Drug-induced osteoporosis/osteopenia: a pharmacovigilance analysis using the FDA Adverse Event Reporting System database

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Abstract

Objective

Drug-induced osteoporosis/osteopenia (OP/OPN) has emerged as a significant public health concern affecting bone health. However, the risk assessment of OP/OPN induced by various drugs remains incompletely understood, necessitating large-scale real-world data analysis to clarify the associated risks. The present study aims to systematically analyse OP/OPN-related adverse events (AEs).

Methods

This study utilised the FDA Adverse Event Reporting System (FAERS) database to identify OP/OPN-related adverse event reports from 2004 to 2023. Disproportionality analysis, including the reporting odds ratio and proportional reporting ratio, was applied to evaluate the signal strength of OP/OPN associated with different drug categories. Additionally, the study analysed drug classifications, time-to-onset, and trends over time.

Results

Among the 43,685 OP/OPN-related reports, anti-retroviral drugs accounted for the highest proportion of reports (20.73%), with a gradual annual increase in reporting frequency (average annual growth rate of 2.20%). This was followed by immunomodulatory/immunosuppressive agents (12.76%), proton pump inhibitors (6.25%), and hormone-related (2.88%). A significant variation was observed in the time-to-onset of OP/OPN-related adverse event among different drug categories: glucocorticoids-induced osteoporosis occurred earliest (median time-to-onset of 164 days), while anti-retroviral drug-induced osteoporosis had the longest time-to-onset (median of 1,508 days). Regarding reporting frequency, tenofovir and its combinations, esomeprazole, adalimumab, methotrexate, medroxyprogesterone, interferon beta-1A, etanercept, and rituximab were the most frequently reported drugs. In terms of signal strength, tenofovir and its combinations, adefovir, pamidronic acid, and esomeprazole the strongest signals, suggesting that these drugs may represent key risk factors for OP/OPN.

Conclusion

This FAERS-based study identified multiple drug classes associated with OP/OPN-related adverse event signals, with anti-viral drugs – particularly tenofovir disoproxil and its combination therapies – exhibiting the strongest signal. Although glucocorticoids had a lower reporting proportion, their short onset time underscores the need for vigilance. These findings provide real-world evidence for drug safety management and highlight the necessity of bone health monitoring in long-term medication users. Future studies should integrate clinical data to validate these findings and explore underlying mechanisms.

Key words

drug-induced, osteoporosis, osteopenia, FAERS, pharmacovigilance, time-to-onset

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Introduction

Osteoporosis is a systemic skeletal disease characterised by decreased bone mass and deterioration of bone microarchitecture, leading to increased bone fragility and a significantly higher risk of fractures (1). According to the operational definition established by the World Health Organisation (WHO) based on bone mineral density (BMD), osteoporosis is diagnosed when BMD is 2.5 standard deviations (SD) or more below the mean peak bone mass of a healthy young adult population (2). The prevalence of osteoporosis has been steadily increasing worldwide, particularly among the elderly (3, 4). Epidemiological data indicate that approximately 200 million people are currently affected by osteoporosis, with nearly 9 million fractures occurring annually (5, 6). In the United States, Canada, and Europe alone, the annual healthcare costs associated with osteoporosis-related fractures have reached $48 billion (7). These fractures not only severely impair patients' quality of life but also impose a significant burden on healthcare resources and pose substantial socioeconomic challenges (8). Consequently, effective prevention and management strategies are critical to mitigating the risk of fragility fractures (9).

Beyond aging, unhealthy lifestyle habits, and genetic predisposition, drug use has been identified as a major risk factor for osteoporosis (10). In recent years, drug-induced osteoporosis has garnered increasing attention. Studies have demonstrated that certain medications, including glucocorticoids (GCs), anti-retroviral drugs, proton pump inhibitors (PPIs), aromatase inhibitors, anti-epileptic drugs, and some anti-psychotics, are strongly associated with increased bone loss and fracture risk (11). These drugs influence bone metabolism through various mechanisms, such as inhibiting osteoblast activity, enhancing bone resorption, and disrupting calcium-phosphorus homeostasis (15).

However, current research on drug-induced osteoporosis remains limited (12). First, many existing studies rely on single-centre or regional datasets, making it difficult to comprehensively assess real-world drug utilisation and its impact on bone health. Second, individual susceptibility to drug-induced bone loss varies significantly, and current evidence remains insufficient in delineating the precise mechanisms, severity, and at-risk populations for drug-induced osteoporosis. Given these challenges, large-scale real-world data analyses are essential for identifying osteoporosis-related drug signals and advancing research in this field.

The FDA Adverse Event Reporting System (FAERS) serves as a critical data source for investigating drug safety (13). Although FAERS is based on voluntary reporting, which may introduce bias and data limitations, its extensive dataset and global coverage provide valuable support for drug safety signal detection (14). Against this background, the present study aims to utilise FAERS to systematically analyse OP/OPN-related adverse event (AE). By leveraging real-world data, this study seeks to identify potential drug safety signals and assess their impact in clinical practice. The findings of this study will contribute to enhancing drug safety management and optimising osteoporosis prevention strategies, ultimately facilitating personalised treatment approaches for patients at risk of osteoporosis.

Methods

Data source

This study is a retrospective pharmacovigilance analysis based on the FDA Adverse Event Reporting System (FAERS) database (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html). The FAERS database comprises seven datasets: Demographic and Administrative Information (DEMO), Drug Information (DRUG), Indications (INDI), Outcome Information (OUTC), Adverse Event Reports (REAC), Report Sources (RPSR), and Treatment Start and End Dates (THER). FAERS data are released on a quarterly basis. In this study, we retrieved and analysed all osteoporosis-related AE reports recorded in FAERS from Q1 2004 to Q3 2023.

Data extraction and cleaning

Following the FDA's best practice recommendations, duplicate reports were

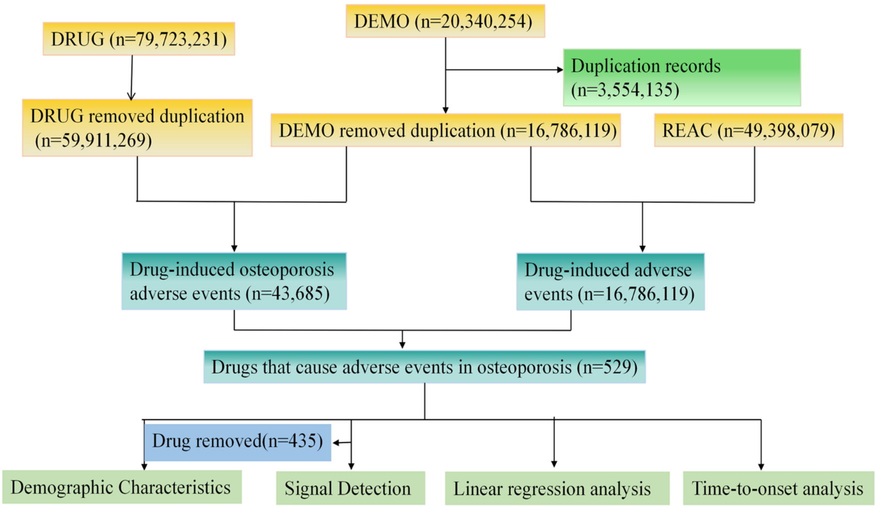


Fig. 1. Flowchart of OP/OPN-related adverse event report selection.
OP: osteoporosis; OPN: osteopenia.

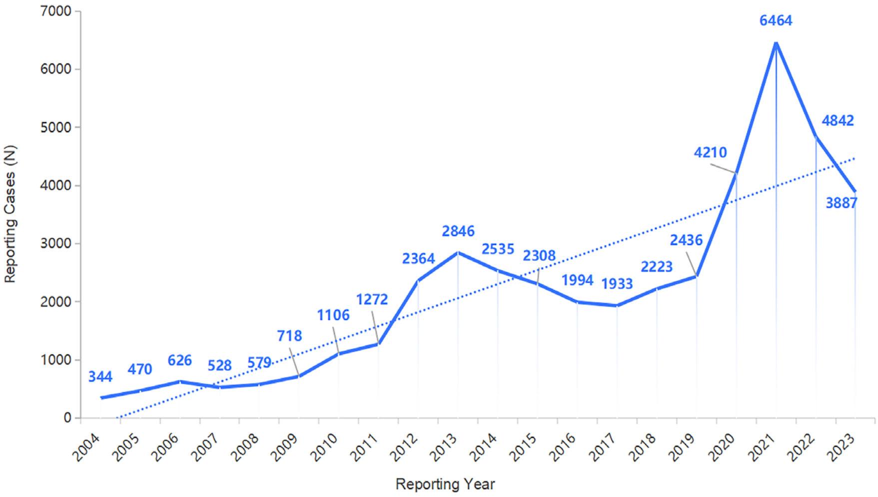


Fig. 2. Annual reporting trends of OP/OPN-related adverse events.
OP: osteoporosis; OPN: osteopenia.

identified and removed by selecting the most recent record based on FDA_DT within the same CASEID. When multiple records shared identical CASEID and FDA_DT values, the report with the highest PRIMARYID was retained to ensure data integrity and avoid redundant counting (15). Reports lacking essential identifiers (*e.g.* CASEID, DRUGNAME, or PT) were excluded. For variables with incomplete demographic or event information, the proportion of missing data was reported, and no imputation was performed to avoid introducing bias.

AEs were identified based on Preferred Terms (PTs) from the Medical Dictionary for Regulatory Activities (MedDRA, v. 26.1). To ensure consistency across the 20-year study period (2004–2023), all AEs were mapped and standardised to MedDRA version 26.1, minimising inconsistencies due to historical updates in terminology. Two PTs were selected to define osteoporosis- or low bone mass-related events: osteopenia and osteoporosis.

Only cases in which the drug was classified as the ‘primary suspect’ for the reported AE were included. Drugs indicated for the treatment of osteoporosis were excluded to avoid confounding effects. The final dataset comprised patient demographics (age, sex), suspected drugs, and associated diagnoses. The data selection process is illustrated in Figure 1.

It should be noted that FAERS reports PT-based AEs without clinical diagnostic confirmation (*e.g.* DXA results, imaging, or self-reported data); therefore, identification of osteoporosis or low bone mass relied solely on MedDRA terminology as reported by the submitter.

Time-to-onset analysis

The time-to-onset (TTO) of adverse events was calculated as the interval (in days) between the treatment start date (START_DT) and the event onset date (EVENT_DT), as recorded in the DEMO and THER datasets. To ensure accuracy, only records with complete and valid date information were included. Cases with missing day, month, or year, entirely missing dates, or implausible sequences (*e.g.* EVENT_DT preceding START_DT) were excluded, representing 38.9% of the dataset.

Statistical analysis

Drug names were standardised to their generic names using DrugBank and subsequently categorised according to the WHO Anatomical Therapeutic Chemical (ATC) classification system (https://www.whocc.no/atc_ddd_index/). Manual adjustments were performed as needed to ensure accurate classification.

AE signal detection was conducted using disproportionality analysis, a widely used pharmacovigilance approach. Specifically, reporting odds ratio (ROR) and proportional reporting ratio (PRR) were calculated from 2×2 contingency tables (Supplementary Table S1) to identify potential drug–event associations. The formulas and threshold criteria for ROR and PRR are detailed in Supplementary Table S2 (17). ROR provides robust risk estimation, while PRR offers higher specificity.

Dynamic temporal trends in OP/OPN-related AE reports were assessed from 2004 to 2023. Linear regression was performed using the annual reporting proportion as the dependent variable and calendar year as the independent variable to estimate the annual rate of change and statistical significance. Year-over-year (YoY) percentage changes were also calculated to capture short-term fluctuations in reporting patterns.

Descriptive statistics were used to

summarise the data: categorical variables were expressed as counts and percentages, and continuous variables as medians with interquartile ranges (IQRs). All data cleaning, processing, and statistical analyses were conducted using Microsoft Excel 2019 and R software (v. 4.3.2), with all AEs mapped to MedDRA version 26.1 to ensure terminological consistency across the 20-year study period.

Table I. Demographic characteristics.

Total (n)	(n=43,685)
Sex	
female (%)	27,376 (62.7%)
male (%)	13,331 (30.5%)
missing (%)	2,978 (6.8%)
Weight	
mean (SD)	71.7 (21.9)
median [min, max]	68 [0, 99.8]
missing (%)	30,692 (70.3%)
Age	
mean (SD)	56.7 (15.4)
median [min, max]	58.0 [0, 100]
missing (%)	16,960 (38.8%)
Reporter type	
Consumer (CN)	16,175 (37.0%)
Lawyer (LW)	10,082 (23.1%)
Physician (MD)	7,933 (18.2%)
Other healthcare professional (OT)	3,246 (7.4%)
Health professional (PHW)	2,256 (5.2%)
Reporting country	
United States of America (USA)	29,820 (68.2%)
Canada (CA)	3,259 (7.5%)
United Kingdom (UK)	988 (2.3%)
Federative Republic of Brazil (BR)	978 (2.2%)
Germany (DE)	917 (2.1%)
Diagnosis	
HIV infection	11,091 (25.4%)
Product used for unknown indication	4,025 (9.2%)
Rheumatoid arthritis	3,493 (8.0%)
Osteoporosis	3,000 (6.9%)
Gastrooesophageal reflux disease	1,297 (3.0%)

Table II. Top 50 drug classes associated with OP/OPN-related adverse event reports in FAERS (2004-2023).

Drug classification	n. (Total proportion)	Most adverse drug events reported (year)	Maximum reporting drug (n. Classification proportion)
Anti-retroviral	9,256 (20.73%)	4,271 (2021)	Tenofovir Disoproxil (4,471, 48.30%)
Immunomodulatory/ immunosuppressive	5,696 (12.76%)	695 (2020)	Adalimumab (1,427, 25.05%)
glucocorticoid	1,165 (2.61%)	129 (2019)	Prednisone (298, 25.58%)
Hormone-related	1,284 (2.88%)	183 (2010)	Medroxyprogesterone (390, 30.37%)
Proton pump inhibitors	2,790 (6.25%)	926 (2013)	Esomeprazole (2,642, 94.70%)
Other drugs	1,112 (2.49%)	155 (2021)	Rofecoxib (213, 19.15%)
Anti-convulsant	245 (0.55%)	26 (2011)	Pregabalin (146, 59.59%)

OP: osteoporosis; OPN: osteopenia.

Table III. Linear regression analysis of OP/OPN-related adverse event reports by drug class.

Drug classification	2004	2023	Year-on-year change (95% CI)	*p*-value
Anti-retroviral	0.87%	42.63%	2.20 (1.36, 3.05)	<0.0001*
Immunomodulatory/ immunosuppressive	18.90%	13.51%	0.24 (-0.15, 0.63)	0.25
glucocorticoid	2.32%	2.39%	0.049 (-0.05, 0.15)	0.34
Hormone-related	6.40%	1.47%	-0.87 (-1.27, -0.48)	0.00038*
Proton pump inhibitors	0.29%	0.46%	-0.20 (-1.03, 0.64)	0.65
Other drugs	12.79%	1.29%	-0.85 (-1.37, -0.34)	0.0043*
Anti-convulsant	2.91%	0.13%	-0.094 (-0.13, -0.05)	0.00034*

OP: osteoporosis; OPN: osteopenia.
*The difference in year-on-year change is statistically significant.

Results

Demographic characteristics

From 2004 to Q3 2023, the FAERS database recorded a total of 49,398,079 AEs. A total of 43,685 patients were identified, involving 529 different drugs with OP/OPN-related AEs. As shown in Figure 2, the number of reported cases exhibited a gradual upward trend over time, reaching its peak in 2021 (6,5464 cases).

Significant demographic differences were observed among these OP/OPN-related AEs (Table I). Gender distribution analysis revealed that female patients accounted for 62.7% (27,376 cases), significantly higher than male patients (30.5%, 13,331 cases), while 6.8% of reports lacked gender information (Fig. 3A). Due to a high proportion of missing weight data (70.3%), a comprehensive assessment of weight distribution was limited. Among available records, the mean patient weight was 71.7 kg (SD = 21.9 kg), with a median of 68 kg (range: 0–99.8 kg). The age data had a missing rate of 38.8%, and among reported cases, the mean patient age was 56.7 years (SD = 15.4), with a median of 58 years (range: 0–100 years).

The distribution of report sources varied significantly. Among the top five sources, consumers (CN) accounted for the highest proportion (37.0%, 16,175 cases), followed by lawyers (LW, 23.1%, 10,082 cases) and physicians (MD, 18.2%, 7,933 cases). Reports from other healthcare professionals (OT, 7.4%, 3,246 cases) and public health workers (PHW, 5.2%, 2,256 cases) were relatively less frequent (Fig. 3B).

In terms of geographical distribution, the United States accounted for the majority of reports (68.2%, 29,820 cases), followed by Canada (7.5%, 3,259 cas-

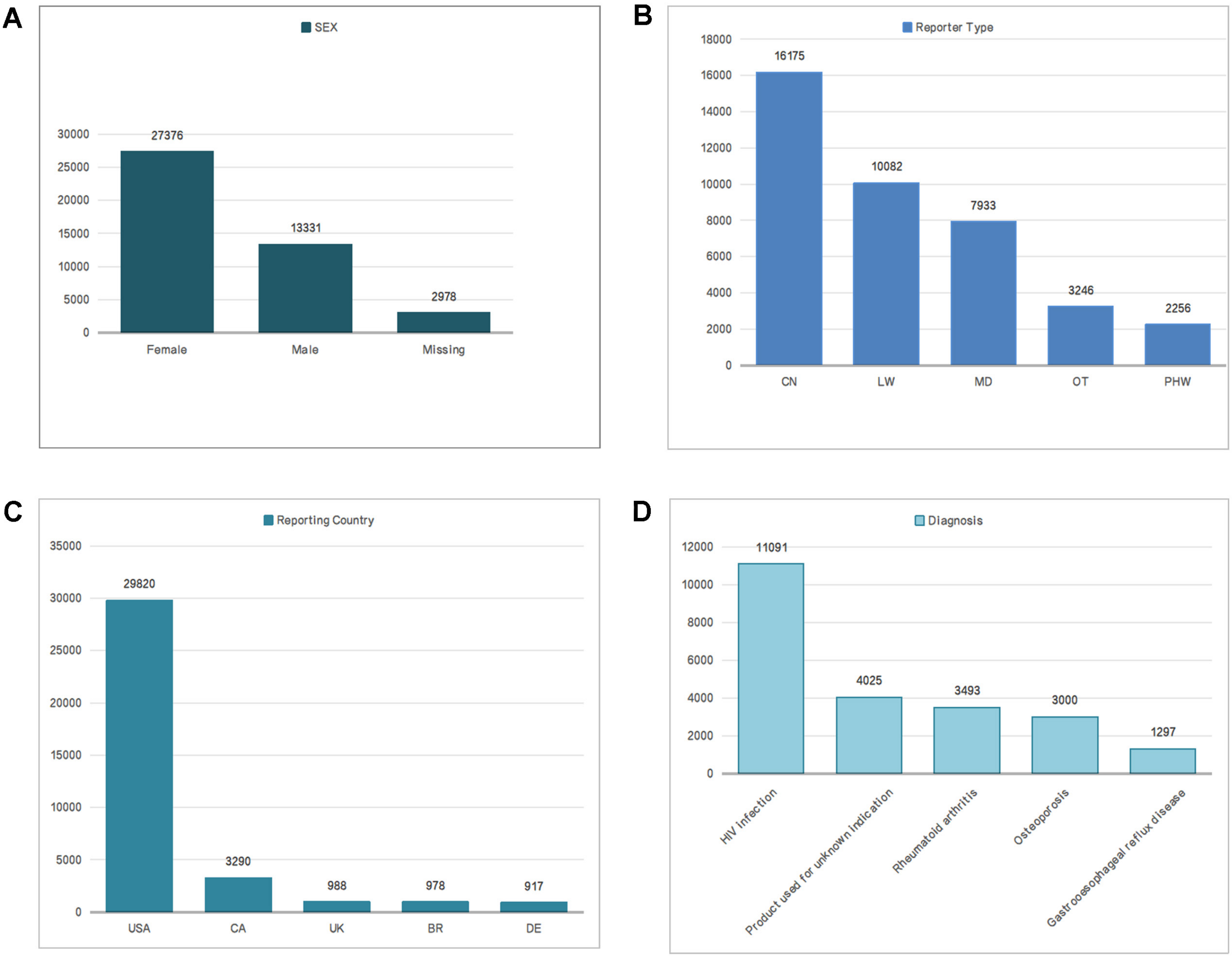


Fig. 3. Overview of OP/OPN-related adverse event reports.
A: Distribution of OP/OPN-related adverse event reports by gender. **B**: Distribution of OP/OPN-related adverse event reports by report source.
C: Distribution of OP/OPN-related adverse event reports by country. **D**: Primary diagnoses with OP/OPN-related adverse events.
OP: osteoporosis; OPN: osteopenia; CN: consumer; LW: lawyer; MD: medical doctor; OT: other healthcare professionals; PHW: public health worker; USA: United States; CA: Canada; UK: United Kingdom; BR: Brazil; DE: Germany.

es), the United Kingdom (2.3%, 988 cases), Brazil (2.2%, 978 cases), and Germany (2.1%, 917 cases) (Fig. 3C).

Among the top five associated diagnoses, HIV infection showed the strongest association with osteoporosis-related AEs (25.4%, 11,091 cases), followed by rheumatoid arthritis (8.0%, 3,493 cases), osteoporosis (6.9%, 3,000 cases), and gastroesophageal reflux disease (3.0%, 1,297 cases) (Fig. 3D).

Major drug categories with osteoporosis-related AEs

An analysis of the top 50 drugs associated with OP/OPN revealed that these drugs collectively accounted for 61.38% of all reported cases. Osteoporosis-related AEs were primarily concentrated in seven major drug categories, including anti-retroviral drugs, immunomodulatory/immunosuppressive agents, GCs, hormone-related drugs, PPIs, -convulsant drugs, and other drugs (*e.g.* non-steroidal anti-inflammatory drugs) (Table II, Suppl. Table S3, Suppl. Fig. 1-2).

Among these categories, anti-retroviral drugs had the highest proportion of reports, accounting for 20.73% (9,256 cases), with a peak occurrence in 2021 (4,271 cases). Tenofovir disoproxil was the most frequently reported drug in this category, contributing 48.30% (4,471 cases). Immunomodulatory/immunosuppressive agents accounted for 12.76% (5,696 cases), with adalimumab being the leading drug (25.05%, 1,427 cases). GCs comprised 2.61% (1,165 cases), predominantly driven by prednisone (25.58%). Hormone-related drugs accounted for 2.88% (1,284 cases), with medroxyprogesterone as the primary drug (30.37%). PPIs were implicated in 6.25% (2,790 cases), with esomeprazole accounting for 94.70% of PPI-related reports. Anti-convulsant drugs and other drugs contributed 0.55% (245 cases) and 2.49% (1,112 cases), respectively, with pregabalin (59.59%) and rofecoxib (19.15%) being the most frequently reported in these categories.

A dynamic analysis from 2004 to 2023 (Table III, Fig. 4) indicated a significant increase in the proportion of reports associated with anti-retroviral

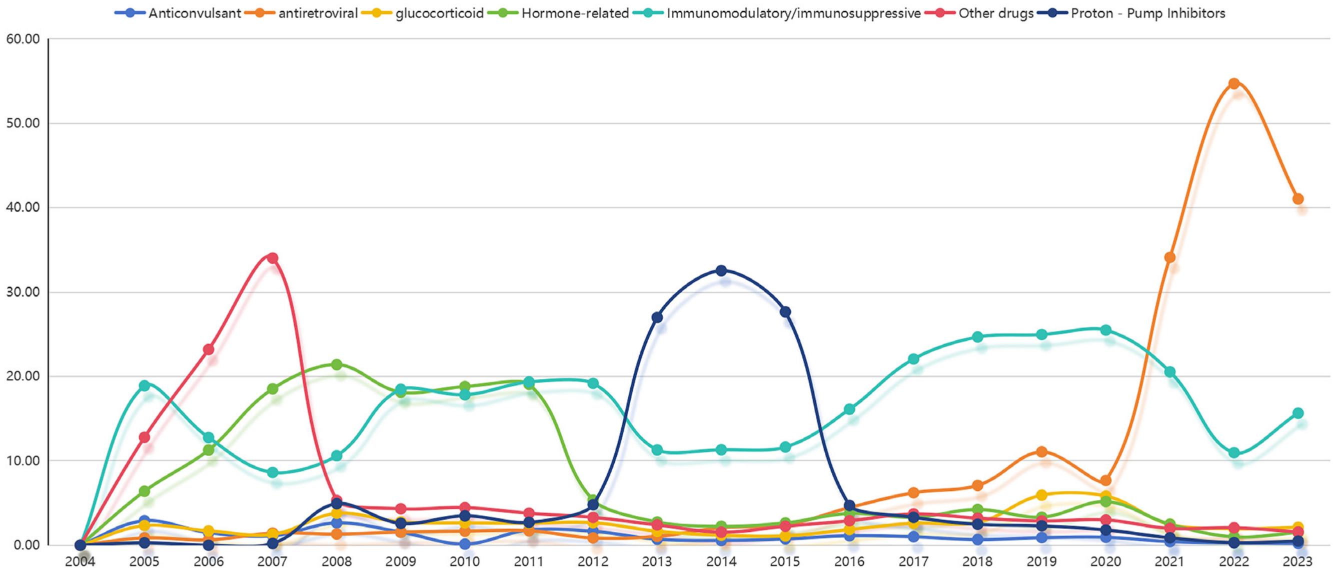


Fig. 4. Temporal trends of OP/OPN-related cases reported to FAERS by drug category.
OP: osteoporosis; OPN: osteopenia.

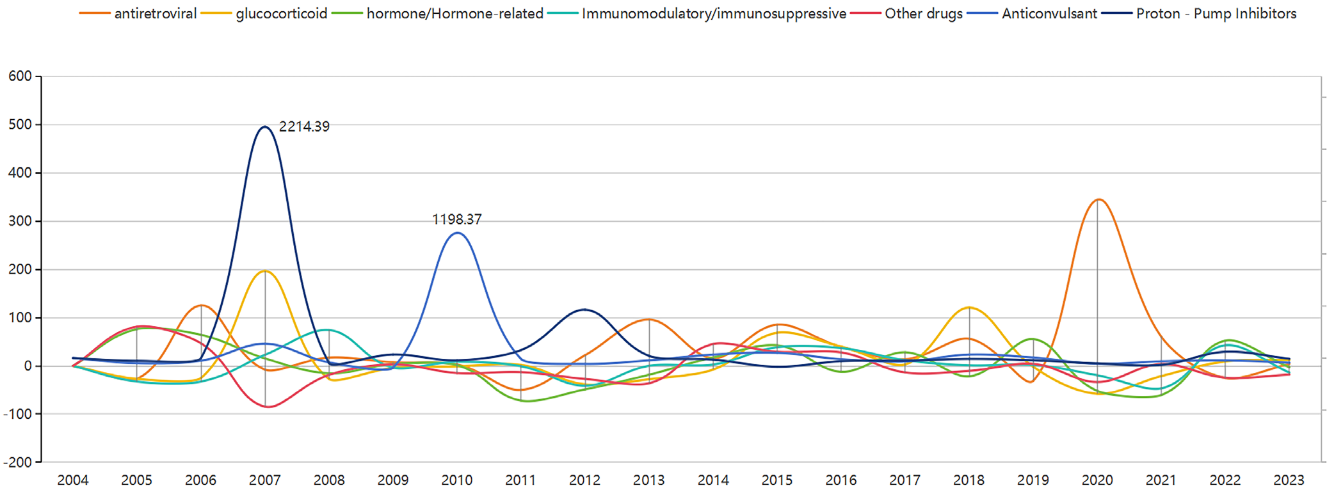
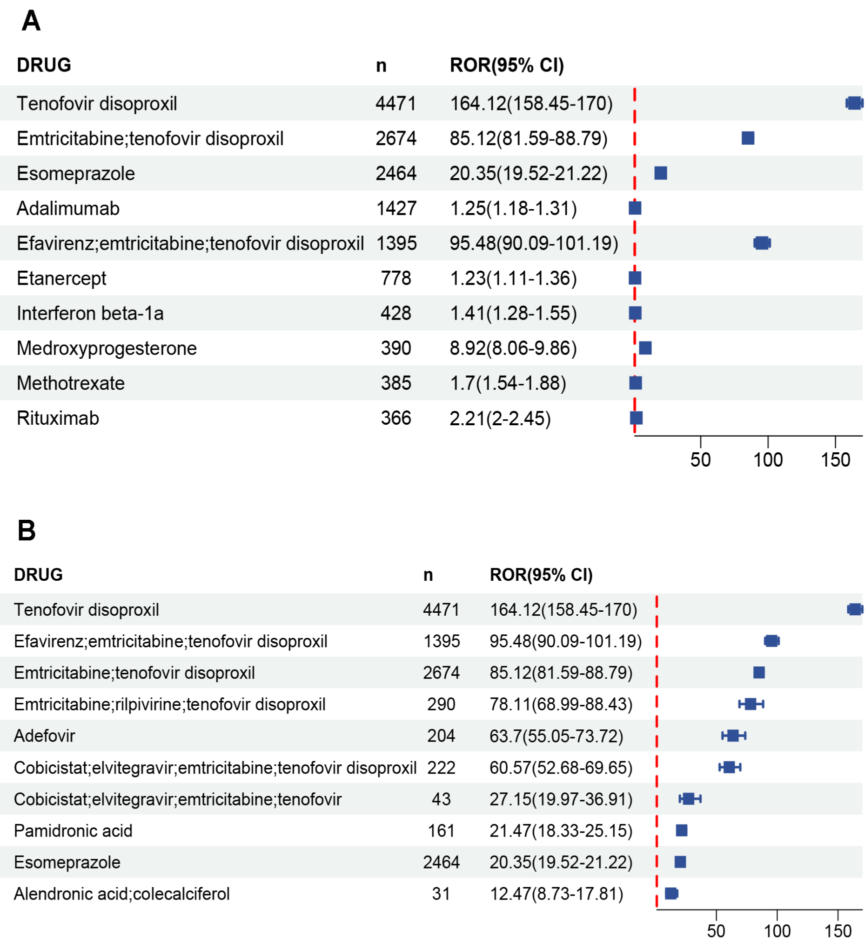


Fig. 5. Year-over-year percentage change of OP/OPN-related cases reported to FAERS by drug category.
OP: osteoporosis; OPN: osteopenia.

drugs, rising from 0.87% in 2005 to 42.63% in 2023, with an average annual growth rate of 2.20% (95% CI: 1.36–3.05, *p*<0.0001). Year-over-year (YoY) change analysis (Fig. 5) showed a 344.33% increase in 2020, followed by a moderate decline, yet the proportion remained high (54.70%) in 2022.

In contrast, GCs-associated reports remained relatively stable, fluctuating from 2.32% in 2005 to 2.39% in 2023 (*p*=0.34). However, YoY changes exhibited significant fluctuations, such as a 120.73% increase in 2018 and a 57.62% decline in 2020. Immunomodulatory/immunosuppressive drug-related reports showed an overall decreasing trend, dropping from 18.90% in 2005 to 13.51% in 2023 (*p*=0.25). Despite this decline, certain years exhibited substantial fluctuations, including a 38.50% increase in 2015 and a 42.72% increase in 2022, both of which correlated with adalimumab usage patterns.

The proportion of hormone-related drugs showed a significant decline, decreasing from 6.40% in 2005 to 1.47% in 2023 (annual change rate: -0.87%, *p*=0.00038). YoY fluctuations were notable, with a 48.56% decrease in 2012, followed by an 52.27% increase in 2022. PPIs exhibited minimal changes in reporting proportion, increasing from 0.29% in 2005 to 0.46% in 2023 (*p*=0.65). Although PPI-related reports peaked in 2013, they subsequently declined, with a 60.20% increase in 2022, followed by a 6.57% decrease in 2023. Anti-convulsant-related reports declined sharply, decreasing from 2.91% in 2005 to 0.13% in 2023 (*p*<0.0001). The highest YoY increase (1,198.37%) occurred in 2010, but a progressive decline followed, culminating in a 43.38% reduction in 2023, likely related to Pregabalin usage trends. Other drugs also showed a decreasing trend, dropping from 12.79% in 2005 to 1.29% in 2023 (*p*=0.00034), with minor fluctuations in specific years, such as a 46.72% increase in 2006.



A

DRUG	n	ROR(95% CI)
Tenofovir disoproxil	4471	164.12(158.45-170)
Emtricitabine;tenofovir disoproxil	2674	85.12(81.59-88.79)
Esomeprazole	2464	20.35(19.52-21.22)
Adalimumab	1427	1.25(1.18-1.31)
Efavirenz;emtricitabine;tenofovir disoproxil	1395	95.48(90.09-101.19)
Etanercept	778	1.23(1.11-1.36)
Interferon beta-1a	428	1.41(1.28-1.55)
Medroxyprogesterone	390	8.92(8.06-9.86)
Methotrexate	385	1.7(1.54-1.88)
Rituximab	366	2.21(2-2.45)

B

DRUG	n	ROR(95% CI)
Tenofovir disoproxil	4471	164.12(158.45-170)
Efavirenz;emtricitabine;tenofovir disoproxil	1395	95.48(90.09-101.19)
Emtricitabine;tenofovir disoproxil	2674	85.12(81.59-88.79)
Emtricitabine;rilpivirine;tenofovir disoproxil	290	78.11(68.99-88.43)
Adefovir	204	63.7(55.05-73.72)
Cobicistat;elvitegravir;emtricitabine;tenofovir disoproxil	222	60.57(52.68-69.65)
Cobicistat;elvitegravir;emtricitabine;tenofovir	43	27.15(19.97-36.91)
Pamidronic acid	161	21.47(18.33-25.15)
Esomeprazole	2464	20.35(19.52-21.22)
Alendronic acid;colecalciferol	31	12.47(8.73-17.81)

Fig. 6. Top 10 drugs associated with OP/OPN AEs based on frequency and signal strength.
A: Top 10 Drugs with the highest frequency of osteoporosis AEs.
B: Top 10 Drugs with the highest signal strength for osteoporosis AEs.
OP: osteoporosis; OPN: osteopenia; AE, adverse event.

Table IV. Time to onset of OP/OPN-related adverse events across different drug classes (days).

Drug classification	25th percentile, days	Median, days	75th percentile, days	Maximum, days
Anti-convulsant	30.5	1,410	6,802	21,550
glucocorticoid	9.5	164	761	4,051
Immunomodulatory/ immunosuppressive	63	337	1,204	14,865
Proton pump inhibitors	470	1,286	2,252	7,852
Anti-retroviral	652	1,508	2,838	8,778
Hormone-related	234	1412	3,095	15,887

OP: osteoporosis; OPN: osteopenia.

Signal detection of drug-related AEs

A total of 94 drugs were included in the signal strength analysis of OP/OPN utilising ROR and PRR. The results (Fig. 6A-B; Suppl. Tables S4-S5) identified the top 10 drugs with the highest reporting frequency, ranked as follows: tenofovir disoproxil (ROR=164.12), emtricitabine;tenofovir disoproxil (ROR=85.12), esomeprazole (ROR=20.35), adalimumab (ROR=1.25), efavirenz;emtricitabine;tenofovir disoproxil (ROR=95.48), etanercept (ROR=1.23), interferon beta-1a (ROR=1.41), medroxyprogesterone (ROR=8.92), methotrexate (ROR=1.7), rituximab (ROR=2.21).

The top 10 drugs ranked by ROR signal strength were consistent with those ranked by PRR, as follows: tenofovir disoproxil (ROR=164.12), efavirenz; emtricitabine;tenofovir disoproxil (ROR=95.48), emtricitabine;tenofovir disoproxil (ROR=85.12), emtricitabine;rilpivirine;tenofovir disoproxil (ROR=78.11), adefovir (ROR=63.7), cobicistat;elvitegravir;emtricitabine; tenofovir disoproxil (ROR=60.57), cobicistat;elvitegravir;emtricitabine; tenofovir (ROR=27.15), pamidronic acid (ROR=21.47), esomeprazole (ROR=20.35), alendronic acid; colecalciferol (ROR=12.47). Figure 6A presents the top 10 drugs with the highest number of osteoporosis-related AEs, while Figure 6B illustrates the top 10 drugs with the highest signal strength for osteoporosis-related AEs.

Time-to-onset analysis

The TTO analysis of the top 50 drugs associated with OP/OPN-related AEs revealed a median TTO of 782 days (IQR: 183–2,145.5 days), with approximately 50% of cases occurring within 2.1 years of drug initiation (Table IV, Fig. 7A-B).

Further analysis indicated significant variations in TTO across different drug categories (Fig. 7C). GCs had the shortest median TTO at 164 days (IQR: 9.5–761 days), while anti-retroviral had a median TTO of 1508 days (IQR: 652–2,838 days). The median TTO for immunomodulatory/immunosuppressive drugs was 337 days (IQR: 63–1,204 days), whereas PPIs exhibited a longer median TTO of 1286 days (IQR: 470–2,252 days). Anti-convulsant drugs had the median TTO at 1,410 days (IQR: 30.5–6,802 days), approximately 4 years, followed by hormone-related drugs, with a median TTO of 1,412 days (IQR: 234–3,095 days).

Overall, GCs were associated with the shortest time-to-onset for OP/OPN-related AEs, whereas anti-retroviral and hormone-related drugs exhibited the longest onset durations.

Discussion

This study highlights the demographic characteristics of drug-induced OP/OPN cases. Females accounted for the majority of cases (62.7%), consistent

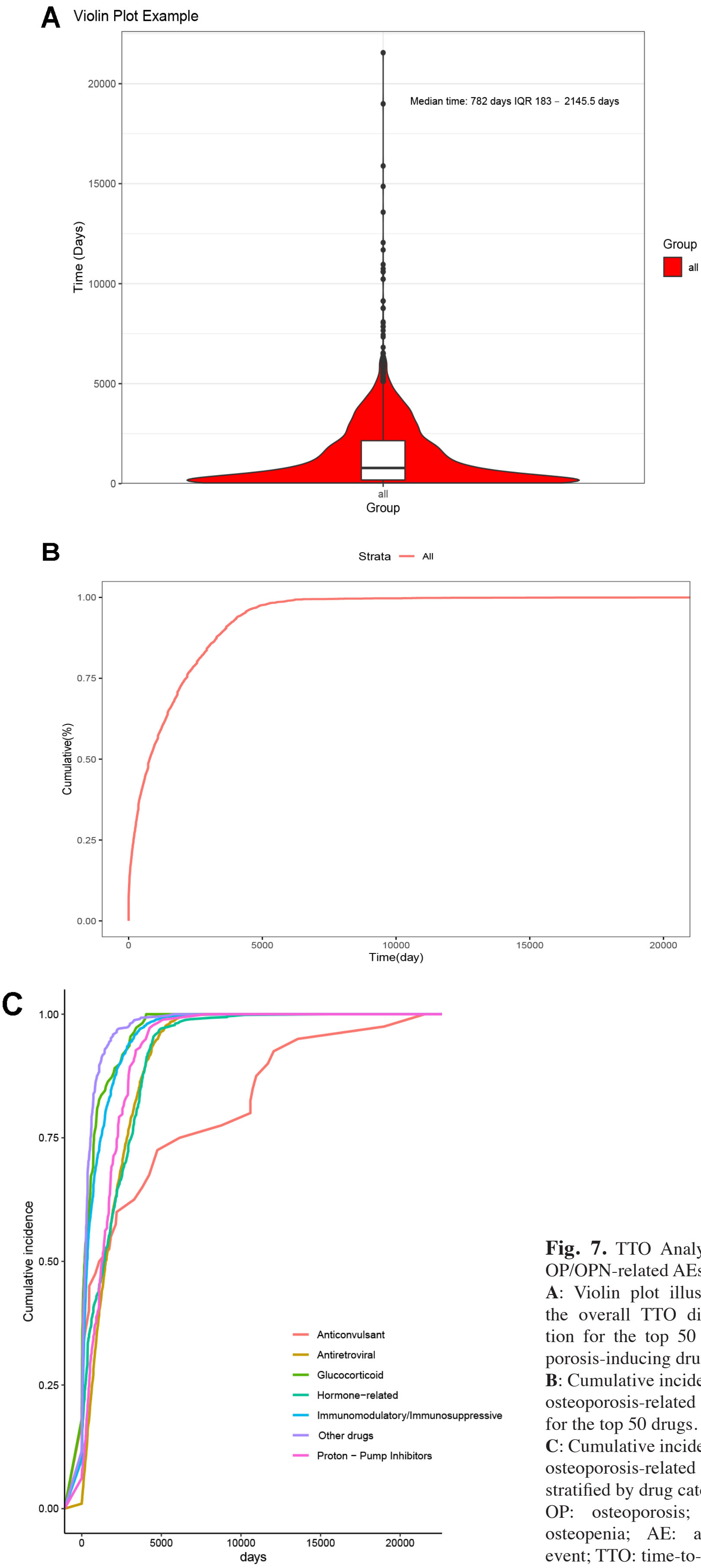


Fig. 7. TTO Analysis of OP/OPN-related AEs.
A: Violin plot illustrating the overall TTO distribution for the top 50 osteoporosis-inducing drugs.
B: Cumulative incidence of osteoporosis-related AEs for the top 50 drugs.
C: Cumulative incidence of osteoporosis-related AEs stratified by drug category.
OP: osteoporosis; OPN: osteopenia; AE: adverse event; TTO: time-to-onset.

with the increased vulnerability of postmenopausal women due to oestrogen deficiency (18). Although this study specifically focused on drug-induced osteoporosis, this sex disparity may partially reflect the higher susceptibility of women to bone loss. Nevertheless, males represented a substantial proportion (30.5%), indicating that drug-induced osteoporosis should not be overlooked in men, especially those receiving long-term hormone therapy or anti-retroviral treatment (19). High missing data for body weight (70.3%) limited a detailed analysis, but the available data suggest that lower body weight may increase susceptibility, aligning with prior evidence that reduced skeletal loading accelerates bone loss (20, 21). although its precise role in osteoporosis requires further investigation. Age analysis showed that adverse events predominantly occurred in middle-aged and elderly individuals (mean 56.7 years, median 58 years), although cases in younger patients – potentially linked to anti-retroviral or hormone-related drugs – warrant further attention (22, 23).

Among the types of AE reporters, consumers accounted for the highest proportion (37.0%), followed by lawyers (23.1%) and physicians (18.2%). The predominance of consumer-reported cases may reflect the chronic nature of osteoporosis, as many patients develop the condition gradually while receiving long-term medication at home rather than being hospitalised due to acute events, leading to less direct physician involvement. Additionally, the relatively low proportion of physician reports suggests that drug-induced osteoporosis may not yet receive sufficient attention in clinical practice, highlighting the need for enhanced recognition and management of drug-induced osteoporosis within healthcare systems.

Most reports originated from the United States, reflecting the coverage and reporting practices of the FAERS database, while data from low- and middle-income countries remain limited, emphasising the need for broader global pharmacovigilance. HIV-infected patients represented a substantial proportion of cases, highlighting the impact of anti-retroviral drugs on bone metabolism (24, 25). Other conditions, such as rheumatoid arthritis and pre-existing osteoporosis, suggest that immunomodulatory agents and drugs affecting bone metabolism may contribute to OP/OPN pathogenesis (26).

Based on our analysis, the top 50 drugs associated with OP/OPN-related AE were classified into seven major categories. While glucocorticoids have traditionally been reported as the primary contributors to drug-induced osteoporosis, our findings indicate that anti-retroviral drugs accounted for the highest proportion (20.73%), with tenofovir disoproxil dominating this category (48.30%). Furthermore, tenofovir disoproxil and its combination therapies ranked among the top six drugs with the highest ROR and PRR signal strengths. A meta-analysis by Brown *et al.* (27) found that individuals receiving anti-retroviral therapy (ART) had a 2.5-fold increased risk of bone mineral density (BMD) loss and a significantly higher risk of osteoporosis compared to untreated individuals. This effect is attributed to anti-retroviral drugs disrupting bone metabolism through multiple mechanisms, including inhibition of osteoblast activity, suppression of bone formation, and stimulation of osteoclast-mediated bone resorption (28-32). Consistently, our analysis of FAERS data showed a significant upward trend in OP/OPN-related adverse events associated with anti-retroviral drugs over time, highlighting the clinical relevance of monitoring bone health in patients receiving these therapies. These findings underscore the importance of investigating drug-induced osteoporosis to optimise treatment strategies and mitigate the burden of osteoporosis-related complications.

Glucocorticoid-induced osteoporosis is characterised by low bone turnover and increased fracture risk, with an incidence of 30–50%, particularly in postmenopausal women and elderly men (33-35). GCs suppress osteoblast differentiation and activity, leading to trabecular bone loss, and indirectly impair bone metabolism by reducing calcium absorption, increasing renal calcium excretion, and inhibiting sex hormone secretion (36, 37). Even low-dose prednisone (2.5 mg/day) increases osteoporosis risk, with higher doses (≥7.5–10 mg/day) substantially elevating hip and vertebral fracture risk (38, 39). Hormone-related drugs, such as aromatase inhibitors and medroxyprogesterone, also reduce bone density and increase fracture risk by altering estrogen production or hormone metabolism (40, 41).

In our FAERS analysis, GCs-related OP/OPN accounted for 2.61% of reports, whereas hormone-related drugs accounted for 2.88% (1,165 cases), with medroxyprogesterone representing 25.58% of these. GCs-related reports remained relatively stable from 2005 to 2023 (p=0.34), whereas hormone-related drug reports declined significantly from 6.40% to 1.47% (annual change rate -0.81%, p=0.00093), despite notable year-to-year fluctuations. TTO analysis indicated that GCs-induced OP/OPN typically occurs early, with 50% of cases within 164 days and 75% within 2 years. In contrast, hormone-related drug-induced OP/OPN tends to manifest later, with 50% of cases within 1,412 days and 75% after approximately 8 years.

These findings highlight the need for careful risk assessment and management of both drug classes. Clinicians should monitor dosage and treatment duration, implement preventive measures such as calcium and vitamin D supplementation or bisphosphonate therapy, and closely track bone mineral density, particularly in patients on long-term hormone-related therapies, to reduce fracture risk and improve long-term outcomes.

The immune system and bone metabolism are intricately interconnected, with immune cells influencing the mechanisms of osteoporosis through cytokine secretion and inflammatory regulation (42). Some studies suggest that immunomodulatory and immunosuppressive drugs may indirectly affect bone metabolism by modulating the immune response (43). However, direct adverse effects of these drugs on bone health remain less well-documented. In the present analysis, immunomodulatory and immunosuppressive drugs accounted for 12.76% (5,696 cases) of OP/OPN-related AEs, making them the second most frequently reported category after anti-retroviral drugs. Among them, adalimumab was the most commonly reported, representing 25.05% (1,427 cases) of this category.

The trend analysis indicated a decline in the proportion of reported OP/OPN-related events associated with immunomodulatory and immunosuppressive drugs, decreasing from 18.90% in 2005 to 13.51% in 2023, though this change was not statistically significant (p=0.25). Despite the overall downward trend, annual fluctuations were substantial, with notable increases in 2015 (36.91%) and 2022 (42.72%). Furthermore, TTO analysis revealed that associated with these drugs typically occurred early, with 50% of cases reported within 337 days of drug initiation. These findings highlight the need for heightened awareness of the potential bone metabolism risks posed by immunomodulatory and immunosuppressive drugs. Given their widespread use and potential impact on skeletal health, clinical practice should incorporate routine osteoporosis risk assessments, particularly for long-term treatment. Personalised bone health management strategies, including regular BMD monitoring, early preventive interventions, and treatment optimisation, are crucial for mitigating drug-related bone AE.

PPIs and anti-convulsants also play a significant role in osteoporosis development (44). PPIs may impair calcium absorption and disrupt bone metabolism by suppressing gastric acid secretion, thereby increasing fracture risk (45). Previous studies have reported that long-term PPI use is associated with a 20–50% increased risk of hip and vertebral fractures (46). In this analysis, OP/OPN-related AE linked to PPIs accounted for 6.25% (2,790 cases), with esomeprazole overwhelmingly dominant, representing 94.70% of these cases. PPIs ranked third in terms of event frequency, and further signal analysis indicated that esomeprazole ranked nine among the top ten drugs with the highest ROR and PRR values (ROR: 20.35, PRR: 19.65), suggesting that it may be a key driver of osteoporosis risk within this category. TTO analysis showed that PPI-induced OP/OPN events had a median onset time of 3.5 years, with 75% of cases occurring within six years. Although the overall OP/OPN risk associated with PPIs is lower than that of high-risk drugs such as GCs, their potential long-term skeletal effects should not be overlooked. Enhanced monitoring and preventive strategies should be implemented for long-term PPI users to minimise osteoporosis and fracture risk.

Anti-convulsants contribute to osteoporosis by accelerating vitamin D metabolism, reducing calcium absorption, and inhibiting bone formation, significantly increasing fracture risk (47, 48). Studies have shown that anti-convulsant use is associated with a 1.2- to 2-fold increase in fracture risk (49). In this study, anti-convulsant-related AE accounted for 0.55% (245 cases), with gabapentin being the most frequently reported drug (59.59%). TTO analysis indicated that OP/OPN-related events associated with anti-convulsants had a median of 1,410 days, suggesting that the risk manifests relatively early.

In summary, the potential impact of PPIs and anti-convulsants on bone health warrants greater attention. Esomeprazole, in particular, stands out due to its high signal strength and substantial case proportion. Long-term users of these medications should undergo regular osteoporosis screening and intervention. Optimising treatment strategies, ensuring adequate calcium and vitamin D supplementation, and implementing bone-protective therapies when necessary may help mitigate fracture risk and improve long-term patient outcomes.

This study provides insights into drug-induced osteoporosis and osteopenia from FAERS; however, several limitations should be acknowledged. First, FAERS is a voluntary reporting system, which may lead to underreporting, reporting bias, and variable data completeness. Although duplicates were removed per CASEID, some may persist. Second, diagnostic certainty may differ between healthcare professionals and consumers, and all reporter types were included, which remains a limitation despite MedDRA standardisation. Third, changes in drug formulations and prescribing patterns over the 20-year study period may affect reporting, though all events were harmonised to MedDRA version 26.1. Fourth, FAERS lacks detailed information on drug dosage, frequency, and cumulative exposure beyond time-to-event data, preventing assessment of dose-response relationships or treatment duration effects. Fifth, disproportionality methods (ROR and PRR) cannot adjust for confounders or polypharmacy, and missing demographic data (70.3% for weight, 38.8% for age) limit stratified analyses. Therefore, all findings should be interpreted as hypothesis-generating rather than confirmatory.

Conclusion

This study highlights the risk of adverse events related to drug-induced osteoporosis/osteopenia, with anti-retroviral drugs showing the highest reporting frequency, differing from previous perceptions. Although glucocorticoids have a lower reporting rate, their shorter onset time and significant risk warrant close attention. Proton pump inhibitors (especially esomeprazole) exhibit higher signal strength in long-term use and should also be carefully monitored. These findings provide essential evidence for optimising drug safety management and clinical practice. Future research should integrate multi-centre real-world data to further explore racial differences, dose-response relationships, and time dynamics to enhance drug safety and improve long-term patient outcomes.

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