Instead of looking at serum biochemical markers of bone turnover or, more importantly, bone density, researchers on most equine studies have used improvement in lameness grade as the endpoint. One research group did examine serum markers of bone turnover in bisphosphonate-treated horses, including two proteins found in bone: osteocalcin (a marker of bone formation) and C-terminal collagen-I telopeptide (a marker of bone resorption). They noticed no change in either marker, as would be expected if bone treatment decreased turnover yet lameness was significantly reduced.

However, in another study using horses casted on one leg, researchers found an increase in serum markers of bone turnover. This was expected because disuse results in increased bone resorption to adapt to decreased weight-bearing. After administering tiludronate, the investigators saw a significant reduction in markers of bone turnover. “This latter report is one of the only studies demonstrating an anti-resorptive effect of bisphosphonates in horses,” Suva said, adding, “These data also suggest alternative mechanisms of action of bisphosphonates to explain the improvement in lameness.”

Examples of such mechanisms that have not yet been proven include anti-inflammatory properties, decreased activity of enzymes that contribute to bone turnover, and altered growth factor effects.

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“While not illegal, off-label use of bisphosphonates may or may not be effective and may potentially be harmful to the horse,” said Suva. “We simply do not have enough data to support widespread recommendations for off-label use.”

In addition, veterinarians have administered some nitrogen-containing bisphosphonates to horses, such as zoledronic acid. Suva said that in a 2013 pharmacology study, researchers gave a single zoledronic acid dose (0.057 mg/kg, intravenous) via a 30-minute infusion. The infusion produced sustained decreases in total serum calcium (at seven days), as expected for such a potent bisphosphonate. It appears that zoledronic acid inhibits bone resorption and is safe in healthy adult horses, he said, noting further studies evaluating potential benefits of zoledronic acid in horses with orthopedic conditions are warranted.

CONCERNS TO CONSIDER
Some adverse effects identified in humans, where bisphosphonate use is far more widespread (in osteoporosis and cancer patients), include osteonecrosis (abnormal breakdown of the bone) of the jaw and atypical femoral (thighbone) fractures. These are very rare events, said Suva, often following long-term use of more potent nitrogen-containing bisphosphonates.

Current manufacturer recommendations are to use FDA-approved bisphosphonates according to label instructions. In studies conducted to garner FDA approval in 4-year-old horses with navicular syndrome, researchers did find a significant beneficial effect. “With the rampant bisphosphonate use in the equine industry, it is important to recognize and follow the approved use of these powerful molecules,” said Suva.

The article, “Bisphosphonate use in the horse: what is good and what is not,” was co-authored by Alexis Mitchell, Ashlee Watts, and Frank Ebertino, all from Texas A&M University’s College of Veterinary Medicine and Biomedical Sciences.

Larry J. Suva, PhD, suggests three ways the veterinary community can help pinpoint the exact role and optimal use of bisphosphonates in horses:

1. Push for more research and clinical trials, especially those focusing on long-term use and safety that measure bone markers and bone density;

2. Offer more continuing education opportunities to keep the equine community abreast of the latest information on bisphosphonates; and

3. Understand the rationale and potential mechanisms for bisphosphonate usage because, based on available data, bisphosphonates’ positive effects might be more connected to non-bone-related effects rather than inhibiting bone resorption.