In 1858, workers in matchmaking factories started to complain of pain, swelling, debilitation and painful exposed bone in the mouth. Labeled “phossy jaw,” the disorder reached epidemic proportions and had a reported mortality rate of 20 percent.

The disorder was linked to yellow phosphorous, the key ingredient in strike-anywhere matches. In the factories, workers—called “mixers,” “dippers,” and “boxers”—were exposed to heated fumes containing this compound. Many workers developed painful exposed bone in the mouth, whereas their office-based counterparts did not. As proper safeguards were put into place, the phossy-jaw epidemic tapered off in the early 20th century, with only a few cases appearing since.1

Until now.

Some troubling, albeit interesting, cases have appeared more than a hundred years later. The exposed bone and clinical course of today’s disease are eerily similar to what our historic counterparts saw in match-factory workers. This time the potential cause is not tied to factory conditions, but instead to people receiving treatment for certain types of cancer. Researchers believe it’s due to bisphosphonates used to treat metastatic cancer deposits in bone or osteoporosis.

Although yellow phosphorus has a simple chemistry of $P_4O_{10}$, when it’s combined with $H_2O$ and $CO_2$ from respiration, and with common amino acids such as lysine, the resulting chemical compound is similar to that found in the prescription medications Fosamax or Aredia.

In patients with phossy jaw, forensic evidence directly points to conversion of the yellow phosphorus to potent amino bisphosphonates by natural chemical reactions in the human body.

The cause of phossy jaw in the late 1800s was actually bisphosphonate-induced osteonecrosis of the jaws, long before clever modern pharmaceutical chemists synthesized bisphosphonates. Today’s bisphosphonate-induced osteonecrosis represents the second epidemic of phossy jaw.1

The three stages of osteonecrosis of the jaw (ONJ):
1. Exposed bone, but no symptoms of pain or infection. Treatment consists of chlorhexidine rinses and monitoring the exposed bone by a dentist or oral surgeon.
2. Exposed bone with symptoms of pain and infection. Treatment consists of oral antibiotic therapy and chlorhexidine rinses with superficial debridement of the infected areas of bone.
3. Exposed bone with extensive pain...
and bone involvement. These patients require the use of chlorhexidine, oral antibiotic therapy, debridement and possible resection to remove the areas of necrotic bone.

**Bisphosphonates today**

For more than a decade, recipients of bisphosphonate drugs have sued pharmaceutical companies over these devastating drug side effects. The plaintiffs allege that the drug, intended as a part of cancer treatment, led to osteonecrosis of the jaw. Many of the lawsuits allege that the pharmaceutical companies either failed to warn the patients of the potential risks, or downplayed the possibility of the associated risks.

Bisphosphonates are a type of drug used to treat bone loss for those who have osteoporosis, bone diseases or cancers that may metastasize to the bones. There can be serious side effects when taking bisphosphonates, especially the IV form, including embolism, myocardial infarction and osteonecrosis. The action of the drug is on the osteoclasts, which deal with the remodeling of bone. When the osteoclasts are shut down, the cells can become infected, leading to exposed bone, infections, pain and numbness.

So far, most of the lawsuits have been decided in favor of the pharmaceutical companies, with courts citing that the drug is fit for the purpose even though there are health hazards to some patients.

**Inside look**

Prior to any modern-day bisphosphonate-related lawsuits, a Dr. Vishtasb Broumand, who now practices in Phoenix, Arizona, began seeing high numbers of patients with necrosis of the bone, as did his mentor at the University of Miami, Dr. Robert Marx, and others across the country. At the time, Broumand was in his advanced training and fellowship in oral and maxillofacial surgery. After completing his position as associate professor of oral surgery at The University of Miami School of Medicine, Broumand relocated to Arizona. He recently shared with me his experience of being an expert witness in a landmark trial involving bisphosphonates.

The patients he’d seen had exposed bone, pain and infection, but had no exposure to radiation, a plausible cause of osteoradionecrosis of the bone.

At the time, the necrosis was of unknown origin. Was it due to an exposure to chemotherapy in these cancer patients? Not all the patients were undergoing chemotherapy. What was the common link?

Other clinicians began to refer similar patients with osteonecrosis of the jaw to Marx and Broumand in Miami. During this time, they researched bisphosphonates heavily, and subsequently published an article at about the same time as Dr. Sal Ruggiero. Both articles established links between bisphosphonate drugs and osteonecrosis of the jaw, and were turning points regarding bisphosphonates.

Patients who had taken IV bisphosphonates as part of their cancer treatments, and then later undergone dental extractions, were more likely to have necrosis of the jaw. This was due, in part, to osteoclastic suppression.

After the publication of their article, patients with ONJ flocked to be treated by Broumand and Marx at University of Miami. The two oral surgeons had no idea that this would inevitably render them authorities in dealing with osteonecrosis.

**An eight-year trial**

Because of his experience in dealing with ONJ, Broumand became an expert witness for the plaintiffs during a class-action lawsuit in which more than 600 patients sued Novartis Pharmaceuticals after suffering osteonecrosis from taking bisphosphonates.

The trial took nearly eight years (2008-2015). During this time, Broumand stayed current with information regarding bisphosphonates. As he was employed by the University of Miami and continued to see patients who were dealing with osteonecrosis, his practice was not adversely affected by the long trial. Additionally, he compiled more than 20 expert reports from his studies on bisphosphonates that were used in testifying during the trial against the big pharmaceutical companies.

Novartis’s earlier clinical trials had revealed that bisphosphonates caused some complications, but those results were never released. Novartis hired paid consultants for the trial, some of whom were oral surgeons (and Broumand’s friends/associates), who suggested that the necrosis was due to periodontal disease or smoking, and not as a result of Zometa (IV bisphosphonate) usage. On the record, he had to disagree with them on their responses.

The trial was exciting but unnerving, Broumand said. “The legal counsel for the defense was pretty harsh when it came to questioning the plaintiff expert witnesses. During my depositions, which had lasted as long as nine hours, I remember thinking to myself that the cross-examining attorney had to be as tired as I was, but they kept going on and on and on and they tried to get me and other witnesses to break. Fortunately, at the end of the case we prevailed and that meant financial freedom and restitution for over 600 participants in the class-action lawsuit. For me it meant going back to being a clinician, which is what I wanted in the first place. I never thought I’d find myself testifying in such a large trial when they first asked me to be an expert witness.”

The defense recently settled with the 600 patients, as a result of the testimonies and expert witness reports shared by Broumand and other experts in the field.

**In practice**

In the dental field, osteonecrosis of the jaw can occur when a patient has been treated using high levels of IV bisphosphonates prior to a dental surgery involving bone. This happens in some 60 percent of the cases of osteonecrosis. The mandible is twice as likely to be affected by osteonecrosis as the maxilla. Current recommendations for patients on oral bisphosphonates are not as rigid as the recommendations for those having been
on intravenous bisphosphonates, and generally treatment can proceed as long as there is no active sign of osteonecrosis.

When a cancer patient must be treated using bisphosphonates, dental clearance should be done ahead of treatment, if possible. Any teeth with poor prognosis should be removed, or treated with root canals.

If the patient has already begun IV bisphosphonate therapy, surgeries involving bone should be avoided. Root canals, rather than extractions, should be performed. Implants or any surgeries involving the bone should be avoided. Cleanings, RCTs and fillings are less risky for these patients and should be done to maintain the patient’s dental health.

A newer osteoclast inhibitor called Xgeva was approved by the FDA in late 2010, which shut down the osteoclasts, but by a different mechanism than the bisphosphonates. The action to the bone was reversible when the drug was discontinued, unlike the bisphosphonates, since Xgeva did not bind to the bone. But this drug could also create osteonecrosis of the jaw due to disruption of the vascular supply to the jawbone; therefore it was found to be the suppression of the osteoclasts themselves that contributed to ONJ.

For the general dentist, treatment recommendations for those who have taken bisphosphonates differ regarding whether the medication was orally or intravenously given.

**Oral Bisphosphonates and Dentistry Recommendations**

- Less than 3 years of treatment, most all dental procedures are safe, including implants.
- Less than 3 years of treatment, but also took steroids or methotrexate, consult with prescribing MD and consider 3 month drug holiday before surgery. (Implant placement would increase risk of ONJ).
- More than 3 years of treatment, increased risk. Consult with prescribing MD and consider 3 month drug holiday before surgery.

**IV Bisphosphonates and Dentistry Recommendations**

Most of these patients are cancer patients. In general, no elective procedures should be performed once a patient has received a dose, unless medically necessary.

**Before the initiation of IV Bisphosphonate Therapy**

- Remove unsalvageable teeth
- Treat periodontitis and gingivitis
- Treat caries
- Defer the start of Bisphosphonates for 2 months

**Recommendations during IV Bisphosphonate Therapy**

- Avoid invasive procedures (extractions, periosurgery, implants)
- Treat caries. If needed, RCT and amputation of crown of tooth, to avoid extraction
- Supragingival scaling
- Splint mobile teeth
- If extractions are unavoidable, provide informed consent of increased risk of ONJ
- Drug holiday is not helpful

**Recommendations for treatment of ONJ with exposed bone**

- Avoid debridements or elective dentoalveolar surgery
- Smooth sharp edges
- Treat with Pen VK 500 mg QID for 3-4 weeks and Peridex TID for life
- Use Levaquin, Zithromycin or Doxycycline in patients allergic to Penicillin
- Add Flagyl 500 mg TID for 10 days in refractory cases
- If surgery is unavoidable, perform alveolectomy or continuity resection

**References**