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REVIEW

A systematic review and meta-analysis of sequential treatment strategies for osteoporosis

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Abstract

Summary We performed a systematic review and meta-analysis of the efficacy of sequential osteoporosis treatment strategies. Sequential strategies resulting in the greatest BMD gain included romosozumab to denosumab or bisphosphonates; teriparatide to romosozumab or denosumab; and bisphosphonates to romosozumab. These findings can help guide sequential medication choice for patients with osteoporosis.

Purpose The purpose of this systematic review and meta-analysis was to evaluate the efficacy of sequential osteoporosis medication strategies on bone mineral density (BMD) and fracture outcomes.

Methods Pubmed, Embase, and Cochrane Library databases were searched, and pre-specified criteria were applied to select relevant primary studies for inclusion in this systematic review and meta-analysis.

Results Thirty-nine primary studies were included. Meta-analysis summary estimates for BMD change on the second medication in a treatment sequence showed robust BMD gain with bisphosphonates followed by 1 year of romozosumab at the lumbar spine (10.1%, 95% CI 9.9–10.4), femoral neck (3.1%, 95% CI 2.9–3.4), and total hip (3.1%, 95% CI 2.7–3.5). Moderate BMD gains were found with romozosumab followed by 1 year of denosumab, with summary estimates of 4.0% (95% CI 1.2–6.7) at the lumbar spine, 2.2% (95% CI 0.5–3.8) at the femoral neck, and 2.8% (95% CI 0.8–4.9) at the total hip; similar gains were found with teriparatide transitioned to 1 year of denosumab. Bisphosphonates followed by 1 year of denosumab resulted in significant BMD gain at the lumbar spine (3.5%, 95% CI 2.8–4.2), femoral neck (1.5%, 95% CI 1.2–1.9), and total hip (2.1%, 95% CI 1.8–2.3). However, bisphosphonates transitioned to 1 year of teriparatide resulted in significant BMD gain at the lumbar spine (5.1%, 95% CI 4.4–5.9) but not at the hip.

Conclusion These findings provide a rigorous summary of the evidence to guide sequential medication choice for patients with osteoporosis.

Keywords Anabolics · Antiresorptives · Bone mineral density · Fracture prevention · Osteoporosis · Sequential therapy

Introduction

Osteoporosis, a bone disease characterized by compromised bone strength and increased risk of fracture, is highly prevalent among older adults, with substantial associated morbidity, mortality, and costs [1–7]. There are many effective medications for treatment of osteoporosis that increase bone mineral density (BMD) and reduce risk of fragility fracture, which can be broadly classified into two categories based on mechanism of action—antiresorptive and anabolic agents. Antiresorptive agents' primary mechanism of action involves inhibiting bone breakdown; examples include bisphosphonates (alendronate, ibandronate, risedronate, zoledronic acid), denosumab (a human monoclonal antibody), and raloxifene (a selective estrogen receptor modulator). Anabolic agents build bone, and include teriparatide (a parathyroid hormone analog), abaloparatide (a parathyroid hormone-related protein analog), and romosozumab (a humanized monoclonal antibody that appears to have dual-action anabolic and antiresorptive properties) [8]. Individual osteoporosis medications should not be continued indefinitely, for a variety of reasons [9]. Bisphosphonates are associated with a risk of rare but serious adverse events (e.g., atypical

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femur fracture, osteonecrosis of the jaw) with increasing duration of therapy [9]. Thus, for patients who have taken bisphosphonates for more than 3 to 5 years, periods of time off treatment, or drug holidays, may be advised to lower risk of adverse events, during which some residual pharmacological activity is maintained [9]. For denosumab drug holidays are not recommended due to rapid decline in BMD and increased risk of vertebral fractures after cessation; thus, if denosumab is discontinued, subsequent treatment with another osteoporosis medication is recommended to prevent bone loss and vertebral fractures [10]. With respect to anabolic therapies, the United States Food and Drug Administration (FDA) previously had a 2-year lifetime regulatory limit on anabolic therapies that target the parathyroid hormone receptor (teriparatide and abaloparatide), due to theoretical risk of increased rates of osteosarcoma. This limit has been removed for teriparatide. Romosozumab use is limited to one year because its anabolic effect wanes afterwards.

Although most individual osteoporosis medications should not be used indefinitely, osteoporosis is a chronic disease that may require treatment over several decades of life, and thus, long-term management of osteoporosis involves transitions between medications. As such, sequential therapeutic strategies, in which different medications are initiated and discontinued over time, are important to consider when planning a treatment course for patients. Currently, physicians and patients face the challenge of making these therapeutic decisions and changing medications without clear scientific guidance. The sequential use of different medications over a patient's lifetime has been identified as a critical knowledge gap in the field by professional societies, practitioners, and the NIH [9, 11, 12]; addressing this gap may help improve osteoporosis care and clinical outcomes.

We performed a systematic review and meta-analysis of primary studies evaluating the efficacy of sequential osteoporosis medication strategies on clinical outcome measures of bone mineral density (BMD) and fractures.

Materials and methods

Data sources and search strategies

We searched PubMed, Embase, and Cochrane Library databases in July 2024 to find clinical studies evaluating the efficacy of sequential treatment with two or more different FDA-approved medications for osteoporosis; the PubMed literature search strategy is shown in Supplemental Table S1. The database search strategies were broad and included terms for osteoporosis, fractures, low bone density, FRAX, all FDA-approved medications for the treatment of osteoporosis, randomized controlled trials and cohort studies, and sequential and other similar terms, and were limited to English-language studies published in the year 2000 or later. We also identified additional studies by reviewing the reference lists of relevant topical studies identified with our database search strategies.

Study selection

Pre-specified inclusion and exclusion criteria were applied to the identified literature to select studies relevant to this systematic review and meta-analysis. We required studies to evaluate a sequential treatment strategy of two or more FDA-approved medications for osteoporosis compared to a comparator (another treatment or placebo); be a clinical trial or observational cohort study; report outcomes of either BMD at the hip (total hip or femoral neck) or lumbar spine, or fractures at any sites; select study participants based on BMD T-scores showing osteoporosis at the hip or spine, prior osteoporotic fracture history, or meeting FRAX criteria; be an English-language publication; and report original results rather than duplicate results reported in another included article. Studies that did not meet all these criteria were excluded. We evaluated the literature for inclusion or exclusion in two stages: first, titles and abstracts were reviewed, and then studies identified as potentially relevant based on their title and abstract were evaluated with an independent full-text review by two investigators.

Data extraction

We extracted information from included studies on sociodemographic characteristics of participants, study location, year of publication, study design and methodology details, medication sequence(s) evaluated, the comparator treatment(s) evaluated, duration of study, BMD outcome results (e.g., change in BMD on treatment), fracture outcome results, serious adverse events rates, and funding sources.

Statistical analysis

We performed separate meta-analyses using a DerSimonian and Laird random-effects meta-analysis model [13] for each different sequential treatment strategy (i.e., specific medication followed by another medication) for which at least two studies reported data on the same outcome(s) such as BMD change at hip and/or spine, and its standard error or sufficient information to calculate standard error. Between-study heterogeneity in each analysis was assessed using the I^2 statistic [14]. We also performed meta-analyses for sequential strategies of medications grouped into the broader category of bisphosphonates. For any treatment sequence which did not have

multiple similar enough studies reporting the same outcomes, we described findings qualitatively. We assessed study methodological quality using Cochrane Collaboration risk of bias criteria for randomized controlled trials (RCTs) and the ROBINS-I risk of bias tool for non-randomized studies [15, 16]. All statistical analyses were performed using Stata software version 11.0 (StataCorp, College Station, TX).

Results

Literature search and study selection

The literature search identified 3270 records for review; 1021 were duplicate records identified by different databases, which were excluded, yielding 2249 unique records. After applying inclusion/exclusion criteria, 48 records (45 full-text articles and 3 abstracts) were included [17–64].

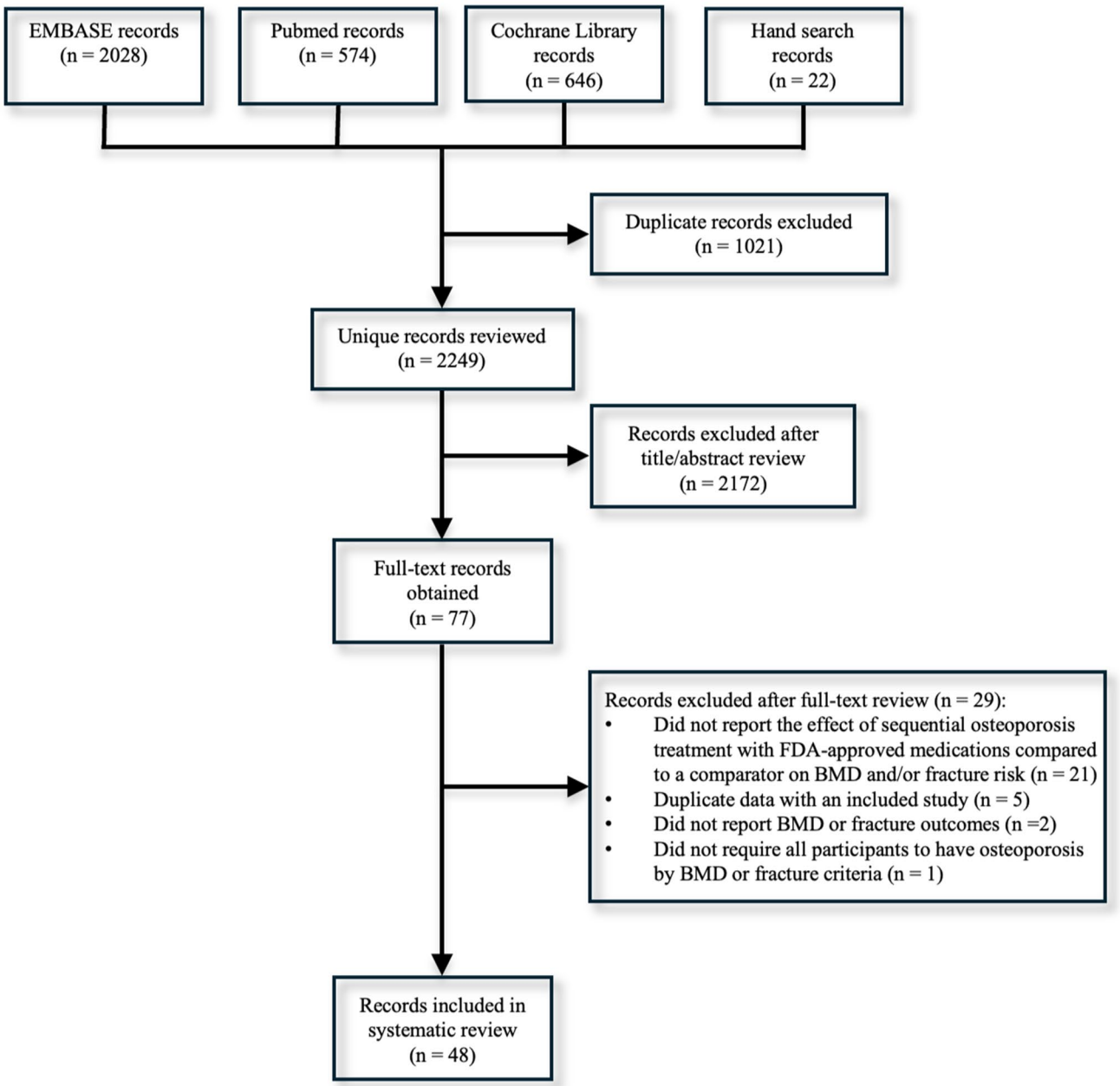

Fig. 1 Flow diagram of literature search and study selection

Figure 1 depicts a flow diagram of the literature search and study selection process.

Study characteristics

The included study characteristics are shown in Supplemental Table S2. The 48 included records reported results from 39 unique studies, 21 randomized clinical trials (RCTs) and 18 non-randomized studies. The studies were published between 2000 and 2024; 11 were performed in Asia, 10 in North America, 8 in Europe, and 10 were international and performed in multiple geographic regions. The number of study participants ranged from 19 to 7180; 32 studies included women only (almost all postmenopausal), 6 included both women and men, and 1 included men only; and study duration ranged from 1 to 4 years. Many different sequences of osteoporosis medications were evaluated; 6 studies evaluated teriparatide followed by denosumab, 4 evaluated alendronate followed by teriparatide, and 3 each evaluated romozosumab followed by denosumab, denosumab followed by romozosumab, bisphosphonates followed by teriparatide, bisphosphonates followed by denosumab, and denosumab followed by zoledronic acid. Twenty-two other sequential strategies were evaluated by fewer than 3 studies each. All included studies reported BMD outcomes, most commonly BMD percent change at the lumbar spine, total hip, and/or femoral neck. A minority of studies also reported fracture outcomes, often as adverse events, with very few studies having adequate statistical power for fracture outcomes. Of the studies reporting rates of serious adverse events (approximately half of included studies), no study reported a statistically significant increase in serious adverse events attributable to sequential therapy compared to the comparator; however, a few did report higher absolute rates of serious adverse events in the intervention group [29, 38]. Approximately three-quarters of studies were either funded by a pharmaceutical company or had authors who received pharmaceutical company fees or support.

Assessment of potential sources of bias

The assessment of study quality/potential sources of bias is shown in Supplemental Table S3 for randomized studies and Supplemental Table S4 for non-randomized studies. Of the 21 included RCTs, 12 were assessed overall as having high risk of bias, 7 were assessed as unclear risk of bias, and 2 were assessed as having low risk of bias. The bias domain that accounted for the high risk of bias assessment in all cases was performance bias due to lack of blinding of participants and personnel; many included studies were open-label in design, and this design feature resulted in the high-risk assessment according to the Cochrane criteria. Despite the open-label nature of many of the included studies, we believe that any resulting bias is not likely to be of significant concern given that the efficacy outcomes of interest (BMD and fractures) were objective measurements; furthermore, these outcomes were often assessed by individuals who were unaware of treatment allocation, and thus less susceptible to bias. Of the studies that were assessed as having an unclear risk of bias, the bias domains which resulted in this assessment included selection bias due to lack of details about random sequence generation and allocation concealment, performance bias due to unclear blinding of participants and personnel, and detection bias due to lack of information about blinding of outcome assessment. We believe that any resulting impact of these unclear study design features on the outcomes of interest is also limited by the objective nature of the measurements.

With respect to the assessment of potential sources of bias in the 18 included non-randomized studies, 9 were assessed as having low risk of bias overall, 8 were assessed as having moderate risk of bias, and one was assessed as having serious risk of bias. The non-randomized studies that were assessed as having moderate risk of bias were due to the risk of confounding and selection bias secondary to the non-random methods of allocation to the evaluated sequential treatments and comparators, which resulted in BMD, the primary outcome measurement of interest, also affecting which treatment group participants were assigned to. The one study assessed as having serious risk of bias was due to the risk of confounding and selection bias secondary to BMD affecting the sequential treatment received, as well as a difference in treatment duration of approximately 6 months between the intervention and comparator groups [44]; this study was not included in any of the meta-analyses performed.

Meta-analyses

Meta-analysis results are shown in Table 1. There were insufficient similar studies reporting fracture outcomes to perform a meta-analysis of the effect of any sequential treatment strategies on fracture outcomes. Most of the studies which were sufficiently similar for meta-analysis only reported BMD change on the second medication in the treatment sequence, rather than for the entire treatment sequence. The two medication sequences for which sufficiently similar studies were available to perform meta-analyses for BMD change on the entire sequence of therapy were 2 years of teriparatide followed by 2 years of denosumab, and 1 year of teriparatide followed by 1 year of raloxifene. The summary estimates of BMD change for teriparatide followed by denosumab showed robust BMD increases at the lumbar spine (18.0%, 95% CI 14.7–21.4), femoral neck (8.3%, 95% CI 6.1–10.5), and total hip (6.6%, 95% CI 5.3–7.9) over the 4 years of treatment. The meta-analysis findings for BMD change on 1 year of teriparatide followed by 1 year

Table 1 Meta-analysis results for osteoporosis sequential treatment

Treatment sequence	Duration of treatment	Included studies	Summary estimates of BMD[a] percent change (%) from meta-analysis[b] (95% CI; I^2 value[c])
Studies that reported BMD change for entire sequence of therapy			
Teriparatide-denosumab	4 years (2 years of teriparatide followed by 2 years of denosumab)	Hirooka 2021 [39] & Leder 2015 [48]	Lumbar spine: 18.0 (14.7–21.4; $I^2 = 0.0\%$) Femoral neck: 8.3 (6.1–10.5; $I^2 = 0.0\%$) Total hip: 6.6 (5.3–7.9; $I^2 = 0.0\%$)
Teriparatide-raloxifene	2 years (1 year of teriparatide followed by 1 year of raloxifene)	Adami 2008 [17] & Eastell 2009 [34]	Lumbar spine: 7.8 (7.0–8.6; $I^2 = 0.0\%$) Femoral neck: 3.4 (2.6–4.2; $I^2 = 0.0\%$)
Studies that reported BMD change on second medication in sequence			
Alendronate-teriparatide	1–1.5 years of teriparatide treatment (after mean of 38–46 months prior alendronate treatment)	Cosman 2009 [28] & Miller 2008 [55]	Lumbar spine: 4.0 (2.9–5.1; $I^2 = 26.4\%$) Total hip: − 0.5 (− 3.0–2.1; $I^2 = 90.4\%$)
Bisphosphonate[d]-denosumab	1 year of denosumab treatment (after mean of 17–84 months prior bisphosphonate treatment)	Lyu 2019 [50], Miller 2016 [56], & Recknor 2013 [61]	Lumbar spine: 3.5 (2.8–4.2; $I^2 = 83.0\%$) Femoral neck: 1.5 (1.2–1.9; $I^2 = 54.3\%$) Total hip: 2.1 (1.8–2.3; $I^2 = 62.9\%$)
Bisphosphonate[d]-romosozumab	1 year of romozosumab treatment (after mean of 28–67 months prior bisphosphonate treatment)	Ebina 2021 [36] & Langdahl 2017 [47]	Lumbar spine: 10.1 (9.9–10.4; $I^2 = 0.0\%$) Femoral neck: 3.1 (2.9–3.4; $I^2 = 0.0\%$) Total hip: 3.1 (2.7–3.5; $I^2 = 41.9\%$)
Bisphosphonate[d]-teriparatide	1 year of teriparatide treatment (after mean of 67–84 months prior bisphosphonate treatment in 2 included studies; 1 study did not report duration of prior treatment)	Langdahl 2017 [47], Lyu 2019[e] [50], & Yoshiki 2017 [64]	Lumbar spine: 5.1 (4.4–5.9; $I^2 = 30.3\%$) Femoral neck: 0.2 (− 0.4–0.8; $I^2 = 30.9\%$) Total hip: − 0.4 (− 0.8 to − 0.1; $I^2 = 0.0\%$)
Romosozumab-denosumab	1 year of denosumab treatment (after 1–2 years prior romozosumab treatment)	Kobayakawa 2022 [45] & McClung 2018 [52]	Lumbar spine: 4.0 (1.2–6.7; $I^2 = 87.2\%$) Femoral neck: 2.2 (0.5–3.8; $I^2 = 63.7\%$) Total hip: 2.8 (0.8–4.9; $I^2 = 74.8\%$)
Teriparatide-alendronate	1 year of alendronate treatment (after approximately 2 years prior teriparatide treatment)	Kurland 2004[f] [46] & Niimi 2018 [60]	Lumbar spine: 3.1 (− 0.6–6.8; $I^2 = 91.3\%$)
Teriparatide-bisphosphonate	1 year of bisphosphonate treatment (after mean of 20–24 months prior teriparatide treatment)	Ebina 2017 [35] & Kurland 2004[f] [46]	Lumbar spine: 3.8 (1.3–6.2; $I^2 = 72.4\%$)
Teriparatide-denosumab	2 years of denosumab treatment after 2 years prior teriparatide treatment	Burkard 2018 [26] & Leder 2015 [48]	Lumbar spine: 7.3 (4.4–10.1; $I^2 = 67.7\%$) Femoral neck: 5.5 (4.0–6.9; $I^2 = 0.0\%$)
	1 year of denosumab treatment after 1–2 years prior teriparatide treatment	Ebina 2017 [35] & Niimi 2018 [60]	Lumbar spine: 5.1 (3.3–7.0; $I^2 = 80.2\%$) Femoral neck: 2.3 (0.3–4.4; $I^2 = 82.9\%$)

[a]Bone mineral density measured using dual-energy X-ray absorptiometry (DXA)

[b]Random-effects meta-analysis using DerSimonian and Laird method

[c]Percentage of variation across studies attributable to heterogeneity

[d]Some studies evaluated bisphosphonates as a category

[e]This study reported annualized BMD change over 2 years of teriparatide therapy

[f]83% of this study's participants who were treated with bisphosphonate after teriparatide received alendronate

of raloxifene also showed substantial increases at the lumbar spine (7.8%, 95% CI 7.0–8.6) and femoral neck (3.4%, 95% CI 2.6–4.2).

Enough similar studies were available to perform meta-analyses of BMD change on the second medication in a treatment sequence for alendronate followed by teriparatide; bisphosphonates as a category followed by denosumab, romosozumab, or teriparatide; romozosumab followed by denosumab; and teriparatide followed by bisphosphonates as a category, or denosumab. Of the studies included in meta-analyses of sequences containing bisphosphonates as a category, the vast majority of participants were treated with oral bisphosphonates, and of those studies that reported which bisphosphonate the participants had taken, most participants had received alendronate. The meta-analysis findings for alendronate followed by 1 to 1.5 years of teriparatide showed significant BMD gain at the lumbar spine (4.0%, 95% CI 2.9–5.1) but not at the total hip (− 0.5%, 95% CI − 3.0–2.1). Similarly, the meta-analyses findings for bisphosphonates followed by 1 year of teriparatide

showed significant BMD gain at the lumbar spine (5.1%, 95% CI 4.4–5.9) but not at the femoral neck (0.2%, 95% CI − 0.4–0.8) or total hip (− 0.4%, 95% CI − 0.8 to − 0.1). In contrast, the summary estimates for BMD change from bisphosphonates transitioned to 1 year of romozosumab showed robust BMD gains at the lumbar spine (10.1%, 95% CI 9.9–10.4) as well as the femoral neck (3.1%, 95% CI 2.9–3.4) and total hip (3.1%, 95% CI 2.7–3.5). Predominantly oral bisphosphonates transitioned to 1 year of denosumab resulted in significant summary estimates for BMD gain at the lumbar spine (3.5%, 95% CI 2.8–4.2), femoral neck (1.5%, 95% CI 1.2–1.9), and total hip (2.1%, 95% CI 1.8– 2.3), though the increases were smaller than with bisphosphonates followed by romozosumab. Figure 2 shows summary estimates from meta-analyses for BMD percent change on 1 year of denosumab, romozosumab, and teriparatide after treatment with bisphosphonates. Romozosumab followed by 1 year of denosumab also resulted in significant BMD gain, with summary estimates of 4.0% (95% CI 1.2–6.7) at the lumbar spine, 2.2% (95% CI 0.5–3.8) at the femoral neck, and 2.8% (95% CI 0.8–4.9) at the total hip.

Teriparatide followed by 1 year of denosumab produced substantial BMD gain of 5.1% (95% CI 3.3–7.0) at the lumbar spine and 2.3% (95% CI 0.3–4.4) at the femoral neck. Teriparatide switching to 1 year of oral bisphosphonates also resulted in significant BMD gain at the lumbar spine of 3.8% (95% CI 1.3–6.2); there were insufficient similar studies to calculate meta-analysis summary estimates for the effect of teriparatide followed by bisphosphonates on BMD at the femoral neck or total hip.

Qualitative summary of findings for other treatment sequences and outcomes

As with the meta-analysis results, most of the descriptive findings from the studies below are for BMD change on only the second medication in the treatment sequence, unless otherwise stated.

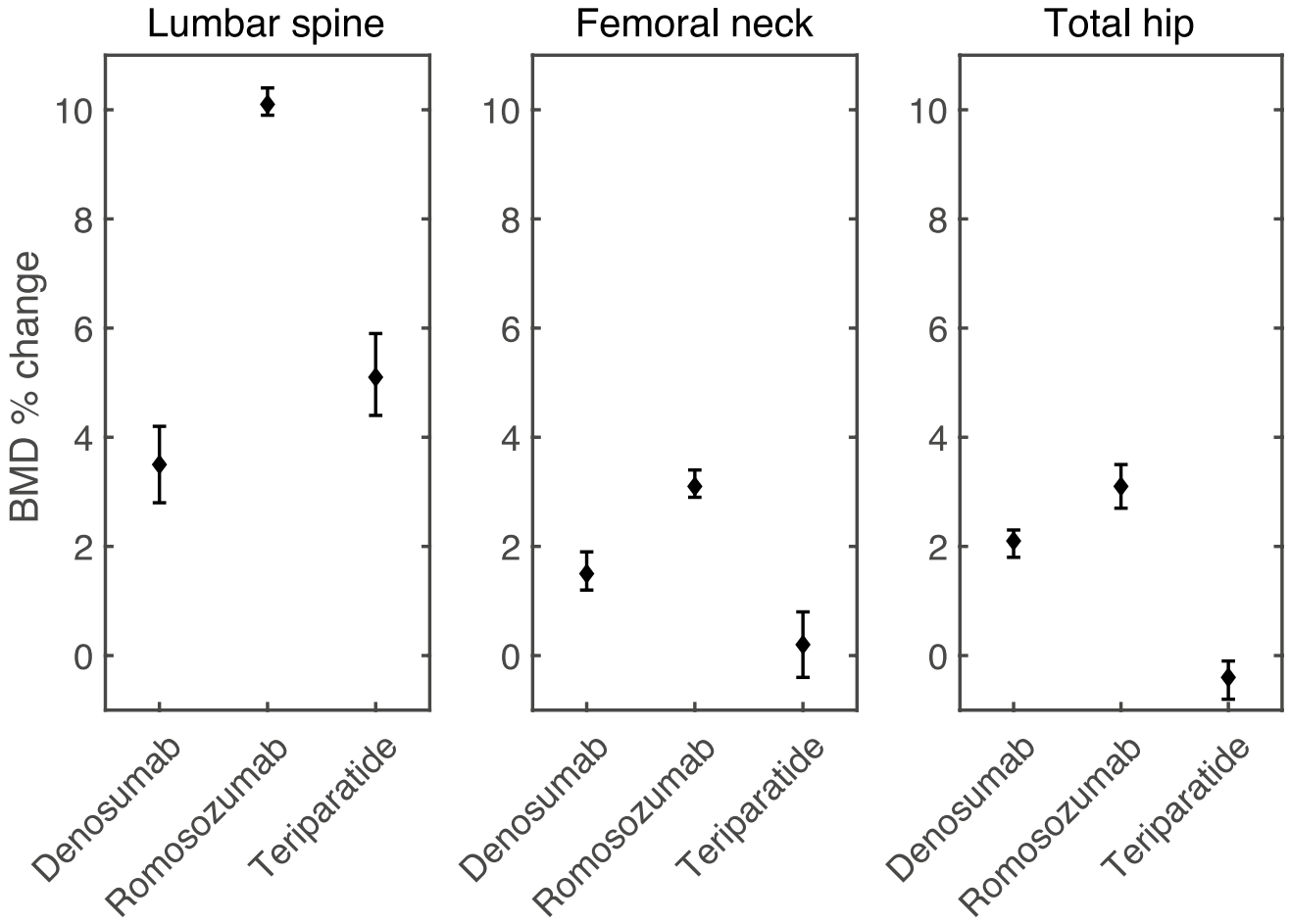

Fig. 2 Summary estimates from meta-analyses for BMD percent change on second medication in treatment sequence after treatment with bisphosphonates. Summary estimates and 95% confidence intervals for BMD change at the lumbar spine, femoral neck, and total hip are shown for 1 year of treatment with denosumab, romozosumab, and teriparatide after bisphosphonates

Sequences including romozosumab

Three studies evaluated denosumab switched to 1 year of romosozumab treatment and found substantial mean BMD gain at the lumbar spine (5.3 to 7.0%), but not at the total hip (−0.9% to 0.9%) or femoral neck (0.7 to 1.3%) [36, 41, 54]. One of these studies reported total BMD gain on a 2-year treatment sequence of 1 year of denosumab followed by 1 year of romosozumab of 11.5% at the lumbar spine, 3.8% at the total hip, and 3.2% at the femoral neck [54]. One large RCT found that on the entire sequence of 1 year of romosozumab followed by 1 year of alendronate, BMD increased by 15.2% at the lumbar spine and 7.1% at the total hip; during the 2nd year of treatment with alendronate only, BMD gain was 1.5% at the lumbar spine and 0.9% at the total hip [63]. This same study was powered for fracture outcomes and reported a significantly lower risk of morphometric vertebral fractures (RR 0.52, 95% CI 0.40–0.66), clinical fractures (HR 0.73, 95% CI 0.61–0.88), nonvertebral fractures (HR 0.81, 95% CI 0.66–0.99), and hip fractures (HR 0.62, 95% CI 0.42–0.92) on the entire sequence of 1 year of romosozumab followed by 1 year of alendronate compared to alendronate therapy alone [63]. One study evaluated 1 year of romosozumab followed by 1 year of ibandronate and found substantial BMD gain on the entire sequence of 14.6% at the lumbar spine, 8.4% at the total hip, and 7.1% at the femoral neck; with BMD gain on ibandronate only of 2.5% at the lumbar spine, 2.5% at the total hip, and 2.7% at the femoral neck [45].

One large international RCT that included over 7000 participants compared 1 year of romosozumab therapy followed by denosumab with an active comparator of denosumab treatment only in a post-hoc analysis [32], and found greater BMD gain on the entire sequence of romosozumab for 1 year followed by denosumab for 1 year than 2 years of denosumab alone, with respective mean BMD changes at the lumbar spine of 16.8% versus 7.5%; total hip of 8.4% versus 4.0%; and femoral neck of 7.6% versus 3.5%. This study also reported fracture outcomes and found a lower 2-year incidence of morphometric vertebral fractures in the romosozumab followed by denosumab group compared to denosumab monotherapy (0.62% versus 1.26%, OR 0.45); however, this study did not find a significant difference in the incidence of nonvertebral fractures, clinical fractures, or hip fractures [32]. Another smaller RCT evaluated 1 year of romosozumab followed by 1 year of denosumab and found robust BMD gain on the entire sequence of 18.0% at the lumbar spine, 8.9% at the total hip, and 8.6% at the femoral neck [45]. Only 1 small study evaluated teriparatide followed by 1 year of romosozumab and found significant BMD increase at the lumbar spine (11.2%), total hip (4.4%), and femoral neck (3.5%) on romosozumab [36].

Sequences including parathyroid hormone analogs

One study evaluated alendronate or risedronate followed by 2 years of teriparatide and found significant gain in femoral neck BMD (3.4% after alendronate, 4.1% after risedronate) and total hip BMD (2.1% after alendronate, 2.9% after risedronate) [25]. Another study that evaluated denosumab transitioned to teriparatide for 2 years reported significantly increased BMD at the lumbar spine (4.8%) and femoral neck (1.2%), but not total hip; however, this study found a transient decrease in total hip and femoral neck BMD for 1 year after the transition, before BMD at the hip began to increase again [48]. Two studies evaluated raloxifene followed by 18 months of teriparatide and found significant BMD gain at the lumbar spine (8.1 to 10.2%) and total hip (1.8%) [28, 38].

One study found that teriparatide followed by 2 years of raloxifene resulted in a significant BMD gain of 2.2% at the femoral neck, but a significant BMD decline of 2.6% at the lumbar spine [17]. Two studies reported significant total hip BMD gain of 4.2 to 4.7% after teriparatide was switched to 1 year of denosumab [35, 48]. Another study reported a significant BMD gain of 1.1% at the total hip after teriparatide was followed by 1 year of oral bisphosphonates [35]. One of the few included studies that was powered for fracture outcomes compared teriparatide therapy for 72 weeks followed by alendronate for 48 weeks with alendronate monotherapy for older postmenopausal women with a high risk of fracture, and found that the entire sequence of teriparatide followed by alendronate significantly reduced the risk of morphometric vertebral fractures compared with alendronate monotherapy (relative risk 0.69, 95% CI 0.54–0.88) [58]. A small study of 2 years of teriparatide switched to 2 years of zoledronic acid therapy for patients with a history of osteoporotic fracture did not find a significant increase in BMD at the lumbar spine or femoral neck on zoledronic acid [26]. One large study that evaluated 18 months of abaloparatide followed by 2 years of alendronate therapy reported significant BMD gain at the lumbar spine (14.4%), total hip (6.4%), and femoral neck (5.3%) on the entire sequence of therapy [22, 24].

Sequences including antiresorptives only

Two studies evaluated oral bisphosphonates followed by intravenous zoledronic acid; one RCT evaluated postmenopausal women who had been receiving alendronate transitioned to 1 zoledronic acid infusion, and found no significant lumbar spine BMD change from prior to the infusion to 1 year after [51]. Another RCT evaluated postmenopausal women previously treated with oral bisphosphonates and found that 1 subsequent zoledronic acid infusion resulted in small but significant increases in BMD at the lumbar spine (1.1%) and total hip (0.6%), but not femoral neck,

1 year after the infusion [56]. Two small studies evaluated zoledronic acid followed by denosumab and found that 2 doses of denosumab over 1 year after a previous zoledronic acid infusion resulted in a 4.4 to 4.5% increase in lumbar spine BMD; one of these studies also reported a significant increase in femoral neck BMD on denosumab [18, 19]. One study evaluated alendronate followed by 1 year of denosumab and found significant BMD gain at the lumbar spine (3.0%), total hip (1.9%), and femoral neck (1.4%); this study found a significantly greater increase in BMD at all sites on denosumab following alendronate compared to continuing alendronate monotherapy [42].

Three small studies evaluated denosumab switched to zoledronic acid and found maintenance of BMD at the lumbar spine and femoral neck but no significant BMD gain 1 year after zoledronic acid infusion [20, 21, 37]. One of these studies also evaluated denosumab followed by oral bisphosphonates and found no significant change in lumbar spine BMD or femoral neck BMD on 1 year of oral bisphosphonate therapy, albeit with slightly lower mean estimates for BMD change on oral bisphosphonates than zoledronic acid [37]. This same study and another study evaluated denosumab followed by 1 year of raloxifene and found a decline in BMD at the lumbar spine (− 2.8 to − 2.7%) and femoral neck (− 3.8 to − 1.7%) [37, 40].

Table 2 briefly summarizes the overall findings of this systematic review and meta-analysis.

Discussion

This systematic review and meta-analysis evaluating the efficacy of sequential osteoporosis medication strategies identified 39 primary studies which assessed many different treatment sequences of FDA-approved osteoporosis medications. All included studies reported BMD outcomes; however, very few were powered for fracture outcomes. We found wide variation in the direction and magnitude of BMD change on different medication sequences, substantiating that the order of administration of osteoporosis medications is a consequential choice for patient outcomes. Our meta-analysis and systematic review findings for specific sequential treatment strategies are summarized below.

Sequences with fracture outcomes

With respect to the few large clinical trials powered for fracture outcomes that compared a sequential treatment strategy to a single active therapy, 1 year of romozosumab followed by 1 year of alendronate was found to significantly lower the risk of morphometric vertebral fractures (RR 0.52, 95% CI 0.40–0.66), hip fractures (HR 0.62, 95% CI 0.42–0.92), clinical fractures (HR 0.73, 95% CI 0.61–0.88), and nonvertebral fractures (HR 0.81, 95% CI 0.66–0.99) compared to 2 years of alendronate alone [63]. One year of romozosumab followed by 1 year of denosumab was found to significantly reduce the risk of morphometric vertebral fractures compared to 2 years of denosumab monotherapy (incidence 0.62% versus 1.26%, OR 0.45); however, this study did not find a significantly reduced risk of nonvertebral fractures, clinical fractures, or hip fractures [32]. Teriparatide for 72 weeks followed by 48 weeks of alendronate significantly reduced the risk of morphometric vertebral fractures compared to alendronate monotherapy for 120 weeks (relative risk 0.69, 95% CI 0.54–0.88); however, this study did not find a significantly reduced risk of any fractures or nonvertebral fractures [58].

Romozosumab to antiresorptives

With regard to BMD outcomes, our meta-analysis found significant BMD gain on romozosumab followed by 1 year of denosumab treatment, with summary estimates of 4.0% (95% CI 1.2–6.7) at the lumbar spine, 2.2% (95% CI 0.5–3.8) at

Table 2 Summary of systematic review and meta-analysis findings for effect of second medication in sequential osteoporosis treatment strategy on axial bone mineral density (BMD)

First medication in treatment sequence	Second medication in treatment sequence					
	Oral bisphosphonate	Zoledronic acid	Denosumab	Raloxifene	Parathyroid hormone analog	Romozosumab
Oral bisphosphonate	N/A[a]	+/–	+	?	+	+ +
Zoledronic acid	?	N/A[a]	+	?	?	?
Denosumab	+/–	+/–	N/A[a]	–	+/–	+
Raloxifene	?	?	?	N/A[a]	+	?
Parathyroid hormone analog	+	+/–	+ +	+/–	N/A[a]	+ +
Romozosumab	+ +	?	+ +	?	?	N/A[a]

+ + substantial BMD gain, + slight to moderate BMD gain, +/– neutral or mixed effect on BMD, – BMD loss, ? evidence lacking

[a]Not applicable

the femoral neck, and 2.8% (95% CI 0.8–4.9) at the total hip on denosumab. For the entire sequence of 1 year of romozosumab followed by 1 year of denosumab, several studies reported robust increases in BMD at the lumbar spine [32, 45, 52], with most of the gain occurring during the romozosumab year of treatment; the largest of these studies, a RCT with over 7000 patients, found mean BMD gain on the entire sequence of 16.8% at the lumbar spine, 8.4% at the total hip, and 7.6% at the femoral neck [32]. One study found comparable BMD gain at the femoral neck and total hip for the entire treatment sequence of romozosumab followed by ibandronate, an oral bisphosphonate [45]; however, this study found greater BMD gain at the lumbar spine with romozosumab followed by denosumab [45]. Another large RCT found similar although slightly less mean BMD gain at the lumbar spine and total hip with the sequence of 1 year of romozosumab followed by 1 year of alendronate [63].

Antiresorptives to romozosumab

Our meta-analysis summary estimates for BMD change from bisphosphonates to 1 year of romozosumab treatment showed robust BMD gains at the lumbar spine (10.1%, 95% CI 9.9–10.4) as well as the total hip (3.1%, 95% CI 2.7–3.5) and femoral neck (3.1%, 95% CI 2.9–3.4) on romozosumab. In contrast, three studies that evaluated denosumab followed by 1 year of romozosumab found lower mean BMD gain on romozosumab at the lumbar spine (5.3 to 7.0%) without substantial BMD gain at the total hip (− 0.9 to 0.9%) or femoral neck (0.7 to 1.3%) [36, 41, 54]. Only one study directly compared a treatment sequence containing romozosumab to a sequence containing a parathyroid hormone analog, a RCT which found that for patients who had previously taken an oral bisphosphonate for 3 or more years, subsequent treatment with romozosumab compared to teriparatide for 1 year produced significantly greater increases in BMD at the lumbar spine (9.8% vs 5.4%), total hip (2.9% vs − 0.5%), and femoral neck (3.2% vs − 0.2%) [47]. Only 1 included study evaluated a treatment sequence including 2 anabolic therapies, a small study that evaluated teriparatide followed by 1 year of romozosumab; this study found significant BMD increase at the lumbar spine (11.2%), total hip (4.4%), and femoral neck (3.5%) on romozosumab [36].

Parathyroid hormone analogs to antiresorptives

With regard to treatment sequences including parathyroid hormone analogs, our meta-analysis summary estimates of BMD change on 2 years of teriparatide followed by 2 years of denosumab showed substantial BMD increases at the lumbar spine (18.0%, 95% CI 14.7–21.4), femoral neck (8.3%, 95% CI 6.1–10.5), and total hip (6.6%, 95% CI 5.3–7.9) over the 4-year treatment sequence. Meta-analysis findings for teriparatide transitioned to 1 year of denosumab showed BMD gain of 5.1% (95% CI 3.3–7.0) at the lumbar spine and 2.3% (95% CI 0.3–4.4) at the femoral neck on denosumab; additionally, 2 small studies reported significant total hip BMD gain of 4.2 to 4.7% on teriparatide switched to 1 year of denosumab [35, 48]. The meta-analysis summary estimate for teriparatide followed by 1 year of oral bisphosphonates also showed significant BMD gain at the lumbar spine (3.8%, 95% CI 1.3–6.2), and 1 small study reported significant BMD gain of 1.1% at the total hip with teriparatide transitioned to 1 year of oral bisphosphonate therapy [35]. One small study of 2 years of teriparatide followed by 2 years of zoledronic acid therapy in patients with a history of osteoporotic fracture did not find a significant increase in BMD at the lumbar spine or femoral neck on zoledronic acid [26]. A large study that evaluated 18 months of abaloparatide followed by 2 years of alendronate found significant BMD gain at the lumbar spine (14.4%), total hip (6.4%), and femoral neck (5.3%) on the entire sequence of therapy [22, 24]. The meta-analysis findings for BMD change on the entire treatment sequence of 1 year of teriparatide followed by 1 year of raloxifene showed substantial increases at the lumbar spine (7.8%, 95% CI 7.0–8.6) and femoral neck (3.4%, 95% CI 2.6–4.2); however, 1 study found that teriparatide transitioned to 2 years of raloxifene treatment significantly increased BMD by 2.2% at the femoral neck, but resulted in 2.6% BMD loss at the lumbar spine on raloxifene [17].

Antiresorptives to parathyroid hormone analogs

Meta-analyses findings for bisphosphonates followed by 1 year of teriparatide showed significant BMD gain at the lumbar spine (5.1%, 95% CI 4.4–5.9) but not at the femoral neck (0.2%, 95% CI − 0.4–0.8) or total hip (− 0.4%, 95% CI − 0.8 to − 0.1); however, 1 study that evaluated teriparatide for a longer duration (2 years) after alendronate or risedronate found significant gain in femoral neck BMD (3.4% after alendronate, 4.1% after risedronate) and total hip BMD (2.1% after alendronate, 2.9% after risedronate) [25]. Another study that evaluated denosumab followed by teriparatide for 2 years found significantly increased BMD at the lumbar spine (4.8%) and femoral neck (1.2%), but not total hip; this study also found a transient decrease in total hip and femoral neck BMD for 1 year after the transition, before BMD at the hip began to increase again [48]. Two studies evaluated raloxifene switched to 18 months of teriparatide and found significant BMD gain at the lumbar spine (8.1 to 10.2%) and total hip (1.8%) [28, 38].

Antiresorptives to antiresorptives

With respect to treatment sequences including antiresorptive agents only, our meta-analysis findings showed that switching from predominantly oral bisphosphonate therapy to 1 year of denosumab treatment resulted in significant BMD gain at the lumbar spine (3.5%, 95% CI 2.8–4.2), femoral neck (1.5%, 95% CI 1.2–1.9), and total hip (2.1%, 95% CI 1.8–2.3). One sizable RCT evaluated postmenopausal women previously treated with oral bisphosphonates and found that 1 subsequent zoledronic acid infusion resulted in small but significant increases in BMD at the lumbar spine (1.1%) and total hip (0.6%), but not femoral neck, 1 year after the infusion [56]. Two small studies evaluated zoledronic acid followed by denosumab and found that 2 doses of denosumab over 1 year resulted in a 4.4 to 4.5% increase in lumbar spine BMD; one of these studies also reported a significant increase in femoral neck BMD on denosumab [18, 19]. Two small studies found moderate mean BMD loss at the femoral neck and lumbar spine with denosumab followed by raloxifene [37, 40]. Several small studies found maintenance of lumbar spine and femoral neck BMD but no significant gain with denosumab followed by zoledronic acid infusion [20, 21, 37]; one of these studies also found that denosumab followed by 1 year of oral bisphosphonate treatment maintained BMD, albeit with slightly lower mean estimates than zoledronic acid at these sites [37]. However, two small studies that evaluated BMD change for patients who transitioned from long-term denosumab treatment (more than 3 years) to zoledronic acid found significant BMD loss at the lumbar spine and hip 1 year after zoledronic acid infusion [65, 66]; thus, the duration of prior denosumab treatment may affect whether zoledronic acid can maintain BMD after transition. For patients who discontinue long-term denosumab use, the European Calcified Tissue Society (ECTS) has advised that intravenous zoledronic acid administered promptly and frequently (e.g., every 6 months) after denosumab discontinuation is preferable to oral bisphosphonates to minimize short-term bone loss [67]. We also found evidence that, at least for short-term denosumab use, transitioning to romosozumab results in BMD gain at the lumbar spine with maintenance of BMD at this hip [36, 41, 54]; thus, we recommend further investigation into whether romosozumab may be a useful medication to switch to after long-term denosumab use.

When considering the entire body of evidence on sequential osteoporosis treatment, we found that the strategies which led to the greatest BMD gain included romosozumab followed by denosumab or bisphosphonates; teriparatide followed by romosozumab or denosumab; and bisphosphonates followed by romosozumab. These strategies include an anabolic or dual-action anabolic/antiresorptive agent followed by an antiresorptive; an anabolic agent followed by a dual-action anabolic/antiresorptive agent; and an antiresorptive followed by a dual-action anabolic/antiresorptive agent. Although our findings do not enable direct comparison between these strategies to rank their relative effectiveness for increasing BMD, a head-to-head clinical trial of these effective strategies may be useful to investigate this question further, if it would be feasible to do a large clinical trial that would be adequately powered to detect BMD differences. We also found many sequential strategies that resulted in slight to moderate BMD gain at the lumbar spine and/or hip, as well as many that resulted in overall neutral or mixed BMD effects at these sites, as summarized in Table 2. We found evidence that denosumab followed by raloxifene leads to moderate bone loss [37, 40], and thus this sequence should be avoided.

This systematic review and meta-analysis is the most comprehensive one to date on the topic of sequential treatment strategies for osteoporosis. We are aware of a single prior meta-analysis on sequential therapy for osteoporosis published in 2016, which reported that sequential therapy, in general, significantly increases BMD at the femoral neck and lumbar spine [68]. This prior study had major limitations, however; it included only 8 primary studies with small sample sizes, failed to report efficacy for specific medication sequences (medications were only grouped into broad categories of anabolics or antiresorptives), and did not report fracture outcomes or adverse events [68]. Our systematic review and meta-analysis further extends previous narrative reviews on this topic [69, 70].

This systematic review and meta-analysis of sequential treatment for osteoporosis had several limitations. Very few studies were powered for fracture outcomes, and BMD is an intermediate outcome; however, BMD change has been shown in a recent meta-regression to be well correlated to fracture risk reduction at the spine and hip [71]. Most of the participants in included studies were postmenopausal women, with information lacking for men and younger women. There was high between-study heterogeneity in several of the meta-analyses performed, which may be a consequence of underlying differences between the study populations in included studies. In terms of study quality, many included studies had design features that could lead to selection bias or performance bias. Some treatment sequences were only evaluated by 1 or a few relatively small studies, and we found a dearth of primary studies evaluating treatment sequences including zoledronic acid, raloxifene, abaloparatide, and sequences with 2 anabolic agents (parathyroid hormone analogs before or after romosozumab); more primary studies to target these gaps in the literature would be useful. Additionally, although no studies reported a significantly increased risk of serious adverse events on a sequential treatment strategy compared to a comparator, many studies did not report adverse events and/or were not

adequately powered to detect an increase in rare adverse events. Furthermore, approximately three-quarters of studies were either funded by a pharmaceutical company or had authors who received pharmaceutical company fees or support, which raises the possibility of conflicts of interest that may affect study findings.

Despite these limitations, our study is the most comprehensive systematic review and meta-analysis to date on the topic of sequential treatment strategies for osteoporosis and provides a rigorous summary of the evidence to guide the consequential decision of sequential medication choice for patients, as well as highlighting areas where more primary studies are needed.

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Declarations

Conflicts of interest None.

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