to prevent bone loss. Although effective for prevention of bone loss, there are no data to support this regimen for the prevention of osteoporotic fracture in these populations. Alternatively, given the reversal of bone loss seen with stopping treatment, cessation of GnRH therapy could be considered in those with significantly accelerated bone loss and at higher risk for fracture. Men commencing GnRH agonist therapy for ADT are at higher baseline risk of fracture. Assessment of fracture risk is reasonable in older men receiving ADT, with treatment of those at high risk of fracture, and intermittent monitoring of others.

**Depot Medroxyprogesterone Acetate**

Injectable depot medroxyprogesterone acetate (DMPA) is an effective and convenient (3 monthly administration) contraceptive agent, which acts by inducing hypogonadotrophic hypogonadism. As such, endogenous oestrogen levels are reduced during DMPA therapy, and accelerated bone loss occurs. Oestrogen therapy prevents this bone loss. Cessation of DMPA use, if accompanied by restoration of menses, leads to at least partial reversal of the bone loss. Women who use DMPA until menopause do not experience bone loss at onset of menopause, presumably because they have already lost the oestrogen-sensitive component of BMD. Consequently, although data are limited, BMD in postmenopausal women who previously used DMPA may not be different from that of women who did not. Data on fracture risk are limited to case–control studies, which suggest a small increase in fracture risk in women exposed to DMPA (relative risk (RR)1·2–1·5). Given that absolute fracture risk in premenopausal women is very low, the putative increase that accompanies DMPA use is of limited clinical importance, particularly when weighed against the risks associated with unplanned or unwanted pregnancy. Although DMPA use in adolescents causes a decline in BMD, the very low baseline fracture risk in that age group, the likely short duration of therapy (>50% discontinue within 1 year) and the evidence for at least partial reversibility of bone loss after drug discontinuation argue against a need for aggressive assessment and/or intervention. Thus, for most women using DMPA, there is little need for assessment of skeletal health; consideration might be given to BMD measurement in those with important risk factors for fracture, such as very low body weight or comorbid conditions that are associated with low BMD. In postmenopausal women, previous use of DMPA might be considered in decisions about whether and when to undertake skeletal health assessments.

**Chemotherapeutic Agents**

**Chemotherapy**

The direct negative effects of agents such as methotrexate, doxorubicin and cisplatin on bone turnover, particularly through depletion of osteoblast precursors, have been demonstrated in animal models and in vitro studies. In children, chemotherapy may
reduce bone growth and final height,\cite{52} and possibly BMD.\cite{53} This may result in permanently reduced BMD and an increased risk of fracture in adulthood.\cite{54} In premenopausal women, the deleterious effects of chemotherapy are predominantly the result of chemotherapy-induced ovarian failure, which is associated with rapid bone loss in the first 6–12 months following chemotherapy.\cite{55} There may be some direct effect of chemotherapy as evidenced by reduced BMD in postmenopausal women receiving chemotherapy.\cite{56} Men treated with combination chemotherapy for Hodgkin's lymphoma\cite{57} and haematologic malignancy\cite{58} had reduced BMD; however, some had evidence of mild hypogonadism. In another study, men who had previously received chemotherapy for lymphoma or testicular cancers did not have reduced BMD.\cite{59} There are no fracture data for any of these populations. Currently, there are no evidence-based protocols for managing bone health in patients undergoing chemotherapy. Intravenous bisphosphonates are effective in preventing chemotherapy-induced bone loss in children\cite{60} and premenopausal women.\cite{61} In children exposed to chemotherapy, monitoring of growth and assessment of BMD in adulthood may be reasonable.

**Tyrosine Kinase Inhibitors**

The tyrosine kinase inhibitors (TKI), imatinib, nilotinib and dasatinib, used in the treatment of chronic myeloid leukaemia (CML),\cite{62} and gastrointestinal stromal cells tumour (GIST),\cite{63} substantially improve the prognosis of the underlying disease. Their molecular targets (PDGFR, c-abl, c-kit) are present in bone and "bystander effects" on bone and calcium metabolism have been observed.\cite{64,65} *In vitro* these drugs inhibit osteoblast proliferation but not function, and osteoclastogenesis.\cite{65–67} Data from animal studies demonstrate reduced bone formation and bone mass after treatment with imatinib.\cite{68} The most consistent effects in patients are alterations in calcium and phosphate metabolism and development of mild secondary hyperparathyroidism.\cite{64,65} In a prospective study, imatinib therapy was associated with altered bone remodelling, but BMD was stable or increased compared with baseline values.\cite{69} In patients treated with nilotinib, BMD tended to be higher than normative values.\cite{65} Overall, data in adults are largely reassuring regarding the skeletal safety of short- or long-term use of imatinib for treatment of CML or GIST. In children, imatinib also leads to development of secondary hyperparathyroidism and dysregulation of bone remodelling and may inhibit linear growth.\cite{70} Some authors recommend periodic monitoring of calcium and phosphate metabolism in patients receiving TKIs,\cite{71} but the current data do not suggest a need to monitor bone health in adults. In children, there may be negative effects on growth, but the nature and magnitude of this effect is unclear, and further studies are necessary before recommendations can be made.

**Calcineurin Inhibitors**

Cyclosporine A (CsA) and tacrolimus are immunosuppressive drugs used to prevent graft rejection following solid organ transplantation and to treat autoimmune disorders.\cite{72,73} *In vitro*, CsA inhibits osteoblasts, particularly at high doses, and osteoclasts,\cite{74,75} and animal studies suggest a detrimental effect of both CsA and FK506 on bone.\cite{76} The specific skeletal effects of calcineurin inhibitors are difficult to evaluate in humans as they are generally used with glucocorticoids, which are associated with bone loss and an increased risk of fracture.\cite{77} Studies examining CsA monotherapy and some studies of regimens
combining CsA and glucocorticoids have shown neutral or protective effects on BMD and fracture.\textsuperscript{[78–81]} As it is likely that those patients receiving calcineurin inhibitors will undergo monitoring and treatment for osteoporosis as a result of concomitant glucocorticoid use and disease-related risk factors, additional surveillance is unnecessary.

**Antiretroviral Therapy**

Antiretroviral therapy (ART) (also known as highly active antiretroviral therapy (HAART) consists of the combination of at least three classes of antiretroviral (ARV) drugs. As a result of the effectiveness of this treatment, patients with HIV have a life expectancy similar to the noninfected population\textsuperscript{[82]} and the focus has shifted to managing the long-term complications of HIV and ART, which may include adverse effects on skeletal health.\textsuperscript{[83]} The small number of preclinical studies investigating the effects of ART suggests an increase in osteoclast function, with inhibition of osteoblast function.\textsuperscript{[84,85]} In patients with HIV infection, the prevalence of low BMD is increased.\textsuperscript{[83]} However, low BMD is present at the time of diagnosis or very early in the course of the disease,\textsuperscript{[83]} and most of the difference in BMD is attributable to lower body weight, suggesting that HIV infection per se does not significantly affect bone health.\textsuperscript{[86]} Whether ART importantly affects skeletal health is uncertain. Initiation of ART induces increases in markers of bone turnover and causes accelerated bone loss in the first 2 years, particularly if treatment includes tenofovir.\textsuperscript{[83]} The mechanisms of these effects are unclear, and they may be attributable to the direct effects on bone cells seen in *in vitro* studies, vitamin D insufficiency\textsuperscript{[87]} or urinary phosphate wasting.\textsuperscript{[88]} Subsequently, however, changes in BMD tend to be positive in ART-treated cohorts and not different to those reported in non-HIV-infected controls. In a pooled analysis of randomized controlled trials of ART, fracture rates were similar in patients established on ART compared with those who were ART-naïve, but were higher in the first 2 years after initiation of ART.\textsuperscript{[89]} Overall, these results suggest that ART may activate osteoclast function with an increase in bone turnover and a fall in BMD in the first 2 years of treatment. The subsequent stabilization of BMD and lack of data showing an increase rate of fracture in the longer term are reassuring. At present, the available evidence suggests that younger healthy adults with adequately treated HIV infection do not need specific skeletal investigation or treatment, and older HIV-infected adults can be assessed and managed as per the existing guidelines for the general population.

**Psychoactive Treatments**

**Selective Serotonin Re-uptake Inhibitors**

Selective serotonin reuptake inhibitors (SSRIs) are commonly used antidepressants that increase levels of 5-hydroxytryptamine (5-HT) (serotonin) by inhibiting the serotonin transporter and thereby preventing serotonin reuptake.\textsuperscript{[90]} Bone cells express 5-HT receptors, and activation of these receptors leads to either stimulatory or inhibitory effects depending upon the subtype of receptor.\textsuperscript{[91]} Animal studies of the effects of SSRIs on the skeleton are inconsistent, reporting both increases and decreases in bone mass.\textsuperscript{[91–93]} In patients, the results of observational studies on BMD have been variable with prospective cohort studies and cross-sectional studies in boys, women and older men finding higher
rates of bone loss and lower BMD,[94–96] but a prospective cohort study of middle-aged women initiating an SSRI and the Women's Health Initiative (WHI) observational study failing to find such an association.[97,98] When adverse effects of SSRIs on BMD have been reported the magnitude of effect is small, of the order of 0·5%/year, and therefore of dubious clinical significance. Observational studies (that identified evidence of publication bias) have found an increased risk of fracture with SSRI use (pooled RR 1·7).[99–101] As this increased risk was independent of BMD, it has been suggested that it may be due to an association between depression and increased fracture risk or may represent an effect of SSRIs to increase the risk of falls, rather than a direct effect on bone mass or strength.[102,103] There is no consensus regarding management of bone health in these patients, although there have been recommendations that SSRI use be considered a secondary cause of osteoporosis.[104] Although there is an absence of consistent data demonstrating adverse effects on bone mass, there may be an indirect effect to increase fracture risk; thus, in older adults (>60 years) receiving long-term SSRI therapy, an assessment of fracture risk could be performed and treatment considered in those at high fracture risk. In younger adults, whose baseline risk of fracture is low, it would seem reasonable for management to be as per the general population.

Antipsychotic Drugs

Antipsychotic drugs are used in the treatment of psychoses, as a result of their ability to block dopamine receptors.[105] There are only a limited number of preclinical studies of antipsychotic drugs, which showing conflicting effects on bone.[106,107] Cross-sectional studies generally show reduced BMD in patients taking antipsychotic drugs compared with normative data, but the magnitude of effect varies, as does the affected site(s).[108] Bone turnover tends to be increased in association with hypogonadism induced by an increased prolactin level.[109] There is evidence from cross-sectional studies that fracture rates are higher in patients taking antipsychotic drugs (OR 1·7–2·6).[110,111] Proposed mechanisms by which antipsychotic agents cause reduced BMD are by inducing hyperprolactinaemia and thereby hypogonadism, by a direct effect on bone metabolism or by increasing the risk of falls.[112] Studies have failed to consistently show a difference in BMD or fracture rate between people taking antipsychotic drugs that increase prolactin and those that do not.[113] Studies of the effects of these drugs are confounded by other risk factors for low BMD in patients with schizophrenia, such as low body weight, reduced exercise, smoking and poor diet.[114] A recent study found that schizophrenia was associated with reduced BMD, after controlling for medications and other risk factors for osteoporosis.[115] It has been recommended that patients with psychosis who have osteopenia/osteoporosis or are at significant risk for reduced BMD be considered for treatment with prolactin-sparing antipsychotic medications.[116] However, in the absence of consistent evidence of a causative relationship between antipsychotic drugs and low BMD and/or fracture, no specific screening or treatment measures outside those for the general population seem indicated.

Anti-epileptic Drugs

Anti-epileptic drugs (AED) are a diverse group of drugs used to treat or prevent epileptic seizures. Many of these drugs are also regularly used in the management of psychiatric
conditions and neuropathic pain. The AEDs most commonly reported to affect BMD and bone metabolism are the inducers of the cytochrome P450 enzyme system (phenobarbital, phenytoin, carbamazepine and primidone) and sodium valproate, an enzyme inhibitor. It has been proposed that CYP450-inducing AEDs increase catabolism of 25(OH) vitamin D, leading to decreased calcium absorption and secondary hyperparathyroidism. In the past, institutionalized patients receiving AEDs were found to have osteomalacia and rickets caused by vitamin D deficiency. In recent studies of community dwelling adults and children, there is an increased incidence of vitamin D insufficiency (levels <20 ng/ml). Increased parathyroid hormone (PTH) levels have been reported in patients receiving AEDs. An increase in markers of bone turnover has been found in a number of small studies of patients receiving AEDs, and this may be associated with a decrease in BMD. Epidemiological studies link AED use to decreased bone mass in adults under 40 years and children, but prospective studies are lacking. In a single prospective study lasting up to 29 months, young male patients with epilepsy treated with a variety of AED (predominantly phenytoin and carbamazepine) experienced an annual 1.8% drop in femoral neck BMD. A recent meta-analysis of observational studies reported a significant increase in fracture risk amongst users of AEDs, however, patients receiving AEDs often have other risk factors for fracture, and the increase in risk may not relate to use of the drugs. In the absence of any evidence-based screening or treatment guidelines for managing bone health in patients receiving AEDs, most authors recommend treatment and surveillance as per the general population, with additional measurement of 25(OH) vitamin D levels.

Other Treatments

Thiazolidinediones (TZDs) are insulin-sensitizing drugs used in management of type II diabetes. Two TZDs, pioglitazone and rosiglitazone, are used in clinical practice. Their molecular target, the peroxisome proliferator-activated receptor gamma (PPARγ) nuclear transcription factor, regulates the differentiation of mesenchymal stem cells into osteoblasts or adipocytes, such that activation (as by TZDs) favours adipogenesis. Preclinical studies, including genetic manipulation of PPARγ expression, reported adverse effects of TZDs on BMD, with mechanistic data suggesting both decreased bone formation and increased bone resorption. No evaluation of bone end-points was undertaken in clinical trials prior to, or for several years after, TZDs were registered for clinical use. Data from small, short-term randomized clinical trials signalled skeletal harm, by demonstrating reductions in biochemical markers of bone formation and accelerated bone loss, and prompted interrogation of adverse events data from TZD trials. Collectively, these data suggested a modest (OR 1.45) increase in fracture risk in patients with type II diabetes exposed to TZDs for 1–4 years. The risk appeared to be confined to women (OR 2.2 vs 1.0 in men) and to fractures in the appendicular skeleton. The randomized trials were conducted in middle-aged populations, in which rates of hip and vertebral fractures were low. Subsequent analyses in observational studies of older cohorts suggested that fracture risk might be increased in men and in the axial skeleton.
More recently, several RCTs have reported the effects of TZDs on surrogate outcomes for bone health, aiming to define the magnitude, mechanism and reversibility of the TZD skeletal effect. Collectively, the results suggest that each TZD induce small decreases (1–2%, compared with placebo) in BMD over 12–18 months of use, without a consistent pattern of changes in markers of bone turnover. It is also not clear to what extent these small short-term effects are reversible after treatment discontinuation; in the 2 trials which reported 6-month off-treatment follow-up data, the TZD effects on BMD persisted. Overall, rigorous evidence exists that TZDs increase fracture risk in the appendicular skeleton in older women; less rigorous evidence suggests that fracture risk in the axial skeleton and in older men might be increased by TZD therapy. Bone loss is mildly accelerated by TZD use, although the mechanism (decreased bone formation and/or increased bone resorption) is uncertain. As people with type II diabetes might be at increased fracture risk because of their disease, consideration of skeletal health and estimation of fracture risk is reasonable in patients for whom TZD therapy is being considered. Alternative treatments should be considered in patients who are estimated to be at high baseline fracture risk.

**Loop Diuretics**

Diuretics lower the blood pressure by inducing sodium and fluid loss and are used in the treatment of hypertension and heart failure. Loop diuretics act on the Na\(^+\)-K\(^+\)-2Cl\(^-\) symporter (cotransporter) in the thick ascending limb of the loop of Henle to inhibit sodium and chloride reabsorption. Treatment with loop diuretics is associated with increased urinary calcium excretion and a compensatory increase in levels of PTH to prevent hypocalcaemia. Some studies of loop diuretic users have shown increases in markers of bone turnover. In several studies, PTH levels also increased and may be the underlying cause for the change in bone turnover. Observational studies have reported inconsistent effects of loop diuretics on bone mass. A 1-year randomized controlled study of postmenopausal women confirmed a decrease in BMD at the hip (−2%) and whole body (−1.4%) in users of loop diuretics when compared with placebo. In a prospective study of a cohort of older women, loop diuretic use was associated with a small but significantly higher rate of hip bone loss than nonuse after a mean duration of 4.4 years. In men, there was a greater decline in total hip BMD in users of loop diuretics (annual rate of decline −0.78 vs −0.33 percent in nonusers). Observational studies generally do not report an increase in fracture risk in patients treated with loop diuretics. The exception is a case–control study of elderly patients, in which the adjusted risk for hip fracture for current frusemide use was 3.9 (CI, 1.5–10.4). In summary, although loop diuretics may increase bone turnover and slightly accelerate bone loss, evidence for an increase in fracture risk is inconsistent. There are insufficient data to recommend additional screening or treatment beyond that of the general population.

**Protein Pump Inhibitors**

Proton pump inhibitors (PPIs) suppress acid secretion and are indicated for several common conditions including gastroesophageal reflux disease and nonsteroidal anti-inflammatory drug (NSAID)-induced peptic ulcers. Several potential mechanisms by which they might affect bone health have been proposed, including impaired intestinal calcium
absorption,\textsuperscript{151} a direct inhibitory effect on osteoclasts\textsuperscript{152} and stimulation of parathyroid hyperplasia.\textsuperscript{152} In vitro, PPIs have been shown to inhibit both osteoblast and osteoclast function.\textsuperscript{153} In some animal studies, omeprazole led to reduced absorption of calcium\textsuperscript{154} and reduced bone mass.\textsuperscript{155} In ovariectomized rats, omeprazole only altered bone turnover in the context of a low calcium diet.\textsuperscript{156} In humans, there have been conflicting results from studies examining the effects of PPIs on calcium and bone metabolism. In a study of postmenopausal women, omeprazole led to reduced absorption of calcium;\textsuperscript{151} however, subsequent studies in postmenopausal women and healthy young individuals did not confirm this finding.\textsuperscript{157,158} leading to speculation that these effects may be age and diet dependent. Several studies, including one in children, found no effect of omeprazole on bone turnover.\textsuperscript{159,160} Data regarding the effects on bone mineral density have been similarly variable. Although a short-term prospective study reported that PPI use was associated with a small reduction in BMD at the spine and hip,\textsuperscript{161} the majority of observational studies have not found PPI use to be associated with significant BMD loss.\textsuperscript{162} Only observational data are available to address the relationship between PPI use and fracture risk – collectively, they suggest that PPI use is associated with increased risk of hip fracture (OR 1·4) and vertebral fracture (OR 1·6).\textsuperscript{163} This association may be explained by the presence of traditional risk factors for fracture is users of PPIs.\textsuperscript{164} In summary, although they probably do not reduce BMD, there is evidence that PPIs may increase fracture risk, implying the coexistence of other risk factors for fracture. In the light of this, assessment of fracture risk in those receiving PPIs could be as for the general population, with management in line with general population guidelines.

Conclusions

There is an expanding list of drugs for which there are concerns regarding adverse skeletal effects. The effect of long-term use of glucocorticoid drugs to cause accelerated bone loss and increase the risk of fracture is well recognized.\textsuperscript{4} For some drugs (TKIs, calcineurin inhibitors and loop diuretics), the available data are inconsistent and/or do not support a definite adverse skeletal effect. Patients receiving these drugs can be managed in line with guidelines for the general population (\textsuperscript{1}). Other drugs (SSRIs, antipsychotics drugs, AEDs and PPIs) do not seem to affect bone metabolism or BMD, but there is evidence for increased fracture risk. However, the evidence is limited to observational data, and any relationship may be attributable either to nonbone effects of the drug or effects of the underlying condition to increase fracture rate. In these patients, evaluation for other risk factors for fracture and management of these risk factors should be considered. In a third group (depot MPA, chemotherapy and ART), there is evidence for increased bone loss and/or fracture, but the patient population is generally at low risk for fracture. In these cases, patients may require an assessment of risk, but will rarely require specific treatment for fracture risk reduction. In the last group (aromatase inhibitors, GnRH agonists and thiazolidinediones), there is evidence of increased risk of bone loss and/or fracture, and the drugs are more frequently prescribed to individuals at higher baseline fracture risk. Patients receiving these drugs require risk assessment and those at high risk of fracture should receive alternative treatments (or "add-back" HRT in the case of GnRH agonists) or, if necessary, specific treatment for osteoporosis.
### Table 2. Summary of management recommendations

<table>
<thead>
<tr>
<th>Example drugs</th>
<th>Evidence for risk</th>
<th>Management recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyrosine kinase inhibitors</td>
<td>No adverse skeletal effect or data inconsistent</td>
<td>Manage as per general population</td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop diuretics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective serotonin re-uptake inhibitors</td>
<td>Evidence for increased fracture risk but fracture risk seems to relate to nonbone effects of the drug or effects of the underlying condition</td>
<td>Evaluate for other risk factors for fracture and manage these risk factors</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-epileptic drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depot medroxyprogesterone acetate</td>
<td>Evidence for increased bone loss and/or fracture, but low risk population</td>
<td>Assessment of fracture risk, but will rarely require specific treatment</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiretroviral therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aromatase inhibitors</td>
<td>Evidence for increased risk of bone loss and/or fracture, and the drugs are more frequently prescribed to individuals at higher baseline fracture risk</td>
<td>Assessment of fracture risk and those at high risk should receive alternative treatments and/or specific treatment for osteoporosis.</td>
</tr>
<tr>
<td>Gonadotrophin hormone-releasing hormone agonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### References


