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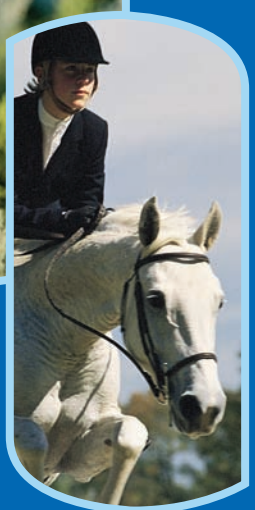
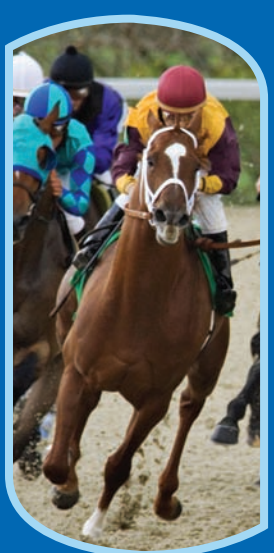
Update on Equine Joint Healthcare

A Roundtable Discussion on Chondroprotective Agents





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About the Participants

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Kent Allen, DVM, is with Virginia Equine Imaging in Middleburg, Virginia, and he also lectures internationally on the subjects of sports medicine, lameness, and equine imaging. His practice interests are lameness, sports medicine, and diagnostic imaging.

Michael Davis, DVM, MS, is founder and CEO of the New England Equine Medical & Surgical Center in Dover, New Hampshire. He is a clinician, lameness diagnostician, and surgeon.

Douglas Langer, DVM, MS, is Vice President, Partner, and Director of Surgery and Diagnostic Imaging at The Wisconsin Equine Clinic and Hospital in Oconomowoc, Wisconsin. He specializes in sport horse lameness and surgery and is also a nutrition consultant with regard to growth-related issues. Dr. Langer also owns Maple Run Farm, a Hanoverian breeding farm.

Brian MacNamara, DVM, is with Warwick Equine Clinic in Warwick, New York, and The Meadowlands Equine Hospital at the Meadowlands Racetrack in East Rutherford, New Jersey. He practices equine surgery and performs lameness and poor performance evaluations.

Richard Stevens, DVM, is with the Conejo Valley Veterinary Hospital in Thousand Oaks, California. His professional interests include sports medicine, equine reproduction, and equine dentistry.

New research on the chondroprotective agents avocado/soybean unsaponifiables (ASU), glucosamine, and chondroitin sulfate has been published recently. At a roundtable held in November 2007, we asked several experts in equine orthopedics their opinions on this research and on the use of these agents in joint health supplement products. They also discussed other modalities for managing joint health in horses. Their discussion follows.

Disease Modification versus Symptom Alleviation

Wayne McIlwraith, BVSc, PhD, DSc, DACVS: As you know, it has been noted that 60% of lameness problems in horses are related to osteoarthritis (OA). Before we begin a discussion on joint healthcare, we first need to clarify what we mean by the term *chondroprotective agent*. What agents belong in this category, and how do we distinguish between a chondroprotective agent (or disease-modifying osteoarthritic drug [DMOAD], the term being used more frequently in human medicine) and symptom-modifying osteoarthritic drugs?

Douglas Langer, DVM, MS: The agents I typically identify as chondroprotective are the oral supplements, such as Cosequin® ASU (Nutramax Laboratories, Inc.); Adequan® (Luitpold Pharmaceuticals), an injectable polysulfated glycosaminoglycan (PSGAG); and Legend® (Bayer Animal Health), an injectable hyaluronate sodium

(also referred to as hyaluronic acid [HA]). The biggest problem I have encountered in private practice is that for many of the oral agents, it is very difficult to know the bioavailability or usefulness of the products in horses. At my practice, we are very proactive in trying to recommend products that have been tested in the research setting because we have an idea of how well they truly work.

Michael Davis, DVM, MS: I agree with classifying the Cosequin-type nutraceuticals and Adequan and Legend as chondroprotective agents or DMOADs. We use these products in my practice. I also think that we have to advise and educate our clients about which compounds are the most appropriate for their horse and in which particular situations they are recommended.

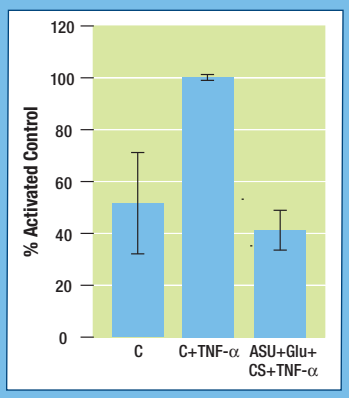
Kent Allen, DVM: I would also say that Legend, Adequan, and Cosequin ASU are definitely DMOADs, and there is good documentation in the literature as to the role each of these agents plays separately in maintaining joint health and repair abilities in equine athletes. The confusing part is whether we are using these products to prevent or repair damage and when each product is indicated, separately or in combination. Periodically examining the available science behind these products is a way to keep us honest in terms of what we tell our clients and to stop us from getting lost in the rhetoric.

Brian MacNamara, DVM: I agree with the classification as well, and those are the products that we primarily use at my clinic. In clinical practice, it's difficult to actually evaluate the chondroprotective or disease-modifying aspects of these products. We focus on whether the agents modify clinical signs, but even that becomes difficult because we're usually relying on owner observations, at least in terms of racehorses and performance horses. I believe there is a degree of placebo effect because the owners are hopeful that the treatment they are paying for works. Also, these agents are seldom the sole treatment

Equine In Vitro Research on ASU, Glucosamine, and Chondroitin Sulfate

The effects of the combination of NMX1000® avocado/soybean unsaponifiables (ASU), FCHG49® glucosamine hydrochloride, and TRH122® low-molecular-weight chondroitin sulfate on cyclooxygenase-2 (COX-2) expression were investigated in equine chondrocytes. Equine chondrocytes were incubated with control media alone or the combination of agents and then stimulated with lipopolysaccharide. COX-2 expression was elevated in stimulated controls. This expression was reduced by the combination of ASU, glucosamine, and chondroitin sulfate; levels were comparable to nonstimulated control.

The effects of the combination were also investigated in equine osteoblasts on COX-2 expression and prostaglandin E_2 (PGE_2) production. Equine osteoblasts were incubated with control media alone or the combination of agents and then stimulated with tumor necrosis factor-α (TNF-α). COX-2 expression and PGE_2 levels were elevated in stimulated controls. COX-2 expression was reduced by the combination of ASU, glucosamine, and chondroitin sulfate; levels were comparable to nonstimulated control. PGE_2 production was decreased by up to 60% versus stimulated controls.



Effect of ASU, glucosamine (Glu), and chondroitin sulfate (CS) on COX-2 expression in TNF-α activated equine osteoblasts. (C = nonstimulated control)

Results of both studies show that the combination of NMX1000 avocado/soybean unsaponifiables (ASU), FCHG49 glucosamine hydrochloride, and TRH122 low-molecular-weight chondroitin sulfate, as found in Cosequin® ASU, inhibited expression and/or production of mediators involved in joint cartilage breakdown and discomfort. The effects on osteoblasts impact subchondral bone health and therefore cartilage health. These results suggest that the combination may be useful in supporting and protecting joint health.

Au RY, Au AY, Rashmir-Raven AM, et al. Pro-inflammatory gene expression in chondrocytes and monocyte/macrophages is inhibited by the combination of avocado soybean unsaponifiables, glucosamine, and chondroitin sulfate. *Proc. 34th Ann Conf Vet Orthoped Soc* 2007;57.

Au RY, Au AY, Snow GE, et al. Cyclooxygenase-2 gene expression and prostaglandin-E_2 production in activated equine osteoblasts are inhibited by avocado soybean unsaponifiables, glucosamine, and chondroitin sulfate. *J Vet Intern Med* 2007;21(3):668.

modality, which makes it even more challenging to evaluate how well an individual agent modifies the symptoms of lameness.

Richard Stevens, DVM: In my view, the symptom-modifying drugs alleviate the clinical signs, but the underlying disease will continue to progress if that is all that is used. On the other hand, I would expect a DMOAD to prevent or slow the progression of the disease. We need research to help us categorize the effects the various products have. I think that some products, such as Legend, fall into both categories because they have an antiinflammatory component as well as activity that either helps restore the matrix or slow disease progression. We also use drugs that are more symptom-modifying, like the NSAIDs, when our goal is simply controlling pain.

Langer: ***I do currently recommend oral joint health supplements, particularly Cosequin ASU, not only in the treatment of joint problems but also as a preventative in young horses starting their training and in growing horses when they are having problems with epiphysitis and other growth-related issues.***

MacNamara: A study by Lippiello discussed the possibility that ASU with chondroitin sulfate and glucosamine reduces the mediators of inflammation and thus both decreases pain and protects the cartilage, but a study performed at Colorado State University (CSU) indicated that there was a different mechanism at work.

ASU: Mechanism of Action and Rationale for Use

McIlwraith: The ASU study that I was part of at CSU used a chip fragment model and was the first time anybody had objectively evaluated an oral product (see page 6). This was the first controlled scientific study demonstrating a positive effect with an oral nutraceutical.

We had various outcome parameters, and the clearly significant ones were at the cartilage level, which fits within the definition of chondroprotective. This contrasts with what was seen when we evaluated Legend using the same model, in which most of the changes occurred at the level of the synovial membrane. When we evaluated Legend we showed decreased prostaglandin E_2 (PGE_2) levels, decreased protein levels in the synovial fluid, decreased hyperemia, and decreased cellular infiltration in the synovial membrane, although we did not demonstrate any difference in the cartilage lesions between treatment horses and controls. This is why the terminology is so perplexing: If the agent cuts down the inflammatory mediators that we know can ultimately cause further cartilage degradation, is it chondroprotective? I tend to think it is.

MacNamara: One of the major takeaway messages I got from the study is that the findings give clinicians a concrete reason to recommend the use of an oral supplement postoperatively. The results show that ASU helps with cartilage repair—not regeneration—at the level where the fragment or fracture is removed. It is very reasonable to recommend the use of ASU for postoperative patients. Furthermore, once a definitive diagnosis of OA has been made in one joint, I think it is reasonable to put the patient on a product like Cosequin ASU as part of the entire treatment protocol, even in nonsurgical cases.

McIlwraith: The OA model used at CSU is a model of progressive degeneration; it is not set up to show whether a repair is being effected. The findings of less fibrillation and less chondrone formation mean that ASU is preventing these events, which are classic histologic events for OA. Based on the model used in this study, we do know that ASU can decrease the amount of articular cartilage degradation; whether it promotes cartilage healing requires further study.

Allen: I was excited to see the CSU study in print. This is proof that there is an oral product that stabilizes the cartilage matrix. Most of the horses we see already have varying degrees of joint inflammation or OA, so we're fairly comfortable with owners using the oral joint health products such as Cosequin ASU along with intraarticular hyaluronic acid, corticosteroids, IRAP (interleukin-1 [IL-1] receptor antagonist protein), and ESWT (extracorporeal shock wave therapy) for injured joints. I've been using Cosequin ASU for several

months now and have been getting positive feedback from my clients, which fits in well with the study findings.

Langer: Dr. Allen, are your clients also using Adequan or Legend, or just Cosequin ASU?

Allen: Many of them have been using Legend and Adequan in various dosage regimens, but for horses that are showing only low-grade OA or that have multiple joint involvement, using a daily supplement that will do what the CSU study revealed—stabilize the cartilage matrix—is really helpful. Other products, such as corticosteroids as well as Legend and Adequan, can be used in addition to the oral supplement. Thus, there are numerous tools to treat the same difficult problem, but I have started using Cosequin ASU as the basis of my treatment approach.

McIlwraith: A number of double-blinded controlled studies in humans in Europe showed that ASU was quite effective in treating OA. In addition, there were some early papers that insinuated that ASU inhibited IL-1, which is the bad guy. Ameye and Chee did a metaanalysis of human clinical trials evaluating the effects of nutritional compounds on OA (studies on glucosamine and chondroitin sulfate were excluded), and ASU was the only ingredient for which there was good evidence of effectiveness; a couple of other products, including methylsulfonylmethane (MSM), had moderate evidence, and the rest had very limited evidence.

Davis: I think the relevancy of the changes in the joint in the CSU study, both grossly and histologically, is what we teach and promote to our clients. I don't think any of us would rely solely on a nutraceutical to treat a clinical case of a chip fracture with associated joint changes. We're always going to treat the joint properly; we now have the research to back the use of ASU as part of the overall therapeutic approach.

Stevens: I see the chip model as an extreme of possible joint damage. I feel that there's a range of joint pathology for which ASU will be effective, but once the damage reaches a certain point, lameness is inevitable. However, the CSU study is important because it has all of the definable criteria by which to judge whether a product is working. The study documented that there was less cartilage erosion in the horses receiving ASU, which was important to establish. I see ASU products as being most valuable in the earlier stages of OA, at least for my patients, and trying to prevent OA in the first place is ideal.

McIlwraith: You bring up an important point: What do you tell your clients? I'm comfortable discussing the results of this study and have no discomfort with the fact that we didn't see a reduction in lameness. The study was short term—we evaluated the horses for only 70 days—and the level of lameness was low even in the controls. Partial- and full-thickness erosions are the critical factors for OA. Many drugs can take away the pain and therefore eliminate lameness without providing any benefit to the articular cartilage (in many instances, this can lead to progression of the degradation as a result of excessive weight bearing). The point is that improvement in the cartilage parameters despite no reduction in lameness is classic for chondroprotection and would have a long-term benefit to the horse.

Langer: The results of this study have led me to change the way I educate my clients. Normally, I'd tell them that if they didn't see any benefit with a product in 30 days, they may as well stop using it. With ASU, I now tell them that they may not see a benefit in 30 days but that they should keep using it because of the chondroprotective action.

McIlwraith: That is the approach we use in surgery as well. Our goal in removing a chip from a joint is to prevent OA. I know that if I don't take the chip out of the distal radial carpal bone and the horse continues to train, it will develop severe OA; that's why we developed the model using a chip fragment off the distal radial carpal bone. Owners have become far more sophisticated over the past 10 years and better understand that therapy is focusing on the long-term goal of preventing OA.

Recommendations Regarding Products and Patients

McIlwraith: Do you use and recommend oral joint health supplements? If so, which products do you prefer?

Langer: I do currently recommend oral joint health supplements, particularly Cosequin ASU, not only in the treatment of joint problems but also as a preventative in young horses starting their training and in growing horses when they are having problems with epiphysitis and other growth-related issues. In the latter group, I use doses similar to what I would use in adults rather than using a weight-based dose, and I see quite a dramatic benefit clinically.

Davis: We use Cosequin ASU in our practice because of the positive results we continue to have with it. I think it adds to the armamentarium that we have in helping these performance horses.

Allen: Cosequin ASU is the first oral joint health supplement I've recommended on a regular basis. I have been reluctant to recommend many of the other products because of the poor or nonexistent research available.

MacNamara: Based on the research, we have started recommending the ASU product. We tend to separate our horses depending on whether the owners and trainers have short- or long-term goals. For the racehorses, especially with claiming horses and the like, we stick with the injectables. With young horses, stakes horses, dressage and event horses, and similar types in which owners are looking more at the long-term results, we tend to recommend oral supplementation as something that may be of value.

Stevens: We steer our sport horse clients toward the companies that we thought did good research, could back up their product, and we felt confident about. We've been carrying Cosequin ASU since it became available and have received excellent feedback about it from clients.

The drawback to the emerging research showing the efficacy of the oral joint supplements is what I call the "coattail companies." One company will do some good research and validate that its product does something, the research is published and referenced in the literature, and the product starts getting recommended; then, other companies will say that their products do the same (and usually for a lot less money), but the coattail companies don't validate that their products are actually equal to the original. They sidestep the issues of whether the quality of the ingredients or the quality control

Evaluation of Avocado Soybean Unsaponifiables Using the Colorado State Equine Osteoarthritis Model

This study was a blinded, experimentally controlled, randomized block design that used 16 horses in an established model of OA. On day 0 of the study, arthroscopic surgery was performed and OA was induced in the midcarpal joint of all horses. Also on day 0, horses were divided into two groups: placebo and ASU-treatment. The placebo group (n = 8) received molasses orally one time daily, whereas the ASU-treated group (n = 8) received 6 g of ASU and a similar volume of molasses orally; both treatments were continued throughout the study period. On day 14, horses began treadmill exercise, which continued for the remaining 8 weeks of the study. All horses completed the study, and no adverse events were recorded. At the termination of the study, horses treated with ASU were observed to have clinically improved total gross examination score (articular cartilage erosion + synovial membrane hemorrhage score) in their OA joints compared with placebo-treated control horses. There was also significant decrease in intimal hyperplasia in the synovial membrane, as well as a decrease in the histologic cartilage disease score. There was a trend for a decrease in lameness. Significant decrease in the cartilage disease points this product toward being a DMOAD.

Kawcak CE, Frisbie DD, McIlwraith, et al. Evaluation of avocado and soybean unsaponifiable extracts for treatment of horses with experimentally induced osteoarthritis. *Am J Vet Res* 2007;68:598-604.

in the manufacturing process is the same. There's no validation that the products contain the labeled ingredients at the levels listed. For me, this is a frustrating issue with many of the nutraceuticals and similar types of products.

There was a very recent report (www.consumerlabs.com/results/gluco.asp) that compared the labeled ingredients versus what was actually in the product. Of the five veterinary glucosamine and chondroitin sulfate products tested as of September 2007, two failed: One contained only 0.7% of the labeled quantity of chondroitin sulfate and 47.2% of the labeled glucosamine hydrochloride amount, and the other had only 2.1% of the labeled chondroitin sulfate amount. Cosequin was tested and approved. The results of this report make it even more difficult for us to give recommendations about products that aren't adequately researched. That's why I found it very helpful that the CSU study provided quantifiable responses in the treatment group.

McIlwraith: The coattail phenomenon has been a problem all along and likely contributes to why companies are reluctant to invest in research—they know their product lines will be copied. In fact, Cosequin is probably the prime victim: You see all these advertisements saying "our product works as well as Cosequin at half the cost."

Do you differentiate in terms of which horses you recommend to receive these products?

Stevens: I tend to look at how much of an athlete a patient is; I think the higher the athletic use, the more important it is to have a multifactorial approach in treating degenerative joint disease. I also allow the clients leeway in terms of economics by trying to help them prioritize what will give them the most benefit for their budget.

Allen: We don't see many young horses in my practice. Our horses are a little bit older and are engaged in some level of performance activity. Since most of my patients have some degree of lameness, I recommend ASU because the goal is not only to help the horse with its current problem but also to prevent future incidents. Many of my patients were receiving Legend and Adequan on a relatively regular basis as part of their "preventative healthcare program," but some of their owners have switched to ASU and are using less of the injectable products. There's still a rationale for using the injectables in many athletic horses, but for the younger horses, the ones with milder degenerative joint disease, and the ones that need all the help they can possibly get, I think ASU is probably very appropriate as well.

Injectable versus Oral Products

McIlwraith: How do you decide when to use an injectable agent versus an oral joint health supplement?

Davis: The first thing I consider is the severity of the joint disease or trauma and the degree of lameness. Then I look at the type of case—is it traumatic arthritis or postoperative chip repair? For the more severe cases of OA, I think the injectables are the standard. Alone, the nutraceuticals or oral supplements we've been discussing today are not going to overcome the threshold of a severely inflamed joint; in these cases, some of the other compounds, including HA and steroids, are needed, and I almost always use them in combination.

Langer: I would say the same thing. I use the oral supplements primarily as a complement to other products for long-term treatment. If the lameness being treated is relatively recent and mild, I often use Adequan or Legend; I frequently use them together initially because I find that not all horses respond to either medication quite the way I'd like. If I think an inflamed joint needs to be treated, I usually use HA along with triamcinolone for the high-motion joints first, followed by Adequan and/or Legend systemically and then Cosequin ASU.

Stevens: ***The most important thing that we can do is to establish a really precise diagnosis so that we know we are trying to treat problems as specifically as possible.***

Allen: I tend to use the oral products as a primary approach in non-lame horses with low-grade multiple-joint OA. I tend to use Legend more for synovitis cases and Adequan more for the cases I suspect are cartilage related. Because of concerns I have about flare, I tend to reserve intraarticular Adequan for the really difficult cartilage cases. I almost always mix HA with a steroid, usually betamethasone or triamcinolone for the high-motion joints and methylprednisolone for the low-motion joints, such as the hocks or sacroiliac joint. For almost all of these horses with more significant OA, I will recommend Cosequin ASU as a supplemental treatment.

I am not a big fan of the current fad of "diagnosis by joint injection" within the horse show industry. With the possible exception of the oral joint health supplements, I think all of the things we put in horses may have unforeseen effects. We need to be logical and careful about which joints we're injecting. I'm sure I use as many intraarticular injectables as anybody here, but I still think the current practice of foregoing diagnostics and just injecting every joint in a horse because it is a little bit sore is inappropriate and needs to be curtailed within the industry.

MacNamara: Most of our therapeutics are intraarticular, usually either a corticosteroid (betamethasone or triamcinolone) in conjunction with HA, even in mild cases. It has been demonstrated that betamethasone esters cause no harm and that triamcinolone acetonide is actually chondroprotective. I think that you get quicker resolution of synovitis or capsulitis with an intraarticular injection than with systemic medications. We also use Adequan intraarticularly quite a bit more than systemically; I have not been impressed with systemic Adequan. We also use Legend. We use Polyglycan (Arthrodynamic Technologies, Versailles, KY; HA and chondroitin sulfate [C4 and C6] in a 10% glucosamine solution) systemically, which is an off-label use, but we've had very good results with it.

I don't distinguish between high- and low-motion joints and won't use methylprednisolone even in a low-motion joint. I stick with either triamcinolone or betamethasone. In fact, I never really quite understood the rationale to justify using methylprednisolone in a low-motion joint. I don't use it because I don't want to see more cartilage damage or destruction in those joints any more than I do in a high-motion joint. I get good results with very, very low doses of triamcinolone in the distal metatarsal and tarsometatarsal joints and the pastern.

Stevens: My approach is similar to Dr. Allen's. The most important thing that we can do is to establish a really precise diagnosis so that we know we are trying to treat problems as specifically as possible. Then, if the patient doesn't respond, I don't have to question whether the problem was with the diagnosis or the treatment. We do inject a lot of joints, but we try to be as specific as possible to the joint(s) involved; we are fortunate that we have access to MRIs and bone scans through our referral hospitals and that our clientele is willing to go to that means. I look to the oral supplements to increase the interval between joint injections and thus use them for their additive effect.

We still use a little methylprednisolone in the hocks, but only on those horses that I know already have a moderate degree of arthritis and whose owners will not let me inject the joint every 2 to 3 months; I may also use methylprednisolone in horses that have had their hocks injected many times with a decreasing interval of response. For young horses, I use triamcinolone and HA.

MacNamara: Dr. Allen talked about the idea of intraarticular injection as a method of diagnosis. Sometimes our clients fail to realize that just because a joint doesn't respond to an intraarticular injection, it doesn't mean that there's not a problem in the joint. For example, if a horse has subchondral bone pain and the cartilage is intact, intraarticular medication will have little effect. It's like saying if you take an aspirin for a headache and it doesn't go away, you didn't have a headache.

Allen: One thing I'm sure we all use but have barely mentioned is IRAP, which has

become a valuable tool in cases that are refractory to some of the more common intraarticular approaches or in animals in which we're very hesitant to use corticosteroids. Examples of the latter include young horses or horses with known cartilage damage.

McIlwraith: At CSU, we investigated the use of IRAP in the same bone chip model used in the ASU study and had positive results. I first became intrigued because of a colleague's unpublished results with coffin joint arthroses that had failed to respond or ceased to respond to triamcinolone and HA and yet responded well to IRAP. We don't know the exact mechanism, but the overall clinical results are impressive.

To recap, if I understand what everyone is saying, you tend to use nutraceuticals for their background antiinflammatory activity in mild cases of OA and then add in specific intraarticular therapies when OA is more severe.

Use of Joint Health Supplements in Conjunction with NSAIDs

McIlwraith: What is the role of joint health supplements in horses with OA that are being treated with an NSAID? Are systemic NSAIDs (oral or intravenous) still being used routinely, for example, in a competing horse with a few knee problems?

Langer: For my clientele, I use NSAIDs as a last resort. I'll use one if the horse really needs it, but only for the short term. I hate to see NSAID therapy being administered continuously for several months. I think NSAIDs are fine in a horse that has a condition we want to treat but needs to get through one or two more competitions before having a break. Of course, in older horses with chronic OA, NSAIDs may be the only thing that will allow them to continue to compete. I prefer to use firocoxib (Equioxx, Merial) whenever possible but also use phenylbutazone and flunixin meglumine.

Davis: When NSAIDs are used, they should generally be given at the lowest possible *effective* dose for the shortest possible time. This appropriate *therapeutic* dosing will help to minimize the masking of more serious disease and the potential for gastric ulcers. Using Equioxx both to treat the horse with a NSAID and to be proactive in minimizing the risk for gastric ulcers is a good approach.

Langer: Again, proper diagnosis is important. We need to know what we're using the NSAIDs for. I recently saw a horse that had been given naproxen through the summer show season; the owner had not talked to me at all, but simply brought the horse in for evaluation about 30 days after naproxen had been discontinued at the end of the season. At this point, the animal was almost four out of five lame. It had a severe meniscal tear that was worsened by the use of the NSAID.

Allen: I had a similar experience in a show horse. The trainer had started out giving naproxen and then added ketoprofen. When the horse eventually hit the wall and couldn't go anymore, the horse was finally brought in for diagnostic work-up—it had collateral ligament desmitis of the coffin joint. It was quite distressing to think about that horse being shown and how hard the trainer was pushing it. As veterinarians, we may not be using NSAIDs very much, but, as a group, our clients are. The use of oral joint health supplements will hopefully reduce the amount of NSAIDs needed. The more we can educate our clients about the need for diagnostics, safer alternatives to multiple NSAIDs, and the use of lower doses of NSAIDs, the better off our patients will be.

McIlwraith: It sounds like there is a general reluctance for random, everyday NSAID treatments because of the associated risks. In addition to the known gastrointestinal and renal risks associated with NSAIDs, is there also the risk of not achieving a diagnosis or of allowing a condition that needs another form of treatment to go undiagnosed and untreated, thereby causing long-term damage? Meniscal tear and collateral ligament desmitis are good examples.

MacNamara: ***Sometimes our clients fail to realize that just because a joint doesn't respond to an intraarticular injection, it doesn't mean that there's not a problem in the joint.***

MacNamara: My practice is a little different. The Standardbred racehorses we see are doing very heavy work on hard tracks, and many of them race every week to 10 days. Most of these horses receive some type of NSAID at least twice a week, either before or right after training and then at some point before racing, depending on the regulations. The hope is that the oral supplements and Polyglycan will allow us to reduce our use of the NSAIDs. In my experience, racehorses that are maintained on a program of Polyglycan (5 ml IV weekly or every other week) seem to require fewer intraarticular injections. I don't have actual numbers, so this is more my impression. Trainer feedback has been very good. We certainly haven't looked at statistical differences in terms of race results or the like. In my own horses, the use of Polyglycan has reduced the number of intraarticular injections that I have to administer.

McIlwraith: ***The manufacturers have to show that their products have some published efficacy, as is the case for Cosequin ASU, which could be looked upon as the gold standard for oral products.***

Alternately, on the pleasure horse side of our practice, we have very little control over the use of NSAIDs. The owners don't report to us every time they give their horse something, and I think the use of phenylbutazone paste and tablets is much more extensive than we realize because owners will give it to a sore horse for 5 days before they call the veterinarian. I always caution my new associates that when they take a history, the first thing they should ask about, even before starting a lameness examination, is whether the horse has been given phenylbutazone and, if so, when was the last dose given. I've had too many experiences where a horse has been on phenylbutazone for 4 or 5 days before the owner calls us to do a lameness examination and then the horse doesn't look that bad.

Stevens: It also depends on what the horse does. Some of my older horses, such as the retired show horses, do get a fair amount of phenylbutazone, and I encourage that to some degree to increase rider safety; I find that a lot of these horses tend to trip and stumble, and the phenylbutazone helps alleviate that. In competition horses, I try to keep the use of phenylbutazone to a minimum.

McIlwraith: Are there any other risks associated with NSAIDs?

Allen: Many horses are receiving multiple NSAIDs, none of which was ever intended to be used in combination. When we consider how common ulcers are in show horses, it raises the question as to whether the ulcers are related to the way the horses are shown or to the use of multiple NSAIDs.

McIlwraith: One reason there is so much interest in nutraceuticals for humans with OA is the high morbidity associated with NSAIDs. They're not innocuous drugs. Even the NSAIDs that inhibit cyclooxygenase-2 (COX-2), which were meant to eliminate the side effects, are associated with ulceration.

Allen: I'm optimistic about firocoxib, and we've started using it quite a bit in our practice.

McIlwraith: In humans, COX-2 inhibitors have reduced the number of ulcers, but the ulcers that develop won't heal until the drug is stopped. Apparently, you need a certain amount of COX-2 to promote healing of ulcers. It's an ironic situation, but the literature is full of such examples. When one pathway in the inflammatory cascade is blocked, another is exacerbated. There's some good evidence that if you get the COX levels low enough with NSAIDs, IL-1 production is upregulated. I've always believed that if we can find something to stop IL-1, which is thought to be at the top of the cascade, you won't have to worry about the rest of the cascade. Dr. Frisbie's work with gene therapy with IL-1 receptor antagonists showed that if you shut down IL-1, you shut down OA. That's why I think biologic therapies that address the cascade at that level are much better than an NSAID.

There was some literature indicating that ASU had anti–IL-1 effects. Lippiello's study concluded that phytosterols account for part of ASU's biologic activity; the sterols could be exerting anti–IL-1 effects, among others. The study basically showed that if you control for sterol levels, the therapeutic effect is

the same. However, the insinuation is that ASU blocks some IL-1 activity, which then translates into decreased synthesis.

Role of ASU as a Preventative

MacNamara: Earlier, we talked about ASU decreasing the amount of cartilage degradation. Can ASU therefore be recommended as a preventative in normal joints?

McIlwraith: I think it's quite appropriate to do so in at-risk horses, for example, a horse that is having some symptoms and is involved in a tough activity. The inhibition of fibrillation and chondrone formation is a significant finding. On a related note, Bayer and Luitpold, as well as practicing veterinarians, tell me that Legend and Adequan are most commonly being used on a prophylactic basis in horses in athletic training.

Stevens: I think we need to consider using the oral joint health product as a preventative. Society is beginning to see the value in preventive medicine rather than reactive medicine once OA has already set in. I want something I can use early on to help horses have a long career, and ASU is a component of that. My patients often compete well into their late teens, so they are facing years of competitive use. We also tend to see more repetitive-type injuries than the catastrophic traumatic injuries associated with racehorses.

McIlwraith: We saw a shift toward prevention after our Legend study was published. Those results changed our thinking about how these drugs worked. The product has a very short half-life, 4 minutes. We administered three injections 8 days apart and were still seeing significant antiinflammatory effects in the joints 50 days after the last injection. People started using it prophylactically because of the long-term benefit.

Stevens: We talk about how one measures success with a given therapy. I'm always amazed about how perceptive my clients are when they ride their horses and what they can "feel" that I can't see. The horse may look the same to me after a particular therapy, but the rider will tell me that the horse is much better.

McIlwraith: What agents do you use as preventatives?

Stevens: In the more expensive horses, I use Adequan in conjunction with Legend and would certainly consider adding Cosequin ASU as an adjunct.

McIlwraith: I've always used Adequan in horses I suspect have cartilage damage, and, based on our results in the experimental model, we do the same with ASU. This approach is rational because the low-grade joint damage from high-powered levels of activity is significant, and anything that can mitigate against cartilage damage is good.

In terms of using Adequan versus Legend, it's not necessarily an either–or choice. In a horse that's sound without any known low-grade cartilage damage and owners who want to prevent future damage, I'd lean toward Legend. If I have any reason to suspect cartilage damage (e.g., a horse that has undergone arthroscopy, been diagnosed with cartilage damage, and treated with IRAP without a good response), I would lean toward Adequan.

Stevens: If I can only use one, I will usually use Legend, but I encourage my clients to use both if they can.

MacNamara: When do you initiate the use of preventatives in an asymptomatic horse? I think you can justify administering one of the oral products beginning at a very early stage and then incorporating the injectables when the horse enters race training.

McIlwraith: Furthermore, many of these young horses are receiving expensive supplements. The oral joint health supplements could be a far better use of the money than simply having a horse on a vitamin or rare earth minerals supplement.

Davis: ***When NSAIDs are used, they should generally be given at the lowest possible effective dose for the shortest possible time.***

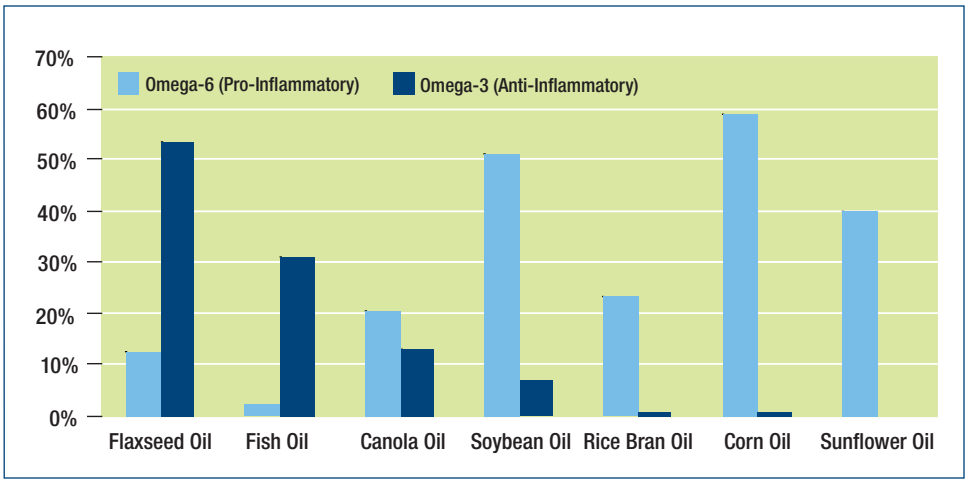


figure 1. Percentage of Omega-6 and Omega-3 Fatty Acids in Various Oil Sources

Langer: If owners and farm managers are willing to give oral supplements, you may be able to improve the horses' feeding program. Many of the horse farms have outdated feeding programs, and simply improving the overall nutrition can have a very dramatic effect. Much has been documented on the role of nutrition in growth and development. When nutrition is not optimal, both joint and physeal changes occur, leading to many of the growth-related problems we see. These inflamed areas have a cartilage component that can benefit from supplementation.

McIlwraith: The supplement market could be huge, but the manufacturers have to show that their products have some published efficacy, as is the case for Cosequin ASU, which could be looked upon as the gold standard for oral products.

Langer: Some companies are starting to include chondroitin sulfate and glucosamine in senior feeds, but questions about

Table 1. Omega-3 Fatty Acid (FA) Content and Omega 6:3 Ratios

Oil Source	% Oil in the Seed	% Omega-3 FA in the Oil*	Omega 6:3 Ratio†
+Flaxseed (linseed)	36.0%	53.3%	1:4
+Menhaden (fish oil)	100%	31.0%‡	1:15
+Canola (rapeseed)	28.0%	12.9%	2:1
+Soybean	18.0%	7.0%	7:1
–Rice bran	20.0%	0.8%	29:1
–Corn (maize)	3.6%	0.7%	84:1
–Sunflower	19.0%	0.2%	199:1

+Recommended.
–Not recommended.
*FA composition as listed by the Nutrition Research Council.
†Rounded to nearest whole number.
‡Total omega-3 containing C20s (EPA and DHA). Other oils listed do not contain EPA or DHA.

the quality of the agents used and whether they are truly effective remain.

Other Supplements

McIlwraith: Do you recommend other supplements, such as omega-3 fatty acids, cetyl myristoleate, MSM, and oral HA?

Langer: I have a master's degree in nutrition, so I frequently look at my patients' feeding programs, particularly in young horses but also in performance horses. I focus on educating people about the omega-3 fatty acids and steer them away from products that have high levels of omega-6 fatty acids, particularly sunflower oil, which is extremely high in omega-6. My goal is to improve the omega fatty acid ratios. Figure 1 and Table 1 provide additional information on the fatty acid content of various products.

Flaxseed is a good source of omega-3 fatty acids. In my practice, mares with foals at their sides and young growing horses are getting ground flaxseed every day as part of their diet.

Allen: Does it have to be ground?

Langer: Yes, horses don't digest it very well. Also, if the flaxseed is not human grade, it starts to mold almost immediately when it's ground. Thus, if you're using feed-grade flaxseed, you almost have to grind it and feed it at the same time.

I don't look at omega-3 fatty acids as a primary treatment but rather as another means to help prevent other problems, even muscle-related problems, in these training horses. When I use an oral agent, it's Cosequin ASU. I do not typically dispense MSM by itself, and I have not recommended oral HA.

Davis: Does anybody here use oral HA?

Langer: I have clients that swear by it and really like it, but I still can't recommend it with confidence.

Stevens: I can't recommend it yet.

McIlwraith: The anecdotal feedback suggests that oral HA is of benefit, particularly in helping older horses get around. It's intriguing. Its use presents an interesting shift in how we think things work. What is left once the product goes through the gastrointestinal tract? A study was published out of Rood and Riddle last year investigating oral HA after hock OCD surgery, and the results were quite impressive.

MacNamara: We frequently use MSM, but for respiratory problems, not arthritis. It seems to have some antiinflammatory properties, at least in respiratory disease.

Langer: I have never been happy with the clinical results when I've prescribed MSM.

McIlwraith: That's interesting, because there was a good double-blinded study published recently that showed positive results in humans with OA. How many use omega-3 fatty acid supplements?

Stevens: I've recommended them.

Allen: I'll use them on horses with dermatitis or poor coats. I also use them in immune-challenged cases, such as horses being shipped in from the southern hemisphere.

Langer: We use omega-3 fatty acid supplements for breeding issues, such as improving stallion semen quality and mare reproductive performance. We also use these supplements in growing and training horses, although it is difficult to tell how dramatic of a benefit we are receiving.

McIlwraith: Do any of you use cetyl myristoleate or Myristol (Tryan Enterprises, Dennis, TX)? It's becoming popular in the cutting horse community in Texas, but it fell into the "limited evidence" category in the metaanalysis by Ameye and Chee. This is a good example of how people have conceptions and then the research disproves them. The same thing happened with chondroitin sulfate: Everybody said you couldn't absorb it, but the evidence is very strong that a low-molecular-weight chondroitin sulfate is a critical factor when it comes to absorption.

***Allen:** The use of oral joint health supplements will hopefully reduce the amount of NSAIDs needed.*

I find it interesting that nobody here has used any oral supplement other than Cosequin.

Quality Issues

MacNamara: I'm sure we're going to start seeing knock-off ASU products or ads for "generic Cosequin," and our clients are going to be asking why they can't use a cheaper product that has the same ingredient list. It will be very hard to advise them as far as dosage and bioavailability on those products.

McIlwraith: Remember, we didn't investigate the Nutramax product; our research used the Vétoquinol product. The ratio of ingredients differs, but the study by Lippiello showed that the ratio wasn't as important as the sterol content. The importance of our study is that it looked at these ingredients in vivo.

Allen: The question is, how do you educate your clients? I've used the Internet to research some of the products my clients use; I can then compare those products with Cosequin ASU and discuss the differences.

Safety of Cosequin® ASU in Horses

A randomized, blinded, placebo-controlled study was conducted to assess the safety of Cosequin® ASU in horses. Each 16.1 g (recommended maintenance level) of Cosequin ASU is formulated to contain 1.05 g NMX1000® avocado/soybean unsaponifiables, 7.2 g FCHG49® glucosamine hydrochloride, 1.2 g TRH122® chondroitin sulfate, 5 g methylsulfonylmethane (MSM), and 50 mg manganese. Twenty horses were divided into five groups: placebo, 1× (16.1 g of Cosequin ASU added to feed), 3× (48.3 g of Cosequin ASU), and two 5× groups (80.5 g of Cosequin ASU). Horses received placebo or product once daily for 84 days. Hematology and serum chemistry were analyzed on days –7, 0, 7, 28, 49, 70, and 84. Body weight was measured on days 0, 14, 28, 42, 56, 70, and 84; and a complete physical examination was conducted on days –7, 0, 7, 28, 56, and 84. Safety of Cosequin ASU was demonstrated as no statistically significant changes were noted in either hematology or serum chemistry values over the course of the study or between the groups. No statistically significant changes were noted in body weight. There were no adverse events or abnormal physical findings associated with administration of Cosequin ASU.

Kettenacker RW, Griffin D. Safety profile evaluation of an equine joint health supplement containing avocado/soybean unsaponifiables (ASU), glucosamine, chondroitin sulfate, and methylsulfonylmethane (MSM). 2007 American Academy of Veterinary Pharmacology & Therapeutics 15th Biennial Symposium; poster presentation.

Stevens: With just a list of ingredients, you don't know if those agents are actually in the product or at what level.

McIlwraith: Research by Oke showed that 78% of equine glucosamine products didn't meet their label claims; 39% had levels below the labeled claim (some even had none of a listed ingredient) and the others had levels significantly higher than indicated. Until the manufacturers have to prove efficacy, there are always going to be problems, but having the products match their labels would be a good start.

When we're discussing these products with clients, we need to remember that the word *generic* is never appropriate in these situations. *Generic* refers to a licensed drug with exactly the same formulation and efficacy as the branded version, so the term doesn't apply here. We should make sure clients understand that. As a profession, the more we support knock-offs and so-called generics, the less incentive there is for the manufacturers to seek a drug license.

Allen: If cost is the major factor driving our clients to the Cosequin competitors, maybe we should try to make Cosequin ASU more affordable. In my practice, we created an online pharmacy. When clients start using Cosequin, we discuss the online savings with them in person when they pick up their first bottle at the clinic. They can then get their refills at a tremendous savings via the online pharmacy. We can offer competitive pricing and still keep its use within our sphere of influence.

Stevens: I believe many of our clients perceive value in oral joint supplement products by comparing the list of ingredients versus the cost. From the summary of the scientific research presented here today, I feel we can state that this is not an accurate way to determine value. It will be important for the veterinary profession to inform our clients about the scientific research that determines what truly are effective oral joint supplements. If our clients understand the value of quality—in terms of *proven* ingredients and a *quality* manufacturing process—they will be willing to pay more for the products that are backed by research.

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