Knowledge, Practices and Opinions of Ontario Dentists when Treating Patients Receiving
Bisphosphonates

by

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for the degree of Masters of Science

Graduate Oral & Maxillofacial Surgery

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Abstract

Background: Bisphosphonate related osteonecrosis of the jaws (BRONJ) is a severe but extremely rare complication of prolonged treatment with bisphosphonates. Improper treatment or misdiagnosis can have serious repercussions. **Objective:** is to measure the awareness of Ontario dentists about BRONJ and to identify any gaps in their knowledge of the condition and its treatment. **Material and Methods:** A survey was sent to a random sample of dentists in Ontario, Canada. Information about their awareness of bisphosphonates, and their awareness of an established BRONJ guideline was collected. **Results:** 60% of responding Ontario dentists had good knowledge of BRONJ, only 23% followed the guideline when surgical treatment was indicated. However, about 50% of responding Ontario dentists are not comfortable treating BRONJ patients. **Conclusion:** The finding reveals that Ontario dentists have moderate knowledge about BRONJ, which suggest greater educational efforts should be made to promote their knowledge.

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1 Introduction and literature Review

1.1 Background

Osteoporosis is a skeletal disorder characterized by reduced bone density, a condition that predisposes individuals to an increased risk of fracture.¹ This particular medical condition is most frequent among people older than 45 with a probable prevalence ratio of up to one in four women and one in eight for men in North America as indicated by the National Institutes of Health.¹ With over five million prescriptions written in North America per year, the overwhelming medication of choice for more than 95% of patients with osteoporosis is bisphosphonates.¹

Osteoporosis has different types like primary osteoporosis which is the most common type. Primary osteoporosis affects women more than men. Secondary osteoporosis has the same symptoms as primary osteoporosis.² But it developed from some medical conditions like hyperthyroidism or leukemia. Idiopathic juvenile is also a rare type of osteoporosis which affects mainly children between the ages of 8 and 14, where there is less bone formation. Which makes them prone to fractures.²

1.2 Bisphosphonates

Bisphosphonates (BPs) are a class of therapeutic drugs derived from pyrophosphates. Bisphosphonates acts on the nonhydrolyzable analogs of ATP which accumulate intracellularly

in the osteoclasts, which results in osteoclast apoptosis. Bisphosphonates also inhibit the enzyme farnesyl diphosphonate in the mevalonate pathway.³ There are several distinct types of BPs that can be differentiated from one another by the active phosphorous carbon side chain.^{4, 5} The first generation of BPs, such as etidronate and clodronate, possess alkyl or halide sidegroups.⁴ The 2nd generation BPs (pamidronate, zoledronic acid, alendronate, risedronate, and ibandronate) contain a side chain amino-terminal cluster which allows for a ten times greater bone anti-resorptive capacity when compared with the first generation BPs.⁶ The 3rd generation BPs, which includes zoledronate, has an imidazole ring in the side chain. This makes them about 100x more potent than the 2nd generation BPs. The cytotoxic cell death of the osteoclast induces osteoclast apoptosis through selective enzyme inhibition.^{5, 6} This is the primary mechanism by which BP's reduce bone resorption and increase bone density/mineralization.^{5, 6}

First generation BP was initially introduced for the treatment of osteoporosis. In contrast, the second and third generations BPs are used to treat malignant bone disease and are prescribed yearly to over two million individuals in North America. This treatment may contribute to the exposed necrotic bone observed in the oral cavity encountered in patients at dental practices.^{7, 8} Pamidronate and zoledronic acids are both administered intravenously. Nitrogen-containing BP agents are at present the most widely used drugs in oncology; 90% of all documented exposed bone cases have been treated with these drugs.⁹

Bisphosphonates were first synthesized in 1865 in Germany and used industrially as they were found to have powerful anti-corrosive properties.⁶ Herbert Fleisch, a German scientist, claims to be the first to use bisphosphonates therapeutically; he employed them because he observed their inhibitory effects on bone resorption in in vitro studies. This was followed by the first medical use of bisphosphonates on a person to treat Myositis ossificans.⁶ BPs may be considered a universal treatment because they slow down osteoclastic bone resorption.⁶ BPs are not only prescribed for patients with osteoporosis, they are also administered to patients with metastatic bone disease, cancer of the breast, multiple myeloma, and hypercalcemia of malignancy in the hopes of increasing survival rates and preserving quality of life.^{10, 11} Bone metastases can lead to pathologic fractures of the bones, bone pain, spinal cord compression and hypercalcemia in metastatic tumors. BPs are used to treat and prevent such skeletal consequences in concert with radiation treatment, surgery and chemotherapy. The primary advantages of these

treatment modalities are that they improve quality of life, as the disease is usually incurable at this stage.^{6, 12}

BPs serve a very useful purpose in the aforementioned disease state, however, they have the potential to cause unwanted consequences and or complications. Complications with the use of BPs include; hypocalcemia, increased parathyroid hormone, eye inflammation, nephrotic syndrome and osteonecrosis of the jaw. The aforementioned complications are more commonly found when BP's are administered intravenously. In particular, BRONJ occurs more frequently in patients on IV BP who then undergo a traumatic dental procedure, such as dental extractions, periodontal surgery or root canal therapy.¹³ The effects on the oral cavity will be discussed in the following pages.

BPs are separated into two subtypes based on the nitrogen atoms in the side chains. The less potent non-nitrogen contains BPs, such as etidronate, clodronate, and tiludronate. They are believed to lyse osteoclast cells due to cytotoxic hormones of adenosine triphosphate (ATP) production.^{5, 6} The process can accumulate and penetrate through intracellular metabolic enzymes that are involved in the BP process.^{5, 6}

Altering the R (in the side chain) containing nitrogen atoms can change the potencies of resorption (Figure 1).^{6, 14} Intracellular scarcity is created by the presence of geranyl and farnesyl diphosphate. Both are required for modifying post-translational lipid (prenylation) of small signaling proteins with GTPase activities.^{6, 14} The dysfunction result hampers the control of osteoclast morphology leading to poor cell apoptosis and functioning.^{6, 14}

Nitrogen containing BPs have been shown in vitro to reduce the metastatic capabilities of cancer cells within bone.^{6, 14} BP's interrupt or alter the interaction between neoplastic cells and osteoclasts by decreasing the levels of insulin-like growth factor-I (IGF-I) and transforming growth factor-13(TGF-13).¹⁴ Zoledronic acid disrupts the process of angiogenesis by reducing the formation of new vessels and thus reducing the amount of circulating vascular endothelial growth factor (VEGF) and suppressing endothelial cell proliferation.⁵

Researchers have focused their work on the nitrogen-containing BPs that affects tumor cells. *In vitro* experiments confirmed that they were able to inhibit the bonding of neoplastic cells to bone, as well as reducing their ability to attack artificial membranes. All doses that do not cause direct cytotoxicity can slow down cell passage.¹² The nitrogen-containing BPs can induce apoptosis and prevent neoplastic cell growth by disrupting the mevalonate pathway processes.^{3, 14} Furthermore, all BPs can prevent complex metalloproteinases, which are a class of enzymes that are zinc-dependent and contribute to standard wound remodeling, a process that has been demonstrated to use tumor cells to assist in metastatic movement to adjoining tissues in various animal experiments.^{14, 15}

BPs can disrupt the intricate relationship that occurs between osteoclasts and cancer cells by preventing the discharge of TGF-0 and TGF-1.^{14, 16} It has been shown in animal studies that the presence of zoledronic acid, which is a nitrogen-containing BP, can affect angiogenesis by decreasing the formation or vascularization of new blood vessels as well as by lowering the number of endothelial cell growth factors.¹⁷ A decrease in the quantity of VEGF (vascular endothelial growth factor) has been confirmed in humans after they have received zoledronic acid.¹⁷ In addition, some patients will develop an acute-phase and self-limiting reaction after the infusion of BPs that results in mild flu-like signs and this is thought to be due to the release of interleukin and tumor necrotic factor hormones.^{12, 18}

1.3 Bisphosphonate- related osteonecrosis of the jaw

Despite the many benefits of bisphosphonates, in the early 2000s several patients presented at dental offices with exposed necrotic bone in the maxilla or mandible of then unknown etiology. Further investigations identified a common variable among all patients who presented with exposed bone: they were all taking bisphosphonates, and most of them had recently undergone a surgical dental procedure.⁹ Marx (2003) was among the pioneers to describe the relationship of treatment with BPs to the occurrence of osteonecrosis of the jaw.¹⁹ After Marx, Ruggiero- along with several colleagues- published a larger case series of

bisphosphonate- related osteonecrosis of the jaws.⁹ This realization led to numerous studies that examined the relationship between bisphosphonates and bone infection, a clinical scenario that is now known as BPs- related osteonecrosis of the jaws (BRONJ).⁹

BRONJ is defined as an area of exposed bone that persists longer than eight weeks in a patient taking a bisphosphonate for bone disease.¹⁹ BRONJ is a severe but extremely rare complication of prolonged treatment with bisphosphonates.^{19, 20} Studies have not yet conclusively established a mechanism by which BPs are responsible for causing BRONJ. However, one hypothesis is that BPs prevents osteoclastic activity by inhibiting farnesyl pyrophosphonate synthase, a key amino acid in the mevalonate pathway.^{5, 21} This action can lead to a decrease in bone absorption. It has also been suggested that BP may prevent normal bone turnover remodeling. Micro-fractures of the bone are no longer repaired and angiogenesis may be inhibited which leads to weakening of the bone structure..^{5, 21}

The literature suggests that the maxilla and mandible are at greater risk of osteonecrosis as compared to other parts of the skeletal portions of the human body.²² The jaw bones are the only bones in the body that are always in contact with the external environment. They are also subjected to repeated micro-trauma due to normal mastication and the teeth/bite force.¹³ In vivo studies on animals have demonstrated that the bone remodelling process can be ten times greater in the alveolar process than in the long bones.^{22, 23} This increased remodelling may indicate a physiological adjustment and may therefore make the human jaw bones more susceptible to BRONJ.¹⁰ By preventing the process of natural bone remodelling and angiogenesis because increased usage of BPs affects the bone's native regenerative capacity.²³ Therefore, a local injury to bone, a non-healing injury, can lead to an osteonecrotic condition that will ultimately result in super-infection when exposed to the normal flora.²⁴ Local trauma caused by teeth extraction, ill-fitting dentures or local surgery are considered to be the most significant risk factors,⁹ even though, interestingly, an estimated 25% of all BRONJ cases appear to occur spontaneously without a known insult.⁹ Approximately 65%-70% of BRONJ cases result after dental surgery.⁹ This observation has led many to assume that the regenerative capability of the alveolar bone can be affected by the disruption of the delicate communication between osteoclasts and osteoblasts.⁹ Animal studies have highlighted the importance of a well-functioning osteoclast in the restorative process of micro-fractures following dental surgery.^{9, 24}

Marx et al. (2003) reported that the presence of periodontitis (84%), dental caries (29%), gingival abscesses (13%), previous root canal treatments (11%), and anatomical differences that include exposure of bone in the mandible (9%) were present in their patients with BRONJ; 94-97% of them received BPs.⁹ The most frequent treatment for cancer patients is chemotherapy.⁷ There is no apparent association with a specific cytotoxic agent of chemotherapeutic agents, such as in cases that had been reported with allylators, anti-metabolites, tumour antibiotics, taxanes, vinca alkaloids and platinum derivatives. In multiple myeloma patients, the use of steroids has been linked to an increase in osteonecrosis. Further investigations are still required to determine the cause and effect relationship.¹⁹

The mandible is supplied by the inferior alveolar artery that reaches out to other small vessels in the periosteum.¹⁰ These vessels play a significant role in the process of wound healing. Angiogenesis involves both vessels of the periosteum and the inferior alveolar artery and hence any inhibition by BPs may interfere with the blood supply into the healing tissue.^{11, 13}

The historic and morphologic analysis comparing BRONJ with infected osteoradionecrosis has revealed promising results in the search for effective therapies. Osteoradionecrosis is a well-defined phenomenon resulting from exposure to radiotherapy and chemotherapy procedures that can develop many years after the initial exposure. Investigators have seen lesions that demonstrate extensive homogenous areas of bone necrosis.^{25, 26} Osteoradionecrosis has however, been successfully treated with surgery debridement and the use of hyperbaric oxygen, which can be used as a preventive option or to treat Osteoradionecrosis.²⁵

BRONJ- affected bone lesions exhibit many of the elements linked to osteoradionecrosis including necrotic bone, loss of soft tissue coverage and hypocellularity.²⁵ With respect to vascularisation, no reduction in capillaries could be demonstrated and destruction of vessels was only seen in certain BRONJ patients. Studies have shown that only 13% of BRONJ cases demonstrated hypovascularity as compared to 30% of cases of osteoradionecrosis. In contrast, increased cellularity was noticed in both the media and intima of the arteries in BRONJ but this finding was not present in the cases of osteoradionecrosis.^{25, 26}

The uncertainty with respect to the causes of pathogenesis remains. Infection is thought to be another vital factor in BRONJ, with both sustaining of bones and causal roles for micro-

organisms. Specific colonies of actinomyces have been discovered in BRONJ patients, most commonly in the area of necrotic bone showing signs of erosion.^{14, 26} These gram-positive bacilli have low virulence capabilities that can produce chronic, gradually developing infections when normal mucosal barriers are disrupted. Furthermore, interactions between bacteria and osteoclasts could lead to increased bone destruction.^{5, 26} Clinical findings in BRONJ classically demonstrate tissues having a chronic non-healing inflammation with purulent secretions; these require the use of anti-microbial drugs over extended periods for resolution. The oral cavity contains an abundance of commensal flora and other organisms that include fungi and yeasts, all of which might be involved as well in the BRONJ presentation. There is a high incidence (58%) of diabetes or impaired glucose tolerance among BRONJ patients, as compared to 14% among age-matched members of society without BRONJ.^{5, 27} Diabetes mellitus has been connected with tissue hypoxia, blight wound healing, decreased bone turnover, and remodelling, and induction of apoptosis of osteoblasts or osteocytes.^{5, 27}

1.4 Incidence of BRONJ

The incidence of BRONJ seen, in oncologic-based cases and for dental patients that are treated with intravenous (IV) BPs, is 4.5 to 8% for multiple myeloma and 1.2 to 12% for metastatic breast cancer.²⁸ The incidence of oral BRONJ has been discussed in a number of studies with significant differences being reported.^{21, 28} The BP drug manufacturers estimate the incidence of BRONJ from patients taking oral BPs is 0.7 cases per 100,000 persons. Etidronate and clodronate do not typically cause osteonecrosis of the jaws despite the fact that they are used in oncological studies at the present time.²⁹ Research in Australia determined that the commonality of BRONJ in osteoporotic and oncologic dental patients can be 1 in 2,260 to 8,470 or 0.01–0.04% for oncologic dental patients. The incidence of BRONJ among all kinds of osteoporotic dental Israeli patients also amounted to about 1 in 4000 or 0.025%.^{8, 28, 30}

Sedghizadeh reviewed at least 208 oncologic dental patients from the University of Southern California Dental School who were using alendronate and found a high incidence rate

of 4.3%.³⁰ Nine of these oncologic dental patients had been diagnosed with BRONJ in connection with the use of alendronate. On the other hand, Pazianas utilized jaw surgeries as alternative markers and reported that there is no relation between osteonecrosis and oral BP use.¹⁸ Studies showed that the risk of BRONJ increases with the duration of BPs use if it's been taken for more than 3 years. Subsequently, there has been considerable discussion the benefits from a drug holiday. A three months drug holiday have been suggested for oral BP if it was taken for more than 3 years, although it is still debatable how long does bisphosphonates affect the bone after it has been stopped.^{19, 31, 32}

Most available data on triggering events are related to dental patients, while similar data for patients with an osteoporosis diagnosis are limited. Marx reported that BRONJ developed spontaneously, without any known triggering event, in 15 out of 30 oncologic dental patients treated with alendronate. The vast majority (13 out of 15) of cases developed BRONJ on the lingual cortex in the mandibular molar area. The reasoning for the propensity of this site is that the overlying mucosa is thin and is easily traumatized, exposing the underlying jawbone to the oral cavity. Among the 15 BRONJ cases that resulted from dentoalveolar surgery, 12 were associated with teeth extraction, two with dental implants placement, and one with the harvesting of a palatal connective tissue graft.^{9, 29}

1.5 Treatment guidelines for BRONJ

BRONJ treatment can be challenging and frustrating. There are a wide variety of treatment modalities available, including surgery, antibiotic/microbial therapy conservative management, hyperbaric oxygen therapy and local ozone therapy.³³ The existing treatment guidelines are based entirely on expert agreement (level 5 or grade D recommendation), due to the lack of randomized and prospective clinical trials. A disease staging system has been proposed in order to select the optimal treatment strategy for an individual patient.^{33 19}

A conservative treatment regimen using an antiseptic rinse, as well as symptomatic use of analgesics and long-term antibiotics remains the standard of therapy.^{4, 26} Before treatment is initiated, cultures should be meticulously gathered in order to narrow the initial practical anti-microbial treatment. All wounds should be cultured for both anaerobic and aerobic microorganisms as well as fungi and yeasts.^{4, 26} Actinomyces species are known to be slow-growing organisms, which mean they can go unnoticed in regular bacterial cultures; it is suggested that there should be close cooperation with microbiologists to overcome this drawback.^{15, 26, 34, 35}

Oral rinses, using 0.12% chlorhexidine gluconate at least 3-4 times a day, can be the basis of a maintenance therapy. Anti-microbial treatments can be also used to treat associated super-infections that reach the necrotic bone as well as to relieve symptoms of swelling, pain, and purulent discharge.^{9, 36} The therapy should be directed against the commensal flora of the mouth penicillin-based antibiotics with or without clavulanate. In cases of sensitivity or penicillin allergy, one of the newer macrolides like azithromycin or a quinolone such as ciprofloxacin can be used as alternates alone or preferably in combination- a preferred option. If initial therapy is unsuccessful, further treatment of anaerobic organisms can be initiated using metronidazole or clindamycin. In addition, if yeasts or fungi prove to be present in cultures, an anti-mycotic such as fluconazole or nystatin can be used. Anti-viral therapy is not regularly recommended and should only be started when clinically appropriate. Therapy usually begins orally, but in severe cellulitis or in refractory cases, intravenous therapy can be also included.^{9, 36}

There are still no specific guidelines concerning the use of anti-inflammatory drugs or analgesic agents even if these medications are useful and can relieve symptoms and work as anti-infective treatments. With this treatment, the majority of patients (90%) achieve a pain-free state without the need for surgical treatment no matter the oral condition or complicated wound care.^{9, 29} It is especially noteworthy that many investigations into optimal treatment regimes do not always interrupt or stop BP usage following BRONJ diagnosis.³⁷ Despite the persistence of areas of exposed bone in approximately 70% of all oncologic dental patients, control of symptoms still appears feasible in BRONJ using the previously mentioned treatments.²⁹

The initial reports of BRONJ clearly showed that surgery was detrimental for the resolution of the affected regions; it rather only served to worsen symptoms and resulted in larger bone and mucosal defects.^{8, 23} These initial studies for surgical techniques were similar to those used in the management of osteoradionecrosis; both diseases were presumed to be responsive to similar treatments. It has been suggested that the aforementioned conservative medical therapies as opposed to major surgery remains the preferred treatment approach.^{8, 14, 38}

Nonetheless, some still believe that there is a role for surgery in BRONJ, such as eliminating the sharp edges of bones that might traumatize all surrounding soft tissues. As an example, when there is involvement of the lingual aspect in the posterior mandible, superficial debridement procedures can prevent further soft tissue damage.^{11, 34} There are two published cases involving surgically enhanced techniques where the primary surgical salvage resulted in successful closure of the mucosal defect.^{11, 34} In order to achieve tension-free closure of the wounds after local debridement, periosteal-releasing incisions were employed in one case and a buccal fat pad local rotational flap was used in the other.^{11, 34}

Investigators have reported that primary surgery is potentially curative, even though there remains the possibility for postoperative complications leading to more bone exposure (29% of cases). A better understanding of the management of BRONJ is needed before these interventions can be routinely recommended. Hyperbaric oxygen (HBO) treatments have been reported to be ineffective and as such have fallen out of favor.³⁹ New data has been published that seems to challenge these earlier clinical findings. One case of BRONJ in a multiple-myeloma patient was reportedly cured using a combination of HBO and antibiotic therapy.³⁹ It should be noted that the investigation showed that various oncologic dental patients had not been exposed to BPs and therefore a diagnosis of BRONJ could not be seen. As the results of the use of HBO are equivocal this therapy must be recommended carefully.³⁹

The latest addition in the search for new therapeutic options is the use of ozone therapy, which is believed to have anti-microbial and neo-angiogenic properties.^{11, 34} A treatment strategy consisting of local minor curettage with post-operative ozone, antibiotics, antiviral and antifungal therapy, chlorhexidine 0.2% mouthwash and ascorbic acid was reported to be successful, resulting in complete mucosal healing. However, the true value of ozone application

still remains to be determined because these reports did not compare both strategies; as well, the number of evaluations of oncologic dental patients in these initial reports are low. The cessation of BP therapy has not been shown to accelerate the process of healing.¹¹ A possible explanation could be a long half-life effect on the bone, which is estimated to be at least 10 years.^{11, 34}

Despite these findings, it is legally questionable and ethically difficult to continue administering an agent that could be responsible for the current condition. Careful consideration of both risks and patient benefits is necessary; decisions have to be reached in consultation with the patient. If more BP therapy is indicated, the use of pamidronate can now be administered every three months instead of using zoledronic acid, although there is still a lack of scientific evidence to support this practice.^{11, 39} Long term follow-up data and prospective comparisons of the different treatment protocols are necessary to validate these preliminary results and should result in more definitive recommendations.^{38,11, 33}

The diagnosis of BRONJ can be based on the clinical manifestations; this is usually quite straightforward. However, sometimes BRONJ needs to be distinguished from other delayed healing circumstances.⁴⁰

According to Rugiero, all kinds of oncologic dental patients may be considered to have BRONJ if all of the following characteristics are in place:

- (1) There is a current or previous treatment with BPs,
- (2) The exposed bone along the maxillofacial region has persisted for more than eight weeks, and
- (3) There is no history of radiation therapy to the jaws.¹⁹

The American Association of Oral and Maxillofacial Surgeons (AAOMS) has developed a staging system that was recently updated with a new definition for Stage 0- for oncologic dental patients who are having asymptomatic necrotic bone and present with clinical and radiographic findings.¹⁹ Signs may include odontalgia not related with an odontogenic cause, dull bone pain in the body of the mandible, sinus pain, or altered neurosensory function.¹⁹ Other clinical findings may include loosening of teeth that cannot be explained by chronic periodontal

disease, or a periodontal fistula not associated with pulpal necrosis due to dental caries. Radiographically, a wound may demonstrate alveolar bone resorption not attributed to chronic periodontal disease, thickening of periodontal ligaments, changes to trabecular patterns, or narrowing in the lower alveolar-canal.¹⁹

These non-particular findings characterize the following:

Stage 0: Refers to oncologic dental patients with a previous history of Stages 1, 2 or 3 BRONJ diseases that have already healed, and that are also asymptomatic.

Stage 1: Refers to exposed necrotic bone for various oncologic dental patients that express no evidence of infection.

Stage 2: Refers to exposed necrotic bone in some oncologic dental patients with attendant pain and with clinical evidence of infection.

Stage 3: Refers to exposed and necrotic bone in oncologic and osteoporotic dental patients who are experiencing pain, infection, and one or more of the following: exposed necrotic bone extending beyond the region of alveolar bone such as inferior border and ramus in the mandible, maxillary zygoma and sinus in the maxilla, extra-oral fistula, pathologic fracture, oral antral or nasal communication, and osteolysis extending to the inferior border of the sinus floor.¹⁹

Though there are recognized guidelines secondary to the treatment of oncologic and osteoporotic dental patients undergoing BP therapy, there are nonetheless dentists who refuse to treat all oncologic dental patients who have a history of BP- related therapies. Their refusal can be related to a lack of awareness of BRONJ.⁴⁰ Despite the low incidence of BRONJ, it is crucial for members of the dental profession to have a fundamental knowledge of BRONJ, as BP use has become the cornerstone in the management of osteoporosis and other metabolic bone diseases.⁴⁰

This is particularly significant because the demographic profiles of numerous oncologic dental patients in visiting dental offices are increasing dramatically as the population ages. The

2010 Canadian census indicates that for the past three decades, the population over 75 years of age has increased significantly, by 130%, while there has been a 225% increase for individuals who are 85 years or older.⁴¹ Which increase the risk of seeing patients on BP and possible occurrence of BRONJ for this population.

The objectives of managing all kinds of oncologic dental patients with an established diagnosis of BRONJ are basically palliative and include: elimination of pain, control of secondary infection of the soft and hard tissue, and minimizing the progression of bone necrosis. As suggested by the AAOMS position paper, dental patients with Stage 1 BRONJ should be treated topically with oral antimicrobial rinses, such as chlorhexidine 0.12%. Oncologic dental patients with Stage 2 BRONJ may benefit from the use of oral antimicrobial rinses in combination with antibiotic therapy. Most isolated microbes have been sensitive to the penicillin group of antibiotics, but actinomyces colonies requiring long-term antibiotic therapy have been demonstrated in many cases.^{11, 42}

For oncologic dental patients who are allergic to penicillin, other antibiotics have been suggested: quinolones, metronidazole, clindamycin, doxycycline, and erythromycin. Oncologic dental patients require a combination of antibiotic therapies for long-term antibiotic maintenance, or a course of IV antibiotic therapy.¹⁹ All oncologic dental patients with severe and complicated diseases (Stage 3) may experience long-term palliation with a resolution of acute infection and pain from debridement, including resection, in combination with antibiotic therapy. Extensive surgical procedures are usually not recommended.¹⁹ Spicules of sharp bone which irritate the adjacent soft tissue such as the tongue or buccal mucosa should be rounded. Detached segments of bony sequestrum should be removed without exposing uninvolved bone at any stage.¹⁹

Improper treatment or misdiagnosis of BRONJ can have serious repercussions. In some cases, the treatment of BRONJ can require jaw resection, prolonged use of antibiotics and long hospitalizations, things that negatively impact the quality of life of all oncologic dental patients who suffer the disease, in addition to putting a large burden on the health care system.¹⁹ Also lack of evidence, refusal to treat patients on BPs and rarity of BRONJ support the need to

investigate knowledge and awareness of BRONJ. However, to the best of our knowledge, no study has measured the knowledge of the dental profession about BRONJ. This study aims to determine Ontario, Canada dentists' knowledge and awareness of the severity of BRONJ.

1.6 Supplements to Chapter 1, Figures

Figure 1 Bisphosphonates structure

Pamidronate: $R^2 = (-CH_2)_2-NH_2$

Generic bisphosphonate structure

Alendronate: $R^2 = (-CH_2)_3-NH_2$

Risedronate:

Zoledronic acid:

The nitrogen-enclosed bisphosphonates such as pamidronate, alendronate, risedronate, ibandronate, zoledronic acids inhibit the mevalonate pathway.

2 Methods

2.1 Objectives

This study aims to evaluate the knowledge, practices and opinions of Ontario dentists about BRONJ when treating patients receiving bisphosphonates. The objectives were to determine Ontario dentists' knowledge about BRONJ; to measure Ontario dentists' knowledge of current treatment guidelines; and to identify how Ontario dentists manage patients on BP therapy.

2.2 Study Design

The aims were achieved by conducting a cross-sectional web-based survey design that was conducted over a period of two months and was approved by the Research Ethics Board at the University of Toronto (Appendix 1)

2.3 Sampling frame

A list of the members of the Royal College of Dental Surgeons of Ontario (RCDSO) was obtained through their membership directory. This list contained 11,151 dentists and dental specialists registered with the RCDSO. From these 11,151, a total of 3,724 did not have their e-mails registered and were excluded from the sample. From the remaining list of 7,427 we also excluded 35 Anaesthesiologists, 14 Oral Pathologists, 11 Oral Radiologists, 315 Orthodontists, 114 Paediatric Dentists, and 18 Public Health Dentists because we assumed they may not have

(or may have minimal) direct surgical interaction with patients taking BPs. Our final list consisted of 6,920 Ontario dentists and dental specialists who may perform dentoalveolar surgeries, namely general dentists, oral surgeons, periodontists, endodontists and prosthodontists.

2.4 Sample size calculation

Sample size calculation (n) was based on Dillman (2000):

$$n = ((N)(P)(1-P)) / ((N-1)(C/Z)^2 + (P)(1-P)),$$

Where the required sample size (n) is based on

N = the size of the population,

P = the proportion of the population expected to choose one of two responses (P= 0.5 to allow for the maximum variance),

C = the assumed sampling error (C= 0.05), and

Z = the Z-statistic of the confidence interval (Z = 1.96 for 95% confidence level).⁴³

The calculated sample size for each subgroup is as follows:

- **Oral Surgeons:** Based on a total of N=171 in Ontario, the sample size was n=92.
- **Periodontists:** Based on a total of N=165 in Ontario, the sample size was n=90.
- **Prosthodontists:** Based on a total of N=67 in Ontario, the sample size was n=57.
- **Endodontists:** based on a total of N=121 in Ontario, the sample size was n=70.

Since the difference between the sample size and the total population for the oral surgeons, periodontists, endodontists and prosthodontists was not large, and in order to account for the non-responders, we changed the sampling frame to use the total population for each specialty. This resulted in a total of 524 specialists.

General Dentists: Based on a total of 10,473 in Ontario, the sample size was 419.

Therefore, the calculated sample size for this survey was 943. However, because of the historically low response rates of dentists population, which can be as low as 19%,⁴³ the sample size of the general dentists was increased by four folds up to 1,676. Therefore, we utilized a sample size of 2,200 to account for the non-responders (Table 1).

2.5 Survey tool

The survey tool included questions about participants' knowledge of BPs (Table 2), their experiences treating patients presenting with osteonecrosis, any treatment modification in performing different surgical procedures (e.g., tooth extraction, dental implant placement, periodontal, and/or endodontic surgery) in patients taking intravenous (IV) or oral bisphosphonates, and their awareness of the BRONJ guidelines suggested by the AAOMS. For further validation and adjustment, the survey instrument was pilot-tested among 15 specialists and dentists at the Faculty of Dentistry, University of Toronto. This field test resulted in revisions to the original questionnaire, from which a final questionnaire (Appendix 2) was drafted based on the following principal domains:

Domain 1 – Perception and Current Practice: Included in this domain were questions that measure participants' general knowledge about ONJ and BRONJ. They were asked questions about BP use, route of administration, incidence and treatment for a patient with BRONJ based on the AAOMS 2009 position paper.¹⁹ They were also asked about the volume of patients they see with BRONJ symptoms, at which stage of BRONJ they would refer the patient to a specialist, and their treatment.

Domain 2 – Scenario Cases: In this domain, the participants were provided with a scenario of a patient who takes BPs and presents for a surgical procedure relevant to the field of specialty of the participant. The scenarios differed based on the duration (≤ 3 years or > 3 years) and route of BPs given (oral or IV). These scenarios were given for extraction, placing dental implants, or performing periodontal or endodontic surgeries. They were asked about their management plan for these different scenarios: whether they would perform the surgical procedure; or would

discontinue bisphosphonate for 3 months then perform the procedure; or would not perform the procedure; or would refer to a specialist.

Domain 3 -- Demographics: Included in this domain were questions pertaining to participants' age, gender, pattern of practice (currently practicing vs. retired/not practicing), primary professional activity (e.g., GP, specialist, military dentist, academic instructor), location and years of practice, specialty field, and population of town/city where they practice.

Domain 4- Knowledge acquisition: Included in this domain were questions that asked about the resources participants use to stay current in their knowledge (educational courses, scientific meetings, journal articles and/or internet), where they first learned about BRONJ, if they feel comfortable treating patients with BRONJ, and their preferred method for continuing education related to BRONJ.

2.6 Data Collection

The online survey tool (<http://sgiz.mobi/s3/BRONG>) was administered using a simple online interface web-based survey (SurveyGizmo, Boulder, CO). The study followed Dillman's recommendation for five varied contacts over a period of two months (September to October 2012).⁴³ The initial contact was an e-mail to inform the participants about the study. In this first contact, the participants were provided with the study contact information in case they chose to receive the survey in hard copy rather than by e-mail, or to opt out. A week after, the second contact was made. An email with complete information about the study, the consent process, and a link to the survey was sent directly from SurveyGizmo[®]. Two weeks after, a third contact was made. This was an e-mail thanking those who had participated and reminding those who had yet to complete the survey. The next contact was an automated resending of the email with the survey link from the SurveyGizmo[®] address which was sent only to non-responders. Our final contact was a fax reminder accompanied by an email sent from SurveyGizmo. This was six weeks after launching the survey. Upon completion of the survey, a link to BRONJ guidelines

and the AAOMS 2009 position paper on BRONJ (www.aaoms.org/docs/position_papers/bronj_update.pdf) was provided to the participants.¹⁹

The study was approved by the Research Ethics Board at the University of Toronto (Appendix 1). SurveyGizmo[®] is compliant and certified under both HIPAA (guidelines for the handling of medical information) and Safe Harbor (European Union privacy protection standards) programs. SurveyGizmo[®]'s privacy policy forbids the use of customer-collected information. All data was held in secure data centers with state of the art back-up and redundancy programs. Account data was password-protected, and only account holders could access these accounts.

2.7 Data Analysis:

The data from the online survey was downloaded from the SurveyGizmo (Boulder, CO) website as a Microsoft Excel[™] file. After recoding the variables, the database was imported to SAS 9.2 (SAS institute, Cary, NC) for management and analysis. The responses to the questions in this survey were summarized using descriptive statistics (percentages for the categorical data and means and standard deviations for continuous variables). The descriptive analyses were conducted for the whole sample and for sub-groups of the participants (*general dentists, periodontists, prosthodontists, oral surgeons and endodontists*). The responses were compared among these subgroups using Chi-square test and Fisher's Exact test for categorical variables and student-t test for continuous variables. The key knowledge questions were defined for each category of respondents. Nine knowledge questions (Domain 1) and six scenario questions (Domain 2) were provided to the participants. The responses to the key knowledge questions were summarized. A score of nine out of nine was given if the participant answered all question correctly in the first domain. A series of bivariate and multivariate analyses were conducted to identify the characteristics of those with good knowledge of the guideline.

Moreover, six scenarios were asked and the results were divided into right treatment answers, wrong treatment answers (based on the guidelines), or thirdly whether they would refer the patient. The percentage of each category was derived for each practitioner. Multivariate regression was applied to analyze the association of the scenario answer percentage with the practitioner characteristics. All tests were conducted at a significance level of 0.05.

2.8 Supplements to Chapter 2, Tables

Table 1 Targeted population and sampling frame

	Population	Minimal number needed based on sample size calculations	Actual Targeted Sample	Respondents
<i>Specialists</i>	524			
Oral Surgeons	171	92	171**	54
Periodontists	165	90	165**	37
Prosthodontists	67	57	67**	18
Endodontists	121	70	121**	18
<i>General practitioners</i>	10,473	419	1,676*	1452
Total	10,997	728	2200	1579

* Increased by four folds from 419 due to expected low responsive rate among GPs.

** Since the difference between the sample size and the total population for the specialists was not large, and in order to account for the non-responders, the sampling frame was changed to include the total population for each specialty.

Table 2 - Knowledge questions

Knowledge Questions	Expected Correct Answers
1) Bisphosphonate is used for the treatment and prevention of which of the following?	Osteoporosis- Osteitis deformans- Bone metastases - Multiple myeloma
2) Through which route can a bisphosphonate be administrated?	Oral- IV
3) What is the incidence of BRONJ in patients taking Oral bisphosphonates?	<11%
4) What is the incidence of BRONJ in patients taking IV bisphosphonates?	<11%
5) How would you treat patients in at risk stage BRONJ?	No treatment- Patient education
6) How would you treat patients in stage 0 BRONJ?	Patient education- Treat symptoms
7) How would you treat patients in stage 1 BRONJ?	Patient education- Treat symptoms- Mouth rinse
8) How would you treat patients in stage 2 BRONJ?	Patient education- Treat symptoms- Mouth rinse- Antibiotics
9) How would you treat patients in stage 3 BRONJ?	Patient education- Treat symptoms- Mouth rinse- Antibiotics- Surgical debridement

Table presents the nine knowledge questions that were asked from participants.

3 Results

3.1 Response Rate

From a total of 6,920 RCDSO dentists with email addresses who may perform dentoalveolar surgeries (namely general dentists, oral surgeons, periodontists, endodontists and prosthodontists), a total of 1,665 e-mails bounced back. From the final active list of 5255, a total of 1,579 survey responses were collected, resulting in a response rate of 30% (Figure 2). This acquired number of responses was 66% more than our *a priori* calculated sample size of 951.

3.2 Demographics

Table 3 shows the different participant groups and their distribution based on their age and specialty. The majority of participants were male (68.0%), general practitioners (82.6%), aged between 45-54 years (29.2%) with more than 20 years of experience as a general dentist (56.1%) or as a specialist (50.0%), and working in areas that have a population of more than 500,000 people (45.7%). The participants' demographics were compared to the available census data from dentists in Ontario (Table 4).⁴⁴ The results revealed that for those demographics that could be compared, differences between the participants and their Ontario counterparts were small.

Knowledge questions Table 5 shows the results of the knowledge questions in the survey. Almost all participants (93.2%) correctly identified osteoporosis as the indication for the BP use. Very few participants identified wrong indications for BP (3.2% for diabetes and 0.7% for hypertension). More than 80% of the participants correctly selected the BP route to be oral or IV, yet 14% were not sure of the BP administration route. Almost a quarter of participants did not know the answer for the question on the incidence of BRONJ in patients taking oral or IV BP.

The remaining knowledge questions pertained to the assessment of the knowledge of participants on treatment strategies of BRONJ in different stages of risk. The least aggressive strategies was selected for the lower degrees of risk, i.e., patient education, treating symptoms, and mouth rinse were mostly selected for respectively at risk, stage 0, and stage 1 patients. The majority of participants selected antibiotics and in particular, surgical debridement for the higher stages of risk with 70% recommended antibiotics for 'Stage 2' treatment and 68.3% recommended 'Surgical Debridement' in stage 3. The distribution of the correct selected strategies relates to the questions of patients at the lower risk categories (at risk or stage 0) or at the highest risk category (stage 3). On the other hand, for the patient in stage 1, almost 13% and 40% of the subjects selected wrong choices of 'no treatment' and 'antibiotics' respectively as their approach to treatment. This pattern of incorrect answers was similar for the scenario of patient in stage 2.

Those who gave correct answers for knowledge and scenario questions are shown in Table 6. Figure 3 depicts the percentage of correct answers for knowledge and scenario questions. This figure shows a pattern where the participants had more correct answers in the knowledge questions and more wrong answers for the scenario questions. Stage 3 BRONJ treatment in has the highest percentage of participant (89%) answering correctly. On the other hand, only 28.3% of participants correctly answered the knowledge question about the incidence of BRONJ in patients who were taking oral BP. Participants more frequently gave correct answer for patients oral BP for less than 3 years, on the other hand, wrong answers increased in the scenario where the patients are taking IV BP and oral BP for more than 3 years.

3.2 Participants' knowledge score

Overall, the mean knowledge score for all participants was 5.6 ± 1.9 . No significant difference was found between participants' knowledge score and their gender or years in practice (Table 7). However, there was a significant difference in knowledge score with age, where those in the age group of 45-54 years had a lower knowledge score compared to other age groups. Being a specialist, and in particular being an oral surgeon, being comfortable treating patients

with BRONJ, having some exposure to BRONJ cases in a given month, and practicing in large urban centres were associated with higher knowledge scores ($P < 0.05$). All these significant variables were analyzed in a linear regression model. Having adjusted for dentists' characteristics a pattern of a better knowledge score was found in those 25-34 years old compared to other groups. In particular, those 45-54 years old had a significantly lower knowledge score as compared to younger practitioners of 25-34 years old ($\beta = -0.73$, 95%CI: -1.07, -0.30). On the other hand, those being comfortable treating patients with BRONJ have significantly higher knowledge score compared to those who are not comfortable treating patients with BRONJ ($\beta = 0.34$, 95% CI: 0.06, 0.62). (Table 8) Clinically, recent graduates show more BRONJ knowledge than older dentists. With increase in knowledge about BRONJ, dentists tend to be more comfortable when treating these patients. In other word, increasing or refreshing the BRONJ knowledge, in particular for older dentists, can significantly make them more comfortable in treating these patients.

3.3 Scenario questions

Table 9 shows the percentage of participants who correctly answered the six scenario questions. In general, no matter of the surgical intervention, participants tend to select referral if the patient has been taking BP for more than three years, or if they have been taking IV BPs no matter of the duration.

Among the three scenarios of tooth extraction (simple, complex, impacted), participants tend not to extract and refer as the complexity of extraction is increased. For data analysis, these variables were defined for each participant, representing the percentage of right answer, wrong answer, and referral answers. The data are presented in Table 9. Participants were more frequently to give right answers in scenarios when treating patients taking oral BP for less than 3 years, while more wrong answers were given in scenarios when treating patients taking oral BP for more than 3 years. With the increase in complexity of extraction, referral to specialists increased. In all IV BP scenarios participants tend to refer the patient. For example, for the

simple tooth extraction scenario, 73.4% of the participants had the right answer for the question about the patient taking oral BPs for less than three years, and 47.2% of them had the wrong answer for the scenario of the patient taking oral BPs for more than three years, 77.6% and 80.1% will refer if the patient is taking IV BPs. Participants were more frequently to have correct management for patients receiving oral BP for less than three years, while in scenarios when the patients were given oral BP for more than three years, they were more frequently choosing the wrong management. When patients were given IV BP, participants were more frequently to refer the patient (Table 10).

In aggregate of all scenarios combined together, 23.8% of participants answered right to all six scenarios, 15.9% answered wrong, and 60.3% referred to others. Two regression models were constructed. The first model identified the characteristics of those who referred vs. those who selected a right treatment strategy. The final model is presented in Table 11 and shows that females, GPs, those works in a city with a population of 50,000- 500,000, and those who are not comfortable with their current knowledge are more likely to refer. The second model identified the characteristics of those who got the wrong answer vs. those who selected a right treatment strategy or refer the patient. The final model is presented in Table 12 and shows that there were no significant differences between participants who gave wrong answers and those who gave correct answers or referred the patient.

3.4 Referral to specialists

Tables 13 demonstrate that the knowledge score remains a significant factor in relation to when practitioners would refer their patients. Those with lower knowledge score would refer BRONJ patients at lower risk category as compared to those with a higher knowledge score who tend to refer later. This pattern remained the same in the logistic regression analysis, adjusting for practitioner's characteristics (Table 14). For example, all other things being equal, those with 1 unit more knowledge score would be 1.42 times (95% CI=1.23-1.64) more likely to treat

patients who are at risk and only refer a patient to specialist when they are showing some early signs of BRONJ (‘stage 0’).

3.5 Knowledge acquisition

Table 15 shows the answers of participants to questions targeting their way of obtaining knowledge. The leading resource that 87% of the participants revealed to be using to stay current in dentistry is CE courses. 86% of the participants consider journal articles to be their primary source of knowledge, followed by scientific meetings (72%), while internet browsing ranked fourth since 63% considered the Internet as their primary source. Majority of participants (56%) learned about BRONJ through journal articles. Almost half (49%) reported that they are not comfortable treating the BRONJ. 55% of participants indicated that they preferred journal articles (55%) or full day/half day courses (51%) as their source of information about BRONJ.

3.6 Summary of key findings

- The majority of participants were male (68%), general practitioners (82.6%), with more than 20 years of experience as a general dentist (56.1%) or as a specialist (50%), and working in areas that have a population of more than 500,000 people (45.7%).
- About 60% of responding Ontario dentists had good knowledge of BRONJ. Recent graduates have more knowledge about BRONJ than dentists of other age groups.
- Results from this survey of Ontario dentists on knowledge and practice guidelines indicate that about 50% of 1579 responding dentists are not comfortable treating BRONJ patients.
- About 42% followed the AAOMS guidelines for surgical procedures.

- About 63% will refer patients.
- Oral surgeons had better knowledge about BRONJ compared to other dental specialists.
- Females, GPs, those who work in a city with a population of 50,000- 500,000, and those who are not comfortable with their current knowledge are more likely to refer the patient.
- Participants more frequently gave correct answer for patients oral BP for less than 3 years, on the other hand, wrong answers increased in the scenario where the patients are taking IV BP and oral BP for more than 3 years.
- Participants were more frequently to give right answers in scenarios when treating patients taking oral BP for less than 3 years, while more wrong answers were given in scenarios when treating patients taking oral BP for more than 3 years.
- With the increase in complexity of extraction, referral to specialists increased. In all IV BP scenarios participants tend to refer the patient.

3.7 Supplements to Chapter 3, Tables and Figures

Figure 2 Response rates for Ontario general dentists

Figure shows the number of completed surveys and the final response rate.

Figure 3 Performance in answering the survey questions

Figure shows the performance of participants in answering the survey questions, the bottom axes shows the percentages of the participants who answered correctly.

Table 3 Descriptive of dentists who participated in survey

Demographics	Number (%)
Gender (male)	678 (68.0%)
Oral Surgeons	48 (85.7%)
Periodontists	30 (73.2%)
Prosthodontists	13 (68.4%)
Endodontists	18 (78.3%)
General practitioners	555 (66.5%)
Age	
25-34	131 (12.9%)
35-44	233 (22.9%)
45-54	297 (29.2%)
55-64	271 (26.6%)
>65	86 (8.4%)
Dental Specialty	
Oral Surgeons	57 (4.9%)
Periodontists	42 (3.6%)
Prosthodontists	20 (1.7%)
Endodontists	26 (2.2%)
General Practitioners	1003 (86.2%)
Other	16 (1.4%)
Working years	
<i>As a GP</i>	
1-5	125 (13.5%)
6-10	89 (9.6%)
11-20	193 (20.8%)
>20	521 (56.1%)
<i>As a Specialist</i>	
1-5	24 (20.3%)
6-10	12 (10.2%)
11-20	23 (19.5%)
>20	59 (50.0%)
Local Population	
<5,000	45 (4.5%)
5,000-50,000	161 (16.1%)
50,000-500,000	338 (33.7%)
>500,000	458 (45.7%)

Table 4 Comparison of survey respondents with Ontario dentist data

		Our survey (n=1579)	Ontario data† (n=7053)
Gender, n(%)	Male	678(68.0%)	5149(73.0%)
Working year, n(%)	0-10	214(23.1%)	1072(15.2%)
	11-20	193(20.8%)	1841(26.1%)
	21+	521(56.1%)	4140(58.7%)
Age(%)	25-34	30.10%	30.60%
	35-44		
	45-54	31.60%	30.70%
	55-64		
	65+	5.70%	6.10%

† from the 2008 registry list of the Royal College of Dental Surgeons of Ontario⁴⁴

Table 5 percentage of answers for the knowledge questions

Knowledge Q1 BP use	Osteoporosis	Diabetes	Osteitis deformans	Bone metases	Multiple myeloma	Hypertension
	93.2%	3.2%	37.4%	47.9%	42.4%	0.7%
Knowledge Q2 BP route	Oral	IV	IM	Not sure		
	85%	81%	7.8%	14%		
Knowledge Q3&4 incidence		>11%	<11%	I don't know		
	Oral	3.5%	72%	24%		
	IV	21%	51%	27%		
Knowledge Q5 to 9 BRONJ treatments	No treatment	Patient education	Treat symptoms	Mouth rinse	Antibiotics	Surgical debridement
At risk	46.1%	80.2%	9.2%	9.7%	5.9%	0.8%
Stage 0	20.6%	78.1%	56.0%	22%	15.5%	1.3%
Stage 1	12.3%	66%	51.1%	61.8%	39.8%	21.1%
Stage 2	12.8%	63.2%	54.6%	58.3%	70.1%	46.4%
Stage 3	12.7%	62.2%	52.4%	55.3%	68.2%	68.3%

- **Bold = correct answers**

Table presents the percentage of participants' answers for each of knowledge questions. Percentages may not add up to 100% as the participants could choose all options which were applicable

Table 6 Performance in answering the survey questions

	N	%
Number of dentists who correctly answered the question about indications of BP	718	63.8
Number of dentists who correctly answered the question about the route of BP	1031	86.5
Number of dentists who correctly answered the question about incidence of BRONJ in patients taking oral BP	335	28.3
Number of dentists who correctly answered the question about incidence of BRONJ in patients taking intravenous BP	567	48.8
Number of dentists who correctly answered the question about treatment of at risk BRONJ stage	674	67.0
Number of dentists who answered correctly the question about treatment of stage 0 BRONJ	612	63.4
Number of dentists who answered the question about treatment of stage 1 BRONJ correctly	388	42.7
Number of dentists who answered the question about treatment of stage 2 BRONJ correctly	376	42.5
Number of dentists who had the question about treatment of stage 3 BRONJ correct	768	89.9
Number of dentists who perform surgical procedures	949	78.9
Number of dentists who had the simple extraction scenario correct		
patient taking oral BP for $\leq$ than 3 years	614	73.4
patient taking oral BP for $>$ than 3 years	151	18.1
patient taking IV BP for $\leq$ than 3 years	114	13.7
patient taking IV BP for $>$ than 3 years	83	10.0
Number of dentists who had the complicated extraction scenario correct		
patient taking oral BP for $\leq$ than 3 years	439	52.7
patient taking oral BP for $>$ than 3 years	138	16.7
patient taking IV BP for $\leq$ than 3 years	75	9.1
patient taking IV BP for $>$ than 3 years	49	5.9
Number of dentists who had the impacted extraction scenario correct		
patient taking oral BP for $\leq$ than 3 years	220	26.5
patient taking oral BP for $>$ than 3 years	84	10.1
patient taking IV BP for $\leq$ than 3 years	46	5.6
patient taking IV BP for $>$ than 3 years	31	3.8
Number of dentists who had the implant scenario correct		
patient taking oral BP for $\leq$ than 3 years	222	60.3
patient taking oral BP for $>$ than 3 years	98	26.9
patient taking IV BP for $\leq$ than 3 years	54	14.7
patient taking IV BP for $>$ than 3 years	30	8.2
Number of dentists who had the periodontal surgery scenario correct		
patient taking oral BP for $\leq$ than 3 years	238	81.0
patient taking oral BP for $>$ than 3 years	49	16.8
patient taking IV BP for $\leq$ than 3 years	79	27.0
patient taking IV BP for $>$ than 3 years	68	23.1
Number of dentists who had the endodontic surgery scenario correct		
patient taking oral BP for $\leq$ than 3 years	133	61.9
patient taking oral BP for $>$ than 3 years	40	18.7
patient taking IV BP for $\leq$ than 3 years	22	10.2
patient taking IV BP for $>$ than 3 years	13	6.1

- IV (intravenous)

Table presents the number and percentage of correct answers for knowledge and scenarios questions.

Table 7 Mean knowledge scores according to different variables

Factors (n)	Mean	SD	P value
Total practitioners (825)	5.6	1.9	
Age			<0.01
25-34 (108)	5.9	1.8	
35-44 (195)	5.5	1.8	
45-54 (240)	5.2	1.9	
55-64 (193)	5.8	1.9	
>65 (58)	5.7	2.2	
Gender			0.61
Male (536)	5.6	1.9	
Female (252)	5.5	1.8	
Practitioner type			<0.01
Specialists (127)	6.3	2.1	
GP (660)	5.4	1.8	
Specialists			0.04
Oral Surgeons(54)	6.8	1.6	
Periodontists(37)	5.7	2.0	
Prosthodontists(18)	6.7	2.2	
Endodontists(18)	5.7	2.9	
Working years			0.46
1-5 (95)	5.5	1.8	
6-10 (73)	5.2	1.6	
11-20 (144)	5.5	1.7	
>20 (321)	5.3	1.9	
Patients per month			<0.01
0 (563)	5.4	1.8	
≥1 (209)	6.0	2.1	
Population			0.05
under 50,000(15)	5.1	2.9	
50,000-500,000(49)	6.5	1.9	
over 500,000(80)	6.4	1.9	
Comfortable with knowledge			0.01
No/ Unsure (442)	5.4	2.0	
Yes/minor supplementation(357)	5.8	1.8	

Table presents comparative knowledge scores between age, gender, practitioner type, specialists, working years patients they see per month, their city population and scenarios answers.

Table 8: The impact of significant practitioner characteristics on participants knowledge score

Variable	Coefficient estimate	95% CI	p value
Age			
35-44	-0.42	(-0.87, 0.03)	0.07
45-54	-0.73	(-1.07, -0.30)	<0.01
55-64	-0.35	(-0.81, 0.11)	0.14
65+	-0.34	(-1.00, 0.31)	0.31
Comfortable with knowledge	0.34	(0.06, 0.62)	0.02

Reference: age (25-34) and not comfortable/unsure with knowledge

Table 9 Percentage of participants who correctly answered the six scenario questions

Scenario 1 Simple tooth extraction	Extract	Discontinue BP for 3 months then extract	Don't extract	Refer
Oral BP $\leq$ 3 years	73%	6%	0.40%	19%
Oral BP > 3 years	46%	18%	1%	34%
IV BP $\leq$ 3 years	13%	5%	3%	77%
IV BP > 3 years	10%	5%	4%	80%
Scenario 2 Complicated tooth extraction	Extract	Discontinue BP for 3 months then extract	Don't extract	Refer
Oral BP $\leq$ 3 years	52%	7%	0.60%	40%
Oral BP > 3 years	29%	16%	0.60%	53%
IV BP $\leq$ 3 years	9%	3%	2%	80%
IV BP > 3 years	5%	4%	3%	85%
Scenario 3 Impacted tooth extraction	Extract	Discontinue BP for 3 months then extract	Don't extract	Refer
Oral BP $\leq$ 3 years	26%	4%	1%	67%
Oral BP > 3 years	13%	10%	2%	74%
IV BP $\leq$ 3 years	5%	2%	4%	87%
IV BP > 3 years	3%	3%	5%	87%
Scenario 4 Implant	Place implants	Discontinue BP for 3 months then place implants	Don't place implant	Refer
Oral BP $\leq$ 3 years	60%	8%	4%	27%
Oral BP > 3 years	29%	26%	6%	37%
IV BP $\leq$ 3 years	14%	6%	22%	56%
IV BP > 3 years	8%	7%	28%	55%
Scenario 5 Periodontal surgery	Perform surgery	Discontinue BP for 3 months then perform the surgery	Don't Perform surgery	Refer
Oral BP $\leq$ 3 years	81%	8%	2%	8%
Oral BP > 3 years	59%	16%	2%	21%
IV BP $\leq$ 3 years	27%	8%	8%	55%
IV BP > 3 years	23%	5%	10%	60%
Scenario 6 Endodontic surgery	Perform surgery	Discontinue BP for 3 months then perform the surgery	Don't Perform surgery	Refer
Oral BP $\leq$ 3 years	61%	6%	1%	29%
Oral BP > 3 years	34%	18%	3%	43%
IV BP $\leq$ 3 years	10%	7%	8%	74%
IV BP > 3 years	6%	8%	10%	74%

- **Bold = correct answers**

Table 10 Answers to scenario questions

			Right answer N – (%)	Wrong answer N – (%)	Refer N – (%)
Extraction	Simple	Oral BP <3 Y	614- (73.4%)	57- (6.8%)	165- (19.8%)
		Oral BP >3 Y	151- (18.1%)	394- (47.2%)	289- (34.7%)
		IV BP <3 Y	114- (13.7%)	72- (8.75%)	645- (77.6%)
		IV BP >3 Y	83- (10%)	82- (9.9%)	664- (80.1%)
	Complicated	Oral BP <3 Y	439- (52%)	65- (7.8%)	329- (39.5%)
		Oral BP >3 Y	138- (16.7%)	248- (30%)	442- (53.4%)
		IV BP <3 Y	75- (9.1%)	52- (6.3%)	697- (84.6%)
		IV BP >3 Y	49- (5.9%)	69- (8.4%)	708- (85%)
	Impacted	Oral BP <3 Y	220- (26.5%)	52- (6.3%)	559- (67.3%)
		Oral BP >3 Y	84- (10.1%)	126- (15.2%)	619- (74.7%)
		IV BP <3 Y	46- (5.6%)	55- (6.7%)	725- (87.8%)
		IV BP >3 Y	31- (3.8%)	71- (8.7%)	717- (87.5%)
Implant		Oral BP <3 Y	222- (60.3%)	46- (12.5%)	100- (27.2%)
		Oral BP >3 Y	98- (26.8%)	130- (35.6%)	137- (37.5%)
		IV BP <3 Y	83- (22.6%)	77- (20.9%)	208- (56.5%)
		IV BP >3 Y	105- (28.5%)	58- (15.8%)	205- (55.7%)
Periodontal		Oral BP <3 Y	238- (81%)	30- (10.2%)	26- (8.8%)
		Oral BP >3 Y	49- (16.8%)	180- (61.6%)	63- (21.6%)
		IV BP <3 Y	79- (27%)	52- (17.7%)	162- (55.3%)
		IV BP >3 Y	68- (23.1%)	49- (16.7%)	177- (60.2%)
Endodontic		Oral BP <3 Y	133- (61.9%)	18- (8.4%)	64- (29.8%)
		Oral BP >3 Y	40- (18.7%)	82- (38.3%)	92- (43%)
		IV BP <3 Y	22- (10.2%)	34- (15.8%)	159- (74%)
		IV BP >3 Y	13- (6.1%)	41- (19.2%)	159- (74.6%)

Table 11 The impact of significant practitioner characteristics on decision of referral vs. selecting a correct treatment strategy

Parameter		Estimate	95% CI		P value
Gender (ref: female)	Male	-3.53	-6.49	-0.56	0.020
Specialist (ref: GP)	Specialist	-17.17	-22.68	-11.67	<0.001
Population (ref: under 50,000)	50,000- 500,000	4.54	0.77	8.322	0.018
	over 5,000,000	1.29	-2.29	4.88	0.48
Comfortable with knowledge (ref: No)	Yes	-8.36	-11.11	-5.63	< 0.001

Table 12 The impact of significant practitioner characteristics on decision of wrong answer vs. right answer/referral

Parameter		Estimate	95% CI		Pr > ChiSq
Age	35-44	-1.42	-9.021	6.18	0.714
	45 -54	4.01	-5.50	13.51	0.409
	55-64	3.09	-7.40	13.59	0.563
	65+	3.478	-8.64	15.59	0.574
Gender	Male	-3.13	-7.14	0.88	0.12657
Specialist		3.60	-1.10	8.30	0.134
Working year	1-5	5.99	-3.71	15.69	0.226
	6-10	-2.68	-11.58	6.22	0.555
	11-20	3.91	-2.70	10.51	0.246
Patients per month	>0	1.46	-2.95	5.87	0.517
Population	50,000- 500,000	2.99	-1.72	7.71	0.214
	over 5,000,000	1.11	-3.35	5.58	0.625
Comfortable with knowledge	Yes	-1.50	-4.90	1.90	0.387

Table 13 The association between referring to a specialist and the knowledge score

When to refer to a specialist	Mean	SD	P value
At risk	4.3	2.2	<0.01
Stage 0	5.5	1.8	
Stage 1	5.9	1.8	
Stage ≥ 2	5.9	1.5	

Table presents the main stage when a dentist will refer a patient with BRONJ.

Table 14 Odds ratio and 95% CI of the time to refer to a specialist with knowledge score in logistic regression adjusted by practitioner characteristics

When refer	Odds ratio	95% CI
Stage 0	1.42	(1.23, 1.64)
Stage 1	1.53	(1.33, 1.77)
Stage ≥ 2	1.58	(1.28, 1.95)

Logistic model adjusted by: practitioner type and comfortable with knowledge

Reference group: 'at risk'

Table 15 Knowledge acquisition questions

What resources do you use (or would you use) to stay current in dentistry?							
Browsing internet	Scientific meetings	Journal articles	CE courses				
63%	72%	86%	87%				
Where did you first learn about BRONJ?							
Graduate program	Residency	No knowledge	Internet	Dental school	Scientific meetings	CE courses	Journal articles
3.3%	5.8%	13%	14%	20%	34%	43%	56%
Do you feel comfortable treating patients with BRONJ with your current knowledge?							
Unsure	Yes	Could use minor supplementation			No		
12%	15%	22%			49%		
Which would be your preference for continuing education related to BRONJ?							
DVD/Videos	Annual meetings	Internet-based courses		Full day/half day courses		Journal article	
28%	33%	36%		51%		55%	

Table indicates the percentage of the participants who use particular resources to stay current in dentistry, where they first learned about BRONJ, and if they felt comfortable treating patients with BRONJ with their current knowledge, and their preference for continuing education.

4 Discussion

This cross-sectional study was designed to investigate the knowledge, practices and opinions of Ontario dentists (generalists, oral surgeons, endodontists, periodontists and prosthodontists), when treating patients receiving bisphosphonates. In particular, we wanted to check if the participants' knowledge and approach to care of BRONJ are consistent with the established guidelines.

In the absence of uniform guidelines, the AAOMS, the American Society for Bone and Mineral Research (ASBMR), and other groups have established similar guidelines for treating BRONJ and decision making for patients taking BPs and undergoing surgical interventions. The ASBMR task force recommended that all patients taking bisphosphonates be informed of the benefits and risks of treatment and be encouraged to maintain good oral hygiene (including regular dental visits). With respect to the clinical management of BRONJ, the ASBMR task force recommendations provide general guidance regarding management of infections, surgical management, and discontinuation of bisphosphonate therapy; the AAOMS Position Paper covers the same ground but provides treatment instructions according to their staging system.¹⁹ The American College of Rheumatology (ACR) guidelines simply note that “in patients with established ONJ, treatment with systemic antibiotics and oral antibiotic rinses may help with pain and infrequently may lead to healing”; that “stopping bisphosphonate therapy may be prudent, as anecdotal evidence suggests that this may help in some cases”; and that “aggressive dental surgery should generally be avoided.”⁴⁵

The AAOMS 2009 positional paper was prepared by clinicians based in multicenter hospitals and was approved by the AAOMS Board of Trustees in January 2009.¹⁹ The purpose of the AAOMS 2009 position paper was to provide perspective on the risk of developing BRONJ and the risks and benefits of BPs, in order to facilitate medical decision-making by both the treating physician and the patient, and provide guidelines for treating BRONJ.¹⁹ The recommendations of this multidisciplinary task force representing oral and maxillofacial surgery, oral medicine, endocrinology, and medical oncology in the AAOMS 2009 position paper, by contrast, provide detailed guidance regarding the use of dental devices and selection of

appropriate antibiotic therapy.^{19,43} Therefore, we used the AAOMS 2009 guidelines to develop the knowledge and scenarios questions and score the answers given by the participants.¹⁹

In this study, nine knowledge questions about BRONJ were asked to determine the overall knowledge of the participants. Further, another six scenarios were asked to understand the participant approach when treating a patient taking BPs with a different route or duration of taking BPS and who are going for extraction, placement of implant, periodontal or endodontic surgery. We found that in total, only 23.8% of 1579 responding dentists followed the AAOMS guidelines. We also found that 49.7% were not comfortable treating BRONJ patients. Females, GPs, those working in a city with a population of 50,000- 500,000, and those who are not comfortable with their current knowledge are more likely to refer the patient. Specialists were less frequently to refer the BRONJ patients, and this decrease can be explained by the fact that specialists are more trained and knowledgeable when compared to GPs.

Recent graduates (<34 years of age) have more knowledge about BRONJ than dentists of other age groups, which can be attributed to the up-to-date education acquired through their training in dental schools. On the other hand, oral surgeons had better knowledge about BRONJ compared to other dental specialists. This rise in knowledge noticed among surgeons can be related to their increased exposure to the BRONJ patients.

Our results show that despite the existence of guidelines, Ontario dentists had conflicting understanding of how or even whether to carry out surgical dental treatment in cases of patients taking BPs. It should also be noted that there is currently no such guideline in the general dentistry forum readership. It is likely that the Ontario dentists are not aware of such specialized guideline and hence, this study suggests having guidelines developed by the Canadian or American Dental Association or Royal College of Dental Surgeons of Ontario so that such important guidelines would be widely circulated to Ontario dentists. Such targeted guidelines and more hands on experience may possibly improve the knowledge and approach to care when treating patients on BP.

Participants more frequently gave correct answers for the scenarios of patients on oral BP for less than 3 years, and more frequently gave wrong answers for the scenarios of patients on oral BP for more than 3 years, or IV BP (regardless of duration). This may be related to the

participants not knowing the different effect of BPs if it has been taken for more than 3 years, or the benefits and disadvantages of continuing or discontinuing IV BPs.

When patients were given IV BP, participants were more likely to refer the patient. These trends in patients' referral may be a result of the increased responsibility and uncomfortable sense that accompanies treating these cases. Moreover, there was a decreased confidence when the complexity of the procedure increased in the scenarios given in the survey. This indicates that the dentists will most likely refer the patient using BP when the complexity of the procedure increases. We did not ask specifically about the reasons for referral in our survey.

However, since the participants were asked to identify the surgical procedures that they generally perform in their practice, we can assume that although they may be comfortable treating the patients, the factor of BP use in more complex situations make them unwilling to accept the responsibility of treating patients with possible BRONJ development.

For the implants scenario based on the AAOMS position paper, there is no direct guidance for placing implants in patients taking BP. AAOMS only mentioned to not place implants in patients taking IV high potent BP (zoledronic acid and pamidronate). In past years, several papers showed no significant difference in placing dental implants in those taking IV BP and they recommend placing the implant, and including the patient in the decision and telling them about the risk of BRONJ.¹⁹ What was interesting is that dentists have more correct answers when responding to the implant scenarios as compared to other surgical interventions. This trend may be because it reflects the fact that those who are actively placing implants are more frequently to attend continuing education courses.⁴⁶

In our study, we identified a knowledge gap among Ontario dentists related to BRONJ. A study by Cabana (1999) identified the barriers to physician adherence to practice guidelines as knowledge, attitude and behaviour barriers.⁴⁷ In this study, the knowledge barrier was affected by factors like lack of awareness, volume of information, time needed to stay informed and guideline accessibility. More than one third of GPs and specialists prescribed antibiotics to treat early stages of BRONJ (up to stage 1) where the use of these antibiotics is not indicated according to the guidelines. This trend is in contradiction with the need to limit over-prescribing of antibiotics and consequently to help in reducing the spread of drug-resistant bacteria.⁴⁸

Decision-making is undoubtedly one of the most challenging aspects of healthcare delivery. Often the formulation of a decision to select a particular treatment option is more complex than might be appreciated, and it may be linked to heuristic principles, which explains how a dentist's specialty education might impact on the knowledge and comfort practiced while making treatment decisions.^{47, 49} In dentistry, treatment decisions can vary widely amongst general dentists and dental specialists, as shown in this study and others.^{47, 49} In the results, there was a significant difference in knowledge scores between GPs and specialists. This difference is most likely due to the extra training specialists have had, knowledge from lectures and/or the greater direct experience with BRONJ patients.

Factors related to the field of dentistry that can be obstacles for following guidelines are:

- gaps between younger and older dentists in evidence based dentistry;
- related knowledge and skills;
- perception of evidence based dentistry as serving a select group of dentists (academics);
- no time or finances to experiment with new evidence-based devices;
- no information exchanges between practitioners and academics;
- patient satisfaction used as the main criterion to justify actions;
- skills that strongly influence outcomes with patients;
- relying on expert advice for problems;
- lack of quality labels to distinguish evidence based products from other;
- dental courses not up-to-date with evidence; and
- heavy workload in dentistry.

Such obstacles would affect whether or not a practitioner is informed about and follows a guideline.^{47, 49}

Considering the nature of the question, we employed the best study design, a survey. "Survey" is a term used to describe a survey tool such as a questionnaire, as well as to describe the entire process of surveying from planning, to conducting a survey to reporting results. Surveys usually administer a questionnaire to a sample of the population, and then use that data to describe, explain or predict the attitudes, knowledge, skills, opinions, feelings, behavior,

needs, affiliations, demographics, or lifestyles of the population. Surveys and censuses have been used throughout history dating back as far as ancient Egyptian civilizations where rulers used censuses to gather data about their subjects.^{43, 50, 51} Compared to other research methods, survey research tends to be less expensive, permits greater standardization in data collection, and permits the sampling of a large population.⁴⁵

The process of survey research is comprised of several steps: defining survey research objectives, identifying the type of data to be collected and the preciseness of the results, specifying a population, developing a sampling frame, determining a sample size, selecting a sample using random or nonrandom methods, selecting one or more survey response modes (e.g., mail, web, interview), designing items, designing and field testing a survey instrument, disseminating the survey and issuing follow-up reminders, and finally collecting, coding, cleaning, reducing and analyzing data.^{45,43} Additional considerations in survey research include response rate, data quality, questionnaire features (e.g., appearance, length, item design), timeliness of results, cost, resource requirements (e.g., staff, equipment, supplies, postage, printing, training, travel), confidentiality, ethics, and politics.⁴⁵

For this study, we employed a web-based survey. Computer-based surveys such as computer-assisted telephone interviewing and computer-assisted personal interviewing started in the 1970s through the 1990s as the use of desktop and laptop computers increased.^{43, 52} Electronic surveys, including both email and web surveys, have important advantages over other traditional survey modes such as lower costs, resources, dissemination time, and response time, and possibly decreased response bias. Compared to email surveys, web surveys offer additional benefits including broader stimuli potential (color, graphics), automated piping and error-checking features (versing, complex branching, skips, pop-up messages, and features to standardize responses), and automated electronic data collection, entry and analysis.^{43, 53, 54} Features such as these are believed to increase a respondent's attention to survey items, producing lower item nonresponse in web surveys compared to other modes.

A web survey has low costs relative to mail, face-to-face interviews and computer-assisted telephone surveys; in addition, massive amounts of data can be quickly processed, returned, and analyzed.^{43, 54} Web surveys have even been shown to be less expensive than email

surveys. Web surveys that compile data electronically substantially reduce or eliminate costs associated with converting data into an electronic format for analysis, reducing or eliminating human data entry error. Also the web survey offer the advantage of having a quick turnaround compared to other survey methods.

The response rate is the percentage of the number of individuals returning completed surveys divided by the number of individuals in a sampling frame.^{50, 54} Response rate is an important value reported in survey research studies because it's an indicator of a sample's representativeness and the validity of its findings.^{43, 54} A higher response rate is generally associated with lower nonresponse error, thus increasing generalizability and confidence that the sample accurately reflects the population.^{43, 51} Nonresponse error is the error created by individuals in a sample who do not respond to a survey, but if they had responded, would have provided different answers than those of individuals who did respond.^{43, 51, 54}

We followed the recommended strategies to reduce survey nonresponses:^{43, 50, 54, 54, 55}

- assuring confidentiality and anonymity
- using appropriately designed questionnaires and items
- having easy and nonthreatening questions
- using emailing reminders and replacement surveys.

The questionnaire was designed to be aesthetically appealing, appropriate in length, easy to complete and with clear instructions. A pilot study was conducted to test and revised the survey before sending the survey to Ontario dentists.

We achieved a response rate of 30% in this study. A response rate of 15–35% is generally obtained in web- based surveys of professional groups,⁴³ and ours is well within this range. As shown in Table 3, there was no large difference between the demographics of the study sample and the available census data on Ontario dentists. This allows for a conclusion stating that, at least from a statistical perspective, it was appropriate to believe that the respondents served as an adequate and representative sample of dentists in Ontario, and that there was unlikely to be a response bias. Moreover, the achieved sample matched the calculated sample target.

4.1 Limitations of the study

A potential limitation of this study was that there were no x-rays or detailed patient histories. By doing this, potential interference with understanding how decision-making was minimized in this study since the participants were provided with all the required information for making the decision. The point was to give dentists standardized scenarios under which to follow the guidelines. As mentioned above, we used the AAOMS position paper as the current best available guideline. It is likely that our participants were not aware of the existence of such guideline. Keeping in mind that guidelines are not the only source of treatment planning that dentists use. Other sources may include case study reports, continuing education courses and their past experience. Another limitation was that a participant was only able to make one decision for each scenario and not able to rank preferences for treatments or decisions. This study included only Ontario dentists/specialists. Therefore, conclusions withdrawn from this study should not be generalized to represent the knowledge of dentists in Canada, US or elsewhere in the world.

Having mentioned these limitations, our study has several strengths. To the best of our knowledge, this study is the first study to measure the knowledge of dentists in Ontario. The study had acceptable response rate of Ontario dentists, where the sample size were representative comparing to Ontario census data. The information gathered from this study can assist us in understanding how dentists are actually treating BRONJ patients and whether further education or guidelines are required to assist in ensuring that patients receive the most appropriate and evidence-based treatment.

5 Conclusion

This survey suggested while 60% of responding Ontario dentists had good knowledge of BRONJ, only 23% followed the guidelines of the AAOMS when surgical treatment was indicated for a patient taking BPs and 63% would refer patients if they are taking BPs. While about 50% of responding Ontario dentists are not comfortable treating BRONJ patients and they prefer to send these patients to specialists, there was also an increased trend of referring the patients when the complexity of the procedure increased, as in the impacted and complicated surgical scenario.

Recent graduates have more knowledge about BRONJ than dentists of other age groups,. On the other hand, oral surgeons had better knowledge about BRONJ compared to other dental specialists. Increased awareness among dentists of the importance of following the guidelines is recommended. Well-planned implementation strategies should be conducted involving, e.g., existing continuing dental education activities such as day courses and national meetings. Future research should therefore focus on methods to successfully implement guidelines. The finding reveals that GPs and specialists have moderate knowledge about BRONJ, which suggest greater educational efforts should be made to promote their knowledge.

The results show that in some scenarios almost 50% of the participants were doing the wrong treatment. This can lead to serious complications for the patient and can lead them to develop BRONJ. The study recommends that CDA or ODA should implement strategies to educate dentists about BRONJ treatment and prevention. We recommend the RCDSO to have a mandatory CE course to educate dentists on how to treat and prevent BRONJ when treating patients taking BPs.

Treatment requirements for the management of BRONJ become more extensive as the patient progresses to a more severe stage of the disease. Identification and appropriate management of patients who are at risk or those presenting with early BRONJ symptoms will improve treatment outcomes, prevent disease progression, and aid in reducing treatment needs and the burden on the health care system. There is a need to explore reasons that stand behind

dentists' decisions to refer BP patients. We recommend to expand the survey to include medical doctors (i.e. Family Physicians) as they are the primary prescribers of BPs for the treatment of osteoporosis and other bone metabolic conditions. We recommend expanding the survey nationwide to compare knowledge acquisition and management in different regions.

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Appendices

Appendix 1 - Thesis ethics approval, Health Sciences Research Ethics Board, University of Toronto

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OFFICE OF THE VICE PRESIDENT, RESEARCH

PROTOCOL REFERENCE # 27571

April 20, 2012

Dr. Amir Azarpazhooh
FACULTY OF DENTISTRY

Dr. Ahmed Alhussain
FACULTY OF DENTISTRY

Dear Dr. Azarpazhooh and Dr. Ahmed Alhussain,

Re: Your research protocol entitled, "Knowledge, practices and opinions of Ontario dentists when treating patients receiving bisphosphonates"

ETHICS APPROVAL

Original Approval Date: April 20, 2012
Expiry Date: April 19, 2013
Continuing Review Level: 1

We are writing to advise you that the Health Sciences Research Ethics Board (REB) has granted approval to the above-named research protocol under the REB's delegated review process. Your protocol has been approved for a period of one year and ongoing research under this protocol must be renewed prior to the expiry date.

Any changes to the approved protocol or consent materials must be reviewed and approved through the amendment process prior to its implementation. Any adverse or unanticipated events in the research should be reported to the Office of Research Ethics as soon as possible.

Please ensure that you submit an Annual Renewal Form or a Study Completion Report 15 to 30 days prior to the expiry date of your current ethics approval. Note that annual renewals for studies cannot be accepted more than 30 days prior to the date of expiry.

If your research is funded by a third party, please contact the assigned Research Funding Officer in Research Services to ensure that your funds are released.

Best wishes for the successful completion of your research.

Yours sincerely,

Judith Friedland, Ph.D.
REB Chair

Daniel Gyewu
REB Manager

Appendix 2 - Survey

Dear Colleague,

My name is Dr. Ahmed Alhussain. I am a MSc/Specialty student in the Department of Oral & Maxillofacial Surgery at the Faculty of Dentistry, University of Toronto.

I would like to invite you to participate in my Masters thesis research, which is concerned with the perceptions and practices of Ontario dentists when treating patients receiving bisphosphonates. In particular, we would like to measure the knowledge of Ontario dentists about bisphosphonate-related osteonecrosis of the jaw (BRONJ).

I am inviting you to participate in this research by completing this online questionnaire. Your participation will help us to:

- 1) measure the awareness of Ontario dentists about BRONJ;
- 2) assist educators to develop future guidelines and protocols related to BRONJ

The survey will take approximately 7 minutes to complete. There is neither cost nor reimbursement for your participation in this study. You have been selected from the pool of Ontario dentists for this study and your participation is voluntary.

All surveys are confidential, and I will be the only one with access to the data. All necessary measures have been taken to safeguard your privacy. No information that discloses personal identity will be released or printed. You are free to withdraw from the study at any time during the survey by clicking on the "Exit survey" button, and if you withdraw, your withdrawal will not have any effect on your present and future relationship with the Faculty of Dentistry, University of Toronto. It is my intention to publish this survey's findings in scholarly publications, as well as presenting such findings in lectures and professional/academic meetings. Your name will not be used in the reporting of the information in publications or conference presentations. By clicking on the "Yes" button, you will enter the survey and your participation in the study is assumed to be your consent, meaning that you are giving permission for the survey contents to be used for the research.

If you have any questions, please feel free to contact me at the address below. If you have questions about your rights as a research participant, please contact Rachel Zand, Director, Office of Research Ethics, rachel.zand@utoronto.ca or 416-946-3389.

Thank you very much for your time and support. Please start the survey now by clicking on the "Yes" button below.

Ahmed Alhussain, DDS, MSc/Specialty candidate (Oral & Maxillofacial Surgery)
Faculty of Dentistry, University of Toronto
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(416) 979-4907
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Co-Investigators at Faculty of Dentistry, University of Toronto
Dr. Sean Peel, Assistant Professor, Orthobiologics Group
Dr. Laura Dempster, Assistant Professor, Department of Biological and Diagnostic Sciences
Dr. Cameron Clokie, Professor, Oral and Maxillofacial Surgery
Dr. Amir Azarpazhooh, Assistant Professor, Dental Public Health and Endodontics

Do you agree to participate in this study? *

- ☐ Yes
☐ No

Before starting this survey please take time to read this introduction to the terms that will be used in this survey.

Introduction:

One of the most commonly prescribed medications for the elderly are bisphosphonates, which have been shown to significantly reduce debilitating and fatal fractures by preserving bone density. There is a serious adverse effect called bisphosphonate-related osteonecrosis of the jaw, which is poorly described and difficult to treat. The difficulty is compounded by the inability of medical personnel to recognize and adequately refer these patients or take adequate precautions before instituting bisphosphonate therapy.

Patients may be considered to have BRONJ if all of the following three characteristics are present:

1. Current or previous treatment with a bisphosphonate.
2. Exposed bone in the maxillofacial region that has persisted for more than eight weeks.
3. No history of radiation therapy to the jaws.

Necrotic bone in the left mandible, posterior to tooth #33

Symptoms of BRONJ are:

1. Odontalgia not explained by an odontogenic cause.
2. Dull, aching bone pain in the body of the mandible, which may radiate to the temporomandibular joint region.
3. Sinus pain, which may be associated with inflammation and thickening of the maxillary sinus wall.
4. Altered neurosensory function.

Reference: Ruggers SJ, Osborn TG, Axelsson LA, Lundberg R, Mann RB, Mervin S. J Oral Maxillofac Surg 2009; 67: 3-12.

Bisphosphonate is used for the treatment and prevention of which of the following? Please select all that apply.

- ☐ Osteoporosis
- ☐ Diabetes
- ☐ Osteitis deformans (Paget's disease)
- ☐ Bone metastasis (with or without hypercalcaemia)
- ☐ Multiple myeloma
- ☐ Hypertension

Through which route can a bisphosphonate be administered? Please select all that apply.

- ☐ Oral
- ☐ Intravenous
- ☐ Intramuscular
- ☐ Not sure

What is the incidence of BRONJ in patients taking bisphosphonates?

	Common: >11%	Infrequent: 6-10%	Rare: 1-5%	Very Rare: 0.1-0.5%	Exceptionally Rare: <0.1%	I don't know
Oral bisphosphonate	☐	☐	☐	☐	☐	☐
Intravenous bisphosphonate	☐	☐	☐	☐	☐	☐

In a given month, how many patients do you think you would see with BRONJ symptoms or who are being treated with bisphosphonates? Please consider an average number based on your estimate for the past year.

	Patients
Patients with BRONJ symptoms?	<input type="text"/>
Patients who are being treated with oral bisphosphonates?	<input type="text"/>
Patients who are being treated with intravenous bisphosphonates?	<input type="text"/>

Patients who have been treated with oral or intravenous bisphosphonates can be placed in the following categories:

At risk	a patient with no apparent exposed/necrotic bone
Stage 0	no clinical evidence of necrotic bone, but non-specific clinical findings and symptoms
Stage 1	a patient with exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection
Stage 2	a patient with exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage
Stage 3	a patient with exposed/necrotic bone with pain, infection, and one or more of the following: pathologic fracture, extra oral fistula, or osteolysis extending to the inferior border

With this knowledge, please respond to the following two questions:

At which stage would you consider referring a patient with BRONJ to a specialist ?

- ☐ At risk
- ☐ Stage 0
- ☐ Stage 1
- ☐ Stage 2
- ☐ Stage 3
- ☐ I am competent to treat all stages
-

How would you treat patients in the following BRONJ stages? For each stage, please select all that apply.

	No treatment	Patient education	Treat symptoms	Mouth rinse	Antibiotics	Surgical debridement or resection
At risk	☐	☐	☐	☐	☐	☐
Stage 0	☐	☐	☐	☐	☐	☐
Stage 1	☐	☐	☐	☐	☐	☐
Stage 2	☐	☐	☐	☐	☐	☐
Stage 3	☐	☐	☐	☐	☐	☐

Do you perform any surgical dentistry such as tooth extraction, implant placement, periodontal surgery, endodontic surgery? *

- ☐ Yes
- ☐ No
-

Back

Next

22%

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What type of surgical procedures do you perform? Please select all that apply. *

- ☐ Extraction
- ☐ Implant placement
- ☐ Periodontal surgery
- ☐ Endodontic surgery
-

The following scenarios describe 4 patients on bisphosphonate differing in route of administration (intravenous or oral) and length of treatment (≤ 3 years or > 3 years).

What is your treatment strategy if you are planning for a simple tooth extraction (ODA code 71101) for these patients?

	Extract	Discontinue bisphosphonate for 3 months then extract	Don't extract	Refer to a specialist
Patient 1, taking oral bisphosphonates for ≤ 3 years	☐	☐	☐	☐
Patient 2, taking oral bisphosphonates for > 3 years	☐	☐	☐	☐
Patient 3, taking intravenous bisphosphonates for ≤ 3 years	☐	☐	☐	☐
Patient 4, taking intravenous bisphosphonates for > 3 years	☐	☐	☐	☐

What is your treatment strategy if you are planning for a complicated tooth extraction (ODA code 71201) for these patients?

	Extract	Discontinue bisphosphonate for 3 months then extract	Don't extract	Refer to a specialist
Patient 1, taking oral bisphosphonates for ≤ 3 years	☐	☐	☐	☐
Patient 2, taking oral bisphosphonates for > 3 years	☐	☐	☐	☐
Patient 3, taking intravenous bisphosphonates for ≤ 3 years	☐	☐	☐	☐
Patient 4, taking intravenous bisphosphonates for > 3 years	☐	☐	☐	☐

What is your treatment strategy if you are planning for an impacted tooth extraction (ODA code 72221) for these patients?

	Extract	Discontinue bisphosphonate for 3 months then extract	Don't extract	Refer to a specialist
Patient 1, taking oral bisphosphonates for ≤ 3 years	☐	☐	☐	☐
Patient 2, taking oral bisphosphonates for > 3 years	☐	☐	☐	☐
Patient 3, taking intravenous bisphosphonates for ≤ 3 years	☐	☐	☐	☐
Patient 4, taking intravenous bisphosphonates for > 3 years	☐	☐	☐	☐

The following scenarios describe 4 patients on bisphosphonate differing in route of administration (intravenous or oral) and length of treatment (≤ 3 years or > 3 years).

What is your treatment strategy if you are planning for a dental implant placement (ODA code 79931) for these patients?

	Place implant	Discontinue bisphosphonate for 3 months then place implant	Don't place implant	Refer to a specialist
Patient 1, taking oral bisphosphonates for ≤ 3 years	☐	☐	☐	☐
Patient 2, taking oral bisphosphonates for > 3 years	☐	☐	☐	☐
Patient 3, taking intravenous bisphosphonates for ≤ 3 years	☐	☐	☐	☐
Patient 4, taking intravenous bisphosphonates for > 3 years	☐	☐	☐	☐

The following scenarios describe 4 patients on bisphosphonate differing in route of administration (intravenous or oral) and length of treatment (≤ 3 years or > 3 years).

What is your treatment strategy if you are planning for a periodontal surgery for these patients?

Periodontal surgery may include:

- Lancing, Scaling, Curettage, Surgery or Medication for Periodontal Abscess or Pericoronitis (ODA codes 42831-2)
- Root Planing (ODA codes 43421-7)
- Gingivectomy (ODA code 42311)

	Perform surgery	Discontinue bisphosphonate for 3 months then perform surgery	Don't perform surgery	Refer to a specialist
Patient 1, taking oral bisphosphonates for ≤ 3 years	☐	☐	☐	☐
Patient 2, taking oral bisphosphonates for > 3 years	☐	☐	☐	☐
Patient 3, taking intravenous bisphosphonates for ≤ 3 years	☐	☐	☐	☐
Patient 4, taking intravenous bisphosphonates for > 3 years	☐	☐	☐	☐

The following scenarios describe 4 patients on bisphosphonate differing in route of administration (intravenous or oral) and length of treatment (≤ 3 years or > 3 years).

What is your treatment strategy if you are planning for an endodontic surgery for these patients?

Endodontic surgery may include:

- Exploratory surgery (ODA codes 34441-6)
- Apicoectomy (ODA codes 3411-2, 34121-3, 34131-4, 34141-2, 34151-3, 34161-4) with or without retrofilling
- Hemisection (ODA codes 34421-3)
- Root amputation (ODA codes 3441-2)

	Perform surgery	Discontinue bisphosphonate for 3 months then perform surgery	Don't perform surgery	Refer to a specialist
Patient 1, taking oral bisphosphonates for ≤ 3 years	☐	☐	☐	☐
Patient 2, taking oral bisphosphonates for > 3 years	☐	☐	☐	☐
Patient 3, taking intravenous bisphosphonates for ≤ 3 years	☐	☐	☐	☐
Patient 4, taking intravenous bisphosphonates for > 3 years	☐	☐	☐	☐

What is your dental specialty?

- ☐ Oral Surgeon
 - ☐ Periodontist
 - ☐ Prosthodontist
 - ☐ Endodontist
 - ☐ General Practitioner
 - ☐ Others
-

What is your primary professional activity?

- ☐ General practice
 - ☐ Specialty practice
 - ☐ Military practice
 - ☐ Other salaried practice position
 - ☐ Teaching institution
 - ☐ Retired
 - ☐ Not practicing
-

What is your gender?

- ☐ Male
 - ☐ Female
-

What is your age range?

- ☐ < 24
 - ☐ 25-34
 - ☐ 35-44
 - ☐ 45 -54
 - ☐ 55-64
 - ☐ 65+
-

In the space below, please enter the year of graduation from your general dentistry training program and the specialty training program (if applicable)

	Graduation year
As a general practitioner	<input type="text"/>
As a specialist (if applicable)	<input type="text"/>

What is the population of the town/city where your primary practice located?

- ☐ under 5,000
- ☐ 5,000- 50,000
- ☐ 50,000- 500,000
- ☐ over 500,000

What resources do you use (or would you use) to stay current in dentistry? Please select all that apply.

- ☐ Continuing dental education courses
- ☐ Scientific meetings
- ☐ Reading medical/dental journal articles or books
- ☐ Browsing internet

Where did you first learn about BRONJ? Please select all that apply.

- ☐ Undergraduate dental school
- ☐ Dental residency program
- ☐ Graduate dental specialty program
- ☐ Continuing dental education courses
- ☐ Scientific meetings
- ☐ Reading medical/dental journal articles or books
- ☐ Browsing internet
- ☐ Have no knowledge of this topic

Do you feel comfortable treating patients with BRONJ with your current knowledge?

- ☐ Yes
- ☐ Could use minor supplementation
- ☐ Unsure
- ☐ No

Of the options listed, which would be your preference for continuing education related to BRONJ? Please select all that apply.

- ☐ Journal article with a self test
- ☐ Full day/half day courses
- ☐ Internet-based courses
- ☐ DVD/Videos
- ☐ Annual meetings

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Thank You for completing this survey The AAOMS developed a staging system that was recently updated with a new definition for cases in which the diagnosis of BRONJ was suspected. [click here](#) for the AAOMS 2009 staging.

For more information about BRONJ and treatment guidelines please [click here](#)

100%