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1 **Associations between osteoporosis and drug exposure: a post-marketing**
2 **study of the World Health Organization pharmacovigilance database**
3 **(VigiBase®)**

4

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18

19 **KEYWORDS**

- 20 • Osteoporosis
- 21 • Drug
- 22 • Pharmacology
- 23 • Pharmacoepidemiology
- 24 • Pharmacovigilance

25

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27 **HIGHLIGHTS**

28

29 *What is already known about the subject?*

- 30 • Several drugs are known to induce osteoporosis and/or increase the fracture risk.
- 31 • Pharmacovigilance and pharmacoepidemiologic studies are crucial for the safety assessment of
- 32 marketed drugs.

33

34 *What this study adds?*

- 35 • New disproportionality signals with a pharmacologically plausible mechanism in bone fragility
- 36 were found for drugs used in the fields of neurology (selective 5-HT₁ agonists, levodopa and
- 37 memantine), hematology (romiplostim), pulmonology (macitentan), ophthalmology (ranibizumab),
- 38 and rheumatology (tofacitinib).

39 **ABSTRACT**

40 **Background:** Bone remodeling is a complex process, and many conditions (including drug exposure)
41 lead to osteoporosis. Here, we sought to detect new disproportionality signals for drugs associated
42 with osteoporosis.

43 **Methods:** We performed a disproportionality analysis of the World Health Organization's VigiBase®
44 pharmacovigilance database through April 12, 2020. The frequency of reports on osteoporosis for all
45 identified drug classes was compared with that for all other drugs and quoted as the reporting odds
46 ratio (ROR) [95% confidence interval (CI)].

47 **Results:** Of the 7,594,968 cases spontaneously recorded to VigiBase®, 4,758 concerned osteoporosis.
48 New disproportionality signals with a pharmacologically plausible mechanism were found for drugs
49 used in neurology (levodopa (ROR [95%CI]: 10.18 [4.33–25.10]), selective serotonin agonists (4.22
50 [2.34–7.00]) and memantine (4.10 [1.56–8.93])), hematology (romiplostim (4.93 [1.15–21.10])),
51 pulmonology (macitentan (3.02 [1.84–4.90])), ophthalmology (ranibizumab (3.31 [1.00–10.51])) and
52 rheumatology (tofacitinib (3.65 [3.00–4.40])). The robustness of these new results is supported by
53 the significant RORs for the vast majority of drugs already known to induce osteoporosis and/or
54 increase the fracture risk, namely glucocorticoids, gonadotropin-releasing hormone analogs, anti-
55 aromatases, androgen receptor blockers, thyroid hormones, proton pump inhibitors,
56 thiazolidinediones, vitamin K antagonists, loop diuretics, protease inhibitors, nucleoside and
57 nucleotide reverse transcriptase inhibitors, and enzyme-inducing antiepileptics including barbiturates
58 and derivatives, hydantoin derivatives, carboxamide derivatives and fatty acid derivatives.

59 **Conclusion:** We established up a comprehensive list of drugs potentially associated with
60 osteoporosis and highlighted those with pharmacologically plausible mechanisms leading to bone
61 fragility. Our results might pave the way for additional exploration of these mechanisms.

62 **ABBREVIATIONS**

63	5-HT	5-hydroxytryptamine (serotonin)
64	ADR	adverse drug reaction
65	AI	aromatase inhibitor
66	ATC	Anatomical Therapeutic Chemical
67	BMD	bone mineral density
68	CI	confidence interval
69	COX	cyclooxygenase
70	DMARD	disease modifying anti-rheumatic drug
71	ET-1	endothelin-1
72	GnRH	gonadotropin-releasing hormone
73	HCQ	hydroxychloroquine
74	ICSR	individual case safety report
75	IL	interleukin
76	IRD	inflammatory rheumatic disease
77	JAK	Janus kinase
78	MedDRA	Medical Dictionary for Regulatory Activities
79	Mpl	myeloproliferative leukemia virus oncogene
80	MS	multiple sclerosis
81	MTX	methotrexate
82	NFκB	nuclear factor-kappa B
83	NMDA	N-methyl-D-aspartate
84	NNRT	nucleoside and nucleotide reverse transcriptase
85	OB	osteoblast
86	OC	osteoclast
87	PDE-5	phosphodiesterase-5

88	PG	prostaglandin
89	PI	protease inhibitor
90	PPI	proton pump inhibitor
91	RA	rheumatoid arthritis
92	RANKL	receptor activator of nuclear factor-kappa B ligand
93	ROR	reporting odds ratio
94	SD	standard deviation
95	sGC	soluble guanylate cyclase
96	SMQ	standardized MedDRA query
97	SSRI	selective serotonin reuptake inhibitor
98	STAT	signal transducers and activators of transcription
99	TPO	thrombopoietin
100	TTR	transthyretin
101	VEGF	endothelial growth factor
102	VKA	vitamin K antagonist
103	WHO	World Health Organization

104 **INTRODUCTION**

105 Osteoporosis is a systemic skeletal disease characterized by low bone mineral density (BMD),
106 microarchitectural deterioration of the bone tissue, and a consequential increase in bone fragility [1].

107 Bone fractures (the main complication of osteoporosis) have a major impact on health and quality of
108 life and constitute a significant economic burden [2].

109 The conditions or factors that lead to osteoporosis and/or an elevated fracture risk include age, sex,
110 race, smoking, alcohol consumption, body weight, poor nutrition or any cause of malabsorption, low
111 calcium and vitamin D intakes, chronic inflammatory rheumatic diseases (IRDs, particularly
112 rheumatoid arthritis (RA)), other inflammatory diseases, endocrine disorders, bone marrow
113 disorders, immobilization, a history of fractures, and the fall risk [3].

114 Furthermore, several drugs are known to induce osteoporosis and/or increase the fracture risk:
115 systemic, inhaled and topical glucocorticoids [4], some hormone preparations (gonadotropin-
116 releasing hormone (GnRH) analogs [5], aromatase inhibitors (AIs) [6], androgen receptor blockers [7],
117 and thyroid hormones [8]), proton pump inhibitors (PPIs) [9], thiazolidinediones [10], vitamin K
118 antagonists (VKAs) [11], loop diuretics [12], protease inhibitors (PIs), nucleoside and nucleotide
119 reverse transcriptase (NNRT) inhibitors [13,14], opioids [15,16], antiepileptics [17], antipsychotics
120 [18,19], benzodiazepines [20], antidepressants (mainly selective serotonin reuptake inhibitors
121 (SSRIs)) [21], vitamin A [22], and heparin during pregnancy [23].

122 Although phase III studies are very robust tools for assess drug effectiveness, they are less able to
123 evaluate adverse drug reactions (ADRs) because of the small sample sizes, highly selected
124 populations, and short follow-up periods [24]. Hence, post-marketing pharmacoepidemiologic
125 studies are important for detecting rare or long-term ADRs, such as osteoporosis in long-term users
126 of PPIs [9] or VKAs [11]. Disproportionality analysis lies at the interface between pharmacovigilance
127 and pharmacoepidemiology. It is usually based on the assessment of spontaneous individual case
128 safety reports (ICSRs) and can detect early disproportionality signals for specific ADRs, which must
129 then be confirmed by more specific pharmacoepidemiologic studies [25]. For example, a

130 disproportionality signal (defined as reports of events that are significantly disproportionate, i.e. an
131 observed/expected ratio exceeding a specific threshold [26]) was detected for rofecoxib and
132 thrombotic ADRs as early as the end of 2001 [27]. The drug was withdrawn from the market for this
133 reason in September 2004.

134 Pharmacovigilance and pharmacoepidemiologic studies have identified a broad range of drug classes
135 associated with an osteoporotic risk. The safety of recently marketed drugs must be assessed
136 regularly. Dardonville et al. recently analyzed drug-induced osteoporosis in the French and Spanish
137 pharmacovigilance databases but did not perform a disproportionality analysis that might have
138 detected new disproportionality signals [28].

139 Consequently, we analyzed a global pharmacovigilance database in order to (i) provide an overview
140 of drugs already known to induce osteoporosis and/or increase the fracture risk, and (ii) detect new
141 disproportionality signals for osteoporosis and discuss potential mechanisms underlying bone
142 fragility.

143

144 **METHODS**

145

146 **2.1. Data source**

147 ICSRs were collected from VigiBase® – the world’s largest pharmacovigilance database, curated by
148 the World Health Organization (WHO) [29]. Each ICSR includes anonymous administrative data (the
149 country, and the reporter’s qualification), patient information (age and sex), drug information (the
150 international non-proprietary name or the trade name, Anatomical Therapeutic Chemical (ATC)
151 classification, indication, start date, withdrawal date, dosage, and administration route), and
152 information on the suspected ADR (coded according to the Medical Dictionary for Regulatory
153 Activities (MedDRA)) [30]. There are five levels in the MedDRA hierarchy, ranging from very general
154 to very specific. MedDRA also includes standardized MedDRA queries (SMQs), which are collections
155 of MedDRA terms consistent with a description of a clinical syndrome associated with an ADR and

156 drug exposure [31]. As such, SMQs are useful for wide-ranging searches. There are two types of
157 SMQ: the narrow SMQ contains fewer MedDRA terms than the broad SMQ and is therefore more
158 specific. If a drug is considered to be at least probably responsible for the ADR, it is defined as
159 “suspect” or “interacting” in the ICSR. If not, it is defined as “concomitant.” Probability scales are
160 based on a variety of temporal, semiologic, and/or bibliographic criteria [32]. Full information on
161 ICSRs is given on the Uppsala Monitoring Centre’s website [26] .

162

163 **2.2. Study design**

164 Using the narrow SMQ “Osteoporosis/osteopenia” (including the MedDRA preferred terms “Bone
165 density decreased”, “Bone formation decreased”, “Bone loss”, “Bone marrow oedema syndrome”,
166 “Osteopenia”, “Osteoporosis”, “Osteoporosis postmenopausal”, “Osteoporotic fracture”,
167 “Resorption bone increased”, “Senile osteoporosis”), we selected ICSRs recorded in VigiBase
168 between January 1, 1967, and April 12, 2020. In order to analyze only the best-documented ICSRs
169 (particular with regard to the nature of adverse drug reactions and the suspected or concomitant
170 medications), we selected ICSRs filed by physicians, pharmacists, or other health professionals.
171 Lastly, we analyzed only ICSRs for which the sex and age (18 or over) were reported. We then
172 analyzed drugs reported as being “suspect” in least in three ICSRs [33]. Given the large number of
173 suspect drugs at the 5th level of the ATC classification, we pooled the active substances at the 3rd
174 level (the pharmacological subgroup) or the 4th level (the chemical subgroup) corresponding to the
175 mechanism of action. In order to avoid the question of poor drug effectiveness, we excluded ICSRs
176 for which the suspected, interacting, or concomitant drugs were indicated in osteoporosis, i.e.
177 bisphosphonates (ATC M05BA and M05BB), denosumab (ATC M05BX04), burosumab (ATC
178 M05BX05), romosozumab (ATC M05BX06), teriparatide (ATC H05AA02), abaloparatide (ATC
179 H05AA04), strontium renalate (ATC M05BX03 and M05BX53), selective estrogen receptor
180 modulators (ATC GX03XC), estrogen replacement therapy (ATC G03AA, G03AB, G03C, G03EA, G03EB,

181 G03F, L02AA), calcitonin preparations (ATC H05BA), calcium (ATC A12A), and vitamin D and its
182 analogs (ATC A11CC).

183

184

185 **2.3. Statistical analysis**

186 In our descriptive analysis, categorical variables were expressed as the number (percentage), and
187 continuous variables were expressed as the mean \pm standard deviation (SD) or, as appropriate, the
188 median (range).

189 Several types of disproportionality analysis are available in the literature. Here, we chose to calculate
190 reporting odds ratio (ROR) and its 95% confidence interval (CI) as a gauge of the association between
191 a suspected drug and osteoporosis in the ICSRs filtered over the study period. This case/non-case
192 approach is the best way to deal with the limitations of a database of spontaneous reports and to
193 interpret the results optimally [34]. The ROR calculation method has been described elsewhere [25].
194 Briefly, $ROR = (a/c)/(b/d)$, where (a) is the number of osteoporosis ADRs with the suspected drug, (b)
195 is the number of osteoporosis ADRs with all other drugs, (c) is the number of ADRs other than
196 osteoporosis with the suspected drug, and (d) is the number of ADRs other than osteoporosis with all
197 other drugs. If the ROR and the lower boundary of its 95%CI are above than 1, the ADR of interest is
198 reported more frequently with the drug of interest than with all other drugs. It has been suggested
199 that an ROR above 4 corresponds to a “large” effect size [25].

200 Given that many conditions can lead to osteoporosis, we expected to see false-positive RORs
201 confounded by the disease itself and “disease spill-over” (i.e. aspects of the treated disease coded as
202 an ADR, namely osteoporosis). In this case, the disproportionality signal would reflect the risk
203 associated with the indication and not with the drug itself. Thus, we minimized this indication bias by
204 stratifying the RORs by therapeutic area; we defined the comparator as the suspected drug’s
205 therapeutic or pharmacological class, rather than all other drugs [35]. The therapeutic areas

206 considered in the analyses are summarized in **Supplementary Table S1**. The RORs were adjusted for
207 age and sex, using logistic regressions.

208 Bias due to competition between events might mask interesting RORs and can be observed when the
209 suspected drug is strongly associated with another ADR [36,37]. This bias can be minimized by
210 removing the competitor event [37]. We therefore performed sensitivity analyses when RORs were
211 not significant for drugs already known to be associated with osteoporosis by removing the most
212 frequently reported ADR for each drug concerned from the analysis. Overall, this case was
213 encountered only for antithrombotic agents, where the SMQ “Haemorrhages” was removed from
214 the analysis for this drug class.

215 We performed sensitivity analyses by applying the above-mentioned method to (i) the broad SMQ
216 “osteoporosis/osteopenia”, which includes ADRs related to fractures, a decrease in BMD, and
217 changes in markers of bone turnover (such as elevated urine levels of collagen cross-linked N-
218 telopeptide and elevated serum levels of collagen C-telopeptide), and (ii) the MedDRA terms related
219 to fractures. The MedDRA terms related to the broad and narrow SMQs and to fractures are given in
220 **Supplementary Table S2**.

221 All analyses were performed using R software (version 3.6.0, R Foundation for Statistical Computing,
222 Vienna, Austria).

223

224 **RESULTS**

225 ***3.1. Study population***

226 After the exclusion of drugs indicated in osteoporosis, 4,758 of the 7,594,968 ICSRs in adult patients
227 of known age and sex reported by physicians, pharmacists or other health professionals to VigiBase®
228 between January 1, 1967, and April 12, 2020, matched the narrow SMQ “osteoporosis/osteopenia”.
229 There was a single suspect drug in 2,798 (58.8%) of the ICSRs. The mean \pm SD age was 57.1 ± 15.6 .
230 The cases predominantly occurred in females (65.9%). The characteristics of the study population are
231 summarized in **Table 1**.

232

233 **3.2. Disproportionality analysis**

234

235 *3.2.1. Drugs already known to induce osteoporosis and/or increase the fracture risk*

236 The adjusted RORs (aRORs) [95%CI] were significant for PPIs (12.12 [6.79–24.21]), thiazolidinediones
237 (1.80 [1.11–2.82]), heparins (3.69 [2.75–4.92]), high-ceiling diuretics (2.37 [1.19–4.84]), systemic,
238 inhaled and topical corticosteroids (14.14 [13.17–15.18], 2.55 [2.02–3.24] and 13.06 [12.17–14.00],
239 respectively), antiandrogens (7.76 [3.78–14.84]), thyroid hormones (2.44 [1.64–3.46]), PIs (1.75
240 [1.38–2.18]), NNRT inhibitors (2.78 [2.37–3.25]), GnRH analogs (4.21 [3.25–5.45]), AIs (4.21 [3.25–
241 4.45]), and enzyme-inducing antiepileptics, including barbiturates and derivatives (7.35 [5.05–
242 10.43]), hydantoin derivatives (7.89 [1.32–2.64]), carboxamide derivatives (1.93 [1.42–2.59]) and
243 fatty acid derivatives (2.06 [1.50–2.79]). The RORs are represented graphically in **Figures 1** and **2**.

244 These results were consistent with sensitivity analyses (**Supplementary Figures S1-S42**), with the
245 exception of the following drugs. The aROR for heparin was not significant in the broad SMQ (0.69
246 [0.58–0.81], **Supplementary Figure S5**) but was significant in the fractures subset (3.69 [2.72–5.00],
247 **Supplementary Figure S6**), The aROR for thyroid hormones was not significant in the broad SMQ
248 (0.83 [0.62–1.08], **Supplementary Figure S17**) but was significant in the fractures subset (2.65 [1.75–
249 3.81], **Supplementary Figure S18**). The aROR for opioids was significant in the broad SMQ (1.67
250 [1.47–1.89], **Supplementary Figure S29**) and not in the fractures subset (1.21 [0.83–1.71],
251 **Supplementary Figure S30**). The aROR for benzodiazepine-related hypnotics and sedatives was
252 significant in the broad SMQ (1.34 [1.12–1.60], **Supplementary Figure S29**) but not in the fractures
253 subset (0.55 [0.22–1.14], **Supplementary Figure S30**). The aROR for retinoids in treatment of
254 psoriasis was significant in the fractures subset (6.16 [1.44–42.22], **Supplementary Figure S12**).

255 For VKAs, the aROR was significant after removing the SMQ “Haemorrhages” from the analysis (1.68
256 [1.52–1.86], **Figure 3**) but not before (0.37 [0.31–0.44]; **Supplementary Figures S4-S6**). The RORs
257 were not significant for platelet aggregation inhibitors, even the SMQ “Haemorrhages” had been
258 removed from the analysis.

259

260 *3.2.2. New disproportionality signals*

261 In group A of the ATC classification, the aROR [95%CI] was significant for imiglucerase (4.87 [1.24–
262 20.33], **Figure 1**).

263 In group B of the ATC classification, the aRORs was significant for romiplostim (4.93 [1.15–21.10]),
264 **Figure 1**).

265 In group C of the ATC classification, the aRORs were significant for antihypertensives for pulmonary
266 arterial hypertension (particularly macitentan (3.02 [1.84–4.90]) and riociguat (2.83 [1.25–5.59]),
267 **Figure 1**).

268 In group G of the ATC classification, the aROR was significant for sildenafil (2.84 [1.29–5.63]), **Figure**
269 **1**).

270 In group L of the ATC classification, the aRORs were significant for interferon beta-1a (9.49 [6.66–
271 13.73], **Figure 1**), mycophenolic acid (2.53 [1.99–3.16]), sirolimus (2.12 [1.02–3.85]), leflunomide
272 (4.84 [3.84–6.03]), abatacept (5.06 [4.08–6.20]), belimumab (3.17 [1.25–6.46]), tofacitinib (3.65
273 [3.00–4.40]), tocilizumab (6.16 [5.08–7.41]), calcineurin inhibitors (1.43 [1.11–1.80]), and
274 azathioprine (2.26 [1.69–2.96]), **Figure 2**).

275 In group M of the ATC classification system, the aRORs were significant for nonsteroidal anti-
276 inflammatory drugs (1.25 [1.11–1.40]), particularly for cyclooxygenase inhibitors (coxibs: 10.28 [8.06–
277 13.19], **Figure 2**).

278 In group N of the ATC classification, the aRORs were significant for selective serotonin (5-HT) agonists
279 (4.22 [2.34–7.00]), dopaminergic agents particularly dopa and its derivatives (10.18 [4.33–25.10]),
280 memantine (4.10 [1.56–8.93]), sodium oxybate (4.79 [2.75–7.66]) and amifampridine (43.60 [13.51–
281 104.15]), **Figure 2**).

282 In group P of the ATC classification, the aROR was significant for hydroxychloroquine (7.91 [6.70–
283 9.26], **Figure 2**).

284 In group R of the ATC classification system, the aRORs were significant for omalizumab (2.38 [1.67–
285 3.29]) and mepolizumab (2.94 [1.51–5.12], **Figure 2**).

286 In group S of the ATC classification, the aROR was significant for ranizumab (3.31 [1.00–10.51], **Figure**
287 **2**).

288 In group V of the ATC classification, the RORs were significant for iron-chelating agents (4.20 [2.58–
289 6.39]) and radium Ra 223 dichloride (5.13 [1.27–13.36], **Figure 2**).

290 All these results were consistent with those of the sensitivity analyses, with the exception of
291 imiglucerase (3.75 [0.86–16.24], **Supplementary Figure S3**), romiplostim (2.43 [0.33–12.68],
292 **Supplementary Figure S6**), and radium Ra 223 dichloride (4.05 [0.67–12.55], **Supplementary Figure**
293 **S42**) in the fractures subset, and for riociguat (1.09 [0.82–1.42], **Supplementary Figure S8**),
294 mycophenolic acid (0.67 [0.57–0.78], **Supplementary Figure S23**), sirolimus (0.87 [0.58–1.24],
295 **Supplementary Figure S23**), belimumab (1.59 [0.95–2.49], **Supplementary Figure S23**), calcineurin
296 inhibitors (0.57 [0.49–0.65], **Supplementary Figure S23**), azathioprine (0.80 [0.66–0.92],
297 **Supplementary Figure S23**), and nonsteroidal anti-inflammatory drugs (0.72 [0.67–0.77],
298 **Supplementary Figure S26**) in the broad SMQ.

299

300 **DISCUSSION**

301 Our results are in line with the literature data and provide a comprehensive overview of drugs
302 associated with osteoporosis and the risk of fracture. Furthermore, we report on new
303 disproportionality signals for (i) drugs previously linked via clinical studies to a lower BMD and/or a
304 higher fracture risk, (ii) drugs whose pharmacological properties provide a rationale for a potential
305 effect on bone metabolism, and (iii) drugs that do not belong to either of the previous categories.

306

307 ***4.1. Drugs with previously published clinical data on a potential association with osteoporosis***

308 The aRORs were significant for the vast majority of drugs already known to induce osteoporosis
309 and/or increase the fracture risk, namely systemic, inhaled and topical glucocorticoids, GnRH

310 analogs, AIs, androgen receptor blockers, thyroid hormones, PPIs, thiazolidinediones, VKAs, loop
311 diuretics, PIs, NNRT inhibitors and enzyme-inducing antiepileptics; however, the aRORs were also
312 significant for opioids and benzodiazepines in the broad SMQ [4–21]. When considering vitamin A
313 and its derivatives, the aROR was significant only for retinoids for the treatment of psoriasis in the
314 fractures subset but not in the broad or narrow SMQs. Their use in clinical studies is associated with
315 a lower BMD and a higher fracture risk [22,38] through osteoblast (OB) inhibition, osteoclast (OC)
316 differentiation, and an antagonism of vitamin D's action [39–41]. Vitamin A and its derivatives are
317 scattered across the ATC classification system (with vitamin A [A11CA01], retinoids for treatment of
318 psoriasis [D05BB], topical retinoids for acne [D10AD], systemic retinoids for acne [D10BA], retinoids
319 for cancer treatment [L01XF], and retinol eye drops [S01XA02]); this prevented us from calculating
320 the overall ROR for this drug class.

321 We found a significant ROR for radium 223 dichloride, which is indicated in metastatic prostate
322 cancer. This calcium-mimetic radioisotope was recently shown to induce osteoporosis with a high
323 risk of vertebral fractures, independently of androgen deprivation therapy and abiraterone therapy
324 [42]. This radioisotope binds selectively to hydroxyapatite in areas of increased bone remodeling; the
325 short-range emission of high-energy alpha particles probably leads to bone fragility [43].

326 Testosterone-5-alpha reductase inhibitors (used in prostate cancer) prevent the conversion of
327 testosterone to dihydrotestosterone. Low concentrations of dihydrotestosterone predispose men to
328 a risk of osteoporosis [44] because this hormone is approximately ten times more potent than its
329 precursor testosterone, and is the preferred ligand for androgen receptor transactivation [45].
330 Nevertheless, observational studies have yielded inconsistent findings [46–48].

331 Methotrexate (MTX, indicated in several chronic IRDs at low doses but also used to treat cancer at
332 very high doses) appears to induce osteoporosis and increase the fracture risk in a dose-dependent
333 manner. At high doses, MTX induces osteoporosis and fractures regardless of corticosteroid use [49–
334 51] in a way that has not yet been not fully elucidated – possibly through increased urinary calcium

335 excretion [52]. At low doses in IRDs, MTX use is not associated with lower BMD or a higher fracture
336 risk [53–57].

337 *In vivo*, calcineurin inhibitors (indicated in patients undergoing organ transplantation) cause bone
338 loss and increase the fracture risk [58] due to increased bone resorption - notably because of
339 changes in T-cell cytokine production and altered vitamin D metabolism, with secondary
340 hyperparathyroidism [59].

341 Azathioprine inhibits purine synthesis and also leads to autophagy [60]. A recent *in vivo* study found
342 that the use of this drug is associated with a deterioration in the bone's trabecular microarchitecture,
343 which might induce the autophagy pathway [60]. Azathioprine's detrimental effects on bone have
344 already been described *in vivo* [61], and the results of an observational study showed an elevated
345 fracture risk [62].

346 The involvement of non-steroidal anti-inflammatory drugs in bone remodeling appears to be
347 complex and depends on the type of cyclooxygenase (COX) inhibited, sex, and hormone status.
348 Prostaglandin (PG)E2 and prostacyclin have complex roles in bone remodeling cycle; they may
349 stimulate bone resorption (particularly PGE2) as well as bone formation [63–65]. The literature data
350 are contradictory. In a systematic review, aspirin (which inhibits COX-1 at low doses and both COX-1
351 and COX-2 at high doses) is associated with a decrease in the fracture risk and an increase in BMD in
352 both men and women [66]. In a multicenter cohort study, COX-2-specific inhibitors are associated
353 with a lower BMD in men and with a higher BMD in postmenopausal women not using estrogen
354 replacement therapy [67]. In a large cohort study, the combination of coxibs with low-dose aspirin
355 was associated with an increase in BMD in both men and women [68]. Nevertheless, we found a
356 significant aROR only for coxibs.

357

358 ***4.2. Drugs with a pharmacological rationale for a potential bone effect but that have not yet been***
359 ***investigated in clinical studies***

360 Romiplostim – indicated in immune thrombocytopenia – activates c- myeloproliferative leukemia
361 virus oncogene (c-Mpl); this is the receptor for thrombopoietin (TPO) present in megakaryocytes and
362 OCs, which are derived from the same hematopoietic precursor [69]. *In vitro*, TPO increases OC
363 formation and differentiation through the mitogen-activated protein kinases, Janus kinases
364 (JAKs)/signal transducers and activators of transcription (STAT), and nuclear factor-kappa B (NFκB)
365 signaling pathways by activating c-Mpl [70]; this mechanism might explain our results.

366 We found a significant aRORs for macitentan - an endothelin-1 (ET-1) receptor antagonist indicated
367 in pulmonary arterial hypertension. This finding is consistent with *in vitro* studies showing that
368 exogenous ET-1 stimulates OB proliferation/differentiation and type I collagen production and
369 inhibits osteoclastic resorption [71–73]. Moreover, ET-1 levels in a clinical study were positively
370 correlated with BMD at the lumbar spine in non-osteoporotic women [74]. However, the drug class’s
371 possible direct effect on bone was not evaluated.

372 It is well known that Parkinson’s disease is associated with bone loss through immobilization or
373 hypokinesia. However, dopaminergic depression alters the sympathetic innervation of bone, which is
374 fundamental for bone homeostasis [75,76]. Furthermore, the breakdown of L-dopa by catechol-O-
375 methyltransferase results in greater homocysteine formation [77]. In turn, high level of
376 homocysteine lead to osteoporosis and fractures - possibly through impaired collagen cross-linking
377 [78]. This has been confirmed in mice but not in humans, where dopamine replacement treatment
378 with levodopa further reduces the bone mass and raises the serum level of homocysteine [76].

379 The use of SSRIs appears to be associated with a reduction in BMD and an elevated risk of fracture
380 [79]. SSRIs increase serum serotonin concentrations, and it has been suggested that serum 5-HT
381 downregulates osteoblast proliferation, bone formation, and bone mass via the 5-HT_{1B} receptor [80–
382 82]. On the same lines, selective 5-HT₁ agonists (some of which are indicated in migraine) bind to 5-
383 HT_{1B/D} receptors, which might impair bone formation. Nevertheless, no clinical data on this topic
384 have been published.

385 The N-methyl-D-aspartate (NMDA) receptor antagonist memantine is indicated in dementia.
386 Mechanical loading (which contributes to the normal bone remodeling process [83]) increases the
387 expression of NMDA receptors on OBs and OCs [84]. Accordingly, experiments *in vitro* and in an
388 animal model showed that the downregulation of NMDA receptor expression decreased
389 osteogenesis [85].

390 Ranibizumab – indicated in age-related macular degeneration – is a vascular endothelial growth
391 factor (VEGF)-A inhibitor that has an important role in angiogenesis and osteogenesis [86]. A recent
392 study showed that enhancing VEGF-A expression promotes osteogenesis in the context of
393 postmenopausal osteoporosis [87]. Hence, ranibizumab might impair bone homeostasis.

394 Tofacitinib – indicated in RA – is a JAK1/JAK3 inhibitor. *In vivo*, JAK1 inhibition can lead to an
395 osteoporotic bone phenotype [88] and JAK3 inhibition *via* the inactivation of signal transducers and
396 activation of transcription 3 (STAT3) in OBs [89]. Moreover, STAT3 deficiency activates
397 osteoclastogenesis [90]. Nevertheless, no clinical data on this topic are available.

398 The drugs with a pharmacologically plausible mechanism of osteoporosis induction are summarized
399 in **Table 2**.

400

401 ***4.3. Drugs with disproportionality signals identified in the present study but that are not in line***
402 ***with the literature data***

403 It is well known that Gaucher's disease (glycocerebrosidase deficiency) induces osteoporosis through
404 the accumulation of glucosylceramide. The enzyme replacement therapy imiglucerase is associated
405 with dose-related, long-term increases in BMD [91]. The significant ROR for imiglucerase might be
406 related to drug ineffectiveness, rather than a direct effect on bone.

407 For certain vasodilator agents (namely the phosphodiesterase-5 (PDE-5) inhibitors sildenafil and
408 tadalafil and the soluble guanylate cyclase (sCG) agonist riociguat, we also found significant RORs – a
409 finding that contrasts with the literature data. In animal models, PDE-5 inhibitors prevent cGMP
410 degradation and thus stimulate cGMP-dependent protein kinase (PKG) 1/2, leading to an increase in

411 BMD via OB proliferation and differentiation [92]. The sGCs (Gucy1a2 and Gucy1a3) are expressed in
412 mouse skeletal tissue, and the sGC agonists' effects appear to be driven by osteoblasts. *In vivo*, the
413 sGC agonist cinaciguat enhanced osteoblast proliferation and differentiation and reversed trabecular
414 bone loss in ovariectomized mice [92].

415 We found significant RORs for disease-modifying antirheumatic drugs (DMARDs) used to treat
416 chronic IRDs: leflunomide, TNF inhibitors, tocilizumab, abatacept, rituximab, and
417 hydroxychloroquine. In the present study population, the use of co-medications (e.g. glucocorticoids)
418 not addressed in the analysis or an indication bias (despite stratification by therapeutic area) might
419 explain these discrepancies. All these DMARDs are known to be associated with a reduction in the
420 osteoporosis risk through a decrease in systemic inflammation. *In vitro* and in an animal model,
421 leflunomide suppresses receptor activator of NFκB ligand (RANKL)-activated intracellular signaling
422 and OC differentiation, and this effect is independent of its suppressive effect on T cells [93].
423 However, a clinical study found that patients with RA exposed to leflunomide for an average of 2.4
424 years did not have a significant change in BMD [94]. It is well known that interleukin (IL)-6 induces
425 osteoporosis by activating osteoclastogenesis [95]. Biologic DMARDs targeting TNF and IL-6 inhibit
426 the expression of RANKL on synovial cells and T cells, which leads to the subsequent suppression of
427 osteoclast maturation and bone damage through RANKL; however, biologic DMARDs are not known
428 to affect bone metabolism and osteoporosis [96]. The use of the IL-6 inhibitor tocilizumab is
429 associated with lower levels of bone-resorbing markers and higher levels of bone formation markers
430 [97,98]. Nevertheless, the use of tocilizumab in RA patients appears to be associated with a bone
431 mass gain only in individuals who are positive for anti-citrullinated protein antibodies [99]. Abatacept
432 (a fusion protein containing the FC region of IgG1 and the extracellular domain of cytotoxic T-
433 lymphocyte-associated protein-4) inhibits the differentiation and maturation of OCs [100]. A clinical
434 study found that patients treated with abatacept had a greater BMD at the lumbar spine than
435 patients treated with tumor necrosis factor inhibitors or tocilizumab [101]. Few literature data on the
436 anti-B-cell (anti-CD20) rituximab are available. The use of this agent appears to be associated with a

437 reduction in levels of the bone resorption marker deoxypyridinoline [102], although the results of a
438 clinical study were not conclusive [103]. Hydroxychloroquine (HCQ) was shown to reduce OC
439 differentiation *in vitro* and levels of β -carboxy-terminal collagen *in vivo* [104]. One clinical study
440 confirmed these preclinical results: HCQ use was associated with higher BMD in patients with
441 systemic lupus erythematosus [105]. However, a recent study did not show an association between
442 HCQ and the fracture risk in postmenopausal women with RA [106].

443 In mice, interferon beta – indicated in multiple sclerosis (MS) – appears to have beneficial effects on
444 bone by interfering with the RANKL-induced expression of c-Fos and thus inhibition of
445 osteoclastogenesis [107]. In one clinical study, the use of interferon beta by patients with MS was
446 associated with lower osteoclastogenesis in response to RANKL [108]. In another clinical study,
447 however, its use was associated with lower BMD in men with MS and no change in BMD in women
448 with MS [109].

449 Omalizumab – indicated in allergic asthma, sinonasal polyposis, and chronic spontaneous urticaria –
450 binds IgE specifically, whereas mepolizumab – indicated in severe eosinophilic refractory asthma –
451 binds IL-5 specifically. These actions results in lower histamine levels and lower leukotriene and
452 proinflammatory mediator levels *via* inhibition of mast cell degranulation and eosinophils,
453 respectively [110,111]. In theory, these mechanisms of action should prevent bone loss [112]; again,
454 no clinical data are available.

455 As mentioned above, iron accumulation harms bone [113,114]. Accordingly, a clinical study found
456 that iron-chelating agents can restore iron-induced bone damage [115].

457

458 ***4.4. Drugs with neither clinical data or nor a pharmacological rationale for a potential association*** 459 ***with osteoporosis***

460 Mycophenolic acid and sirolimus inhibit inosine-5'-monophosphate dehydrogenase and IL-2 and
461 other cytokine receptor-dependent signal transduction mechanisms *via* an action on mTOR. The two

462 drugs inhibit T and B lymphocyte proliferation and do not appear to harm bone in kidney transplant
463 patients [116].

464 Amifampridine – indicated in MS and Lambert-Eaton myasthenic syndrome, respectively – are broad-
465 spectrum voltage-dependent potassium channel blockers that enhance synaptic transmission. No
466 clinical or preclinical data are available.

467 Tafamidis – indicated in transthyretin (TTR) amyloidosis – binds the TTR tetramer and prevents it
468 from dissociating into monomers. Only one clinical study has shown that TTR levels were positively
469 correlated with BMD but only in patients without amyloidosis; in this context, TTR is a nutritional
470 marker [117]. Bone effects of TTR accumulation in the subset of patients with amyloidosis were not
471 investigated.

472 The mechanism of action of sodium oxybate – indicated in narcolepsy with cataplexy or excessive
473 daytime sleepiness – is not well understood [118]. Hence, no hypothesis can be made as to its
474 possible harmful bone effects.

475

476 **4.5. Study limitations and strengths**

477 Our study had several limitations, most of which are inherent to all pharmacovigilance and case/non-
478 case designs [25]. Firstly, we were not able to provide the absolute frequency of drugs associated
479 with osteoporosis – notably because of underreporting. However, widespread underreporting would
480 not affect the results of a disproportionality analysis [25]. Secondly, we did not have information on
481 the severity of the diseases for which the studied drugs were administered; this might have created
482 false positives in the ROR calculation. As a result, several RORs might be falsely significant even after
483 stratification by therapeutic area: certain drugs used to treat IRDs, the imiglucerase used in
484 Gaucher's disease. The significant ROR in this example probably reflects certain aspects of the
485 disease itself. Nevertheless, many of the contrasting literature data comes from preclinical studies
486 and have not always been confirmed in clinical studies. On the same lines, our analyses did not
487 address the concomitant use of certain medications (e.g. glucocorticoids in patients with IRDs) or

488 previous medication use that was not documented in the database, which could have led to falsely
489 significant RORs. Thirdly, our analyses took account of age and sex but not other conditions leading
490 to osteoporosis (due to lack of data), which could result in confounding bias. Fourthly, event
491 competition bias (as seen with VKAs) might have prevented us from detecting other
492 disproportionality signals masked by other ADRs strongly associated with the drugs of interest.
493 Fifthly, we cannot assert that fracture events in ICSRs are all low-energy osteoporotic fractures.
494 In contrast, our study has several major strengths, due to its case/non-case design [25]. We studied
495 the world's largest pharmacovigilance database, which reflects routine medication use. The
496 case/non-case design is a validated means of investigating disproportionality between reports and
497 drugs [25]. A recent study showed that in most cases, the ADR risk obtained in meta-analyses is
498 correlated with the ROR from the disproportionality analysis [119]. In the present study, the RORs for
499 the vast majority of drugs already known to induce osteoporosis or increase the fracture risk were
500 significant, which testifies to the robustness of our results.

501

502 **CONCLUSION**

503 Our results are consistent with the literature data on drugs already known to induce osteoporosis or
504 increase the fracture risk: glucocorticoids, GnRH analogs, AIs, androgen receptor blockers, thyroid
505 hormones, PPIs, thiazolidinediones, VKAs, loop diuretics, PIs, NNRT inhibitors, opioids, enzyme-
506 inducing antiepileptics, benzodiazepines, heparin, radium 223 dichloride, and high-dose MTX. We
507 found new disproportionality signals with a pharmacologically plausible mechanism (requiring
508 confirmation in clinical studies) in the fields of neurology (selective 5-HT₁ agonists, levodopa and
509 memantine), hematology (romiplostim), pulmonology (macitentan), ophthalmology (ranibizumab),
510 and rheumatology (tofacitinib).

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515 **Conflict of interest disclosure**

516 The authors declare that they have no competing interests.

517 **Ethics approval statement**

518 Not applicable

519 **Patient consent statement**

520 Not applicable

521 **Data availability statement**

522 The data that support the findings of this study are available on request from the corresponding
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528 **Authors' contributions**

529 BB and SL were the major contributors to the study conception and design and acquisition, analysis,
530 and interpretation of the data; they drafted the article and revised it critically for important
531 intellectual content. VGC, KM, SB, ASHL, SK and YB were major contributors to the analysis and
532 interpretation of the data and revised the article critically for important intellectual content. All
533 authors read and approved the final manuscript.

534 **Disclaimer**

535 The interpretation of data in the present study represents the opinions of the authors only and not
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967

968 **FIGURE LEGENDS**

969 **Figure 1:** Significant RORs for osteoporosis (narrow SMQ) with drugs in the ATC groups A, B, C, D, G,
970 H, J and L.

971 *ROR calculation performed for the corresponding therapeutic area

972 ** ROR calculation not stratified by therapeutic area (the corresponding drugs are almost the only
973 ones in their therapeutic area)

974 *ATC, Anatomical Therapeutic Chemical; CI, confidence interval; ROR, reporting odds ratio.*

975 **Figure 2:** Significant RORs for osteoporosis (narrow SMQ) with drugs in the ATC groups L, M, N, P, R, S
976 and V

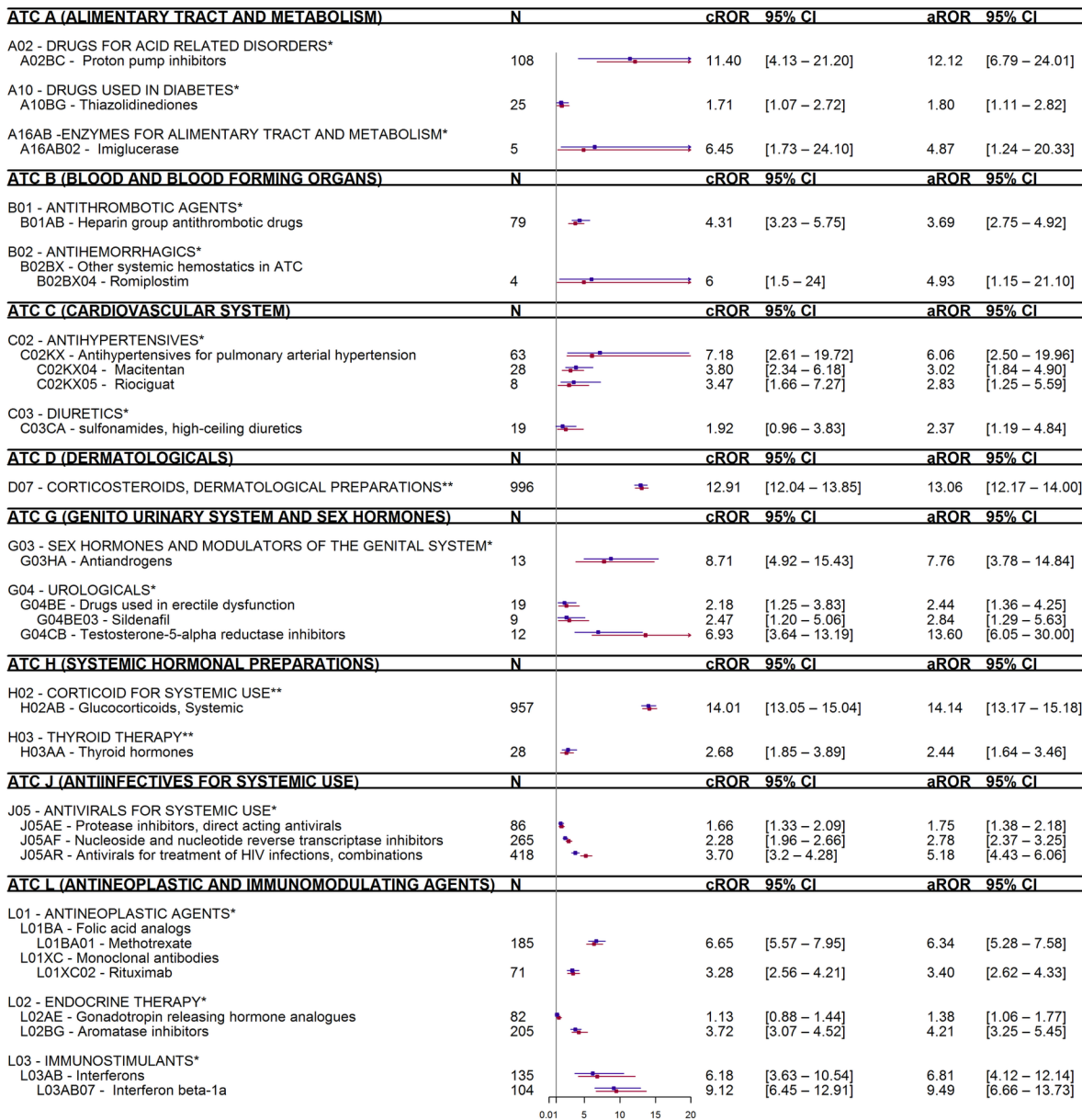
977 *ROR calculation performed in the corresponding therapeutic area

978 ** ROR calculation not stratified by therapeutic area (the corresponding drugs are almost the only
979 ones in their therapeutic area)

980 *ATC, Anatomical Therapeutic Chemical; CI, confidence interval; ROR, reporting odds ratio.*

981 **Figure 3:** RORs for osteoporosis (narrow SMQ) with antithrombotic agents after exclusion of the SMQ
982 "Haemorrhages"

983 *ATC, Anatomical Therapeutic Chemical; CI, confidence interval; MAO, monoamine oxidase; ROR,*
984 *reporting odds ratio; SMQ, standardized MedDRA query;*



■ crude ROR ■ adjusted ROR

ATC L (ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS)		N	cROR	95% CI	aROR	95% CI
L04 - IMMUNOSUPPRESSANTS*						
L04AA - Selective immunosuppressants						
L04AA06 - Mycophenolic acid	80	1.94	[1.55 – 2.44]	2.53	[1.99 – 3.16]	
L04AA10 - Sirolimus	9	1.64	[0.85 – 3.17]	2.12	[1.02 – 3.85]	
L04AA13 - Leflunomide	82	5.49	[4.38 – 6.87]	4.84	[3.84 – 6.03]	
L04AA24 - Abatacept	98	6.20	[5.04 – 7.64]	5.06	[4.08 – 6.20]	
L04AA26 - Belimumab	6	3.10	[1.38 – 6.88]	3.17	[1.25 – 6.46]	
L04AA29 - Tofacitinib	119	4.35	[3.60 – 5.27]	3.65	[3.00 – 4.40]	
L04AB - Tumor necrosis factor alpha (TNF-) inhibitors	586	1.50	[1.30 – 1.66]	1.53	[1.36 – 1.72]	
L04AC - Interleukin inhibitors						
L04AC07 - Tocilizumab	124	7.07	[5.86 – 8.52]	6.16	[5.08 – 7.41]	
L04AD - Calcineurin inhibitors						
L04AX - Other immunosuppressants in ATC	72	1.13	[0.89 – 1.44]	1.43	[1.11 – 1.80]	
L04AX01 - Azathioprine	52	1.81	[1.37 – 2.40]	2.26	[1.69 – 2.96]	
ATC M (MUSCULO-SKELETAL SYSTEM)		N	cROR	95% CI	aROR	95% CI
M01A - ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STERIODS**						
M01AH - Coxibs*	209	12.42	[9.77 – 15.8]	10.28	[8.06 – 13.19]	
ATC N (NERVOUS SYSTEM)		N	cROR	95% CI	aROR	95% CI
N02 - ANALGESICS*						
N02C - ANTIMIGRAINE PREPARATIONS						
N02CC - Selective serotonin (5HT1) agonists, antimigraine drugs	14	4.39	[2.57 – 7.53]	4.22	[2.34 – 7.00]	
N03 - ANTIEPILEPTICS*						
N03AA - Barbiturates and derivatives						
N03AB - Hydantoin derivatives	34	7.28	[5.06 – 10.48]	7.35	[5.05 – 10.43]	
N03AF - Carboxamide derivatives	39	1.84	[1.30 – 2.59]	1.89	[1.32 – 2.64]	
N03AG - Fatty acid derivatives	56	1.93	[1.43 – 2.60]	1.93	[1.42 – 2.59]	
N03AX - Other antiepileptics in ATC	52	2.00	[1.48 – 2.73]	2.06	[1.50 – 2.79]	
N03AX16 - Pregabalin	43	1.40	[1.00 – 1.94]	1.41	[1.00 – 1.96]	
N04 - ANTI-PARKINSON DRUGS*						
N04BA - Dopa and dopa derivatives	20	4.82	[2.36 – 9.86]	10.18	[4.33 – 25.10]	
N06 - PSYCHOANALEPTICS*						
N06D - ANTI-DEMENTIA DRUGS						
N06DX - Other anti-dementia drugs in ATC	6	3.81	[1.68 – 8.68]	4.10	[1.56 – 8.93]	
N06DX01 - Memantine	6	3.81	[1.68 – 8.68]	4.10	[1.56 – 8.93]	
N07X - OTHER NERVOUS SYSTEM DRUGS**						
N07XX - Other nervous system drugs in ATC						
N07XX04 - Oxybate sodium	15	4.56	[2.74 – 7.57]	4.79	[2.75 – 7.66]	
N07XX05 - Amifampridine	4	44.66	[16.53 – 120.67]	43.60	[13.51 – 104.15]	
ATC P (ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS)		N	cROR	95% CI	aROR	95% CI
P01B - ANTIMALARIALS**						
P01BA02 - Hydroxychloroquine	153	8.46	[7.20 – 9.95]	7.91	[6.70 – 9.26]	
ATC R (RESPIRATORY SYSTEM)		N	cROR	95% CI	aROR	95% CI
R03 - DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES*						
R03BA - Glucocorticoid inhalants for obstructive airway disease						
R03DX - Other systemic drugs for obstructive airway diseases in ATC	167	2.55	[2.01 – 3.22]	2.55	[2.02 – 3.24]	
R03DX05 - Omalizumab	41	2.42	[1.74 – 3.37]	2.38	[1.67 – 3.29]	
R03DX06 - Mepolizumab	11	2.98	[1.63 – 5.46]	2.94	[1.51 – 5.12]	
ATC S (SENSORY ORGANS)		N	cROR	95% CI	aROR	95% CI
S01L - OCULAR VASCULAR DISORDER AGENTS*						
S01LA04 - Ranibizumab	6	3.97	[1.38 – 11.45]	3.31	[1.00 – 10.51]	
ATC V (VARIOUS)		N	cROR	95% CI	aROR	95% CI
V03AC - Iron chelating agents**	19	4.10	[2.61 – 6.44]	4.20	[2.58 – 6.39]	
V10XX - Various therapeutic radiopharmaceuticals						
V10XX03 - Radium Ra 223 dichloride**	3	4.59	[1.48 – 14.26]	5.13	[1.27 – 13.36]	

0.01 5 10 15 20

■ crude ROR ■ adjusted ROR

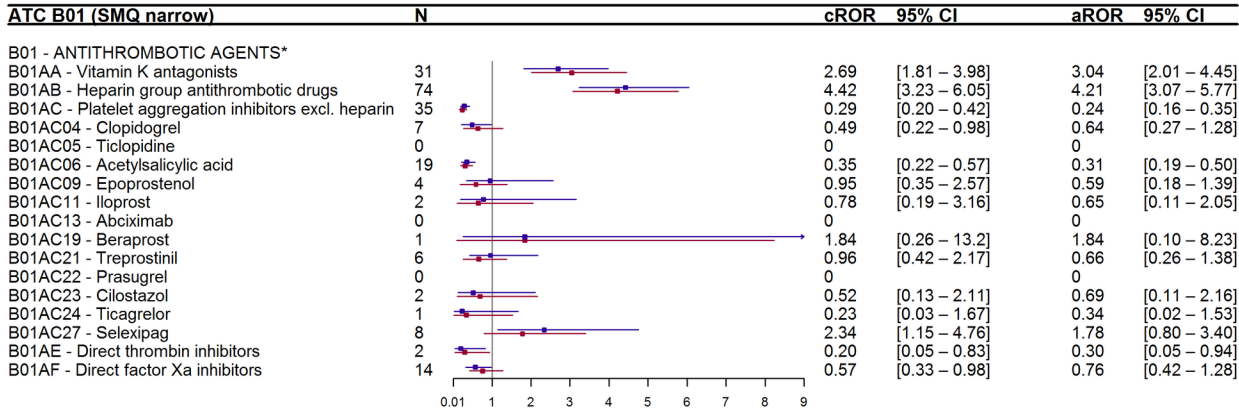


Table 1: Characteristics of ICSRs

Characteristics	Broad SMQ « Osteoporosis » n = 4,758
Age (years) \pm SD	51.1 \pm 15.6
Sex, n (%)	
Male	1,621 (34.1)
Female	3,137 (65.9)
Reporter qualification, n (%)	
Physicians	2,933 (61.6)
Pharmacists	383 (8.0)
Other health professionals	1,059 (30.4)
Continent, n (%)	
North America	2,184 (45.9)
Europe	1,785 (37.5)
Asia	645 (13.6)
Other regions ¹	144 (3.0)
Seriousness of ADRs ² , n (%)	
Death	157 (3.3)
Life-threatening event	62 (1.3)
Disability/incapacity	542 (11.4)
Hospitalization (caused or prolonged)	2,679 (56.3)
Others	2,684 (56.4)

¹including Oceania, Africa and South America

²ADRs of a unique ICSR can have a different seriousness

ADR, adverse drug reaction; ICSRs, individual case safety reports; SMQ, standardized medical dictionary for regulatory activities queries;

Table 2: Indications and mechanisms of action of molecules having a pharmacological plausibility to induce osteoporosis

Molecules	Indications	Mechanisms of action	Pharmacological plausibility
Selective 5-HT₁ agonists	Migraine	Selective 5-HT ₁ agonists	Binding to 5-HT _{1B} OB receptors → ↓ OB proliferation [80–82]
L-dopa	Parkinson disease	Dopamine substitution	Breakdown of L-dopa by COMT → ↑ Hcy → ↓ collagen cross-linking [78]
Memantine	Dementia	NMDA receptor antagonist	Down-regulation of NMDA receptors → ↓ osteogenesis [85]
Romiplostim	ITP	TPO receptor activation (c-Mpl)	Activation of MAPK, JAK/STAT and NFκB → ↑ OC formation and differentiation [70]
Macitentan	Pulmonary arterial hypertension	ET-1 receptors antagonists	ET-1 antagonism → ↓ OB proliferation and differentiation → ↓ type I collagen production → ↑ OC resorption [71–73]
Ranibizumab	Age-related macular degeneration	VEGF-A inhibitor	↓ VEGF-A → ↓ osteogenesis [86,87]
Tofacitinib	Rheumatoid arthritis	JAK1/JAK3 inhibitor	JAK1 inhibition → osteoporotic bone phenotype [88] JAK1/JAK3 inhibition → ↓ STAT3 → osteoclastogenesis [90]

c-Mpl, myeloproliferative leukemia virus oncogene; COMT, catechol-O-methyltransferase; CRBN, cereblon; ET-1, endothelin-1; Hcy, homocystein; ITP, immune thrombocytopenic purpura; JAK, Janus kinases; MAPK, mitogen-activated protein kinases; NFκB, nuclear factor-kappa B; NMDA, N-methyl-D-aspartate; OB, osteoblast; OC, osteoclast; sGC, soluble guanylate cyclase; VEGF, vascular endothelial growth factor;