Informing evidence-based clinical practice guidelines for children with cerebral palsy at risk of osteoporosis: an update

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ABBREVIATION
BMD Bone mineral density

AIM To investigate the impact of new evidence for weight-bearing, bisphosphonates, and vitamin D and calcium interventions, towards updating the systematic review and clinical practice guidelines for osteoporosis in children with cerebral palsy (CP) published in 2011.
METHOD Computer-assisted literature searches were conducted for articles published from 2010 to 2016. Searches focused on children with CP functioning at Gross Motor Function Classification System levels III to V and limited to weight-bearing activities, bisphosphonates, and vitamin D and/or calcium supplementation. Articles were classified according to the American Academy of Neurology guidelines to update the grading of the evidence for improving bone mineral density (BMD) and decreasing fragility fractures.
RESULTS Six new articles underwent full-text review and data abstraction. These included one weight-bearing, three bisphosphonate, and two mixed intervention studies (bisphosphonate and vitamin D/calcium supplementation). Overall, there continues to be 'probable' evidence for bisphosphonates, 'possible' evidence for vitamin D/calcium, and 'insufficient' evidence for weight-bearing activities as effective interventions to improve low BMD in children with CP. There is 'possible' evidence for bisphosphonates in reducing fragility fractures.
INTERPRETATION The grading of evidence to support the use of weight-bearing activities, bisphosphonates, and vitamin D and calcium supplementation in pediatric CP osteoporosis clinical practice guidelines remained the same.

Individuals with a physical disability such as cerebral palsy (CP), are at risk for low bone mineral density (BMD) and associated osteoporosis and fragility fractures.[1] Risk factors for this are multifactorial, and include decreased weight-bearing, inadequate calcium and vitamin D intake, and exposure to medications such as anticonvulsants that adversely affect BMD. Low BMD is asymptomatic; however, fragility fractures, commonly in the shaft of long-bones such as the distal femur, are painful and are 20% more common in non-ambulatory individuals with CP.[1]

Research has evaluated prevention and treatment strategies in adult and pediatric CP populations. In 2011, Fehlings et al.[2] published a systematic review and evidence-informed clinical practice guideline looking at the effects of weight-bearing, bisphosphonates, and vitamin D and calcium interventions on BMD and fracture rate in children and young people with CP functioning at a Gross Motor Functional Classification System (GMFCS) level III or higher. The process paired a systematic review grading the therapeutic evidence using the American Academy of Neurology standards with expert opinion to develop the pediatric osteoporosis clinical practice guideline (Fig. 1). The therapeutic evidence was classified into two arms: impact on improving BMD, which was placed in a prevention of fragility fracture arm in the clinical practice guideline; and impact on fragility fractures, which was placed in the treatment arm of the guideline.

This article is an update to the 2011 systematic review and clinical practice guidelines, investigating whether new research evidence for weight-bearing, bisphosphonates, and vitamin D and calcium interventions on BMD and fracture rate in children and young people with CP has changed. This process was completed to inform the existing clinical practice guidelines and to see if the additional evidence warranted changing the grade of evidence in these guidelines.

METHOD

Similar methods were used to ensure consistency between the original 2011 publication and this update. Computer-assisted literature searches were completed for relevant articles published between January 2010 and March 2016. Databases comprehensively searched were MEDLINE, PubMed, CINAHL, AMED, Cochrane Reviews, EMBASE, and EBM Reviews. A similar search was used to that described in the 2011 paper by Fehlings et al.[2]; however, there were some alterations in that additional truncated keywords were added to this search strategy to account for other similar words that may have otherwise been missed, and keywords related to

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weight lifting were excluded from this search, because they did not return any additional results when searches were compared with and without the terms. An example of the search strategy for MEDLINE is shown in Table SI (online supporting information).

Consistent with Fehlings et al.,[2] the inclusion criteria were as follows: (1) English-language full-text studies; (2) participants under the age of 18 years; (3) the participants had CP; and (4) at least 10 participants were receiving the studied interventions. Studies that involved a mixed sample of children with multiple diagnoses were included if at least 50% of the participants had CP.

Each article was reviewed, abstracted, and classified in two stages. The first review was conducted by a research student. The second review was conducted by a research project manager who was blinded to the initial review and classification. Any discord in classification rating between the two reviews was resolved by a third independent reviewer (developmental pediatrician). Similar to the original 2011 publication, articles were classified into four hierarchical classes of therapeutic evidence used to designate the risk of bias as per Amendment II of the American Academy of Neurology Clinical Practice Guideline Process Manual (approved June 2014).[3] This system for classifying research evidence defines randomized controlled trials and crossover trials, with both period and carryover effects examined and statistical adjustments performed as class I. Matched prospective cohort studies and randomized crossover trials with either period and crossover effects examined or statistical adjustments performed are considered class II. All other controlled and crossover trials are class III, and all other studies not meeting the requirements for classes I to III are considered as class IV. As in the original 2011 publication, a study was downgraded a class level if it met all of the necessary criteria but did not perform any statistical significance testing and/or cited lack of power as a limitation.

Recommendation level classifications were again generated based on the strength of evidence for all the articles as per the American Academy of Neurology Clinical Practice Guideline Process Manual, including Amendment I approved June 2014.[3] The recommendation levels for an intervention are as follows: level A (established as effective/ineffective) required at least two consistent class I studies; level B (probably effective/ineffective) required at least one class I study or at least two consistent class II studies; and level C (possibly effective/ineffective) required at least one class II study or at least two consistent class III studies. Level U (data inadequate or conflicting) resulted when studies did not meet class I to III requirements or included studies that were conflicting.

RESULTS

A total of 230 abstracts were initially identified through the search process (Fig. 2). Of these, 57 were eliminated as duplicates from each other and from the previous Fehlings et al. manuscript based on title, and 48 trials were identified as possible articles for inclusion. A total of 15 articles met the criteria and underwent a full-text review; six fulfilled all the inclusion criteria and underwent data abstraction. The six articles that were reviewed and had their data abstracted included one weight-bearing study, three bisphosphonate studies, and two mixed intervention studies. Of the two mixed intervention studies, one evaluated bisphosphonate administration in addition to calcium and vitamin D supplementation as a combined intervention on BMD, and the other studied simultaneous bisphosphonate and vitamin D administration. There were no additional vitamin D/calcium supplementation intervention articles published since 2010 that met the criteria for inclusion.

What this paper adds

- Updated systematic review and clinical practice guidelines for children with cerebral palsy at risk of osteoporosis.
- Bisphosphonates had 'probable', vitamin D/Calcium 'possible', and weight bearing activities 'insufficient' evidence for improving bone mineral density.
- Bisphosphonates had 'possible' evidence to reduce fragility fractures.

Weight-bearing activity intervention

One weight-bearing activity study was reviewed, and the data abstracted are detailed in Table SII (online supporting information). The design was a non-blinded randomized controlled trial with the intervention consisting of 12-weeks of home-based cycling training, including a warm-up, loaded sit-to-stand exercises, progressive resistance cycling, and cool down.[4] They saw a significant increase in distal femur BMD, but no significant difference in lumbar spine BMD after the intervention, compared with the comparison group.[4] This was a class I study for weight-bearing intervention. This class I study did not provide adequate new information to produce a change in the evidence to support weight-bearing activities as an effective intervention for improving BMD, because mixed results were reported in the distal femur and lumbar spine. The authors did not evaluate for decreasing fragility fractures in children and young people with CP.[4] Therefore, the data remain inadequate (level U) as shown in Table I for both the prevention arm of improving BMD and the treatment arm of decreasing fragility fractures. No significant adverse events associated with a weight-bearing intervention were reported.

Bisphosphonate intervention

The reviewed bisphosphonate studies are detailed in Table SIII (online supporting information). Two studies used intravenous pamidronate,[5,6] and the third used intravenous zoledronic acid.[7] Two of the studies were class III evidence supporting the use of bisphosphonate therapy for increased BMD.[6,7] However, these two studies did not provide adequate new information to produce a change in the level of evidence to support bisphosphonates as an effective intervention for improving BMD in children and young people with CP, therefore it remained level B (probably effective) as shown in Table SIII.

Two class III studies demonstrated a decrease in fracture rate, but only one was statistically significant.[5,6] One study

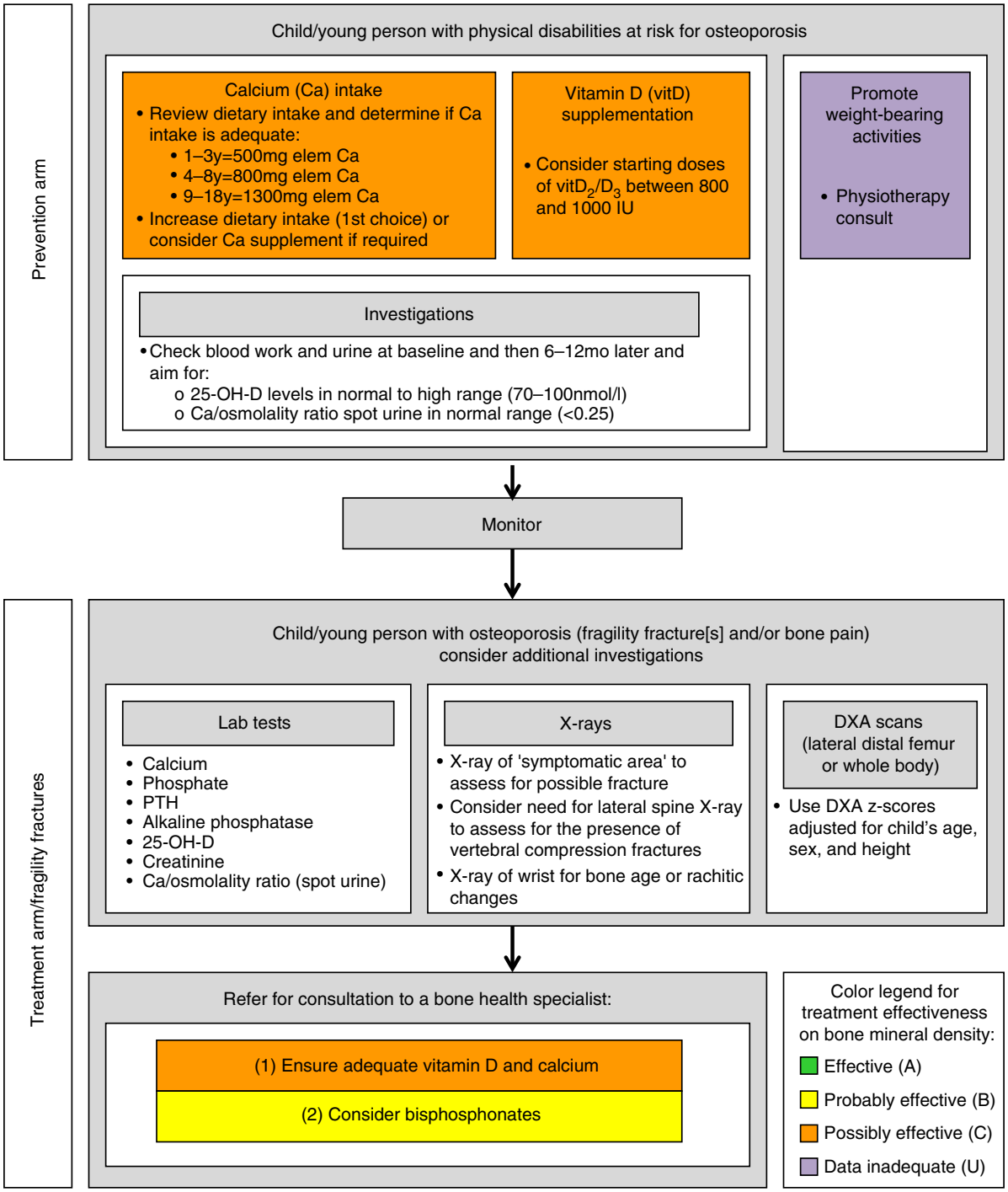

Figure 1: Osteoporosis clinical practice guidelines for children and young people with cerebral palsy. *The figure has been modified slightly from the original 2011 clinical practice guideline with respect to color coding of evidence and location of dual energy X-ray absorptiometry (DXA) scan (e.g. lateral distal femur or whole body).

demonstrated a trend in decreasing fragility fractures, as no new fractures were reported during the intervention period, but no statistical testing was done to measure the effect so it was downgraded to class IV support.[7] These findings did not provide adequate new information to provide a change in the evidence to support bisphosphonates as an effective intervention for decreasing fracture rate in children and young people with CP, therefore it remained level C (possibly effective) as shown in Table II. Short-term adverse events reported in these two articles included asymptomatic hypocalcemia, low-grade fever, aches/pains, and nausea.

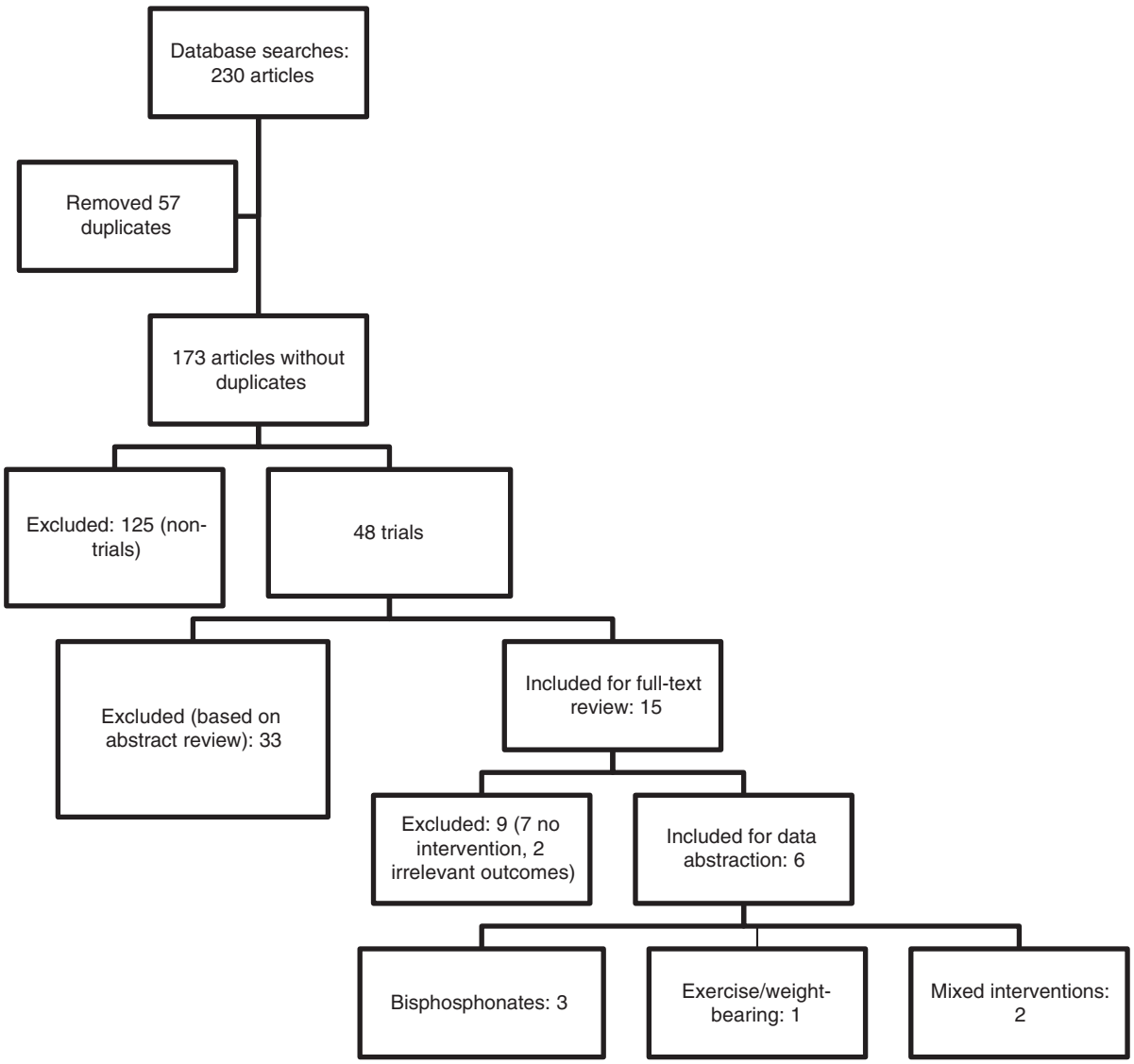

Figure 2: Search strategy results.

Table I: Weight-bearing intervention evidence summary

	Grade level		
Outcome	2011[2]	2016	Overall
Improved BMD	U=data inadequate YES: 2 class I, 1 class II, 1 class III NO: 3 class I, 2 class II	U=data inadequate YES: 1 class I NO: 1 class I	U=data inadequate YES: 3 class I, 1 class II, 1 class III NO: 4 class I, 2 class II
Decreased fracture rate	U=data inadequate YES: Nil NO: Nil Further research will be necessary	U=data inadequate YES: Nil NO: Nil Further research will be necessary	U=data inadequate YES: Nil NO: Nil Further research will be necessary

Vitamin D and calcium intervention

There was no additional literature published since 2011 that met the inclusion criteria of use of vitamin D and/or calcium as an intervention for improving BMD or decreasing fragility fracture rate. The evidence table remains the same as shown in Table III.

Mixed interventions

The two reviewed mixed intervention studies are detailed in Table SIV (online supporting information). One study used oral alendronate in addition to calcium and vitamin D supplementation.[8] The other study used oral risedronate with alfalcidol.[9] Both studies were class III evidence,

Table II: Bisphosphonates intervention evidence summary

	Grade level		
Outcome	2011[2]	2016	Overall
Improved bone mineral density	B=probably effective YES: 2 class I; 4 class III NO: 1 class I	B=probably effective YES: 2 class III NO: 1 class I	B=probably effective YES: 2 class I; 6 class III NO: 1 class I
Decreased fracture rate	C=possibly effective YES: 1class II; 1 class III NO: 1 class III Additional research will be beneficial	C=possibly effective YES: 1 class III NO: 1 class III Additional research will be beneficial	C=possibly effective YES: 1 class II; 2 class III NO: 2 class III Additional research will be beneficial

Table III: Vitamin D and calcium intervention evidence summary

	Grade level		
Outcome	2011[2]	2016	Overall
Improved bone mineral density	C=possibly effective YES: 2 class III NO: Nil Note: There is Grade A evidence in other pediatric populations (e.g. nephrotic syndrome, and ambulatory children on anticonvulsants)	C=possibly effective YES: Nil NO: Nil	C=possibly effective YES: 2 class III NO: Nil
Decreased fracture rate	U=data inadequate YES: Nil NO: Nil Further research will be necessary	U=data inadequate YES: Nil NO: Nil Further research will be necessary	U=data inadequate YES: Nil NO: Nil Further research will be necessary

Table IV: Mixed intervention evidence summary

	Grade level	
Outcome	2016	Overall
Improved bone mineral density	C: possibly effective YES: 2 class III NO: Nil	C: possibly effective YES: 2 class III NO: Nil
Decreased fracture rate	U=data inadequate YES: Nil NO: Nil Further research will be necessary	U=data inadequate YES: Nil NO: Nil Further research will be necessary

supporting the use of mixed interventions for increasing lumbar BMD.[8,9] Taken together, the studies provide possible evidence (level C) to support the use of mixed interventions to increase BMD in children with CP as shown in Table IV. Neither study evaluated fracture rate. No significant adverse events were reported associated with these mixed interventions.

DISCUSSION

Based on the results of this systematic review update, there was inadequate new research to provide a change to the grading of therapeutic evidence to support the use of weight-bearing activities, bisphosphonates, and vitamin D and calcium supplementation to improve BMD and decrease the rate of fractures in children and young people with CP. Consistent with Fehlings et al.,[2] there continues to be 'probable' evidence for bisphosphonates, 'possible' evidence for vitamin D and calcium, and 'insufficient' evidence for weight-bearing activities as effective interventions in the prevention arm of the guideline to improve low bone mineral density in children with CP. Overall, there continues to be less evidence to review the impact of these interventions on fracture rate, but there is 'possibly effective' evidence for bisphosphonates in reducing fragility fracture occurrence.

The updated clinical practice guidelines for osteoporosis originally published in 2011 are presented in Figure 1. It is important to note that a clinical practice guideline combines a systematic review of the published literature with clinical expert opinion to develop a more complete treatment/care pathway to inform clinicians. Hence, weight-bearing continues to be recommended in the guidelines despite the evidence being inadequate. Despite the evidence supporting the use of bisphosphonates for a positive impact on BMD, regular use of bisphosphonates in the prevention arm of the clinical practice guideline has not been recommended because of lack of knowledge on the long-term impact of bisphosphonates on growing bone.

It is interesting to note that the reviewed studies evaluating bisphosphonate interventions as an isolated intervention used intravenous bisphosphonates, whereas the mixed interventions in this review used oral bisphosphonates in conjunction with vitamin D supplementation. A recent review on the use of bisphosphonates in pediatrics looked at whether oral and intravenous administration of bisphosphonates differ in effectiveness in improving BMD and decreasing fracture rate in children with osteogenesis imperfecta.[10] One study using oral alendronate for 2 years

found that it decreased bone turnover and increased lumbar BMD, but did not change fracture rates, compared with the placebo group.[11] However, a second study using oral risedronate for 2 years found that treatment did not lead to any significant differences in cortical width, trabecular bone volume, or parameters of bone turnover. This suggests that, although it led to an increase in lumbar BMD, oral risedronate did not have as strong an effect on skeletal structure as intravenous pamidronate.[10] More research is required to determine whether oral bisphosphonate administration is as effective as intravenous administration in children.

Although this review used a thorough research strategy, only English-language articles were included; thus, findings from potentially relevant non-English articles were excluded. A number of included studies in this review had small sample sizes and were of short duration, demonstrating methodological limitations. The weight-bearing study included a small sample size of 27 children (13 in the treatment group and 14 in the comparison group), and only followed participants for 12 weeks.[4] Within such a short timeframe it is challenging to evaluate the effect of weight-bearing on fractures. Research of a longer duration is required to evaluate the impact of weight-bearing on fracture rates.

The included bisphosphonate studies also present methodological limitations that may have affected their outcomes. Two of the bisphosphonate studies were retrospective and measured the effect of bisphosphonates over 1 year.[5,7] Considering the length of treatment, it is difficult to obtain significant results regarding the effect of bisphosphonates on fracture rate.

The sample sizes of the studies were generally small, limiting the power of the studies. The short duration of many of the studies also limited their potential ability to evaluate the impact of the treatments on fracture rate. While it is difficult to enroll an adequate number of children and to maintain long follow-up periods, it is important to note that insignificant results may not be a matter of treatment inadequacy, but rather a result of methodological barriers.

Further research continues to be warranted. For future research, the designation of a primary location for BMD outcome evaluation (e.g. distal femur) is recommended for comparability between studies and to avoid mixed findings on the impact of these interventions on BMD. Researchers are also encouraged to assess the impact of the interventions on both BMD and fragility fractures.

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SUPPORTING INFORMATION

The following additional material may be found online:

Table SI: Search strategy used for MEDLINE (OVID) and adapted for other databases

Table SII: Weight-bearing activity interventions evidence

Table SIII: Bisphosphonate interventions evidence

Table SIV: Mixed interventions evidence

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