## Title
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## Journal
Journal of Bone and Mineral Research, 35(6)

## ISSN
0884-0431

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## Publication Date
2020-06-01

## DOI
10.1002/jbmr.4049

Peer reviewed

PERSPECTIVE

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# Osteoporosis Management in the Era of COVID-19

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**ABSTRACT**

Osteoporosis is a chronic condition that reflects reduced bone strength and an associated increased risk for fracture. As a chronic condition, osteoporosis generally requires sustained medical intervention(s) to limit the risks for additional bone loss, compromise of skeletal integrity, and fracture occurrence. Further complicating this issue is the fact that the abrupt cessation of some therapies can be associated with an increased risk for harm. It is in this context that the COVID-19 pandemic has brought unprecedented disruption to the provision of health care globally, including near universal requirements for social distancing. In this Perspective, we provide evidence, where available, regarding the general care of patients with osteoporosis in the COVID-19 era and provide clinical recommendations based primarily on expert opinion when data are absent. Particular emphasis is placed on the transition from parenteral osteoporosis therapies. It is hoped that these recommendations can be used to safely guide care for patients with osteoporosis until a return to routine clinical care standards is available. © 2020 American Society for Bone and Mineral Research.

**KEY WORDS:** ABALOPARATIDE; BISPHOSPHONAT; COVID-19; DENOSUMAB; FRACTURES; OSTEOPOROSIS; ROMOSOZUMAB; TERIPARATIDE

## Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) initially caused clusters of severe respiratory illness in Wuhan, China, in late 2019[(1)] and has since rapidly spread in Europe and the United States. As of May 5, 2020, a total of 3,517,345 persons were reported to be infected by SARS-CoV-2 and 243,401 persons to have died of coronavirus disease (COVID-19). COVID-19 was characterized as a pandemic by the World Health Organization on March 11, 2020.[(2)] In response, many countries have implemented a series of unprecedented measures to mitigate the spread of the virus, including large-scale social isolation, travel bans, restriction of public gatherings, and nationwide lockdowns. Although these social distancing strategies have been necessary from a public health standpoint, they have understandably introduced challenges in the management of many chronic medical conditions.[(3)]

Because osteoporosis is a chronic disease, continued treatment is a prerequisite in many patients in order to sustain therapeutic benefits, as is the case with other chronic conditions. With the exception of bisphosphonates, which have a long biologic half-life, other anti-osteoporosis drugs need to be provided in a regularly scheduled manner. Delaying the administration of certain categories of osteoporosis drugs can have ominous consequences for patients, ranging from loss of bone mass to increases in bone turnover and fracture risk. Hip fractures, the most devastating type of fracture, significantly impair mobility and independence and lead to an approximately 25% 1-year mortality rate.[(4)] Recognizing the potential detrimental effects of abruptly terminating anti-osteoporosis therapy, the American Society of Bone and Mineral Research (ASBMR) formed a Steering Committee of bone specialists to address this issue.[(5)] Here we review available evidence and provide clinical guidance for the management of patients with osteoporosis during the COVID-19 pandemic. We acknowledge both that there is a paucity of data to provide evidence-based clinical recommendations and that treatment modalities are likely to vary according to the status of local and national facilities, such as phlebotomy and infusion therapy centers, as well as outpatient clinics. Thus, these recommendations are based primarily on expert opinion and will require reassessment as the worldwide response to COVID-19 evolves.

Received in original form April 28, 2020; revised form May 6, 2020; accepted May 8, 2020. Accepted manuscript online May 14, 2020.
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The peer review history for this article is available at https://publons.com/publon/10.1002/jbmr.4049.

Journal of Bone and Mineral Research, Vol. 00, No. 00, Month 2020, pp 1–5.
DOI: 10.1002/jbmr.4049

## Bone mineral density scans

Although bone mineral density (BMD) testing is a helpful tool to assist in the identification and management of patients at high risk of fractures,[6] these scans should be considered as elective. Thus, BMD examinations may need to be postponed when public health guidance recommends the halting of elective imaging procedures. In the absence of BMD testing, fracture risk stratification can still be performed for treatment-naive adults with the use of the Fracture Risk Assessment Tool (FRAX).[7]

## Laboratory monitoring

Standard pretreatment laboratory studies, including serum calcium, creatinine, and/or 25-hydroxyvitamin D, are often obtained before the administration of potent antiresorptive agents, such as intravenous (iv) bisphosphonates and denosumab, in order to minimize risk of inducing hypocalcemia. In patients who are initiating new osteoporosis treatment with a potent antiresorptive agent, we recommend obtaining relevant laboratory studies before first administration. However, the absolute risk of inducing clinically significant hypocalcemia after treatment with either zoledronic acid[8] or denosumab[9] is very low in the absence of significant renal insufficiency. Both to facilitate social distancing guidelines and to minimize patient exposure at phlebotomy centers, we suggest that pretreatment laboratory studies before retreatment with iv bisphosphonates and/or denosumab need not be performed if laboratory values obtained within the preceding year were normal and it is the clinical judgment of the medical provider that the patient's health has been stable. However, we do recommend obtaining laboratory studies for patients with fluctuating renal function and for those who are at higher risk of developing hypocalcemia, such as those with malabsorptive disorders, hypoparathyroidism, or advanced renal dysfunction (chronic kidney disease stages 4 or 5) or those maintained on loop diuretics.

## Pharmacologic osteoporosis treatment

The initiation of osteoporosis therapy can be done as an outpatient via a non-face-to-face (ie, telephone or video) visit and should not be delayed in patients at high risk for fracture (eg, patients who have recently sustained an osteoporotic fragility fracture or patients taking chronic high-dose glucocorticoids). In particular, oral osteoporosis regimens can be easily initiated during a telemedicine visit; teriparatide and abaloparatide initiation may also be considered but require additional patient training for subcutaneous self-injections that may be more difficult to arrange. Patients who have fractures requiring hospital admission should be considered for osteoporosis medication initiation while hospitalized to minimize the risk of being lost to follow-up in the post-discharge period, which may be further fragmented during the COVID-19 pandemic. Specifically, there is no evidence for impaired fracture healing in patients who receive early initiation of osteoporosis treatment, including bisphosphonates.[10] It should be acknowledged, however, that the administration of iv bisphosphonates may cause a post-infusion inflammatory reaction, particularly in treatment-naive patients. Symptoms of the inflammatory reaction, including fever and myalgias, have the potential to complicate the care of hospitalized patients by triggering a COVID-19 evaluation and may prolong hospitalization.

When possible to do safely, patients who are already treated with osteoporosis medications should continue to receive ongoing therapies including oral and iv bisphosphonates, denosumab, estrogen, raloxifene, teriparatide, abaloparatide, and romosozumab. There is no evidence that any osteoporosis therapy increases the risk or severity of COVID-19 infection or alters the disease course (in either a positive or negative way). However, there are early signals that COVID-19 may be accompanied by an increased risk for hypercoagulable complications,[11,12] in which case caution may be warranted for estrogen and raloxifene use, both of which may modestly increase thrombotic risk.[13,14] It may therefore be prudent to instruct patients to temporarily discontinue these hormonal agents if they develop viral respiratory symptoms. Denosumab also bears particular consideration because it is a monoclonal antibody that inhibits receptor activator of NF-κB ligand (RANKL), and RANKL plays a role in T-cell activation. Studies of denosumab in postmenopausal osteoporosis indicate an increased risk of skin and soft tissue infections.[15] However, no infection safety signals have been found in studies of denosumab in patients receiving concurrent immunomodulatory treatment for rheumatoid arthritis[16–18] and among patients receiving concomitant chemotherapy for solid-organ tumors.[19,20]

Depending on the severity of the local COVID-19 outbreak, we acknowledge that there may be disruptions in the administration of osteoporosis treatments. We thus aim to provide guidance about (i) alternative methods of delivering parenteral osteoporosis treatments that are not self-administered (eg, iv bisphosphonates, denosumab, and romosozumab); and (ii) how to handle temporary disruptions in the pharmacologic management of osteoporosis patients.

### Alternative methods of delivering parenteral osteoporosis treatments

- Off-site clinics: The administration of treatments at locations geographically isolated from COVID-19 "hot spots" should be considered whenever possible. However, it should be recognized that this may disadvantage socioeconomically challenged communities if public transportation options are not available.
- Home delivery and administration: This is an option if available but may be logistically difficult to arrange due to reliance on home-visiting medical staff. Self-injection of denosumab (and/or romosozumab) has been proposed and is reportedly available in some locales. However, there are important medico-legal issues to consider surrounding the proper product handling and administration, including the small risk of drug-related hypersensitivity reactions that could occur in the absence of a medical provider, although steps to mitigate such potential risks may be in place in some communities.
- Drive-through administration of denosumab and/or romosozumab: This may also be logistically difficult to arrange. Further, it is recommended that patients be monitored by a medical provider for 15 minutes after injection in the unlikely event of a hypersensitivity reaction.

### Temporary disruptions of pharmacologic osteoporosis treatment

In the event that temporary disruption of osteoporosis treatment is necessitated due to COVID-19, we have reviewed evidence about treatment discontinuation effects and have provided

recommendations for the delay or temporary transition to other osteoporosis agents. In general, we recommend the resumption of the original osteoporosis treatment plan once circumstances allow.

*Bisphosphonates*

After bisphosphonate discontinuation, suppressed bone turnover markers (BTMs) slowly return to their baseline concentrations and BMD remains stable or decreases very gradually over a period of years.[21–23] The persistent antiresorptive effect of bisphosphonates after treatment discontinuation is dependent on their high affinity for binding hydroxyapatite. To this effect, bisphosphonates with a more pronounced binding capacity for hydroxyapatite, such as alendronate and zoledronate, have been shown to have a more sustained effect on maintenance of BMD and suppression of BTMs compared with risedronate.[24] Some studies also indicate a persistent anti-fracture effect after bisphosphonate discontinuation, although these data are less well-substantiated.[25,26] Finally, randomized controlled trials indicate that less frequent dosing of zoledronic acid may provide skeletal benefit and protection against fractures.[27–29] In summary, for patients in whom continued treatment with iv bisphosphonates is not feasible, delays of even several months are unlikely to be harmful.

*Denosumab*

There is evidence that delay of denosumab treatment causes rebound high bone turnover,[30,31] rapid bone loss within 1 year,[30,31] and increases the risk for the development of multiple vertebral fractures.[32] Reports of vertebral fractures after denosumab discontinuation have occurred as early as 7 months after the last denosumab injection.[33] The optimal regimen of antiresorptive drugs to mitigate the rebound phenomenon that characterizes denosumab discontinuation is currently being investigated in a number of randomized controlled trials. There is some evidence that oral alendronate may provide protection from denosumab-discontinuation rebound bone loss, especially in the setting of a short period of previous denosumab treatment.[34,35] However, multiple vertebral fractures have been described in two patients provided with alendronate after treatment with denosumab for an average of 3.5 years.[36] In comparison to oral bisphosphonate treatment, there is conflicting evidence regarding whether zoledronic acid can prevent rebound bone loss associated with denosumab discontinuation, with most data showing this potent antiresorptive agent to be less effective at maintaining BMD when previous denosumab treatment exceeded 2 years compared with a shorter duration of denosumab therapy.[37–39] Furthermore, there is controversy over the optimal timing and dosing of bisphosphonate therapy after denosumab discontinuation, although ongoing randomized controlled trials are expected to shed more light into this matter. It also remains unclear whether less potent antiresorptive medications, such as raloxifene, may be able to prevent the high bone turnover state after denosumab discontinuation.[40,41] Regarding transitioning from denosumab to osteoanabolic treatment, there is evidence that switching to teriparatide leads to a high bone turnover state and a temporary but rapid decrease in BMD, especially at cortical skeletal sites.[42] Finally, recent evidence has shown that romosozumab treatment after denosumab discontinuation results in BMD gains, albeit of a smaller magnitude compared with romosozumab administration alone in treatment-naive patients.[43]

Based on the available data, we strongly recommend the temporary transition to an oral bisphosphonate (such as weekly alendronate) for patients in whom continued treatment with denosumab is not feasible within 7 months of their most recent prior denosumab injection. For patients with known upper gastrointestinal (GI) disorders, we suggest that these patients be transitioned to monthly ibandronate or weekly/monthly risedronate based on reports that these medications may have fewer upper GI side effects.[44,45] Bisphosphonates are contraindicated for patients with chronic renal insufficiency (estimated glomerular filtration rates [eGFR] levels <30 to 35 mL/min); however, in such patients, the off-label provision of lower-dose oral bisphosphonate (eg, alendronate 35 mg weekly, or alendronate 70 mg every 2 weeks) may be cautiously considered. We note that there is no published evidence to support these off-label regimens, and therefore clinicians should weigh the unknown benefits and potential risks of these regimens against the concern for rebound-associated loss of bone mass and vertebral fracture occurrence after denosumab discontinuation in the setting of the COVID-19 pandemic.

*Teriparatide and abaloparatide*

After teriparatide discontinuation, BMD progressively declines over the course of the first year,[46] but there is no evidence of increased rebound fracture risk. On the contrary, follow-up of the pivotal Fracture Prevention Trial with teriparatide (FPT)[47] suggested that some anti-fracture efficacy was maintained for up to 18 months after teriparatide was discontinued.[48] However, given the aforementioned progressive bone loss after discontinuation, it is likely that most of the beneficial anti-fracture effects of teriparatide will eventually dissipate unless followed by an antiresorptive agent. Multiple antiresorptive agents have been demonstrated to further increase BMD after teriparatide discontinuation.[42,49–51] Interestingly, regimens of cyclical teriparatide treatment (ie, 3 months on-treatment followed by 3 months off-treatment) given for 4 years cumulatively showed similar increases in BMD compared with standard daily teriparatide treatment provided over 2 years,[52,53] demonstrating proof of concept that short-term interruptions of teriparatide may not negatively impact long-term BMD increases, so long as treatment can be restarted within 3 months. On the other hand, pretreatment with bisphosphonates appear to blunt the efficacy of teriparatide,[54–56] evidence that may dampen enthusiasm for using bisphosphonates as bridging agents during a temporary disruption of teriparatide treatment.

Given that abaloparatide has a similar physiologic action as teriparatide, it is presumed that abaloparatide also has no prolonged BMD effects after its discontinuation. Fewer data are available about approaches to transition from abaloparatide to other osteoporosis agents, although the specific regimen of abaloparatide followed by alendronate has been shown to be an effective sequential regimen in postmenopausal osteoporosis.[57]

Based on the data above, for patients in whom continued treatment with teriparatide or abaloparatide is not feasible, we suggest a delay in treatment. If this delay exceeds 2 to 3 months, consider a temporary transition to an oral bisphosphonate.

*Romosozumab*

There is evidence that romosozumab discontinuation causes rapid bone loss within 1 year if not followed by another osteoporosis treatment.[58] Indices of bone resorption also increase within 3 months of romosozumab cessation,[58] although there

is no indication that discontinuation leads to an increased risk of fractures. There is evidence that transitioning from romosozumab to either alendronate or denosumab leads to continued gains in BMD.[59,60] However, pretreatment with alendronate might somewhat blunt the increases in hip BMD anticipated to occur with romosozumab[61] compared with the increases found in treatment-naive patients.[59,60] Finally, bone turnover marker data suggest that the most active period of bone formation with romosozumab occurs within the first 6 months of treatment, after which time romosozumab mirrors the biomarker profile of an antiresorptive agent.[59,60]

Based on the available evidence, we suggest a delay in treatment for patients in whom continued treatment with romosozumab is not feasible. If this delay exceeds 2 to 3 months, consider a temporary transition to oral bisphosphonate. In patients who have already received >6 months of romosozumab treatment, it is possible that a more permanent transition to oral bisphosphonates could be considered.

## Conclusion

Although it is hoped that widespread lockdowns may begin to be eased as we gain better control of COVID-19, it is increasingly likely that intermittent social distancing will be required over the next 18 months.[62] During this time of uncertainty, it is imperative that we continue to provide the best care possible for our patients by addressing the clinically important issue of osteoporosis, while acknowledging various logistic challenges that have the potential to disrupt care. We hope that these recommendations can provide a practical guide to the management of osteoporosis patients during this unprecedented pandemic.

## Disclosures

EWY has received an investigator-initiated grant from Amgen. ET has received research funding from MSD, honoraria for lectures from Amgen, UCB, Shire, and Kyowa Kirin, and educational grants from Shire and UCB. BLC, DAB, and MTD have no relevant disclosures.

## Acknowledgments

This work was not supported by any grant.

Authors' roles: Drafting manuscript: EWY, ET, and MTD. Revising manuscript content: EWY, ET, BLC, DCB, and MTD. Approving final version of manuscript: EWY, ET, BLC, DCB, and MTD.

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