

OPEN WIDE Infection from unchecked periodontal disease has several significant local and potentially systemic consequences.

MANAGEMENT STRATEGIES

Current Concepts in Periodontal Disease

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Of the most common health problems of companion animals throughout their life, dental disease stands out as the number 1 concern. While studies from previous decades list the prevalence of periodontal disease in the 60% to 70% range,¹⁻⁴ a 2018 study found that almost 90% of all canine patients had some degree of periodontal disease.⁵ Another 2018 study using more accurate diagnostics found evidence of periodontal disease in 100% of canine subjects and concluded that periodontal disease is underdiagnosed based on visual examination alone.⁶ In cats, the incidence is reported to be as high as 70% by 2 years old.⁷ Based on its chronicity,

prevalence, and impact on overall health, dental disease was considered the number 1 health-related welfare concern in dogs in the United Kingdom in 2019.⁸

Sadly, many owners and veterinarians still misunderstand the significant effects of periodontal disease, believing them to be limited to bad breath and tooth loss. This lack of understanding, combined with improper or outdated diagnostic methods, can lead to delayed therapy at best and misdiagnosis at worst. Both of these situations are concerning, as significant pain and infection from unchecked periodontal disease have several local and potentially systemic consequences (**BOX 1**). Intervention by veterinarians and educated owners is the only solution to improving health and alleviating distress in these patients.

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PATHOGENESIS

There are two recognized stages to periodontal disease—gingivitis and periodontitis—but they often present concurrently. In the initial stage, gingivitis, the inflammation is confined to the gingiva. This is a reversible process. When gingivitis progresses due to lack of or inappropriate treatment, periodontitis typically ensues. Periodontitis is defined as an inflammatory disease of the deeper supporting structures of the tooth (the periodontal ligament and

alveolar bone) that is caused by bacteria and their byproducts. Progressive destruction of the periodontal tissues leads to attachment loss. Periodontitis is considered an irreversible process, unless the patient is treated with advanced periodontal surgery techniques including guided tissue regeneration.

Periodontal disease begins with the formation of plaque.¹¹ Plaque, one of many biofilms that naturally occur, is made up almost entirely of oral bacteria that adhere to the teeth and are held together by a matrix of extracellular polysaccharides and salivary glycoproteins. Plaque can be found on tooth surfaces within 24 hours of dental cleaning.

When plaque is visible on the surface of the tooth, it is known as *supragingival* plaque. Once it extends below the gumline, it is called *subgingival* plaque. While supragingival plaque is easier to see, the damaging effects of periodontal disease come from the presence of subgingival plaque within the gingival sulcus or periodontal pocket.¹² Calculus, or tartar, is also relatively nonpathogenic. Therefore, control of supragingival plaque or tartar alone, as is found with non-anesthesia dentistry, is ineffective in controlling the progression of periodontal disease.^{5,13}

When subgingival bacteria are able to proliferate, the combination of the inflammation produced by the bacteria themselves and the host's own immune response begins the irreversible damage of periodontitis. Inflammation of the soft tissue weakens attachment, while osteoclastic activity decreases the bony support. Current studies suggest that there is a

BOX 1 Potential Consequences of Periodontal Disease

Local⁹

- Oronasal fistulas
- Class II periodontic-endodontic lesions
- Pathologic fractures
- Ocular problems
- Osteomyelitis
- Oral cancer

Systemic¹⁰

- Renal, hepatic, and cardiac disease
- Increased inflammatory markers
- Anemia of chronic disease
- Arthritis
- Diabetes mellitus

strong genetic component to periodontal disease, potentially related to the amount of damage attributed to the host response.^{2,13,14} Periodontal disease culminates in tooth loss; however, significant problems can precede tooth exfoliation.

CLINICAL FEATURES

Healthy gingiva should look coral pink and have a thin edge. When gingivitis starts, the first clinically notable sign is erythema of the gums, followed by halitosis and gingival edema (**FIGURE 1**). While color change is a



FIGURE 1. Left maxilla of a dog with early to moderate gingivitis. Note the red and slightly swollen gingiva.



FIGURE 2. Mandibular right canine (404) of a dog with normal-appearing gingiva, but bleeding on probing. This is the first sign of gingivitis.

An oronasal fistula forms when periodontal disease progresses apically from the palatal surface of a maxillary tooth, most commonly a canine.

reliable sign of disease, bleeding on probing, chewing, or brushing is now recognized as the earliest clinical sign of gingivitis (**FIGURE 2**).^{15,16}

Dental calculus is often present alongside gingivitis, but plaque bacteria are the true cause of gingivitis and periodontal disease. Therefore, gingivitis can occur in the absence of calculus. By the same logic, widespread supragingival calculus may be notable, with little to no gingivitis accompanying it.¹⁷

The hallmark clinical feature of periodontitis is attachment loss. This is considered to be periodontal pocket formation and/or gingival recession >3 mm in dogs or >1 mm in cats.¹⁸ Both presentations of attachment loss can occur in the same patient and, occasionally, on the same tooth.

LOCAL CONSEQUENCES

One of the most common of the severe local



FIGURE 3. Oronasal fistula on the left maxillary canine of a dog. The diagnosis is made by introducing a periodontal probe into the defect.

consequences of periodontal disease is oronasal fistulation (**FIGURE 3**).^{9,19} Oronasal fistulas can occur in cats as well as any breed of dog, but they are typically found in older small- and toy-breed dogs. An oronasal fistula forms when periodontal disease progresses apically from the palatal surface of a maxillary tooth, most commonly a canine. While it can be apparent during a conscious oral examination, definitive diagnosis typically requires periodontal probing under general anesthesia. A fistula can exist even when the gingiva looks relatively healthy and the tooth is well attached; therefore, probing every aspect of every tooth in the mouth is a vital part of an oral examination. Appropriate treatment of a fistula entails extraction of the tooth and closure of the defect with a mucogingival flap.¹⁹

When periodontal disease progresses toward the apex of the tooth and bacteria gain access to the endodontic system through the apical delta, the result is a class II periodontal-endodontic lesion.^{18,20,21} In these cases, the affected tooth dies and the infection can then spread via the common pulp chamber to other root(s) (**FIGURE 4**).

In some patients with apical progression of severe periodontal disease, especially brachycephalic patients, the proximity of the tooth root apices of the maxillary molars and distal root of the fourth premolars allow for infection transmission into the area behind the globe. This can lead to infection and abscessation of the



FIGURE 4. Radiograph of the left mandibular first molar (309) of a dog with a class II periodontal-endodontic lesion. The disease has caused loss of the alveolar bone down to the apex of the distal root (white circle). The tooth has become non-vital and the infection has spread through the common pulp chamber to create the endodontic lesion on the mesial root (orange arrow).

TABLE 1 Potential Negative Consequences of Periodontal Disease on Systemic Health^a

| ORGAN/SYSTEM AFFECTED | PROPOSED LINK TO PERIODONTAL DISEASE | ASSOCIATED CLINICAL EFFECTS |
|-----------------------|---|---|
| Liver | Bacteremia ²⁸ | <ul style="list-style-type: none"> ▪ Parenchymal inflammation (dogs)^{28,29} ▪ Portal fibrosis (dogs)²⁸ ▪ Cholestasis (dogs)²⁸ |
| Kidney | Chronic stimulation of the immune system leading to presence of immune complexes in the kidney ³⁰ | <ul style="list-style-type: none"> ▪ Glomerulonephritis³⁰ ▪ Chronic kidney inflammation and secondary scarring³⁰ ▪ Decreased kidney function and filtration ability³¹ ▪ Chronic kidney disease (dogs and cats)^{32,33} |
| Heart | Bacteria in bloodstream attach to roughened heart valves | <ul style="list-style-type: none"> ▪ Cardiopulmonary changes (dogs)³⁴ ▪ Increased risk of endocarditis (dogs with stage 3 periodontal disease; 6× that of controls)³⁵ ▪ Hypertension³⁶ ▪ Endothelial effects³⁷ |
| Metabolic | Increased C-reactive protein and other inflammatory markers that improve with periodontal care ³⁸⁻⁴¹ | <ul style="list-style-type: none"> ▪ Increased inflammatory lipids ▪ Overall lipidemic state (human and animal studies)^{29,40,42-45} ▪ Insulin resistance^{44,45} |

^aUnless otherwise noted, studies are in human medicine.

periorbital tissue of the eye and may result in eye loss or blindness.^{22,23}

When chronic periodontal loss weakens the bone, pathologic fracture of the jaw can occur (**FIGURE 5**).^{18,24} This condition is seen almost exclusively in small- and toy-breed dogs, in which the teeth are large in proportion to the jaws, and most frequently affects the mandible around the canines and first molars. It occasionally affects the mandibular canine area in cats.

Chronic osteomyelitis or osteonecrosis (**FIGURE 6**) are well-known sequelae of periodontal disease.²⁵ Once periodontal bacteria gain access to them, deeper bony

tissues become infected and die. Necrotic bone no longer has a functioning blood supply, so it can no longer respond to antibiotic therapy. In patients with suspected osteonecrosis, aggressive surgical debridement is necessary and may require partial or complete mandibulectomy. These animals can live long and comfortable lives after surgery, providing disease has been completely addressed.

In people, chronic periodontal disease has also been linked to an increased incidence of oral cancer.^{26,27} While the mechanism for this is currently unknown, the chronic inflammatory state that exists with periodontitis is the likely cause. Further studies in veterinary medicine are needed to establish this relationship in dogs and cats.

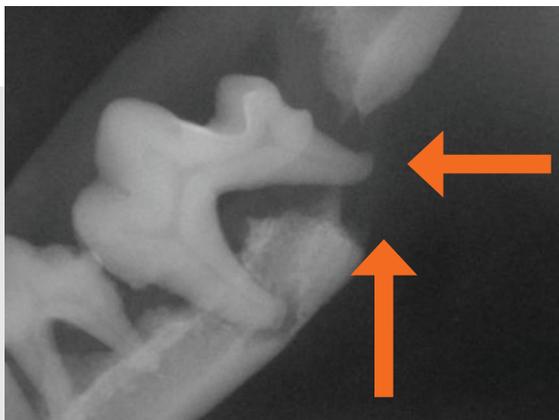


FIGURE 5. Radiograph showing a pathologic mandibular fracture at the distal root of the left mandibular first molar (309) in a small-breed dog (orange arrows). The bone has been weakened to the point of fracture.

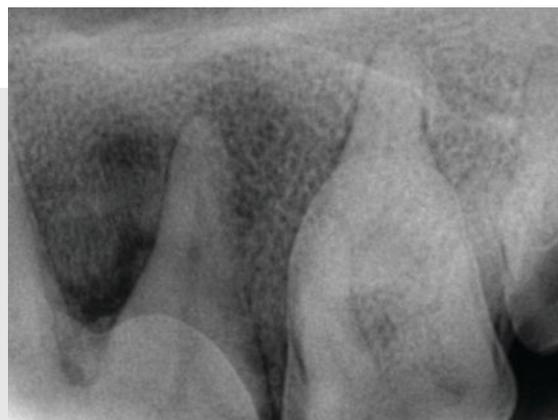


FIGURE 6. Radiograph showing osteomyelitis of the left maxilla of a dog.

Veterinary patients require both doctors and owners to provide frequent, clinically effective dental care to support good health and quality of life.

SYSTEMIC CONSEQUENCES

Systemic health consequences of periodontal disease have seen a strong uptick in research over the last few decades. While no causal relationship has been identified, and much of the research is in human medicine, the evidence that periodontal disease has negative consequences on systemic health is mounting, based on the ability of oral bacteria to gain access to the bloodstream through inflamed periodontal tissue. Once the bacteria have access to the rest of the body, multiple negative sequelae are possible (**TABLE 1**).

While further veterinary studies are needed to fully investigate the deleterious effects periodontal disease can have on companion animals, studies in people have correlated poor periodontal health with increased rates of gastrointestinal, kidney, pancreatic, and hematologic cancers,⁴⁶⁻⁴⁸ as well as a major contributor to

complications of diabetes mellitus.^{44,45} Periodontal disease has been shown to be a significant predictor of early mortality in humans,⁴⁹⁻⁵¹ with one study reporting that severe periodontal disease is linked to a higher risk factor of early death than smoking.⁵²

HEALTH AND WELFARE BENEFITS OF PERIODONTAL THERAPY

Veterinary patients require both doctors and owners to provide frequent, clinically effective dental care to support good health and quality of life. Owners, therefore, must be educated about the impact of periodontal disease on an animal's health-based welfare. Additionally, while it may seem counterintuitive, patients rarely show obvious behavioral changes in response to oral pain, so waiting for these signs simply lengthens time to appropriate therapy and increases the severity of disease for the patient. Veterinarians are considered leaders in the assessment and improvement of animal welfare globally;⁵³ however, incorporating animal welfare conversations into daily practice can be challenging, especially when an animal's needs differ from the client's desires.

The Five Animal Welfare Needs (FAWN) framework (**BOX 2**) provides veterinarians with a context in which patient welfare may be more easily evaluated and discussed with clients in language they can understand and embrace.⁵⁴ The need to be protected from pain, suffering, injury, and disease is the most obvious FAWN element in the assessment of periodontal disease. Remembering the need for a suitable diet and the need to be able to exhibit normal behavior patterns may also lead to discussions that uncover potential improvements that can be realized through adequate dental care.

For a patient to truly benefit from dental care, both the veterinarian and owner must understand, accept, and incorporate the changes necessary to effectively control periodontal disease. Discussing ways that periodontal disease can negatively affect an animal's daily welfare may help the pet owner understand how dental health affects their pet's quantity and quality of life and increase compliance with treatment instructions.⁵⁵

CONCLUSION

Patients with periodontal disease are exposed to oral bacteria in the systemic bloodstream daily, creating a state of chronic disease. Veterinarians and pet owners must learn to view periodontal disease as not merely a

BOX 2 The Five Animal Welfare Needs⁵⁴

- 1. Health:** To be protected from suffering, injury, disease states, and pain, and to be treated if illness or injury occurs
- 2. Behavior:** To behave in a normal species-specific manner (e.g., to dig, chew, scratch, play)
- 3. Companionship:** To live with, or apart from, other animals as is appropriate to the species and individual animal's preference
- 4. Diet:** To be fed a biologically appropriate diet for the age, species, and activity level of the animal that provides adequate nourishment without obesity or poor body condition, and to have access to freely available fresh water
- 5. Environment:** To live in a suitable, safe, comfortable environment that contains places to rest, hide, explore, and exercise



dental problem, but as an initiator of more severe local and systemic consequences. With this knowledge, both veterinary professionals and clients can feel confident they are making informed, welfare-centric decisions for the pet's oral care.

Drs. Niemiec and Stewart are contributors to the WSAVA Global Dental Guidelines, which contain expanded information on periodontal disease. These guidelines are available at: wsava.org/global-guidelines/global-dental-guidelines. **TVP**

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Mirataz™ (mirtazapine transdermal ointment)

For topical application in cats only. Not for oral or ophthalmic use.

CAUTION: Federal law (USA) restricts this drug to use by or on the order of a licensed veterinarian.

Before using this product, please consult the product insert, a summary of which follows:

INDICATION: Mirataz™ is indicated for the management of weight loss in cats.

DOSAGE AND ADMINISTRATION: Administer topically by applying a 1.5-inch ribbon of ointment (approximately 2 mg/cat) on the inner pinna of the cat's ear once daily for 14 days. Wear disposable gloves when applying Mirataz™. Alternate the daily application of Mirataz™ between the left and right inner pinna of the ears. **See Product Insert for complete dosing and administration information.**

CONTRAINDICATIONS: Mirataz™ is contraindicated in cats with a known hypersensitivity to mirtazapine or to any of the excipients. Mirataz™ should not be given in combination, or within 14 days before or after treatment with a monoamine oxidase inhibitor (MAOI) [e.g. selegiline hydrochloride (L-deprenyl), amitraz], as there may be an increased risk of serotonin syndrome.

HUMAN WARNINGS: Not for human use. Keep out of reach of children. **Wear disposable gloves when handling or applying Mirataz™ to prevent accidental topical exposure.** After application, dispose of used gloves and wash hands with soap and water. After application, care should be taken that people or other animals in the household do not come in contact with the treated cat for 2 hours because mirtazapine can be absorbed transdermally and orally. However, negligible residues are present at the application site and the body of the cat at 2 hours after dosing. In case of accidental skin exposure, wash thoroughly with soap and warm water. In case of accidental eye exposure, flush eyes with water. If skin or eye irritation occurs seek medical attention. In case of accidental ingestion, or if skin or eye irritation occurs, seek medical attention.

PRECAUTIONS: Do not administer orally or to the eye. Use with caution in cats with hepatic disease. Mirtazapine may cause elevated serum liver enzymes (See **Animal Safety** in the product insert). Use with caution in cats with kidney disease. Kidney disease may cause reduced clearance of mirtazapine which may result in higher drug exposure. Upon discontinuation of Mirataz™, it is important to monitor the cat's food intake. Food intake may lessen after discontinuation of mirtazapine transdermal ointment. If food intake diminishes dramatically (>75%) for several days, or if the cat stops eating for more than 48 hours, reevaluate the cat. Mirataz™ has not been evaluated in cats < 2 kg or less than 6 months of age. The safe use of Mirataz™ has not been evaluated in cats that are intended for breeding, pregnant or lactating cats.

ADVERSE REACTIONS: In a randomized, double-masked, vehicle-controlled field study to assess the effectiveness and safety of mirtazapine for the management of weight loss in cats, 115 cats treated with Mirataz™ and 115 cats treated with vehicle control were evaluated for safety. The vehicle control was an ointment containing the same inert ingredients as Mirataz™ without mirtazapine. The most common adverse reactions included application site reactions, behavioral abnormalities (vocalization and hyperactivity), and vomiting. **See Product Insert for complete Adverse Reaction information.** To report suspected adverse events, for technical assistance or to obtain a copy of the SDS, contact Kindred Biosciences, Inc. at 888-608-2542. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at <http://www.fda.gov/AnimalVeterinary/SafetyHealth>.

EFFECTIVENESS: The effectiveness of Mirataz™ (mirtazapine transdermal ointment) was demonstrated in a randomized, double-masked, vehicle-controlled, multi-site field study involving client-owned cats of various breeds. Enrolled cats were ≥ 1 year of age and had existing documented medical history of ≥ 5% weight loss deemed clinically significant. The most common pre-existing conditions included renal insufficiency, vomiting, and hyperthyroidism. Some cats had more than one pre-existing condition. Cats were randomized to treatment groups in a 1:1 ratio of Mirataz™ to vehicle control. A total of 230 cats were enrolled and received either Mirataz™ (115 cats) or a vehicle control (115 cats) containing the same inert ingredients without mirtazapine. The cats were 2.8-24.6 years of age and weighed 2.1-9.2 kg. The dosage was a 1.5-inch ribbon (approximately 2 mg/cat) mirtazapine or vehicle ointment administered topically to the inner pinna of the cat's ear. A total of 177 cats were determined to be eligible for the effectiveness analysis; 83 cats were in the Mirataz™ group and 94 cats were in the vehicle control group. The primary effectiveness endpoint was the mean percent change in body weight from Day 1 to the Week 2 Visit. At Week 2, the mean percent increase in body weight from Day 1 was 3.94% in the mirtazapine group and 0.41% in the vehicle control group. The difference between the two groups was significant (p<0.0001) based on a two-sample t-test assuming equal variances. A 95% confidence interval on the mean percent change in body weight for the Mirataz™ group is (2.77, 5.11), demonstrating that the mean percent change is statistically different from and greater than 0.

STORAGE: Store below 25°C (77°F). Multi-use tube. Discard within 30 days of first use.

HOW SUPPLIED: Mirataz™ is supplied in a 5 gram aluminum tube.

MANUFACTURED FOR:

Kindred Biosciences, Inc.
1555 Bayshore Highway, suite 200
Burlingame, CA 94010

NADA 141-481, Approved by FDA

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NDC 86078-686-01
REG-MTZBS-008 Rev. 26Apr2018
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