Fracture risk associated with drugs: a search for candidate drugs in the same way as for candidate genes

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Oral corticosteroids increase fracture risk, while topical corticosteroids do not. The effect of the corticosteroids is probably linked to negative effects on calcium metabolism, with a negative calcium balance and effects on gonadal function. Insulin and oral antidiabetics, except glitazones, decrease fracture risk by countering the negative skeletal effects of diabetes. Glitazones appear to be associated with an increased risk of fractures, which is probably linked to their negative effects on bone cells. Antithyroid drugs *per se* decrease fracture risk by inducing euthyroidism. Some, but not all, antiepileptic drugs are associated with a very limited increase in fracture risk. The mechanisms probably relate to liver induction with vitamin D deficiency. Anxiolytics and neuroleptics are associated with a very limited increase in fracture risk, which is probably linked to the risk of falls. Among antidepressants, selective serotonin-reuptake inhibitors carry a larger increase in relative fracture risk than tricyclic antidepressants. Lithium is associated with a decrease in fracture risk, which may be the result of an effect on bone metabolism, but further research is required. Most, but not all, opioids are associated with an increase in fracture risk, which is probably due to an increased risk of falls owing to dizziness. Some, but not all, NSAIDs are associated with an increase in fracture risk, which is probably linked to dizziness. Proton-pump inhibitors are associated with an increased fracture risk, which is probably linked to decreased calcium absorption with secondary hyperparathyroidism, while histamine H2 receptor antagonists are associated with a decrease in fracture risk, although the mechanism of the latter is unknown. Histamine H1 receptor antagonists and oral contraceptives are not associated with significant changes in fracture risk.

Drugs are in widespread use to treat a number of common and less common conditions. However, besides their desired effects on the skeleton, that is, to prevent fractures in patients with osteoporosis, they may have a number of side effects on the skeleton, calcium metabolism, bone mineral density (BMD) and the risk of traumas (e.g., fractures). Some of these side effects may be detrimental, with decreased BMD and increased fracture risk. However, some drugs may affect signal systems in calcium metabolism, which may lead to positive effects on the skeleton and a reduced risk of fractures. These effects may be important, as differences in the skeletal effects of different drugs within the same class (e.g., diuretics) may be important when choosing the optimal treatment for older patients who are at a high risk of fractures. Choosing, for example, a thiazide diuretic, which has been associated with a decrease in fracture risk [1], may be preferable to, for example, a loop diuretic, which is associated with an increased fracture risk [2,3], in an elderly subject with heart failure and concomitant osteoporosis. Drugs with hitherto unknown positive effects on bone metabolism and fracture risk may lead to development of new therapeutic principles for treating calcium-metabolism disorders and preventing fractures [4]. The search for such drugs can be compared with the search for candidate genes for discovering new therapeutic principles. Due to the widespread use of drugs, even small changes in fracture risk may have considerable effects on a population level.

A change in fracture risk compared with the general population can be brought about through alterations in bone biomechanical competence (bone strength) or altered risk of traumas (e.g., falls leading to fractures). As a major part of the biomechanical competence is determined by BMD, alterations in BMD are important. However, changes in fracture risk may also be brought about by alterations in, for example, the risk of falls, as even the strongest bone will fracture if subject to a major force, such as that resulting from a fall from a substantial height or an automobile accident.

Keywords: antidepressants, antidiabetics, antiepileptic drugs, antithyroid drugs, corticosteroid, fracture, insulin, lithium, morphine

future medicine part of fsg

Besides the effects of the drugs *per se* on bone metabolism and BMD and potential side effects affecting fracture risk (risk of falls from sedation, dizziness or effects on postural balance or cardiovascular system, such as heart rhythm or blood pressure), any effects that the drugs may have in modulating the disease for which they are administered may also have an influence on the risk of fractures.

In order to ease overview, the drugs have been categorized into:

- Drugs with endocrine actions (including corticosteroids)
- CNS-active drugs
- Cardiovascular drugs
- Analgesics (divided into weak and strong analgesics)
- Other drugs

In the analysis, the emphasis has been put on the effects on overall fracture risk and the known effects on BMD and risk of traumas. Drugs known to or developed to affect bone metabolism (bisphosphonates, selective estrogen receptor modulators, strontium, estrogen–progestin therapy [EPT], calcitonin and parathyroid hormone) will not be discussed. As fractures are the clinical end point of interest, tables have been constructed (**Tables 1–6**) on available studies showing overall fracture risk (risk of any fracture) compared with controls, and risk of major osteoporotic fractures that are typically linked to reduced BMD (hip, forearm and spine fractures). The tables present a selection of prior studies on drugs associated with fracture risk within the categories mentioned. They present the relative risk of fractures among drug users compared with nonusers (relative risk [RR] and 95% confidence intervals [CI]).

Drugs with endocrine effects

These drugs are principally the corticosteroids, insulin and oral antidiabetic agents and agents used to treat thyroid disorders.

As it is well-known that EPT, and estrogen alone therapy (ET), has positive effects on BMD and fracture risk [5–9], these will not be discussed further. Growth hormone has also been shown to have positive effects on BMD, and this will not be discussed further [10].

Corticosteroids

Corticosteroids have a number of detrimental effects on the skeleton. These include [11,12]:

- Decreased intestinal calcium absorption and decreased renal calcium reabsorption, leading to a negative calcium balance
- Decreased synthesis and secretion of gonadal steroids
- Possibly increased parathyroid hormone (PTH) sensitivity
- Alterations in insulin-like growth factor (IGF) synthesis and actions
- Increased osteoclastic bone resorption and decreased bone formation, with decreased bone remodeling
- Decreased formation of collagen matrix

The corticosteroids affect trabecular bone more than cortical bone, and their effects develop rapidly within the first months of therapy [13]. Corticosteroids are among the most frequent causes of secondary osteoporosis; 25% of patients on long-term corticosteroids may suffer a fracture [14,15], and 47% of hip and 72% of spine fractures occurring among users of oral corticosteroids and are attributable to the corticosteroids [16].

However, the disease for which corticosteroids are administered may also *per se* affect fracture risk, as seen, for example, with rheumatoid arthritis [17–19] and Crohn's disease [20,21], where inflammatory cytokines may play a role [22]. The effect of the underlying disease can be seen from the fact that fracture risk starts to increase before corticosteroids are initiated [23].

From large studies it seems that only orally administered corticosteroids increase fracture risk [23,24], while topical corticosteroids, in general, have no such effect (**Table 1**) [24–26]. The increase in fracture risk with oral corticosteroids seems linked to daily, rather than cumulative, dose [27]. This means that corticosteroids administered as intermittent series may be less detrimental than the same cumulative dose divided as a daily dose over a prolonged time interval [27]. This is probably why injected corticosteroids seemed less detrimental than daily oral corticosteroids [24]. The practical implication for further research is to devise dosing schemes for patients needing systemic corticosteroids, whereby shifting to intermittent administration as, for example, intravenous series may be less detrimental to bone, while still maintaining the same effect on the disease in question. Only in very large doses did inhaled corticosteroids appear to be associated with a small decrease in BMD [28] and increase in fracture risk [24]. One study even indicated that, upon adjustment for severity of the underlying

Table 1. Relative risk of fractures in patients receiving drugs with endocrine actions compared with controls.

Drug	Dose	RR (95% CI)				Ref.
		Any	*Hip*	*Forearm*	*Spine*	
Corticosteroids	***(mg/day)***					
Oral	<2.5	0.97 (0.93–1.91)	0.97 (0.87–1.08)	0.99 (0.89–1.09)	1.16 (0.95–1.41)	[24]
	2.5–7.49	1.15 (1.09–1.22)	1.27 (1.11–1.44)	1.14 (0.98–1.33)	1.54 (1.18–1.99)	
	≥7.5	1.59 (1.49–170)	1.45 (1.25–1.69)	1.19 (0.99–1.43)	2.08 (1.54–2.79)	
Inhaled	<2.5	1.01 (0.97–1.04)	0.88 (0.78–1.00)	0.99 (0.90–1.09)	1.03 (0.84–1.26)	
	2.5–7.49	0.99 (0.93–1.06)	0.79 (0.66–0.95)	0.97 (0.82–1.16)	0.86 (0.62–1.19)	
	≥7.5	1.17 (1.00–1.38)	1.13 (0.68–1.87)	1.01 (0.70–1.64)	0.81 (0.36–1.82)	
Injected	<2.5	1.04 (1.01–1.07)	0.84 (0.77–0.91)	1.04 (0.97–1.12)	1.05 (0.91–1.22)	
	2.5–7.49	1.15 (0.82–1.61)	0.78 (0.28–2.21)	0.95 (0.37–2.43)	0.18 (0.02–1.47)	
	≥7.5	0.84 (0.43–1.64)	2.34 (0.38–14.2)			
Dermal	<2.5	1.00 (0.98–1.01)	0.90 (0.86–0.95)	0.99 (0.95–1.04)	0.99 (0.90–1.08)	
	2.5–7.49	0.91 (0.84–0.98)	0.96 (0.80–1.15)	0.87 (0.72–1.07)	1.13 (0.79–1.60)	
	≥7.5	1.09 (0.95–1.25)	0.98 (0.69–1.40)	1.15 (0.78–1.68)	0.81 (0.39–1.66)	
Locally in mouth	<2.5	0.95 (0.88–1.03)	0.93 (0.75–1.15)	1.12 (0.92–1.36)	1.01 (0.67–1.51)	
	2.5–7.49					
	≥7.5					
Nasal	<2.5	0.97 (0.94–1.00)	0.78 (0.70–0.86)	1.06 (0.99–1.14)	0.86 (0.52–1.11)	
	2.5–7.49	1.01 (0.68–1.50)	0.21 (0.03–1.61)	0.69 (0.20–2.46)	2.67 (0.40–17.8)	
	≥7.5	1.01 (0.42–2.42)	1.90 (0.12–30.8)	4.12 (0.20–83.8)		
Eye/ear	<2.5	0.97 (0.95–1.00)	0.89 (0.84–0.95)	0.95 (0.89–1.01)	1.03 (0.91–1.16)	
	2.5–7.49	0.84 (0.47–1.49)	0.39 (0.03–4.31)	0.57 (0.11–2.92)	1.73 (0.15–19.5)	
	≥7.5	1.11 (0.53–2.30)			1.10 (0.11–11.0)	
Rectally	<2.5	1.09 (0.92–1.30)	0.93 (0.55–1.57)	1.18 (0.74–1.87)	1.59 (0.59–4.25)	
	2.5–7.49	0.84 (0.55–1.44)	0.74 (0.18–3.12)	1.30 (0.40–4.28)	0.38 (0.03–5.17)	
	≥7.5	0.24 (0.06–1.03)		1.76 (0.15–21.2)		
Diabetes	***DDD***					
Insulin	<1000	1.04 (0.92–1.18)	1.18 (0.88–1.57)	0.99 (0.70–1.39)	0.53 (0.26–1.09)	[31]
	1000–1999	0.85 (0.73–1.00)	0.70 (0.69–1.01)	1.13 (0.74–1.72)	0.21 (0.09–0.52)	
	≥2000	0.88 (0.76–1.02)	0.80 (0.54–1.20)	0.94 (0.62–1.41)	0.49 (0.22–1.11)	
Metformin	<150	0.87 (0.76–1.01)	0.70 (0.49–1.02)	0.71 (0.48–1.04)	1.16 (0.58–2.34)	
	150–499	0.81 (0.71–0.94)	1.05 (0.76–1.46)	0.89 (0.60–1.31)	0.52 (0.23–1.14)	
	≥500	0.81 (0.70–0.93)	0.76 (0.55–1.04)	0.72 (0.49–1.06)	0.92 (0.45–1.87)	
Sulphonylureas	<400	0.88 (0.80–0.96)	0.86 (0.70–1.05)	0.91 (0.71–1.15)	0.89 (0.57–1.38)	
	400–1299	0.82 (0.75–0.90)	0.77 (0.63–0.95)	0.81 (0.63–1.03)	1.03 (0.65–1.62)	
	≥1300	0.86 (0.76–0.95)	0.74 (0.58–0.93)	0.82 (0.60–1.11)	0.88 (0.51–1.53)	
Other oral antidiabetics	<45	1.03 (0.79–1.36)	1.22 (0.64–2.33)	1.01 (0.53–1.95)	1.66 (0.52–5.31)	
	45–199	0.89 (0.68–1.17)	0.90 (0.49–1.65)	0.61 (0.25–1.48)	0.33 (0.04–2.81)	
	≥200	1.17 (0.90–1.52)	1.27 (0.69–2.33)	1.43 (0.77–2.65)	0.92 (0.28–3.05)	
Glitazones (thiazolidinediones)		1.74 (1.31–2.31)				[32]
Thyroid	***DDD/day***					
Antithyroid drugs	<0.4	0.84 (0.75–0.95)	0.66 (0.51–0.85)	0.83 (0.63–1.11)	1.53 (0.88–2.65)	[42]
	0.4–0.659	0.79 (0.69–0.91)	0.88 (0.67–1.15)	0.87 (0.63–1.22)	0.95 (0.47–1.92)	
	≥0.66	0.84 (0.73–0.95)	0.87 (0.67–1.17)	0.81 (0.60–1.10)	1.38 (0.72–2.63)	
Levothyroxine	<0.4	1.01 (0.92–1.10)	0.98 (0.80–1.19)	1.08 (0.88–1.32)	0.84 (0.53–1.33)	
	0.4–0.659	0.91 (0.83–0.99)	0.87 (0.71–1.06)	0.92 (0.75–1.14)	0.77 (0.47–1.27)	
	≥0.66	0.94 (0.87–1.02)	0.84 (0.69–1.02)	0.91 (0.76–1.10)	0.65 (0.42–1.01)	

**Prednisolone equivalents.*

CI: Confidence interval; DDD: Defined daily dose; RR: Relative risk.

disease, no increase in fracture risk was present [26]. Topical corticosteroids, such as dermal preparations and preparations used locally in the mouth, in the eyes, ears and nose, and rectally, were not associated with an increased risk of fractures [24], probably owing to low absorption into systemic circulation and the low and intermittent doses used. For oral corticosteroids, an increase in fracture risk was seen with more than 2.5 mg/day [23,24], which equals approximately 900 mg/year (2.5 mg/day × 365 days/year). However, the increase in fracture risk was rather rapid and seen within 1 month of initiation of prednisolone therapy [23]. Patients undergoing prolonged oral prednisolone therapy should thus be considered for preventive measures against osteoporosis. One example could be oral prednisolone for chronic obstructive pulmonary disease (COPD), where prednisolone 40 mg/day for a 10-day course would result in prednisolone 400 mg. Two such courses per year would be close to the limit of 900 mg of prednisolone and would thus indicate that considerations for bone mineral measurements and initiation of antiresorptive therapy should be made.

The major aims for further research are to develop and test safe algorithms to reduce the use of oral prednisolone, to shift use to topical applications, and to test intermittent use, to examine if this can reduce skeletal complications without compromising the effect on the disease for which the drugs are prescribed. The major clinical implications are extensive screening for risk factors, including measurements of BMD before and during corticosteroid therapy, in order to select patients for preventive treatment against osteoporosis.

Drugs to treat diabetes mellitus

Type 1 diabetes mellitus (T1D) is associated with decreased BMD and increased fracture risk [29], while patients with Type 2 diabetes (T2D) have increased BMD but also increased risk of fractures [29]. The difference between T1D and T2D in BMD is linked to differences in BMI, as patients with T2D tend to be overweight, while patients with T1D tend to be normal weight or even underweight [29]. The overweight may also be the reason why patients with T2D have a smaller excess fracture risk than patients with T1D [29]; however, the patients with T2D still have a higher fracture risk than normal controls. The decrease in BMD and increase in fracture risk in T1D is linked to a number of pathophysiological factors, including hypercalciuria due to hyperglycemia, impaired vitamin D metabolism (especially in patients with renal impairment), altered glycation of collagen, increased risk of falls due to hypoglycemia and impaired vision [30]. These factors may also explain why patients with T2D have an increased fracture risk despite their greater average weight.

Table 1 shows a trend towards a decrease in fracture risk with all types of drugs used to treat diabetes, irrespective of whether they were insulin or oral antidiabetic agents. This could indicate that the drugs counter the detrimental effects of diabetes on the skeleton, thus reducing fracture risk, rather than possessing bone-anabolic effects *per se*. Metformin acts by increasing insulin sensitivity and by decreasing glucose absorption and decreasing gluconeogenesis in the liver. Metformin thus does not increase insulin secretion, as the sulphonylureas do. Metformin therefore cannot act on bone via an increase in insulin. Patients with T1D have absolute insulinopenia and require insulin to maintain insulin levels. Insulin treatment thus partially restores normal insulin levels. Patients with T2D are insulin resistant, that is, they may have increased levels of insulin, which is anabolic. The effect of decreasing fracture risk in both T1D and T2D thus points at an indirect effect mediated through the antidiabetic effects [31].

However, as the only group of drugs to treat diabetes, the glitazones (thiazolidinediones) have been associated with an increase in fracture risk [32], probably as a class effect [33]. The glitazones have negative effects on bone marrow cells [34] and have been associated with a decreased BMD [35] and an increased risk of fractures [32].

The main implication for further research is to identify the exact mechanisms of action for the negative effects of glitazones in order to prevent fracture risk.

Drugs to treat thyroid disorders

Hyperthyroidism is accompanied by an increased fracture risk that decreases after euthyroidism is achieved [36,37]. In the same way, BMD is decreased at the time of diagnosis and increases to normal levels when euthyroidism is achieved [38]. The mechanism behind this is increased bone turnover and a negative calcium balance during hyperthyroidism, which is reversed upon achievement of euthyroidism [39]. In patients with hypothyroidism a transient decrease in BMD is observed when substitution with levothyroxine is initiated [37,40]. In the same way, a transient increase in fracture risk is observed [37,41,42].

Table 1 shows that antithyroid drugs are associated with a decrease in fracture risk. However, no clear dose–response relationship was observed. The decrease is probably more the result of the normalization of the hyperthyroidism rather than a bone-anabolic effect of the antithyroid drugs *per se*. Levothyroxine was *per se* not associated with any change in fracture risk. The transient increase in fracture risk after initiation of levothyroxine may thus be linked to the replacement of old bone with new bone due to the normalization of the thyroid hormone levels, rather than a negative effect of levothyroxine *per se*. When thyroid-stimulating hormone is kept within normal range, BMD is not decreased in postmenopausal women substituted with levothyroxine [43]. However, suppression of thyroid-stimulating hormone leads to decreased BMD and thus, potentially, increased fracture risk [43].

CNS-active drugs

This is a large group of drugs with several effects on calcium-metabolism pathways and postural balance.

Antiepileptic drugs

Some antiepileptic drug (AEDs), especially among the older AEDs, may induce liver enzymes and thus lead to vitamin D deficiency through increased catabolism, and thus decrease BMD [44]. Use of AEDs for more than 2 years, and especially use of liver-enzyme inducing AEDs, may be linked to a decrease in BMD [45]. However, the decrease in BMD is limited and does not explain the increase in fracture risk seen in patients with epilepsy [44]. A recent case–control study using data from the UK General Practice Research Database, including 1018 cases (first fracture under AED) and 1842 matched controls, found that the risk of fractures increased with cumulative duration of exposure to drugs (risk higher in women) without difference between cytochrome P450 inducers and noninducers [46]. Most of the increase in fracture risk seems linked to seizures that lead to traumas [44]. AEDs that decrease seizure frequency may thus actually result in a net decrease in fracture risk. Some AEDs, especially among the older drugs, are *per se* associated with a small increase in fracture risk (Table 2) [47]. Overall, most AEDs, especially among the newer AEDs, seem relatively safe in terms of fracture risk [44].

As most studies on AEDs have been performed in children, further research in adults, in particular on the newer AEDs, is needed.

Antidepressants

Older antidepressants, such as the tricyclic antidepressants, have been associated with an increased risk of fractures through an increased risk of falls. However, in general, patients with depression may have a decreased BMD [48,49]. The mechanisms behind this may be diverse, but could be linked to decreased physical activity and decreased exposure to the sun with decreased vitamin D levels, although falls are also an important risk factor [50]. The newer selective serotonin-reuptake inhibitors (SSRIs) have also been associated with decreased bone growth [51] and an increased risk of fractures (Table 2) [52] and falls [53]. The SSRIs may have selective effects on bone cells [51].

The increase in relative fracture risk seems to be higher with SSRIs than with tricyclic antidepressants [52]. The reasons for this are not known in detail, but may give rise to concern due to the widespread used of antidepressants.

The group of other antidepressants did not seem to be associated with an increased risk of fractures (Table 2) [52]. However, more research is needed before definitive conclusions can be drawn.

The main focus for further research is to identify the mechanisms behind the effects of SSRIs on bone, to identify whether fracture risk is in fact higher than with tricyclic drugs, and to see if differences exist between the various SSRIs and if fracture risk is truly lower with the group of other antidepressants.

Anxiolytics & sedatives

These drugs may be associated with an increased risk of falls and thus an increased risk of fractures [52]. An increased fracture risk was observed at all doses without a dose–response relationship (Table 2). These findings were confirmed by a further study finding no association between hip-fracture risk and dose of antipsychotics [54]. Most studies on the use of benzodiazepines have confirmed a weak trend towards an increase in hip and spine fractures [55,56] due to injuries [57]. The small increase with no particular dose–response relationship may be due to the fact that at the initiation of the treatment, when small doses are administered, the patients are more susceptible to the effects of the drugs than when they have been taking them for a while. At higher doses, an effect on postural balance may still be seen, but

Table 2. Relative risk of fractures in patients receiving CNS-active drugs compared with controls.

Drug	Dose	RR (95% CI)				Ref.
		Any	*Hip*	*Forearm*	*Spine*	
Antiepileptic drugs	***Ever use***					
Carbamazepine		1.18 (1.10–1.26)	1.33 (1.13–1.58)	1.05 (0.88–1.25)	0.91 (0.63–1.30)	[47]
Clonazepam		1.27 (1.15–1.41)	1.91 (1.43–2.56)	1.38 (1.06–1.80)	1.71 (0.99–2.96)	
Ethosuximide		0.75 (0.37–1.52)	1.25 (0.06–23.5)			
Phenobarbital		1.79 (1.64–1.95)	1.69 (1.34–2.15)	1.93 (1.53–2.43)	2.03 (1.31–3.15)	
Phenytoin		1.20 (1.00–1.43)	1.41 (0.94–2.15)	1.10 (0.71–1.70)	1.34 (0.47–3.83)	
Lamotrigine		1.04 (0.91–1.19)	1.30 (0.85–2.00)	0.81 (0.55–1.21)	2.47 (1.13–5.39)	
Oxcarbazepine		1.14 (1.03–1.26)	1.48 (1.11–1.97)	1.31 (0.99–1.74)	1.13 (0.69–1.84)	
Primidone		1.18 (0.95–1.48)	1.10 (0.66–1.85)	1.06 (0.62–1.81)	3.82 (1.16–12.6)	
Tiagabine		0.75 (0.40–1.41)	4.01 (0.35–45.5)	0.39 (0.09–1.71)		
Topiramate		1.39 (0.99–1.96)	0.90 (0.20–4.03)	1.12 (0.35–3.55)	0.40 (0.06–2.78)	
Valproate		1.15 (1.05–1.26)	1.06 (0.84–1.34)	1.28 (1.00–1.55)	1.07 (0.68–1.70)	
Vigabatrin		0.93 (0.70–1.22)	0.52 (0.09–3.19)	1.13 (0.53–2.40)	2.49 (0.68–9.19)	
Antidepressants	***DDD/day***					
Tricyclic drugs	<0.15	1.07 (1.02–1.13)	0.90 (0.79–1.02)	0.99 (0.86–1.14)	1.08 (0.85–1.38)	[52]
	0.15–0.74	1.14 (1.07–1.21)	1.39 (1.20–1.61)	1.12 (0.95–1.32)	1.48 (1.10–1.98)	
	≥0.75	1.27 (1.13–1.42)	1.35 (0.99–1.84)	1.30 (0.97–1.75)	1.98 (1.22–3.22)	
SSRI	<0.15	1.13 (1.09–1.18)	1.32 (1.20–1.46)	1.08 (0.98–1.21)	1.25 (1.03–1.52)	
	0.15–0.74	1.32 (1.27–1.37)	1.91 (1.75–2.09)	1.32 (1.19–1.47)	1.54 (1.27–1.87)	
	≥0.75	1.40 (1.35–1.46)	2.02 (1.85–2.20)	1.62 (1.46–1.79)	1.56 (1.29–1.88)	
Other antidepressants	<0.15	1.10 (1.03–1.17)	1.30 (1.12–1.52)	0.98 (0.83–1.15)	1.27 (0.94–1.72)	
	0.15–0.74	0.97 (0.91–1.03)	0.97 (0.84–1.12)	0.87 (0.73–1.03)	1.31 (0.97–1.77)	
	≥0.75	1.09 (1.01–1.18)	1.13 (0.95–1.34)	1.20 (0.98–1.49)	1.48 (1.03–2.13)	
Anxiolytics	***DDD/day***					
	<0.1	1.07 (1.05–1.10)	1.06 (0.99–1.14)	1.03 (0.97–1.10)	1.10 (0.97–1.25)	[52]
	0.1–0.33	1.09 (1.05–1.12)	1.20 (1.11–1.29)	1.01 (0.93–1.09)	1.38 (1.18–1.61)	
	≥0.33	1.10 (1.07–1.13)	1.22 (1.15–1.30)	1.05 (0.98–1.12)	1.34 (1.18–1.52)	
Neuroleptics	***DDD/day***					
	<0.1	1.11 (1.07–1.16)	1.23 (1.13–1.35)	1.07 (0.97–1.18)	1.16 (0.97–1.39)	[52]
	0.1–0.33	1.20 (1.12–1.28)	1.76 (1.54–2.01)	1.02 (0.85–1.24)	1.27 (0.91–1.78)	
	≥0.33	1.18 (1.12–1.25)	1.83 (1.63–2.05)	1.16 (1.00–1.35)	1.22 (0.94–1.58)	
Lithium	***DDD***					
	<250	0.96 (0.78–1.18)	0.75 (0.42–1.36)	1.61 (0.94–2.75)	2.32 (0.75–7.17)	[4]
	250–849	0.71 (0.57–0.89)	0.78 (0.47–1.30)	0.61 (0.33–1.16)	0.90 (0.25–3.26)	
	≥850	0.72 (0.59–0.89)	0.85 (0.52–1.40)	0.58 (0.34–0.99)	0.31 (0.10–1.02)	

CI: Confidence interval; DDD: Defined daily dose; RR: Relative risk; SSRI: Selective serotonin-reuptake inhibitor.

patients who have been treated for some time may display adaption. Care should be taken when prescribing these drugs to patients with a decreased postural balance and who are at an increased risk of falls.

Neuroleptics

These drugs have antidopaminergic effects and may thus increase serum prolactin, which in turn may lead to a decrease in BMD [58]. On the other hand, the drugs may also be associated with anitcholinergic effects and a decreased postural balance. A limited increase in fracture risk without any dose–response relationship was observed (**Table 2**). This, again, could point at an increased risk of falls with low doses after initiation of the drugs.

Lithium

Lithium, which is used to prevent manic–depressive episodes and treat episodes of mania, has an interesting relationship with the skeleton and calcium metabolism. Patients treated with lithium had a decrease in fracture risk in contrast to patients treated with other types of psychotropic

drugs (Table 2). A recent case–control study within the UK General Practice Research Database also found that current use of lithium was associated with a decreased risk of fractures (adjusted odds ratio [OR]: 0.75; 95% CI: 0.64–0.88); however, the risk reduction did not vary with cumulative duration of therapy [59]. Lithium has several effects on calcium metabolism that are potentially interesting, indicating that it may have bone-anabolic properties. Lithium increases serum PTH, which may have a bone-anabolic effect [60]. Furthermore, lithium affects Wnt signaling, which may also have bone-anabolic effects [61]. Lithium only seems to possess bone-anabolic effects in low doses and not in high doses [4]. Lithium in low doses may thus be a candidate for new osteoporosis therapies. However, more research is needed.

Cardiovascular drugs

Cardiovascular drugs have many and diverse effects on calcium metabolism.

Diuretics

These drugs alter renal calcium handling and lower blood pressure. Thiazide diuretics decrease calcium excretion in the urine, whereas loop diuretics increase calcium excretion. From this point of view, BMD should increase with thiazide diuretics and fracture risk should decrease, while BMD should decrease and fracture risk should increase with loop diuretics. One randomized, controlled trial did show a decrease in BMD with loop diuretics [3], while an observational study reported an increased fracture risk with loop diuretics (Table 2) [2]. However, fracture risk tended to decrease with increasing doses of loop diuretics, perhaps due to adaptive mechanisms. With thiazide diuretics, a dose–response relationship was seen with decreasing fracture risk with increasing dose, probably due to the calcium-conserving effect. In elderly osteoporotic subjects, thiazides may perhaps be preferred over loop diuretics if possible.

Antihypertensive drugs

This is a class of many different types of drugs (Table 3) with various pharmacodynamic effects on the cardiovascular system. Early studies indicated that β-blockers decreased fracture risk and it was speculated whether this was the result of an effect on the β-adrenergic receptors in the osteoblasts [62]. A recent study confirmed the protective effect of β-blockers in postmenopausal women, illustrated by a reduction of fracture risk at femoral neck, with higher BMD and a better trabecular micro-architecture [63]. However, recent research has demonstrated that a decreased fracture risk seems to be a class effect of all antihypertensives (Table 3) [64]. This seemingly fracture-reducing potential may be the result of the antihypertensives correcting negative calcium-metabolism effects of hypertension. It has actually been shown that patients with increasing blood pressure tend to have lower BMD [65]. The exact nature of the mechanisms behind the apparent fracture-reducing potential of antihypertensive drugs is not known. The class effect on fracture risk may be one explanation why the fracture risk decreased with increasing doses of loop diuretics (see earlier) – the loop diuretics have negative effects on calcium balance, but these effects are offset by a general positive effect on fracture risk by the blood pressure lowering.

The main focus is identifying the mechanisms of action on fracture risk for the antihypertensive drugs.

Vitamin K antagonists

Vitamin K is an essential part of bone formation as it is used in the carboxylation of osteocalcin [66], a protein that is a vital part of bone formation. Lack of vitamin K leads to undercarboxylation of osteocalcin and a potential increase in fracture risk [66]. However, on a population scale, no larger changes in fracture risk were observed, and there was no dose–response relationship for fracture risk. This could indicate that the doses used were in a range that did not significantly affect bone turnover in a clinical setting. The small increase for low doses may be due to other factors linked to the underlying disease for which vitamin K antagonists were administered (confounding by indication).

Cholesterol-lowering drugs

These drugs have effects on the mevalonate pathway in the same way as bisphosphonates, and thus potentially possess antiresorptive effects and fracture-preventing effects [67]. Results from observational studies have indicated a lower fracture risk in users of statins than in controls (Table 3) [68]. No such effect was seen in users of nonstatin cholesterol-lowering drugs [68]. However, randomized, controlled trials have failed to demonstrate a decrease in fracture risk among users of statins [69]. A randomized, controlled trial failed to show a positive effect of simvastatin on hip and spine BMD [70]. However, a meta-analysis showed a small increase in hip but not in spine BMD, and a reduction in hip but not in spine fracture risk [71]. A further meta-analysis also showed a reduction in

Table 3. Relative risk of fractures in patients receiving cardiovascular drugs compared with controls.

Drug	Dose	RR (95% CI)				Ref.
		Any	*Hip*	*Forearm*	*Spine*	
Current use ≤1 year	***DDD***					
Thiazides	<1000	1.06 (1.02–1.10)	1.27 (1.17–1.38)	0.95 (0.86–1.04)	1.23 (1.04–1.47)	[1]
	1000–1999	0.80 (0.76–0.85)	0.88 (0.78–0.98)	0.79 (0.69–0.90)	0.96 (0.75–1.24)	
	≥2000	0.74 (0.71–0.78)	0.81 (0.73–0.90)	0.69 (0.61–0.78)	0.95 (0.75–1.21)	
Current use ≤1 year	***DDD/day***					
Loop diuretics	<0.25	1.43 (1.28–1.59)	1.75 (1.40–2.18)	1.10 (0.84–1.45)	1.94 (1.19–3.19)	[2]
	0.25–0.99	1.23 (1.18–1.30)	1.56 (1.42–1.71)	0.96 (0.85–1.09)	1.16 (0.92–1.44)	
	1.00–1.99	1.00 (0.95–1.04)	1.10 (1.01–1.20)	1.02 (0.91–1.15)	0.99 (0.81–1.22)	
	≥2	1.00 (0.95–1.06)	1.13 (1.03–1.25)	0.89 (0.77–1.02)	1.07 (0.84–1.37)	
Antihypertensives	***DDD***					
β-blockers	<75	0.95 (0.91–0.99)	1.03 (0.91–1.15)	1.03 (0.91–1.15)	0.91 (0.72–1.15)	[64]
	75–499	0.89 (0.85–0.93)	0.87 (0.78–0.97)	1.00 (0.89–1.11)	0.90 (0.72–1.11)	
	≥500	0.89 (0.85–0.93)	0.87 (0.78–0.97)	0.97 (0.86–1.09)	0.86 (0.68–1.07)	
Calcium channel blockers	<400	0.98 (0.94–1.03)	0.98 (0.89–1.08)	0.96 (0.86–1.07)	1.16 (0.95–1.42)	
	400–1399	0.93 (0.89–0.97)	0.91 (0.83–1.00)	1.07 (0.96–1.19)	0.81 (0.66–1.01)	
	≥1400	0.94 (0.90–0.98)	0.95 (0.86–1.04)	1.08 (0.97–1.21)	0.78 (0.63–0.96)	
ACE and ATII inhibitors	<400	0.98 (0.94–1.03)	0.88 (0.79–0.97)	1.08 (0.96–1.21)	1.07 (0.86–1.32)	
	400–1399	0.92 (0.87–0.96)	0.83 (0.75–0.93)	0.96 (0.84–1.08)	0.92 (0.72–1.17)	
	≥1400	0.95 (0.91–1.00)	0.96 (0.86–1.08)	0.93 (0.82–1.05)	0.91 (0.72–1.14)	
Vitamin K antagonists	***DDD***					
Current use	<100	1.49 (1.31–1.69)	1.43 (1.09–1.87)	1.42 (1.02–1.97)	1.50 (0.83–2.72)	[103]
	100–499	1.10 (0.99–1.23)	1.08 (0.86–1.36)	0.88 (0.65–1.20)	0.96 (0.58–1.58)	
	≥500	0.90 (0.82–1.00)	0.71 (0.67–0.89)	0.98 (0.75–1.27)	0.90 (0.60–1.36)	
Cholesterol-lowering drugs	***DDD***					
Statins	<100	0.83 (0.71–0.98)	0.82 (0.49–1.38)	0.90 (0.60–1.35)	0.45 (0.21–0.97)	[68]
	100–999	0.86 (0.80–0.93)	0.60 (0.47–0.76)	0.86 (0.72–1.04)	1.00 (0.70–1.44)	
	≥1000	0.91 (0.83–1.00)	0.48 (0.35–0.67)	0.95 (0.76–1.19)	0.68 (0.41–1.12)	
Nonstatins	<100	1.12 (0.89–1.42)	0.76 (0.35–1.64)	0.61 (0.30–1.24)	3.50 (0.98–12.6)	
	100–999	0.95 (0.74–1.22)	0.57 (0.22–1.44)	0.91 (0.48–1.74)	1.48 (0.53–4.16)	
	≥1000	0.90 (0.70–1.16)	1.32 (0.62–2.79)	0.61 (0.29–1.26)	0.79 (0.20–3.15)	
Anti-arrhythmics	***DDD***					
Digoxin	<250	1.18 (1.08–1.29)	1.60 (1.38–1.85)	1.09 (0.86–1.39)	1.13 (0.75–1.71)	[104]
	251–750	0.70 (0.64–0.76)	0.69 (0.59–0.80)	0.80 (0.64–1.00)	0.80 (0.55–1.17)	
	≥750	0.63 (0.59–0.67)	0.59 (0.53–0.67)	0.67 (0.56–0.79)	0.70 (0.52–0.93)	
Amiodarone	<250	1.41 (0.99–2.03)	1.69 (0.83–3.42)	0.98 (0.37–2.64)	1.59 (0.33–7.60)	
	251–750	1.45 (1.05–2.01)	1.53 (0.75–3.10)	2.59 (1.21–5.57)	12.2 (1.35–110))	
	≥750	1.40 (1.04–1.88)	1.52 (0.78–2.95)	1.62 (0.77–3.41)	2.22 (0.70–7.09)	
Current use	***DDD***					
Flecainide		1.12 (0.84–1.49)				
Quinidine		0.97 (0.77–1.22)				
Nicorandil		1.02 (0.69–1.51)				
Propafenone		1.08 (0.82–1.43)				
Sotalol		0.92 (0.83–1.03)				
Nitroglycerin	<20	0.91 (0.86–0.96)	0.90 (0.81–1.00)	0.93 (0.82–1.06)	0.94 (0.74–1.19)	[73]
	20–249	0.87 (0.82–0.91)	0.86 (0.77–0.96)	0.82 (0.72–0.95)	1.08 (0.85–1.37)	
	≥250	0.89 (0.84–0.94)	0.80 (0.72–0.99)	0.99 (0.86–1.14)	0.97 (0.76–1.23)	

ACE: Angiotensin-converting enzyme; ATII: Angiotensin 2 receptor; CI: Confidence interval; DDD: Defined daily dose; RR: Relative risk.

hip-fracture risk and a trend towards a reduction in nonvertebral fractures [72]. However, these meta-analyses were mainly based on observational, rather than randomized, controlled trials. The randomized, controlled trials did not show an effect of statins on fracture risk [72]; however, none of them were specifically designed to investigate this issue. These results thus stem from *post hoc* analyses. The seemingly positive effect of statins on fracture risk may therefore not be real, but further research is needed to establish whether a fracture-preventing effect is present or not.

Anti-arrhythmics

Table 3 shows that several types of anti-arrhythmics were not associated with fracture risk. However, two groups differed. Digoxin was associated with a decrease in fracture risk, while amiodarone was associated with an increase (**Table 3**). The mechanisms behind this difference are not entirely clear. One mechanism for the positive effects of digoxin may be a strengthening of the skeletal muscles in the same way as digoxin affects the smooth muscles of the heart, through its effects on the Na–K-ATPase, thus leading to a decreased risk of falls. However, this is, at present, only speculative, as only limited experimental evidence is present. The increased fracture risk in patients treated with amiodarone may perhaps be explained from deficiency in vitamin D – amiodarone leads to cutaneous photosensitivity, and patients are encouraged to protect their skin from the sun, thus leading to vitamin D deficiency. For both digoxin and amiodarone, more research is needed on the risk of fractures and mechanisms of action on the skeleton.

Nitroglycerin

Nitroglycerin appears to be associated with a decrease in fracture risk [73]. Previous studies have also demonstrated an increased BMD in users of nitroglycerin, possibly due to its effect as a nitric oxide donator [74]. However, one possibility is also that nitroglycerin has the same positive effects on the underlying cardiovascular disease as some of the other cardiovascular drugs mentioned above. As nitroglycerin represents an interesting principle with regards to fracture reduction via NO donation, more research is needed on the biochemical mechanisms of fracture-risk reduction and increase in BMD.

Heparin

Heparin has traditionally been associated with osteoporosis, with a decreased BMD [75,76] and a significant prevalence of vertebral fractures in pregnant women undergoing heparin therapy [77]. Low-molecular-weight heparin (LMWH) has been associated with a less negative effect on bone than unfractionated heparin [78], and recent research has been unable to detect a larger bone loss in LMWH-treated pregnant women than in normal pregnant women [79]. Up to a third of patients on long-term heparin treatment have a subclinical reduction in BMD [76].

The exact mechanism of action of heparin is not known, and several of the groups studied have been patients who *a priori* are at an increased risk of bone loss.

Analgesics

Like the cardiovascular drugs, this is a large group of drugs in frequent use. However, two major subgroups can be identified: strong analgesics, which are drugs derived from opium (morphine and opiates of various sorts, including partial antagonists and agonists); and weak analgesics, which mainly consist of NSAIDs, including acetylsalicylic acid (ASA) and acetaminophen.

Strong analgesics

These are based on morphine and derivatives. They may affect postural balance by inducing dizziness and thus lead to falls and fractures. Most, but not all, drugs in **Table 4** were associated with increased risk of fractures; however, no clear dose–response relationship was present. This may be owing to the fact that at larger doses, an adaptation takes place where the individual no longer experiences the same dizziness as was seen with the first dose of the drug. The reason for the discrepancies between the drugs was not obvious, as it was not linked to pharmacological properties [80]. More research is needed within the field on the mechanisms of the increased risk of fractures and the extent of the problem.

Weak analgesics

NSAIDs affect the prostaglandin system and may thereby potentially have anabolic properties on BMD [81]. However, no lowering of fracture risk was seen (**Table 5**). On the contrary, an increase in fracture risk was seen with some, but not all, types of NSAIDs [19]. The reason for the increase in fracture risk may be the altered postural balance and dizziness seen with some types of NSAIDs [82]. However, the differences could not readily be explained by the pharmacological properties of the various NSAIDs [19], and therefore more research is needed into the mechanisms of action.

Table 4. Relative risk of fractures in patients receiving strong analgesics compared with controls.

Drug	Dose	RR (95% CI)				Ref.
		Any	*Hip*	*Forearm*	*Spine*	
Opiates	***DDD***					
Morphine	<10	1.47 (1.37–1.58)	1.61 (1.39–1.86)	1.07 (0.87–1.30)	3.01 (2.17–4.18)	[80]
	10–89	1.48 (1.39–1.58)	1.35 (1.18–1.54)	1.23 (1.02–1.49)	2.76 (2.09–3.65)	
	≥90	1.27 (1.18–1.37)	1.36 (1.17–1.58)	1.03 (0.84–1.27)	1.97 (1.38–2.82)	
Fentanyl	<10					
	10–89	2.23 (1.89–2.64)	2.78 (2.04–3.78)	1.51 (0.93–2.45)	5.36 (2.43–11.8)	
	≥90	1.71 (1.48–1.97)	1.89 (1.43–2.50)	0.95 (0.62–1.47)	1.66 (0.93–2.94)	
Methadone	<10	1.39 (1.05–1.83)	1.06 (0.51–2.18)	1.22 (0.54–2.73)	0.99 (0.20–5.03)	
	10–89	1.37 (1.11–1.68)	0.77 (0.42–1.42)	0.83 (0.42–1.65)	3.84 (1.19–12.4)	
	≥90	1.46 (1.27–1.67)	1.22 (0.77–1.96)	1.69 (1.12–2.54)	1.21 (0.53–2.78)	
Oxycodone	<10	1.36 (1.08–1.69)	1.09 (0.63–1.91)	1.43 (0.84–2.46)	5.04 (1.64–15.5)	
	10–89	1.48 (1.23–1.77)	1.63 (1.07–2.48)	1.20 (0.74–1.94)	4.19 (1.91–9.20)	
	≥90	1.31 (1.07–1.60)	1.44 (0.96–2.17)	0.67 (0.36–1.25)	1.22 (0.52–2.86)	
Nicomorphine	<10	1.57 (1.38–1.78)	2.02 (1.52–2.68)	1.17 (0.81–1.70)	1.53 (0.81–2.89)	
	10–89	1.38 (1.16–1.64)	1.36 (0.95–1.94)	0.98 (0.60–1.59)	4.05 (1.61–10.2)	
	≥90	0.92 (0.68–1.25)	1.24 (0.64–2.42)	0.43 (0.19–0.96)	1.37 (0.49–3.84)	
Ketobemidone	<10	1.07 (1.02–1.13)	1.09 (0.96–1.24)	1.03 (0.90–1.18)	1.01 (0.79–1.28)	
	10–89	1.03 (0.97–1.10)	1.04 (0.91–1.19)	1.09 (0.92–1.29)	1.28 (0.97–1.68)	
	≥90	1.05 (0.97–1.13)	0.93 (0.79–1.10)	1.18 (0.97–1.44)	1.01 (0.69–1.47)	
Buprenorphine	<10	0.86 (0.79–0.95)	0.75 (0.59–0.96)	0.89 (0.69–1.15)	0.58 (0.35–0.95)	
	10–49	1.00 (0.89–1.14)	1.31 (0.94–1.81)	0.97 (0.68–1.38)	0.34 (0.15–0.78)	
	≥50	0.89 (0.77–1.04)	1.21 (0.82–1.79)	0.70 (0.43–1.14)	0.81 (0.39–1.69)	
Pethidine	<10	0.98 (0.89–1.08)	1.30 (1.04–1.63)	0.90 (0.69–1.17)	0.90 (0.53–1.52)	
	10–49	0.71 (0.59–0.86)	0.61 (0.40–0.93)	0.74 (0.46–1.18)	1.28 (0.57–2.89)	
	≥50	0.89 (0.71–1.11)	0.94 (0.55–1.62)	1.06 (0.60–1.85)	2.88 (0.76–10.8)	
Opioids	***DDD***					
Tramadol	<10	1.54 (1.49–1.58)	1.66 (1.53–1.80)	1.41 (1.31–1.52)	2.53 (2.18–2.93)	
	10–49	2.23 (2.16–2.33)	3.02 (2.78–3.27)	1.74 (1.58–1.92)	6.18 (5.28–7.23)	
	≥50	1.96 (1.89–2.04)	2.35 (2.17–2.55)	1.44 (1.29–1.60)	5.43 (4.55–6.47)	
Codeine	<10	1.16 (1.12–1.20)	0.93 (0.83–1.06)	1.25 (1.13–1.38)	1.14 (0.92–1.42)	
	10–49	1.20 (1.16–1.24)	1.10 (1.00–1.21)	1.10 (1.01–1.21)	1.50 (1.25–1.79)	
	≥50	1.14 (1.10–1.19)	1.18 (1.08–1.30)	1.10 (0.99–1.23)	1.38 (1.13–1.69)	
Dextropropoxyphene	<10	1.02 (0.90–1.16)	0.66 (0.47–0.91)	1.20 (0.85–1.70)	0.91 (0.46–1.78)	
	10–49	0.99 (0.98–1.10)	0.89 (0.73–1.10)	0.89 (0.68–1.15)	1.54 (0.91–2.59)	
	≥50	1.06 (0.98–1.14)	1.00 (0.85–1.17)	1.04 (0.85–1.28)	0.76 (0.52–1.13)	
Codeine + ASA	<20	0.94 (0.88–1.01)	0.89 (0.76–1.05)	0.99 (0.84–1.17)	1.26 (0.89–1.79)	
	20–79	1.03 (0.94–1.13)	1.11 (0.91–1.37)	1.00 (0.79–1.26)	0.92 (0.56–1.49)	
	≥60	0.94 (0.87–1.01)	0.87 (0.74–1.03)	1.15 (0.97–1.37)	0.64 (0.42–0.96)	

ASA: Acetylsalicylic acid; CI: Confidence interval; DDD: Defined daily dose; RR: relative risk.

In a murine femoral fracture model, a randomized, controlled trial compared the NSAID rofecoxib with placebo and found that the COX-2 inhibitor significantly reduced blood flow across the fracture gap and inhibited fracture repair [83]. Thus, an inhibition of angiogenesis might explain the inhibitory effect of NSAIDs on fracture repair.

Acetaminophen was also associated with an increased risk of fractures, the reason for this being unclear [19]. More research is thus needed.

Other drugs

Antacids

These drugs have several effects on bone metabolism. In theory, proton-pump inhibitors should decrease acid secretion from the osteoclasts and thus act as antiresorptive drugs [84]. However, no decrease, but rather an increase, in fracture risk was seen (**Table 6**). There may be several reasons for this. First, the concentration of proton-pump inhibitors in bone is very low after oral administration [84].

Table 5. Relative risk of fractures in patients receiving weak analgesics compared with controls.

Drug	Dose	RR (95% CI)
ASA	Last use ≤1 yr ago	0.92 (0.76–1.12)
Aceclofenac		1.09 (0.92–1.28)
Celecoxib		0.94 (0.84–1.08)
Diclofenac		1.39 (1.35–1.44)
Diflunisal		1.13 (0.85–1.50)
Etodolac		1.14 (1.06–1.22)
Flurofen		0.70 (0.32–1.55)
Ibuprofen		1.76 (1.72–1.81)
Indomethacin		1.22 (1.09–1.38)
Ketoprofen		1.17 (1.04–1.32)
Lornoxicam		1.74 (1.23–2.46)
Meloxicam		1.03 (0.85–1.26)
Nabumeton		1.16 (0.99–1.36)
Naproxen		1.37 (1.29–1.46)
Phenylbutazon		0.70 (0.41–1.18)
Piroxicam		1.19 (1.09–1.30)
Rofecoxib		1.02 (0.96–1.07)
Sulindac		0.73 (0.43–1.24)
Tenoxicam		1.32 (1.14–1.54)
Tiaprofen		0.87 (0.72–1.06)
Tolfenam		0.97 (0.85–1.12)
Acetaminophen		1.45 (1.41–1.49)

ASA: Acetylsalicylic acid; CI: Confidence interval; RR: Relative risk.
Data from [19].

Furthermore, the decreased acidity in the stomach may lead to calcium malabsorption, with a negative calcium balance and secondary hyperparathyroidism [85].

In contrast to proton-pump inhibitors, histamine H2 receptor antagonists were associated with a decreased fracture risk (**Table 6**). The reason for this is not entirely clear, but osteoclasts have histamine H2 receptors, and perhaps these drugs possess bone-anabolic properties [86]. However, the current evidence is preliminary, and more research is needed into the mechanisms of action and the extent of the problem before any firm conclusions can be drawn on the differences between proton-pump inhibitors and the histamine H2 receptor antagonists.

Other types of antacids are rather heterogeneous. Some contain bicarbonate and calcium and may thus have positive effects on bone, while others may contain aluminium, which may inhibit intestinal phosphate absorption, leading to impaired mineralization due to phosphate deficiency [87].

In contrast to histamine H2 receptor antagonists, histamine H1 receptor antagonists did not seem to affect fracture risk [87]. This may be owing to different effects on the osteoclasts [86].

Oral contraceptives

These are in wide use. They do not seem to affect fracture risk, and thus seem safe in terms of skeletal health. However, they do not appear to be useful in preventing fractures in younger women.

Chemotherapeutics

Patients with cancer may have osteoporosis owing to a number of reasons: malnutrition due to impaired food intake, hypogonadism from the disease *per se* or from the treatment (surgery, radiation or drug therapy), or production of cytokines or other hormones in the tumor. From available evidence for orally administered chemotherapeutics (methotrexate, cyclosporine, azathipoprine), these do not appear to be associated with fracture risk (**Table 6**). Selective estrogen receptor modulators such as tamoxifen are associated with an increased BMD and thus, potentially, a decreased risk of fractures [88–90]. However, one study indicated an increased risk of femoral-neck fractures in users of tamoxifen [91].

In contrast to tamoxifen, which possess bone-anabolic effects due to its partial estrogen-agonist effects, aromatase inhibitors decrease serum estradiol and thus increase the risk of fractures [92] and decrease BMD [93].

In the same way as the aromatase inhibitors, luteinizing hormone-releasing hormone agonists may induce hypogonadism and thus increase fracture risk, as is seen in men with prostate cancer [94].

Immunomodulators

These drugs are used in a variety of inflammatory disorders and to prevent rejection of solid-organ transplants (e.g., kidney, liver, heart). Patients undergoing organ transplantation have a rapid bone loss within the first year after transplantation, but even after this time, bone loss continues, particularly in the femoral neck, although discrepancies exist in the findings between studies [95–97]. Among this class of drugs, cyclosporine A has been associated with varying effects on BMD in organ-transplant recipients. Some studies have suggested that cyclosporine A may be associated with an

Table 6. Relative risk of fractures in patients receiving various drugs compared with controls.

Drug	Dose	RR (95% CI)				Ref.
		Any	*Hip*	*Forearm*	*Spine*	
Proton pump inhibitors	***DDD***					
	<25	1.16 (1.06–1.26)	1.51 (1.21–1.89)	0.89 (0.69–1.15)	1.44 (0.95–2.18)	[87]
	25–99	1.34 (1.26–1.42)	1.85 (1.61–2.13)	1.09 (0.93–1.28)	2.10 (1.60–2.75)	
	≥100	1.14 (1.09–1.19)	1.27 (1.15–1.40)	1.04 (0.93–1.16)	1.44 (1.18–1.75)	
Histamine H2 antagonists	***DDD***					
	<25	0.93 (0.84–1.03)	0.94 (0.67–1.30)	0.92 (0.68–1.23)	1.08 (0.63–1.84)	[87]
	25–99	1.02 (0.93–1.11)	0.73 (0.56–0.95)	1.11 (0.88–1.40)	1.13 (0.73–1.77)	
	≥100	0.88 (0.83-.093)	0.75 (0.65–0.85)	1.02 (0.89–1.18)	0.90 (0.69–1.17)	
Other antacids	***DDD***					
	<15	1.18 (1.01–1.38)	1.75 (1.22–2.50)	1.14 (0.73–1.78)	2.25 (1.10–4.64)	[87]
	15–59	1.95 (1.81–2.09)	2.93 (2.57–3.34)	1.27 (1.03–1.56)	3.98 (2.96–5.36)	
	≥60	1.00 (0.94–1.07)	1.23 (1.09–1.38)	0.92 (0.78–1.09)	1.15 (0.87–1.53)	
Histamine H1 antagonists	***DDD***					
	<10	1.07 (1.02–1.13)	0.96 (0.80–1.15)	1.02 (0.88–1.19)	1.04 (0.76–1.42)	[87]
	10–49	1.02 (0.98–1.05)	0.81 (0.73–0.90)	1.01 (0.92–1.10)	1.17 (0.89–1.39)	
	≥50	1.02 (0.99–1.06)	0.92 (0.82–1.03)	1.02 (0.93–1.12)	0.95 (0.78–1.16)	
Oral contraceptives	***DDD/day***					
	<25 years					[105]
	<0.30	0.97 (0.91–1.03)	1.16 (0.42–3.21)	0.96 (0.79–1.16)	1.05 (0.69–1.62)	
	0.30–0.99	0.96 (0.92–1.01)	1.38 (0.52–3.68)	1.02 (0.87–1.20)	1.08 (0.77–1.51)	
	≥1	0.92 (0.86–0.98)	0.37 (0.08–1.76)	0.87 (0.71–1.06)	0.74 (0.47–1.17)	
	25–49 years					
	<0.30	0.91 (0.82–1.00)	0.74 (0.33–1.69)	0.85 (0.67–1.09)	0.82 (0.34–1.95)	
	0.30–0.99	0.90 (0.77–1.05)	0.64 (0.12–3.57)	0.70 (0.47–1.05)	0.44 (0.07–2.94)	
	≥1	0.87 (0.64–1.18)		0.70 (0.32–1.53)		
	≥50 years					
	<0.30	0.92 (0.77–1.10)	0.79 (0.46–1.35)	0.85 (0.57–1.29)	0.85 (0.34–1.95)	
	0.30–0.99	0.69 (0.45–1.05)	0.77 (0.16–3.59)	1.52 (0.66.3.46)		
	≥1	0.62 (0.27–1.41)	0.64 (0.06–6.91)			
Immunosuppressive (ever use vs never use)						
Methotrexate		1.17 (1.03–1.33)	0.82 (0.55–1.22)	0.79 (0.53–1.17)	0.93 (0.50-.1.72)	[101]
Azathioprine		1.20 (0.88–1.64)	0.59 (0.21–1.64)	0.75 (0.29–1.94)	2.93 (0.32–27.2)	
Cyclosporine		1.01 (0.91–1.12)	1.13 (0.87–1.47)	0.74 (0.55–1.00)	1.15 (0.71–1.86)	
Other		1.49 (1.17–1.88)	1.97 (1.12–3.46)	1.40 (0.71–2.74)	2.70 (0.83–8.84)	
Aromatase inhibitors	vs tamoxifen	1.21 (1.03–1.43)				[92]

CI: Confidence interval; DDD: Defined daily dose; RR: relative risk.

increase in BMD [98,99], probably due to better disease control with less bone loss mediated by cytokines in patients with inflammatory diseases, although one study discovered a negative effect of cyclosporine [100]. The effects of cyclosporine *per se* have not been fully elucidated due to the often-concomitant treatment with corticosteroids. No increase or decrease in fracture risk has been observed with cyclosporine [101]. Tacrolimus may have neutral-to-positive effects on bone after transplantation, and may have a more positive effect than cyclosporine [15,102].

Conclusion

Oral corticosteroids increase fracture risk, while topical corticosteroids do not. Antidiabetics decrease fracture risk by countering the negative skeletal effects of diabetes, except for glitazones, which appear to be associated with an increased risk of fractures. Antithyroid drugs *per se* decrease fracture risk by inducing euthyroidism. Some, but not all, antiepileptic drugs are associated with a limited increase in fracture risk. Anxiolytics and neuroleptics are associated with increased fracture risk. Among antidepressants,

SSRIs carry a larger increase in relative fracture risk than tricyclic drugs. Lithium is associated with a decrease in fracture risk. Most, but not all, opioids are associated with an increase in fracture risk. Some, but not all, NSAIDs were associated with an increase in fracture risk. Proton-pump inhibitors were associated with an increased fracture risk, while histamine H2 receptor antagonists were associated with a decrease in fracture risk. Histamine H1 receptor antagonists and oral contraceptives were not associated with significant changes in fracture risk.

Future perspective

Existing drugs may form an interesting platform for discovering potential new therapies for osteoporosis and to highlight calcium metabolic pathways of interest for new therapeutic principles. Further investigation must take place both at the cellular level, the pharmacoepidemiological level and through randomized, controlled trials.

Executive summary

- Drugs have different effects on the risk of fractures. Even drugs from the same therapeutic category may have different effects.
- Drugs associated with a reduced risk of fractures include insulin, oral antidiabetics other than glitazones, histamine H2 receptor antagonists, lithium, thiazide diuretics, digoxin, nitroglycerin, statins and antihypertensives of all classes.
- Drugs associated with an increased fracture risk include proton-pump inhibitors, antidepressants, glitazones, loop diuretics, amiodarone, aromatase inhibitors, a number of strong analgesics and a number of weak analgesics, including acetaminophen.
- Knowledge is therefore important when prescribing drugs for patients at risk of osteoporosis. Thiazide diuretics could, for example, be preferred over loop diuretics, digoxin over amiodarone, lithium over other antipsychotics, and histamine H2 receptor antagonists over proton-pump inhibitors, where possible. However, more research is needed before firm guidelines can be issued.
- Pharmacoepidemiology may prove a valuable tool not just for identifying drugs that increase the risk of fractures but also for identifying drugs that are potentially associated with a decreased risk of fractures, which may lead to the discovery of new signaling pathways of importance to bone turnover and, potentially, to new treatment modalities.

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