How common medicines can affect bone health

In this article...

- Review of common drugs that adversely affect bone health
- Mechanisms that have a negative effect on bone density
- Overview of prevention strategies

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Many people have weak bones and this is a global public health concern. Lifestyle factors can reduce bone density, as can some common drugs. This article describes some of these drugs, the conditions for which they may be prescribed and how they can threaten bone health. Strategies to reduce the risk of fracture and weak bones are outlined.

Weak bones are a major public health problem, with associated fractures affecting one in three women and one in five men aged over 50-years-old worldwide (Ström et al, 2011). Many factors threaten bone health, particularly in ageing populations. Lifestyle factors including diet, exercise, smoking and alcohol intake, morbidities such as cancer and endocrine disease, genetics and some common drug groups such as corticosteroids all contribute to low bone mass.

A continually renewing and adaptable tissue, bone is controlled by factors that alter the balance between bone-building cells (osteoblasts) and bone-resorbing cells (osteoclasts). Osteocytes, which are embedded in the bone matrix, regulate bone mass, receiving signals from hormones, local mediators and growth factors.

If an imbalance between bone breakdown and bone production arises, for example from a drop in oestrogen levels during the menopause, bone can lose mass and become brittle. Such changes are identified as a loss of bone mineral density on a dual-energy X-ray absorptiometry (DEXA) scan, with osteoporosis defined as a bone mineral density <2.5 standard deviations below the average for young, healthy adults (World Health Organization, 1994). This makes fracture more likely in events not usually associated with fracture such as a minor injury; this is sometimes called a low-energy/trauma fracture.

This article focuses on drugs that harm bone density; some common ones are set out in Table 1. The British National Formulary (British Medical Association and Royal Pharmaceutical Society, 2014) shows this in various ways, sometimes listing osteoporosis as a side-effect – for example, for corticosteroids and methotrexate – or describing an “increased risk of fracture” for example, with proton pump inhibitors (PPIs). If the BNF or the Summary of Product Characteristics (Electronic Medicines Compendium, 2013) do not mention bone mass loss as a side-effect, it should be taken to mean that there is insufficient evidence of an effect.

Corticosteroids

The systemic effects of corticosteroids, such as oral prednisolone, are the most common cause of secondary osteoporosis (osteoporosis resulting from another illness/condition) (Mazzotti et al, 2006). The systemic effects on bones have two phases, which are characterised as follows:

- Phase one - rapid bone loss from reduced calcium absorption from the gut and increased parathyroid hormone activity (enhanced osteoclastic activity raises serum calcium levels);
- Phase two - decreased bone formation and turnover, further compromising bone structure (Pennisi et al, 2006).

Keywords: Drug-induced osteoporosis/ Fracture/Bone health/Bone protection

This article has been double-blind peer reviewed

Weaker bones are a major public health issue; related fractures affect one in three women and one in five men aged >50 years worldwide

Lifestyle factors including diet, exercise, smoking and alcohol intake affect bone health

Common drug groups such as corticosteroids, proton pump inhibitors and heparins contribute to low bone mass

Nutritional advice, weight-bearing and strength-building exercise, stopping smoking and limiting alcohol intake can improve bone health

Prophylactic intervention is recommended with some drugs, such as corticosteroids, to reduce the risk of osteoporosis
Hormone therapy
As part of their role, oestrogens, androgens and corticosteroids regulate the production and lifespan of bone cells; it follows that hormone therapy could damage bone. Contraceptive drugs such as medroxyprogesterone acetate (Depo-Provera injection) are anti-oestrogenic and are associated with a reduction in bone mineral density in the first two to three years of use, which then stabilises (BMA and RPS, 2014). The lower oral doses of medroxyprogesterone acetate used to treat endometriosis and infertility. These drugs reduce oestrogen and androgen production and this is associated with loss of bone mass, although the literature does not contain clinical data on osteoporosis and fracture. Some forms of breast cancer require oestrogen-lowering drugs, such as letrozole, which is associated with osteoporosis, and fractures are common side-effects (McCaig et al, 2010; Roux et al, 2009). Anti-androgen drugs such as cyproterone acetate, used to treat hypersexuality and prostate cancer, can cause osteoporosis.

Proton pump inhibitors
Two mechanisms are proposed regarding how PPIs increase fracture risk (Lau et al, 2012; Roux et al, 2009). Decreased gastric-acid production could discourage the absorption of calcium salts but, although drugs such as cimetidine reduce gut acid, they do not have this effect (Yu et al, 2008). The current focus is on the effect that PPIs have on osteoclast cells. An inhibiting effect on osteoclasts could reduce bone breakdown; this could improve bone mass as osteoblasts continue to build bone but, as bone turnover is prevented, bone quality may deteriorate (Costa-Rodrigues et al, 2013). Investigations into the effect of PPIs on bone health have been carried out mainly in people aged over 70 years who are at risk of osteoporosis (Eom et al, 2011; Roux et al, 2009), but some studies have shown an impact on bone in other populations, such as post-menopausal female smokers who have been using PPIs for more than two years (Khalili et al, 2012).

Table 1: Common Drugs that Affect Bone Density

<table>
<thead>
<tr>
<th>Drug/drug group</th>
<th>Risk</th>
<th>Risk level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Osteoporosis, particularly in older people</td>
<td>Very common</td>
</tr>
<tr>
<td>Piroliotazone</td>
<td>Increased risk of fractures in women and older people</td>
<td>Rare</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>Increased risk of fractures, particularly when used at high doses for &gt;1 year in older people</td>
<td>Very rare</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>Osteoporosis, including osteoporotic fractures, BMD loss (frequency unknown)</td>
<td>Common</td>
</tr>
<tr>
<td>Medroxyprogesterone acetae</td>
<td>Reduction in BMD</td>
<td>Rare</td>
</tr>
<tr>
<td>Hormonal contraceptive</td>
<td>Osteoporosis (rare)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Cyproterone acetate</td>
<td>Osteoporosis</td>
<td>Rare</td>
</tr>
<tr>
<td>Triptorelin Gonadotrophins hormones (GnRH) agonists</td>
<td>Use of gonadotrophin hormones (GnRH) agonists may cause a reduction in bone mineral density</td>
<td>Not stated</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>Osteoporosis</td>
<td>Not stated</td>
</tr>
<tr>
<td>Low-molecular-weight heparins</td>
<td>Osteoporosis (risk lower with low-molecular-weight heparins than unfractionated heparin)</td>
<td>Rare</td>
</tr>
</tbody>
</table>

For drugs used in children, the effects are the same unless otherwise stated. Risk-level key: very common ≥10%; common ≥1% and <10%; uncommon >0.1% and <1%; rare < 0.1%; very rare <0.0001%; unknown (cannot be estimated from the available data)

BNF = British National Formulary. SPC = summary of product characteristics

Source: British Medical Association and Royal Pharmaceutical Society (2014); Electronic Medicines Compendium (2013)
TABLE 2. GUIDELINES FOR BONE PROTECTION

<table>
<thead>
<tr>
<th>Drug</th>
<th>Guideline (where available, source stated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Doses of &gt;75mg prednisolone or equivalent per day &gt;3 months for any age, assess and consider prophylaxis with bisphosphonate (&gt;65 most at risk) (Clinical Knowledge Summaries, 2013)</td>
</tr>
<tr>
<td></td>
<td>No drug protection information stated for children (BNF for Children) (BMA and RPS, 2013)</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Assess for fracture risk before starting (CKS, 2013)</td>
</tr>
<tr>
<td>Letrozole</td>
<td>Assess susceptibility to osteoporosis (bone mineral density) before treatment and at regular intervals (BMA and RPS, 2014)</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Monitor bone density if given for &gt;6 months (BMA and RPS, 2014)</td>
</tr>
</tbody>
</table>

PPIs are sometimes used to offset the gastrointestinal side-effects of bisphosphonate drugs used to treat osteoporosis. Using PPIs in this instance may make bisphosphonates less effective (Abrahamsen et al, 2011). National Institute for Health and Care Excellence guidelines recommend caution is exercised when prescribing PPIs and bisphosphonates together (NICE, 2008).

**Anti-epileptic drugs**
Fractures in people taking anti-epileptic drugs are reported for phenytoin, carbamazein and primidone (Ali et al, 2004; Ensrud et al, 2004) but the BNF states fracture is a risk for carbamazepine only. These drugs are thought to accelerate the metabolism of vitamin D, which lowers the availability of calcium for bone formation (Ali et al, 2004; Ensrud et al, 2004). Other biochemical abnormalities found in patients taking anti-epileptic drugs that may affect bone health include:

- Hypocalcaemia;
- Hypophosphataemia (low phosphate);

**Drugs for diabetes**
Pioglitazone is used to treat people with type 2 diabetes who are resistant to insulin; it works by improving the sensitivity of muscle and fat cells (adipocytes) to insulin. However, the stem cells that make fat cells and bone-building cells share the same precursor. Pioglitazone increases the production of the more insulin-responsive fat cells and, as a consequence, fewer bone-building cells are produced, leading to osteoporotic changes (Rzonca et al, 2004).

**Heparin**
Long-term use of heparin is associated with bone density loss (Bhandari et al, 1998). High-dose whole heparin (unfractionated) inhibits bone-building cells while encouraging activity in bone-absorbing cells (Hansen and Vondracek, 2004). The osteoporotic risk is lower with low-molecular-weight heparins as the smaller fragments have less binding capacity to bone cells (Hirsh et al, 2008).

**Managing risk**
The following lifestyle factors can all help to improve bone health:

- Sound nutritional advice;
- Engaging in weight-bearing and strength-building exercise;
- Stopping smoking;

There are some drugs – for example, corticosteroids – for which prophylactic intervention using a bisphosphonate drug (which slows down bone resorption) is recommended to reduce osteoporosis risk. However, as Table 2 shows, in most cases there is no guide to risk reduction. When the risk of fracture is common, for example with pioglitazone, counselling may be appropriate as well as monitoring through clinical reviews and DEXA scans.

**Conclusion**
Drugs that are commonly prescribed can have a detrimental effect on bone health and their risks and benefits must be considered and discussed with patients. Nurses need to consider the implications of the side-effects of drugs and have knowledge so they can discuss these with their patients. NT