Drug-associated osteonecrosis of the jaws (ONJ) remains a timely topic, a frequent occurrence, and a difficult condition to manage. Since 2003 and the first reports of ONJ, epidemiologic studies have shown that ONJ occurs in \( \leq 0.04\% \) of persons taking oral bisphosphonates (BPs), increasing about tenfold for those taking intravenous BPs and another tenfold if extractions are performed. Although the etiologic mechanisms of bisphosphonate-related (BR) ONJ are considered to involve altered bone function, additional studies are clarifying that BPs are also antiangiogenic, and several antiangiogenic chemotherapeutic agents (sunitinib, bevacizumab, denosumab) are now recognized to be involved in the development of ONJ. BPs are also cytoinhibitory against monocytes, keratinocytes, and fibroblasts, and these cells contribute to critical aspects of defense and wound healing that are likely involved in ONJ. Risk factors include intravenous BP use, prolonged BP use, tooth extractions, and concurrent use of steroids.

In this month’s article, Subramanian et al. (page 744) synthesize information from 6 case reports regarding teriparatide and its off-label use for the treatment of BRONJ and review the literature to hypothesize that the pathogenesis of BRONJ centers on a defective remodeling process secondary to weakened synergism between key cell types that interact during bone remodeling: osteoblasts, osteoclasts, osteocytes, and bone lining cells. In this model, ineffective bone remodeling is influenced by the relationships between: 1) the underlying health/disease status of the patient that can compromise osteoblast function; and 2) type and action of the bisphosphonate medication that can suppress osteoclast function. The authors review key biologic pathways of bone homeostasis, including osteoblast and osteoclast crosstalk and attenuated activity, Wnt signaling, the importance of nuclear factor \( \kappa B \), and a cascade of events involving cytotoxicity and poor vascularization of bone. This model presents insight into bone-related factors, but missing from the article is mention that BPs can inhibit mucosal cell proliferation and are cytotoxic against monocytes and macrophages. These cells lend important defense against mucosal breakdown, ingress of bacterial, and infection and are likely critical for preventing BRONJ.

Teriparatide is proposed to counteract the mechanisms of failed bone remodeling by stimulating processes that lead to bone remodeling through stimulation of Wnt signaling and its anabolic effect on osteoblasts. Consistent with this premise, the authors note that a prerequisite of healing is that damaged or necrotic bone is removed and new healthy bone is laid down at the remodeling/repair site. Teriparatide is a synthetic peptide that corresponds to the N-terminal (1-34) residues of human parathyroid hormone. Its anabolic effect on osteoblasts has been well documented and persists regardless of pretreatment with antiresorptive agents, such as alendronate, estradiol, or raloxifene. Furthermore, substituting teriparatide for BPs has been shown to help alleviate the underlying disease phenotype of osteoporosis. However, teriparatide is not without adverse effects. In addition to the side effects of positional hypotension, hypercalcemia, leg cramps, joint aches, and injection site pain, teriparatide carries a black box warning that osteosarcoma has occurred in rats and people who took the drug (Forteo; Eli Lilly Co., Indianapolis, IN). Teriparatide also is contraindicated in patients with osteosarcoma or metastatic bone disease—the population in which BRONJ is most commonly observed—and is not recommended for use for \( \geq 2 \) years of life.

Despite the drug’s limitations, there are several promising dentally related outcomes resulting from the short-term use of teriparatide. Subramanian et al. reported on the off-label use of teriparatide for BRONJ in which healing occurred in 6 cases within 5 months of initiating treatment. Teriparatide also has been shown to help resolve periodontal osseous defects and enhance osseointegration of titanium implants. These recent findings led me to speculate if teriparatide is at an early
tipping point for use in patients with osseous issues of the jaws, including BRONJ. To address this issue, I refer to Malcom Gladwell’s book *The Tipping Point*.18 In *The Tipping Point*, Gladwell identifies 3 key factors that influence whether a particular trend will “tip” into widespread popularity. These include the Law of the Few, the Stickiness Factor, and the Power of Context. I examine these factors in the context of a teriparatide’s use in medicine and dentistry.

The Law of the Few contends that a few key types of people must champion an idea or concept before it can reach the tipping point where widespread appeal and use is attained. Gladwell describes a discrete group of persons who are connectors, mavens, and salesmen, who if they endorse and advocate a new idea, the idea is much more likely to tip into exponential success. Regarding teriparatide, this concept seems to apply. A discrete group of people have tested and initially purported its utility. A search of PubMed revealed 25 papers that are hit with the terms “teriparatide and jaw or osteonecrosis,” 11 with “teriparatide and mouth,” and 5 with “teriparatide and periodontal.” Thus, a few people have championed the idea so far, and diffusion is offered from journals that circulate the concept to readers whereupon its worthiness is determined. Dissemination and conveyance is further reinforced through the present editorial where greater attention is directed. Helping the concept along is the fact that the Subramanian et al. article received peer-review scrutiny as did the 6 case reports which originally appeared in the *New England Journal of Medicine*, *Journal of Oral and Maxillofacial Surgery*, *Journal of Rheumatology*, *Head and Neck*, and *Special Care Dentistry*. My role as a teacher and my compulsion to pass knowledge on and to help clinicians and patients is also likely to result in the spreading of this concept a bit further. However, I remain balanced by the fact that additional scientific evidence is required through more case reports, case-controlled studies, and eventually placebo-controlled clinical trials. These latter efforts can be achieved through government or industry sponsored funding and/or the topic being incorporated into the National Institutes of Health’s strategic plan which is open to suggestion annually.

Gladwell defines the second step in the attainment of a tipping point as the Stickiness Factor. Stickiness in the dental and medical professions is unique in that it requires evaluations from randomized controlled trials that demonstrate effectiveness and reliability while affording minimal adverse effects. Interestingly, stickiness, as defined by Gladwell, is often counterintuitive to the prevailing wisdom. In this case, the prevailing wisdom would be to avoid BPs or invasive procedures in those at risk, but this is not always possible. The counterintuitive possibility is that intravenous BPs may place only some patients at greater risk (e.g., those carrying select gene polymorphisms),19 or that teriparatide may demonstrate utility in patients who have BRONJ together with metastatic bone disease. In the latter, teriparatide may prove to be therapeutic in a unique subset of patients whose metastatic lesions are discriminated by phenotype or genotype. These types of intuitive and counterintuitive studies would require bold thinking and a willingness of patients and clinician-scientists to challenge the expected.

The Power of Context is the third concept mentioned by Gladwell required for a tipping point to be attained. Here, context is the view taken by clinicians and investigators regarding teriparatide’s potential utility as worthy or not worthy of further investigation. If teriparatide’s utility has perceived potential, then investigators will write grant proposals and a small cadre of grant reviewers or industry sponsors would need to view these projects as worthy of funding. Funded grant proposals would result in clinical investigations, and potentially clinical successes could be achieved. Eventually these investigations could lead to rejection of the concept or insight critical for a new drug indication. Subsequently, drug modifications and refinements could develop, leading to a class of drugs that act by similar principle.

As a profession, we should always challenge new concepts and be careful not to be too impressionable or “tip” too quickly toward adoption. After all, there are historical examples of pathologic science, including Fleischmann and Pons reporting of “cold fusion”20 and Sudbo et al.’s reporting of “DNA content as prognostic markers.”21 These examples help to illustrate the flaws in early adoption just because the significance could be great. So, as we examine this potential tipping point, I need to encourage this promising concept and likewise demand scientific rigor in the experiments I predict will be eventually performed. If our scientific community does its job, then we can hope that the cumulative evidence support the findings of Subramanian et al. and that new recommendations and advocacy for the use of drugs such as teriparatide for select diseases of the jaws results. In parallel, studies that investigate methods for prevention of ONJ are required.

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REFERENCES