Musculoskeletal Disease in Aged Horses and Its Management

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KEYWORDS

• Osteoarthritis • Laminitis • Geriatric horse • Pain management
• Degenerative joint disease

KEY POINTS

- Musculoskeletal disease is the most prevalent health and welfare issue in aged horses with osteoarthritis (OA) and chronic laminitis being the most common single disorders.
- The prevalence of OA is greater than 50% in horses older than 15 years and up to 80% to 90% in horses over 30.
- Management of OA in the elderly horse is multifocal and focuses, apart from pain management, also on optimizing the exercise regimen and improving living conditions.
- Laminitis in the geriatric horse is related to pituitary pars intermedia dysfunction (PPID) in many cases.
- Laminitis in geriatric horses is managed as in the general horse population, with additional benefit from pergolide administration in PPID cases.

INTRODUCTION

It is a well-known fact that musculoskeletal disease is the principal cause of wastage in the equine industry. More than 30 years ago, this was demonstrated in epidemiologic research in Thoroughbred racing.[1,2] More recently, Bertuglia and co-workers,[3] in a cohort of 356 Standardbreds, reported an overall exercise-related musculoskeletal injury rate of 4.79 per 100 horse-months, a figure substantially higher than the injury rate of 1.8 per 100 horse-months found in a prospective study in Thoroughbreds in training, although these injuries concerned joint-related injuries only.[4] Musculoskeletal disease-related wastage is not only in the racing breeds. In a study on 126 elite show jumpers, 55% and 22% of days lost to training for medical reasons were owing to non-acute and acute orthopedic injuries respectively.[5] Combined, this figure is similar to

The authors have nothing to disclose.

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Vet Clin Equine 32 (2016) 229–247
http://dx.doi.org/10.1016/j.cveq.2016.04.003 **vetequine.theclinics.com**
0749-0739/16/$ – see front matter

the 72.1% of days lost in a study on racehorses in South Africa.[2] Even in young horses subjected to a standard riding horse quality test, moderate or severe orthopedic clinical findings were reported in 24% of cases, against only 6% moderate or severe clinical medical findings.[6] Of the musculoskeletal tissues (muscle, bone, joints, tendons/ligaments) the latter two are by far of greatest clinical relevance in most disciplines, mainly because of their poor healing capacity and the consequent tendency to develop chronic disorders.

In the aging human population, musculoskeletal disorders have a huge influence on quality of life and rank first as cause of years lived with disability.[7] Given the high prevalence of musculoskeletal disease in nongeriatric horses, as outlined, it is not surprising that this is the case for the elderly horse as well. In a study of 69 horses aged 30 years and older, a staggering 77% was found to be lame at clinical examination with virtually all (97%) having a reduced range of motion in at least 1 joint.[8] When reducing the age above which a horse was deemed to be geriatric to 15 years, these figures were still 51% and 84% in a population of 200 animals.[9] In this group, owners reported lameness only in 23% of cases (and reported hoof abnormalities in 27% against 80% diagnosed by the veterinarian).[10] Hence, owner perception of musculoskeletal problems in aging horses is significantly less than expert diagnosis, which is of great importance from both the veterinary and welfare perspectives. In line with these figures on the prevalence of musculoskeletal disease in the elderly horse, lameness was found to be the principal reason for euthanasia of geriatric horses (24%), just before colic (21%).[11]

The vast majority of lameness cases in geriatric horses are owing to chronic degenerative joint disease or osteoarthritis (OA), as evidenced by the high prevalence of reduced range of motion in 1 or more joints. This is similar to the human situation. Another frequent cause of disablement in the elderly horse that does not have a homologue in human medicine is (chronic) laminitis. Therefore, this review focuses on the clinical aspects and related care and management of chronic joint disorders (OA), and on how to deal with laminitis in the elderly horse. Because pain management is an important common aspect of both conditions, it is an area of focus in this review.

CHRONIC JOINT DISEASE OR OSTEOARTHRITIS IN THE GERIATRIC HORSE

Definition, Pathogenesis, and Clinical Signs

Equine OA has been defined as a group of disorders characterized by a common end stage, namely, progressive deterioration of the articular cartilage accompanied by changes in the bone and soft tissues of the joint.[12] The basic pathogenic mechanism of OA is a disturbance of the joint homeostasis leading to an imbalance of the anabolic and catabolic processes in the joint. Whereas damage to the articular cartilage is among the hallmarks of OA and is generally seen as emblematic for the disease, it is not the only tissue that is affected. In OA, the subchondral bone is also affected and changes in the subchondral bone have even been suggested to be primary events rather than secondary ones.[13] The synovial membrane is also involved and the composition of the synovial fluid will be altered to a certain extent, reflecting the current concept of seeing the joint as a complex multicomposite organ, rather than as a structure consisting of a variety of separately reacting tissue types.[14]

There are various etiologic factors involved in OA, including synovitis, single events producing major joint trauma, and repeated microtrauma as a result of repeated overloading. In the horse, the last 2 pathways are probably most important with use-related wear and tear being highly prevalent. In a post mortem study using

50 metacarpophalangeal joints from racehorses one-third of all 2- and 3-year-old horses had partial- or full-thickness cartilage lesions and signs of OA; the severity of OA increased until age 6.[15] Once OA has commenced, it tends to advance slowly but inexorably in severity and to spread over the joint. In the horse, this process has been investigated in the metacarpophalangeal joint by determining the so-called Cartilage Degeneration Index, a technique based on the fact that Indian ink particles will be retained by damaged, but not by intact, cartilage (**Fig. 1**).[16,17] Independent of the cause of OA, the end stage is common and it is often end stage disease that is encountered in geriatric horses (**Fig. 2**).

OA is an insidious disease par excellence. Articular cartilage is aneural and the damage may have become substantial before pain to some degree is perceived through triggering of nerve endings in the subchondral bone, the very richly innervated periosteum at the joint margins, or the synovial membrane. Nevertheless, articular homeostasis will already be disturbed before this stage as a sequel to the catabolic processes that are ongoing in the cartilage layer, which will result in low-grade inflammation that may become clinically apparent as joint effusion. A typical characteristic of the clinical features of OA is its intermittent character. Horses may be lameness free for a long period and then, mostly because of inadvertent overloading, suddenly become symptomatic with joint effusion and lameness. These signs tend to wear off over time, but, if no treatment is installed, this may take a long time. A more consistent clinical feature is the often a substantial decrease in joint range of motion, which is a very frequent finding in the older horse, as noted.[8] This is caused by stiffening of the periarticular structures and joint capsule and by the osteophytes that frequently form at the joint margins. These are structural changes that do not wear off with time, but tend to become more severe with advancing age. Whereas the diagnosis of OA in the geriatric horse will in general not present problems, because it often represents end-stage disease, the sustainable management of the condition is a greater challenge.

Pain in Osteoarthritis

Pain is the major symptom of OA in humans.[18] It has been described as "the most prominent, but least well-studied feature of OA."[19] Basic knowledge of the physiologic

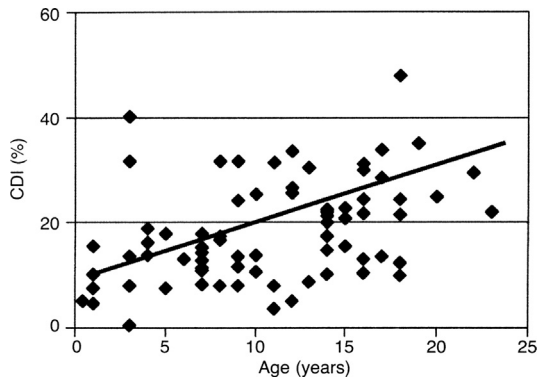

Fig. 1. Correlation between the cartilage degeneration index (CDI; %) of the proximal articular cartilage surface of the first phalanx and age of the horses (years; $r = 0.41$; $P<.001$). Regression line indicated. (*From* Brommer H, van Weeren PR, Brama PA, et al. Quantification and age-related distribution of articular cartilage degeneration in the equine fetlock joint. Equine Vet J 2003;35(7):699; with permission.)

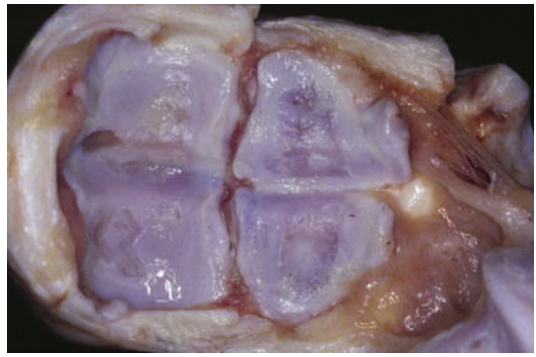

Fig. 2. End-stage osteoarthritis in a metacarpophalangeal joint, characterized by severe cartilage erosion. The synovial membrane is inflamed.

and pathophysiologic aspects of joint pain is necessary for a rational treatment of clinical OA.

Joint pain

There are 2 general types of pain stimuli in synovial joints: mechanical stimuli, originating from mechanical changes in the environment of the joint (eg, through direct trauma), and chemical stimuli caused by inflammation. In case of chronic OA, both mechanical alterations and inflammation are present, but most of the pain is generated by the recurrent and intermittent inflammation that is triggered by the interaction of tissue damage and mechanical loading. These stimuli are detected and forwarded by different mechanoreceptors and nociceptors and the signal is then forwarded by Aδ or C-nerve fibers in peripheral nerves to the dorsal horn of the spinal cord. In the dorsal horn, neuromodulators and neurotransmitters are located within synapses between primary and secondary neurons. These secondary neurons run via the spinal cord to the brain where the signal is modulated and perceived.[20]

Nociception in the joint

Articular cartilage is aneural, but all other constituting elements of the joint are innervated and some of them very richly. In joints, 4 types of afferent receptors can be discerned.[21] The type 1 receptors are low-threshold mechanoreceptors that are connected to medium-sized myelinated nerve fibers and principally have a proprioceptive function. They are located in the joint capsule, but not in the synovial membrane. Type 2 receptors are large encapsulated end organs connected to myelinated nerve fibers that function as low-threshold mechanoreceptors and are typically found at the junction of the fibrous joint capsule and the subsynovial adipose tissue. They are activated only when the joint is in motion and act as dynamic proprioceptive sensors. Type 3 receptors are relatively large, thinly encapsulated end organs that are located close to the bony insertions of intraarticular and periarticular ligaments. Their threshold is high and they are only activated when joint motion reaches its physiologic limits. They are both mechanoreceptive and nociceptive, are connected to very rapidly conducing myelinated fibers, and act as safety mechanisms. Receptors of type 4 receptors consist of free nerve endings of afferent nonmyelinated C-fibers or small myelinated Aδ fibers. They are widely distributed over the entire joint capsule including the synovial membrane. They are also abundant in the periosteum directly adjacent to the joint margins. These receptors have a high threshold and respond to thermal, chemical, and mechanical stimuli. Chemical stimuli provoked

by inflammation may increase their responsiveness to mechanical stimuli and thus lead to sensitization of the joint, thereby causing hyperalgesia and/or allodynia.

Sources of joint pain in osteoarthritis

In OA, there are numerous interacting processes that can contribute to the perception of joint pain and it is rare that a single, precise tissue origin of pain can be identified in the individual patient (**Fig. 3**). Depending on individual disease stage, the fluctuating degree of inflammation and activity of the patient, the richly innervated subchondral bone, marginal periosteum, synovial membrane and joint capsule will all, to a variable extent, contribute to pain and loss of function in OA. In human medicine, it is generally accepted that there is no straightforward relationship between tissue damage and pain level.[18] In human OA patients, alterations of central nervous system pathways associated with chronic pain (central sensitization) have been identified. This phenomenon may, to a certain extent, explain the difficulties encountered in long-term management of OA pain.[22] It is not known whether this plays a role in the horse as well. Synovitis is an important factor in OA because it contributes to pain through joint effusion, swelling, and/or fibrosis, leading to activation of mechanoreceptors in the joint capsule and direct chemical stimulation of nociceptors.

Management of Chronic Joint Disease in the Geriatric Horse

There is no therapy that succeeds in the regeneration of hyaline cartilage once substantial damage to the articular cartilage layer has occurred and the famous statement from William Hunter (1743) that "ulcerated cartilage when destroyed is never recovered" (**Fig. 4**)[23] still stands, despite great efforts in biomedical research (**Box 1**). This applies to young and middle-aged individuals, but obviously more so

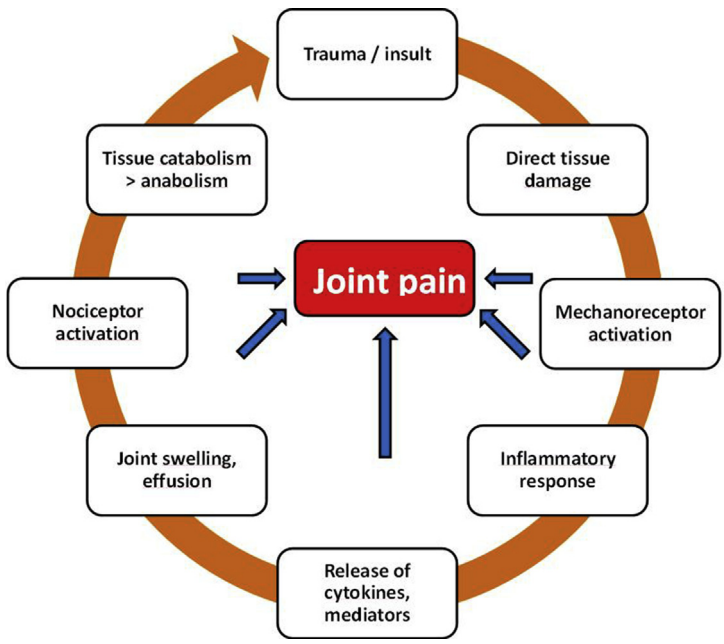

Fig. 3. Simplified scheme representing processes that may lead to joint pain in the vicious cycle of events occurring in osteoarthritis. (*From* van Weeren PR, de Grauw JC. Pain in osteoarthritis. Vet Clin North Am Equine Pract 2010;26:624; with permission.)

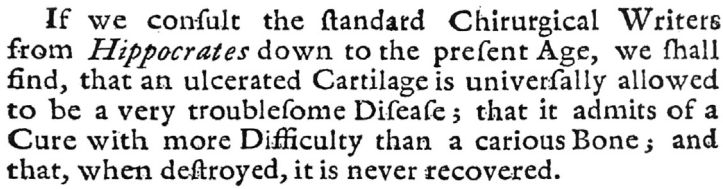
If we conſult the ſtandard Chirurgical Writers from *Hippocrates* down to the preſent Age, we ſhall find, that an ulcerated Cartilage is univerſally allowed to be a very troubleſome Diſeaſe; that it admits of a Cure with more Difficulty than a carious Bone; and that, when deſtroyed, it is never recovered.

Fig. 4. Facsimile reproduction of the original text by William Hunter as published in the *Philosophic Transactions of the Royal Society of London* in 1743.

to geriatric patients in whom the disease is more advanced. The aim of treatment is, however, different in the latter category. In the performance horse, therapeutic efforts will focus on bringing the animal back in competition as soon as possible and doping issues may be relevant. In geriatric horses, the aim is to reach a sustainable and preferably steady condition in which the horse is as comfortable as possible and doping is not an issue. These factors will influence the choice of treatment. Treatment may consist of local treatment of the affected joint(s), pain management, and supportive treatments such as farriery, physiotherapy, and exercise management, and is often a combination of these. Another important aspect of the management of chronic joint disease is the exercise regimen that is applied.

Local treatment of osteoarthritis in the elderly horse

The choice of possible intraarticular treatments of OA has increased considerably over the past decade with the advent of biologic therapies consisting of either (stem) cells or cellular products, such as platelet-rich plasma and autologous conditioned serum. For recent overviews, see Frisbie 2016.[24,25] There is some preliminary and/or anecdotal evidence that some of these treatments may be beneficial and, although any data are lacking, there is no known reason why they could in principle not be applied to geriatric horses. However, these therapies are meant to be disease modifying in active performance horses rather than palliative, and are expensive. This makes them certainly not first-choice treatments in geriatric horses with end-stage disease and they will not be considered further in this text, limiting intraarticular treatment options to corticosteroids and some other drugs such as hyaluronan and polysulfated glycosaminoglycans (PSGAGs).

The principal use of corticosteroids in OA is the rapid treatment of the intermittently occurring flares. Untreated, the effects of flares may linger on for a prolonged period,

Box 1
Principles of management of chronic joint disease in the geriatric horse

- Treat every flare-up directly (in severe cases, short- or medium-acting corticosteroids; pain management through systemic nonsteroidal antiinflammatory drugs).
- Reduce weight, if obese.
- Optimize housing conditions, and soft surfaces.
- Consider specific orthopedic shoeing.
- Improve or maintain joint stability and balance as much as possible through controlled exercise.

because the inflammation will only fade slowly. This prolonged inflammation leads to long periods of disturbed joint homeostasis and hence to further deterioration of the already affected articular tissues, rendering them more vulnerable for a next event. Immediate treatment with a potent antiinflammatory drug such as a corticosteroid in case of severe flares will not only lead to the animal becoming more comfortable, but also limit the aggravation of the existing damage. Several corticosteroids are available for clinical use (**Table 1**). Of these, the use of methylprednisolone acetate is currently discouraged because of deleterious side effects, whereas no such effects have been reported for betamethasone or triamcinolone acetonide, which have even been shown to be chondroprotective.[26] The chance of development of laminitis, which traditionally has been associated with the use of intraarticular corticosteroids and certainly would be a concern in the elderly horse, has been shown to be very limited. A study from the 1980s showed no laminitis in 1200 horses treated with triamcinolone acetonide at a maximal dose of 18 mg[27] and in a more recent study only 3 cases were seen in 2000 horses, many of which were treated with higher doses.[28] Therefore, there is no basis for discouraging the judicious use of intraarticular corticosteroids in case of serious flares of OA.

Hyaluronan (hyaluronic acid [HA]) and PSGAG are widely used in the treatment of equine OA. In a recent survey among 831 equine practitioners more than 50% used regular injections of HA to treat chronic cases of OA, also if there were radiographic changes, that is, in advanced stages of the disease.[29] PGAGs were also frequently used (in almost 60% of chronic cases and in just <50% of cases with radiographic evidence), but here the intramuscular application was generally chosen, not the intraarticular route. Both drugs claim to be both symptom-modifying (ie, palliative) and disease modifying (ie, to a certain extent curative), for which claims there is better evidence for PSGAGs than for HA.[30,31] Although not much can be expected from any disease-modifying action in advanced OA in geriatric horses, there are also no contraindications to use these products in this population, apart from increased costs.

Systemic treatment of osteoarthritis in the elderly horse

Pain is the most important clinical feature of OA with the greatest impact on both welfare and performance. The recurrent lameness episodes that are emblematic for OA in the horse are manifestations of pain. There are 2 important issues that should be considered and that are of greater concern in pain management in geriatric horses

Table 1
Overview of the most commonly used corticosteroids for intraarticular use in the horse

Name of the Drug	Duration of Action	Dosage (mg)	Remarks
Methylprednisolone acetate	Long	40–100	The lower end of the dosage range is recommended for an optimal effect while avoiding damage at a longer term
Betamethasone acetate	Medium to long	3–18	—
Triamcinolone acetonide	Medium	6–18	Most commonly used

From van Weeren PR, de Grauw JC. Pain in osteoarthritis. Vet Clin North Am Equine Pract 2010;26:630; with permission.

with end-stage OA than in younger animals featuring less joint damage. First, pain treatment is palliative and does not treat the underlying disease process (but still may have its influence on that process). Second, prolonged and often even life-long treatment may be necessary, making possible side effects as well as cost aspects very relevant.

Nonsteroidal antiinflammatory drugs (NSAIDs) form by far the most important category of drugs used for the treatment of musculoskeletal pain. These drugs inhibit the enzyme cyclooxygenase (COX) in the arachidonic acid cascade, thus affecting prostaglandin production. Of the isoenzymes COX-1 and COX-2, COX-1 exerts physiologic functions such as the protection of mucosal barriers in the gastrointestinal tract and the latter is more inflammation related. For this reason, selective COX-2 inhibitors have been developed as opposed to the older generation of general COX inhibitors. Selective COX-2 inhibitors have also become available for the treatment of OA in the horse, but older generation nonselective NSAIDs are still widely used, with phenylbutazone (PBZ) as most prominent example (**Table 2**).

PBZ, or "bute," has been used in horses for more than 50 years and is still the most widely used drug in equine orthopedic practice, in which it is seen as the most cost-effective treatment for OA pain.[32] In human medicine, the drug is no longer approved in many countries because of its association with a (slightly) increased risk of aplastic anemia.[33] For the same reason, the drug has been withheld registration for equine use in some countries. PBZ is typically used orally in a dose of 2.2 mg/kg twice a day (BID) or tapered to once a day (QD) after an initial loading dose of 4.4 mg/kg BID over 2 days. The drug is generally seen as very effective in musculoskeletal pain by equine practitioners. Recent in vivo research has shown that at joint level the drug does not limit inflammation-induced cartilage catabolism and may reduce collagen anabolism

Table 2
Overview of the most commonly used NSAIDs with their route of administration and dosage

Name of the Drug	Application	Dosage	Remarks
Phenylbutazone	Oral	2.2 mg/kg BID (initial loading dose often 4.4 mg/kg for 2 d and in case of long-term use standard dose tapered to QD)	Use in some countries not authorized because of perceived human health risk
Flunixin	Oral/IV	1.1 mg/kg QD	—
Carprofen	IV/oral	0.7 mg/kg (IV) QD 1.4 mg/kg (oral) QD	—
Ketoprofen	IV/IM	2.2 mg/kg QD	In oral form not bioavailable
Vedaprofen	Oral	Initial dose 2 mg/kg BID, maintenance 1 mg/kg BID	—
Meloxicam	Oral	0.6 mg/kg QD	Only NSAID with shown positive effect on cartilage metabolism in vivo
Naproxen	Oral/IV	10 mg/kg BID or QD	—

Abbreviations: BID, twice a day; IM, intramuscular; IV, intravenous; NSADI, nonsteroidal antiinflammatory drug; QD, once a day.

From van Weeren PR, de Grauw JC. Pain in osteoarthritis. Vet Clin North Am Equine Pract 2010;26:627; with permission.

transiently as evidenced by Synovial fluid markers.[34] PBZ has a relatively narrow safety margin and may have severe toxic side effects when recommended dosages are exceeded, during prolonged treatment, and/or in susceptible animals (such as geriatric horses, ponies, foals, and animals with vascular, renal, or hepatic compromise[35]). The potentially lethal adverse effects include gastrointestinal ulceration, renal papillary necrosis, and thrombosis.

Flunixin is used most widely for the treatment of abdominal pain. It is, however, also effective for the alleviation of lameness[36] and was shown to be equally efficacious to PBZ in horses with navicular disease.[37] There are no in vivo data on possible effects of the drug on joint homeostasis. Flunixin is generally administered at a dose of 1.1 mg/kg QD orally or intravenously (IV). Toxicity is low; adverse effects became only apparent at 5 times the recommended daily dose.[38]

Carprofen is a relatively potent analgesic in horses that is administered at 0.7 mg/kg IV or orally at a dose of 1.4 mg/kg. Several in vitro studies have suggested positive effects on joint homeostasis,[39,40] but no in vivo data exist for horses. Carprofen has a relatively narrow therapeutic index; adverse effects may develop at twice the recommended dose.[41]

Ketoprofen has been shown to accumulate in inflamed tissues, but was found to be inferior to PBZ in treating acute joint inflammation in a synovitis model.[42] The recommended dose of is 2.2 mg/kg IV QD. It is a safe drug, but has as its main disadvantage that it is not orally bioavailable, precluding routine use in chronic joint disease.

Vedaprofen has been registered for oral use (initial dose 2 mg/kg BID, maintenance 1 mg/kg BID) in several countries. Vedaprofen seems to have more affinity for COX-1 than COX-2.[43] Nothing is known about its effects on the primary process of OA. The clinical impression exists that the analgesic efficacy of vedaprofen for orthopedic pain compares unfavorably with PBZ, which may explain the fact that in countries where the use of PBZ is either illegal or restricted meloxicam rather than vedaprofen is the preferred oral NSAID for orthopedic diseases.

Meloxicam (orally dosed at 0.6 mg/kg QD) is a potent antiinflammatory and analgesic drug. Meloxicam was also the most selective COX-2 inhibitor of 4 examined NSAIDs (with PBZ, flunixin, and carprofen).[44] Meloxicam is the only NSAID for which evidence exists for favorable in vivo effects on cartilage metabolism. In a lipopolysaccharide-induced arthritis, model meloxicam was able to mitigate the catabolic effects of acute joint inflammation on articular cartilage.[45] However, it remains to be seen whether this is also true for chondroprotection in the longer term.

Naproxen is rarely used for the alleviation of equine musculoskeletal pain, but was proven more potent than PBZ in an equine myositis model[46] and has a wide safety margin. It is administered orally or IV at a dose of 10 mg/kg BID or QD.

Some other systemically administered OA drugs, such as IV applied HA and intramuscular PSGAGs (see above) also provide analgesia to some extent, but this is secondary to their influence on the primary disease process. They are not generally used for their analgesic effect in OA and there is no *rationale* for their use to this end in geriatric horses suffering from end-stage disease.

New developments in pain control of chronic joint disease

Pain medication in chronic joint disease often has to be administered over prolonged periods. Many, if not all, of the NSAIDs may produce severe side effects if used in this way. This is a big problem in human medicine and, together with the fact that OA is

mostly restricted to a limited number of joints, it has prompted the quest for local delivery systems that permit the controlled release of medication in the joint cavity. The obvious advantage is that much lower doses are necessary than in case of systemic application, thus avoiding undesired side effects. Some of these systems have been tested in the horse with promising preliminary results. Larsen and colleagues[47] reported the injection into equine carpal joints of 2 mL in situ forming depot composed of polyethylene glycol and the NSAID celecoxib loaded at 290 mg celecoxib per gram of solution. They reported low concentrations (less than the detection level of approximately 1 ng/mL) of celecoxib in serum samples for 10 days after intraarticular administration, but did not report synovial fluid concentrations. In another study the intraarticular tolerability and suitability for local and sustained release of an in situ forming polymer-based gel, loaded with 2 dosages of celecoxib, 50 mg/g ('low celecoxib gel') and 260 mg/g ('high celecoxib gel') was investigated in horse joints.[48] In the synovial fluid, concentrations of celecoxib were detected until 4 weeks after administration (**Fig. 5**). Celecoxib was also detected in plasma, but peaked at very low concentrations (150 ng/mL) and was detectable until day 3 after administration, after which its concentration was less than the detection limit. Controlled intraarticular release using either gel or nanoparticle technology seems promising therefore, especially for use in geriatric horses in which liver function may be compromised and where doping issues normally are not relevant.

Nutraceuticals

Feed additives or nutraceuticals are used at a very large scale worldwide and many of them claim to be beneficial for (chronic) joint disease. Many of these supplements contain glucosamine and/or chondroitin sulfate, both natural components of articular cartilage, with or without addition of a large variety of other compounds. For a recent overview see McIlwraith (2016).[49] The evidence for in vivo efficacy remains very thin,

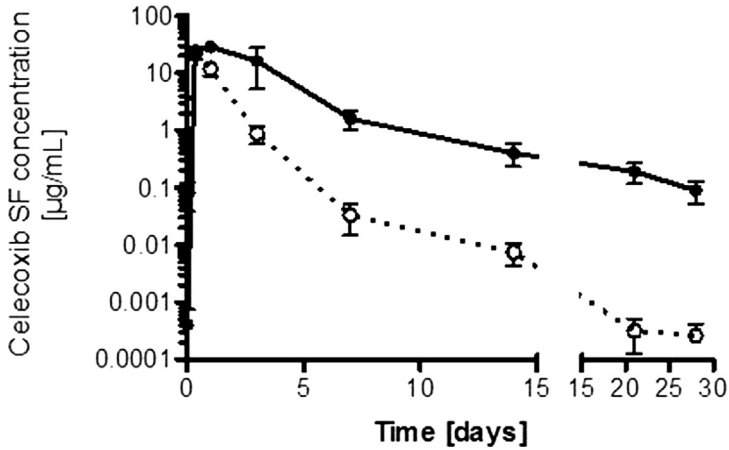

Fig. 5. Celecoxib concentrations in synovial fluid after intraarticular administration in the talocrural joint of a polymer-based gel, loaded with 2 dosages of celecoxib (CLB), 50 mg/g ('low CLB gel', *open circles*) and 260 mg/g ('high CLB gel', *closed circles*). The high dose retained a concentration of greater than 100 ng/mL for more than 4 weeks. In serum the concentration had fallen to less than 50 ng/mL within 3 days and became undetectable shortly after (data not shown). (*From* Petit A, Redout EM, van de Lest CH, et al. Sustained intraarticular release of celecoxib from in situ forming gels made of acetyl-capped PCLA-PEG-PCLA triblock copolymers in horses. Biomaterials 2015;53:434; with permission.)

but a number of studies have shown a (limited) beneficial effect of some products. In a study on the effect of supplementation with extract from green-lipped mussels (*Perna canaliculus*) in 26 horses with primary fetlock lameness, subjective lameness parameters improved in treated horses versus placebo-treated animals.[50] In a study on the effects of avocado and soybean unsaponified extracts in experimentally induced joint disease, no clinical effect on lameness was seen, but the histologic appearance of the treated joints was better.[51] In the only study focusing specifically on geriatric horses (age 29 $\pm$ 4 years) in which kinematic outcome criteria were used to test the effect of a compound containing glucosamine, chondroitin sulfate and methyl sulfonyl methane, no effect on gait parameters was found and the claim that the product would improve stiff gait in elderly horses could hence not be substantiated.[52] Whereas joint supplements will not do harm and some of them may have a certain benefit; their cost-effectiveness ratio can be questioned.

Surgical Treatment

Various surgical interventions have been described for the treatment of heavily osteoarthritic joints that are beyond the stage that any intrinsic repair can still be expected and for which palliative treatment is insufficient to create an acceptable state of comfort for the animal. It can be questioned to what extent application of these mostly very invasive procedures in geriatric patients is ethically acceptable. Further, the application of major surgery to patients that have a reduced life expectancy will likely to be economically viable for only very valuable animals. For these reasons, surgical options are not discussed further in this context.

Supportive Treatments

There are various options for supportive treatments and management procedures for the treatment of OA in the geriatric horse in addition to the pharmaceutical approach of flare-ups and pain management.

Repeated mechanical overloading is a well-known cause of OA. Two factors are important here: the number of repeats and the intensity of loading. The most important determining factor of the latter is the impact peak just after the hoof hits the ground with the high deceleration at that moment creating severe impact vibrations that put heavy stress on the tissues of the lower limb. This impact peak is determined by both the surface and the hoof and can be influenced by shoeing. Impact vibrations have been shown to be 15% less in unshod hooves compared with steel-shod hooves.[53] In some cases, leaving horses unshod may not be an option and for those cases various types of rims between the hoof wall and the shoes or padding of the sole have been developed that may dampen impact vibrations significantly[54] and that can be used to make the horse affected by chronic degenerative joint disease more comfortable.[55]

Optimization of joint stability and proprioception is important to prevent aberrant loading of joints. This is of special importance in geriatric patients, because neuromuscular changes associated with aging are known to manifest as a decrease in strength and coordination preceding a loss in muscle mass.[56] There are various physiotherapy techniques that aim at improving muscular fitness, strength, and coordination.[57,58] Controlled exercise may play a role here too, but care should be taken to ensure that the surface is even and horses should not be forced to exercise during flare-ups of joint disease. To prevent aggravation of chronic OA, care should be taken that exercise is discontinued when signs of fatigue become apparent, because fatigue-induced incoordination may lead to increased joint instability. Manual flexing exercises to improve joint range of motion can be carried out, but are laborious and

are of little benefit in elderly horses with end-stage disease. Low-grade continuous (pasture) exercise is more efficient in such cases.

Obese horses should lose weight, not only to reduce mechanical loading of the articulations, but also to decrease the low-grade inflammation that is a consequence of the systemic inflammatory load caused by cytokine production from adipose tissue, which is known to be an important etiologic factor of OA in humans.[59] It is not known whether a similar mechanism exists in the horse, but it has been demonstrated in small rodents, so it is likely that this is the case. Obesity is a widespread, although still insufficiently perceived problem in horses.[60] Additional measures that can be taken in the management of the geriatric horse with OA are supplying well-protected stabling of sufficient size to get up and lie down easily, providing good and dry bedding and, where possible, avoiding damp and cold weather.

CHRONIC LAMINITIS AND HOOF CARE OF THE GERIATRIC HORSE

Pathogenic Mechanisms

The etiology of laminitis is complex and will not be dealt with in detail in this context, but there is consensus that the main causal factors are inflammatory toxins, mechanical overloading, or metabolic and endocrine influences.[61] Underlying endocrinopathy may play an important and hitherto underestimated role in laminitis. Evidence of endocrinopathy was present in 89% of horses in a hospital in Finland. Of these horses, one-third had a diagnosis of pituitary pars intermedia dysfunction (PPID), and two-thirds showed basal hyperinsulinemia indicative of insulin resistance, without evidence of hirsutism.[62] In another study, the prevalence of PPID as defined by high plasma adrenocorticotropic hormone concentration in a single sample was 70% in a cohort of laminitic horses.[63] The suggested pathogenic pathway is a dysfunction of the brain resulting in a shortage in dopamine release from the hypothalamus. This shortage induces an increase in the release of adrenocorticotropic hormone and other peptides from the hypophysis, ultimately resulting in insulin resistance, higher insulin levels, and vascular constriction.[64]

There are several pathogenic pathways of laminitis, but all lead to structural failure of the attachments between the horny hoof capsule to the third phalanx, which is called the suspensory apparatus of the distal phalanx.[65] Bypass of the blood circulation in the hoof wall by vascular anastomosis with ischemia of the primary and secondary lamellae is one of these pathways.[66]

At older ages and thus in geriatric horses the chance of developing lameness owing to laminitis increases significantly.[67] In principle, all causal factors may play a role in the geriatric horse as in the nongeriatric horse, but endocrine disorders are more prevalent in geriatric horses than in younger ones. Pituitary dysfunction is the most common specific post mortem diagnosis in older horses.[68] In the study by Karikoski and colleagues,[62] horses with laminitis associated with an underlying endocrinopathy were significantly older and more likely to be pony breeds than the general nonlaminitic hospital population during the same period.

Treatment Considerations

The ultimate goal of treatment in geriatric horses, for whom performance is generally no longer a major consideration, is to attain a stable situation that will have the least possible impact on equine welfare (**Box 2**). Fatal progression of disease (**Fig. 6**) has to be avoided at all cost. This implies first of all treatment of the primary cause. In cases of PPID, treatment with pergolide has been reported to lead to significant improvement in clinical signs.[69] Pain management using NSAIDs (see above) is

Box 2
Principles of management of laminitis in the geriatric horse

- Treat every flare-up directly, that is, pain management through systemic nonsteroidal antiinflammatory drugs, first week: full dose, then half dose or every other day.
- Treat primary cause: pergolide.
- Adjust diet: remove concentrates, fresh grass and silage. Provide only hay (plus vitamin and mineral supplement).
- Take off shoes (if possible).
- Reduce toe length and rasp dorsal hoof wall.
- Apply wet hoof bandages every 2 days for a total of 4 days or put on wet shavings at the feeding location in combination with thick, soft stall bedding for lying down.
- Antiinflammatory/nonsteroidal antiinflammatory drugs: systemic, until 1 week after the horse has been shod.
- Vasodilation: acepromazine, until the horse is shod.
- Antithrombotic: calcium carbasalate, until 1 week after the horse has been shod.
- After improvement to Obel grade 2: apply open toe shoes with damping sole and firm hoof pad at the location of the frog.
- Start hand walking on a flat, soft surface three times a day.
- Repeat orthopedic shoeing at least once.
- Cold water on the feet more than 10 minutes each time twice a day depending on effect.

imperative, because laminitis is an extremely painful condition and, although inflammation in endocrine laminitis is less than with many other causes of the disorder,[70] some inflammation is occurring. The use of local anesthetics is not advised, because their use may lead to increased loading of the distal limb and more traction on the lamellae, with possibly fatal outcome. Food intake, especially of easily digestible carbohydrates, needs to be restricted and grain and concentrates should be withheld from the diet and replaced by good-quality hay.[71] To prevent microthrombosis in the hoof, the use of heparin, acetylsalicylic acid, or calcium carbasalate has been reported. Heparin would work prophylactically, but there are doubts regarding its clinical effectiveness.[72] Acepromazine is effective as a peripheral vasodilator and it increases the blood flow to the lamellae.[73] It can be applied orally or parenterally in low dosages, producing minimal sedative effects, although sedation can be beneficial because horses tend to lie down and thus relieve the pressure from their feet.[74] Glyceryl trinitrate pads have been applied locally, but there is no evidence for their effectiveness.[75]

Apart from the pharmaceutical treatment outlined, adaptations in the management of the horse with laminitis are crucial. The acutely laminitic horse needs to be strictly box rested to prevent further damage to the lamellae. Shoes must be removed at first instance and hooves need to be trimmed to distribute the forces exerted on the hoof as evenly as possible and thus to maximally reduce pressure. Maximal distribution of pressure together with an antiinflammatory effect can be achieved by putting the feet in wet bandages or stabling the horse on wet sand or soft bedding.[76] Wet bandages have the advantage that thick straw bedding can be provided for the horse to lay down comfortably.[71] Another option would be to have 1 part of the box filled with thick straw and the other part with wet sand where the horse eats its meals. Shortening the toe will facilitate break over and hence reduce the momentum on the site of attachment of the deep digital flexor tendon, reducing traction on the damaged lamellae.[77] In a

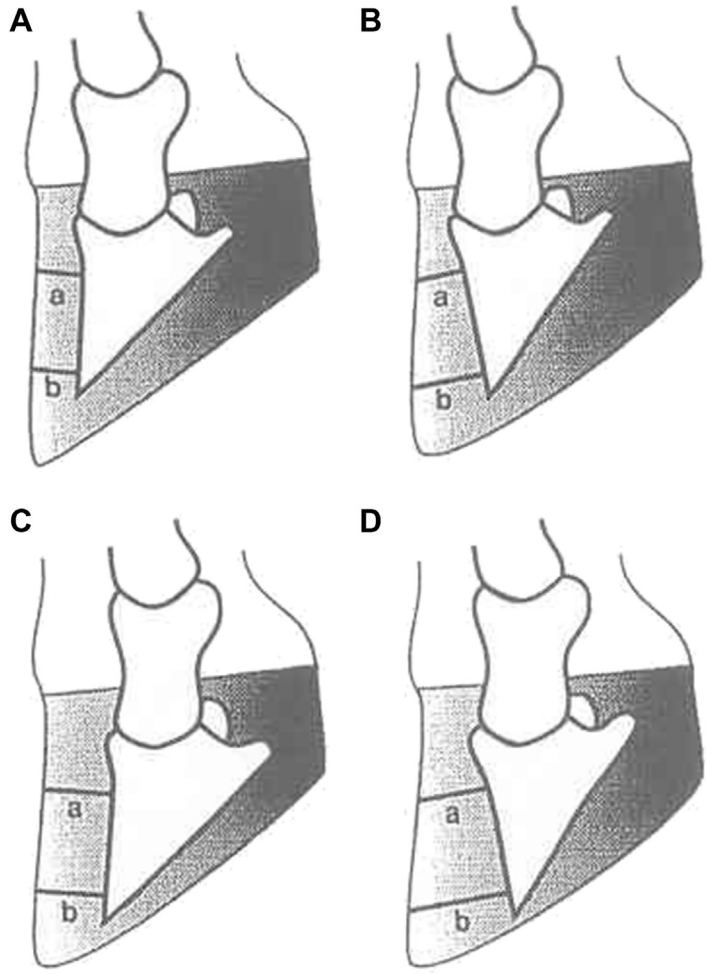

Fig. 6. Schematic radiologic Lateromedial view of the distal limb with (*A*) normal location of the third phalanx in the hoof capsule (a,b 19 ± 1 mm in warmbloods, 5° angle with the ground floor), (*B*) rotation, (*C*) sinker, and (*D*) rotation and sinker. (*From* Sloet van Oldruitenborgh-Oosterbaan MM. Laminitis in the horse: a review. Vet Q 1999;21(4):123; with permission.)

somewhat more chronic stage, a similar effect can be obtained by putting the horse on wedges.[78] Tenotomy of the flexor tendon is sometimes practiced, but should be considered a salvage procedure, because horses will not return to full athletic function.[79] Recently, research has started into the possible usefulness of *Clostridium botulinum* toxin type A as a muscle relaxant of the deep digital flexor muscle that may, either therapeutically or even preventively be used to reduce traction on the third phalanx in laminitis cases.[80,81]

For the more chronic situation, a large variety of shoes and frog supporting devices have been developed. Heart bar shoes can be purchased in an adjustable form.[82,83] The use of heart bar shoes has been shown to improve perfusion of the dorsal lamellae,[84] but substantial clinical improvement should not be expected during the first 7 days after therapeutic shoeing.[85] In our clinic, we advise open toe shoes at

the time the horse allows lifting the feet (Obel grade 2). The palmar/plantar part of the feet is filled using a filler paste with a higher shore value to support the not painful and still well perfused frog.[86]

SUMMARY

As in humans, musculoskeletal disorders are the most prevalent health problem in aging horses. They are not life threatening, but are often painful and debilitating, and therefore are an important welfare issue. Chronic joint disease (OA) and chronic hoof problems (chronic laminitis) are the most prevalent single disorders. Treatment of OA in the elderly horse is basically similar to treatment of performance horses, but aims more at providing a stable situation with optimal comfort rather than at regaining the ability to compete. Immediate medical treatment of flare-ups, long-term pain management, and adaptation of (exercise) management and living conditions form the mainstay of treatment of OA in geriatric horses. Laminitis in the geriatric horse is related to pituitary dysfunction in many cases, which has an increased prevalence with age. Treatment of laminitis is basically similar to nongeriatric horses, but in PPID cases additional pergolide treatment has been shown to significantly improve clinical signs including a lameness/laminitis reduction for some time.

REFERENCES

1. Rossdale PD, Hopes R, Wingfield Digby NJ, et al. Epidemiological study of wastage among racehorses 1982 and 1983. Vet Rec 1985;116(3):66–9.
2. Olivier A, Nurton JP, Guthrie AJ. An epizoological study of wastage in thoroughbred racehorses in Gauteng, South Africa. J S Afr Vet Assoc 1997;68(4):125–9.
3. Bertuglia A, Bullone M, Rossotto F, et al. Epidemiology of musculoskeletal injuries in a population of harness Standardbred racehorses in training. BMC Vet Res 2014;10:11.
4. Reed SR, Jackson BF, McIlwraith CW, et al. Descriptive epidemiology of joint injuries in Thoroughbred racehorses in training. Equine Vet J 2012;44(1):13–9.
5. Egenvall A, Tranquille CA, Lönnell AC, et al. Days-lost to training and competition in relation to workload in 263 elite show-jumping horses in four European countries. Prev Vet Med 2013;112(3–4):387–400.
6. Jönsson L, Roepstorff L, Egenvall A, et al. Prevalence of clinical findings at examinations of young Swedish warmblood riding horses. Acta Vet Scand 2013;55:34.
7. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;386(9995):743–800.
8. Ireland JL, McGowan CM, Clegg PD, et al. A survey of health care and disease in geriatric horses aged 30 years or older. Vet J 2012;192(1):57–64.
9. Ireland JL, Clegg PD, McGowan CM, et al. Disease prevalence in geriatric horses in the United Kingdom: veterinary clinical assessment of 200 cases. Equine Vet J 2012;44(1):101–6.
10. Ireland JL, Clegg PD, McGowan CM, et al. Comparison of owner-reported health problems with veterinary assessment of geriatric horses in the United Kingdom. Equine Vet J 2012;44(1):94–100.
11. Ireland JL, Clegg PD, McGowan CM, et al. Factors associated with mortality of geriatric horses in the United Kingdom. Prev Vet Med 2011;101(3–4):204–18.
12. McIlwraith CW. Frank Milne lecture: from arthroscopy to gene therapy – 30 years of looking in joints. Proc Am Assoc Equine Pract 2005;51:65–113.

13. Radin EL, Rose RM. Role of subchondral bone in the initiation and progression of cartilage damage. Clin Orthop 1986;213:34–40.
14. Samuels J, Krasnokutsky S, Abramson SB. Osteoarthritis. A tale of three tissues. Bull NYU Hosp Joint Dis 2008;66(3):244–50.
15. Neundorf RH, Lowerison MB, Cruz AM, et al. Determination of the prevalence and severity of metacarpophalangeal joint osteoarthritis in Thoroughbred racehorses via quantitative macroscopic evaluation. Am J Vet Res 2010;71(11):1284–93.
16. Brommer H, van Weeren PR, Brama PA. New approach for quantitative assessment of articular cartilage degeneration in horses with osteoarthritis. Am J Vet Res 2003;64(1):83–7.
17. Brommer H, van Weeren PR, Brama PA, et al. Quantification and age-related distribution of articular cartilage degeneration in the equine fetlock joint. Equine Vet J 2003;35(7):697–701.
18. Perrot S. Osteoarthritis pain. Best Pract Res Clin Rheumatol 2015;29(1):90–7.
19. Goldring MB, Goldring SR. Osteoarthritis. J Cell Physiol 2007;213(3):626–34.
20. Raffa RB. Mechanism of action of analgesics used to treat osteoarthritis pain. Rheum Dis Clin North Am 2003;29:733–45.
21. van Weeren PR. General anatomy and physiology of joints. In: McIlwraith CW, Frisbie DD, Kawcak CE, et al, editors. Joint disease in the horse. 2nd edition. St Louis (MO): Elsevier; 2016. p. 1–24.
22. Gwilym SE, Keltner JR, Warnaby CE, et al. Psychophysical and functional imaging evidence supporting the presence of central sensitization in a cohort of osteoarthritis patients. Arthritis Rheum 2009;61(9):1226–34.
23. Hunter W. Of the structure and diseases of articulating cartilages. Proc R Soc Lond 1743;9:514–21.
24. Frisbie DD. Biologic therapies. In: McIlwraith CW, Frisbie DD, Kawcak CE, et al, editors. Joint disease in the horse. 2nd edition. St Louis (MO): Elsevier; 2016. p. 229–35.
25. Frisbie DD. Stem cells. In: McIlwraith CW, Frisbie DD, Kawcak CE, et al, editors. Joint disease in the horse. 2nd edition. St Louis (MO): Elsevier; 2016. p. 236–42.
26. McIlwraith CW. Intra-articular corticosteroids. In: McIlwraith CW, Frisbie DD, Kawcak CE, et al, editors. Joint disease in the horse. 2nd edition. St Louis (MO): Elsevier; 2016. p. 194–206.
27. Genovese RL. The use of corticosteroids in racetrack practice. In: Proc Symposium Effective Use of Corticosteroids in Veterinary Practice. Princeton, NJ: Veterinary Learning Systems; 1983. p. 56–65.
28. Bathe AP. The corticosteroid laminitis story: 3. The clinician's viewpoint. Equine Vet J 2007;39(1):7–11.
29. Ferris DJ, Frisbie DD, McIlwraith CW, et al. Current joint therapy usage in equine practice: a survey of veterinarians 2009. Equine Vet J 2011;43(5):530–5.
30. Frisbie DD. Hyaluronan. In: McIlwraith CW, Frisbie DD, Kawcak CE, et al, editors. Joint disease in the horse. 2nd edition. St Louis (MO): Elsevier; 2016. p. 215–9.
31. McIlwraith CW. Polysulfated glycosaminoglycan (Adequan®). In: McIlwraith CW, Frisbie DD, Kawcak CE, et al, editors. Joint disease in the horse. 2nd edition. St Louis (MO): Elsevier; 2016. p. 220–3.
32. Goodrich LR, Nixon AJ. Medical treatment of osteoarthritis in the horse – a review. Vet J 2006;171:51–69.
33. Risks of agranulocytosis and aplastic anemia. A first report of their relation to drug use with special reference to analgesics. The International Agranulocytosis and Aplastic Anemia Study. JAMA 1986;256:1749–57.

34. De Grauw JC, van Loon JP, van de Lest CH, et al. In vivo effects of phenylbutazone on inflammation and cartilage-derived biomarkers in equine joints with acute synovitis. Vet J 2014;201(1):51–6.
35. Owens JG, Clark TP. Analgesia. Vet Clin North Am Equine Pract 1999;15(3):705–23.
36. Houdeshell JW, Hennessy PW. A new non-steroidal, anti-inflammatory analgesic for horses. J Equine Med Surg 1977;1:57–63.
37. Erkert RS, MacAllister CG, Payton ME, et al. Use of force plate analysis to compare the analgesic effects of intravenous administration of phenylbutazone and flunixin meglumine in horses with navicular syndrome. Am J Vet Res 2005;66(2):284–8.
38. Trillo MA, Soto G, Gunson DE. Flunixin toxicity in a pony. Equine Pract 1984;6:21–9.
39. Frean SP, Abraham LA, Lees P. In vitro stimulation of equine articular cartilage proteoglycan synthesis by hyaluronan and carprofen. Res Vet Sci 1999;67:183–90.
40. Armstrong S, Lees P. Effects of R and S enantiomers and a racemic mixture of carprofen on the production and release of proteoglycan and prostaglandin E2 from equine chondrocytes and cartilage explants. Am J Vet Res 1999;60:98–104.
41. May SA, Lees P. Nonsteroidal anti-inflammatory drugs. In: McIlwraith CW, Trotter GW, editors. Joint disease in the horse. Philadelphia: WB Saunders; 1996. p. 223–37.
42. Owens JG, Kamerling SG, Stanton SR, et al. Effects of pretreatment with ketoprofen and phenylbutazone on experimentally induced synovitis in the horse. Am J Vet Res 1996;57:866–74.
43. Lees P, May SA, Hoeijmakers M, et al. A pharmacodynamic and pharmacokinetic study with vedaprofen in an equine model of acute nonimmune inflammation. J Vet Pharmacol Ther 1999;22:96–106.
44. Beretta C, Caravaglia G, Cavalli M. COX-1 and COX-2 inhibition in horse blood by phenylbutazone, flunixin, carprofen and meloxicam: an in vitro analysis. Pharmacol Res 2005;52:302–6.
45. De Grauw JC, van de Lest CHA, Brama PAJ, et al. In vivo effects of meloxicam on inflammatory mediators, MMP activity and cartilage biomarkers in equine joints with acute synovitis. Equine Vet J 2009;41:693–9.
46. Jones EW, Hamm D. Comparative efficacy of PBZ and naproxen in induced equine myositis. J Equine Med Surg 1978;2:341–7.
47. Larsen SW, Frost AB, Ostergaard J, et al. In vitro and in vivo characteristics of celecoxib in situ formed suspensions for intra-articular administration. J Pharm Sci 2011;100(10):4330–7.
48. Petit A, Redout EM, van de Lest CH, et al. Sustained intra-articular release of celecoxib from in situ forming gels made of acetyl-capped PCLA-PEG-PCLA triblock copolymers in horses. Biomaterials 2015;53:426–36.
49. McIlwraith CW. Use of oral joint supplements in equine joint disease. In: McIlwraith CW, Frisbie DD, Kawcak CE, et al, editors. Joint disease in the horse. 2nd edition. St Louis (MO): Elsevier; 2016. p. 277–80.
50. Cayzer J, Hedderley D, Gray S. A randomised, double-blinded, placebo-controlled study on the efficacy of a unique extract of green-lipped mussel (Perna canaliculus) in horses with chronic fetlock lameness attributed to osteoarthritis. Equine Vet J 2012;44(4):393–8.
51. Kawcak CE, Frisbie DD, McIlwraith CW, et al. Evaluation of avocado and soybean unsaponifiable extracts for treatment of horses with experimentally induced osteoarthritis. Am J Vet Res 2007;68(6):598–604.

52. Higler MH, Brommer H, L'Ami JJ, et al. The effects of three-month oral supplementation with a nutraceutical and exercise on the locomotor pattern of aged horses. Equine Vet J 2014;46(5):611–7.
53. Willemen MA, Jacobs MW, Schamhardt HC. In vitro transmission and attenuation of impact vibrations in the distal forelimb. Equine Vet J Suppl 1999;30:245–8.
54. Benoit P, Barrey E, Regnault JC, et al. Comparison of the damping effect of different shoeing by the measurement of hoof acceleration. Acta Anat (Basel) 1993;146(2–3):109–13.
55. Back W, Pille F. The role of Hoof and Shoeing. In: Back W, Clayton HM, editors. Equine locomotion. 2nd edition. London: Elsevier; 2013. p. 147–74.
56. Hepple RT, Rice CL. Innervation and neuromuscular control in aging skeletal muscle. J Physiol 2015;594(8):1965–78.
57. Haussler KK. King MR physical rehabilitation. In: McIlwraith CW, Frisbie DD, Kawcak CE, et al, editors. Joint disease in the horse. 2nd edition. St Louis (MO): Elsevier; 2016. p. 243–69.
58. Stubbs N, Menke E, Back W, et al. Rehabilitation of the locomotor apparatus. In: Back W, Clayton HM, editors. Equine locomotion. 2nd edition. London: Elsevier; 2013. p. 381–417.
59. Roos EM, Arden NK. Strategies for the prevention of knee osteoarthritis. Nat Rev Rheumatol 2016;12(2):92–101.
60. Owers R, Chubbock S. Fight the fat! Equine Vet J 2013;45(1):5.
61. Katz LM, Bailey SR. A review of recent advances and current hypotheses on the pathogenesis of acute laminitis. Equine Vet J 2012;44:752–61.
62. Karikoski NP, Horn I, McGowan TW, et al. The prevalence of endocrinopathic laminitis among horses presented for laminitis at a first-opinion/referral equine hospital. Domest Anim Endocrinol 2011;41(3):111–7.
63. Donaldson MT, Jorgensen AJ, Beech J. Evaluation of suspected pituitary pars intermedia dysfunction in horses with laminitis. J Am Vet Med Assoc 2004;224:1123–7.
64. Gauff F, Patan-Zugaj B, Licka TF. Hyperinsulinaemia increases vascular resistance and endothelin-1 expression in the equine digit. Equine Vet J 2013;45(5):613–8.
65. van Eps AW. Acute laminitis: medical and supportive therapy. Vet Clin North Am Equine Pract 2010;26:103–14.
66. Hood DM, Grosenbaugh DA, Slater MR. Vascular perfusion in horses with chronic laminitis. Equine Vet J 1994;26(3):191–6.
67. Brosnahan MM, Paradis MR. Demographic and clinical characteristics of geriatric horses: 467 cases (1989-1999). J Am Vet Med Assoc 2003;223(1):93–8.
68. Miller MA, Moore GE, Bertin FR, et al. What's new in old horses? Postmortem diagnoses in mature and aged equids. Vet Pathol 2016;53(2):390–8.
69. Donaldson MT, LaMonte BH, Morresey P, et al. Treatment with pergolide or cyproheptadine of pituitary pars intermedia dysfunction (equine Cushing's disease). J Vet Intern Med 2002;16(6):742–6.
70. Karikoski NP, McGowan CM, Singer ER, et al. Pathology of natural cases of equine endocrinopathic laminitis associated with hyperinsulinemia. Vet Pathol 2015;52(5):945–56.
71. Sloet van Oldruitenborgh-Oosterbaan MM. Laminitis in the horse: a review. Vet Q 1999;21(4):121–7.
72. Moore BR, Hinchcliff KW. Heparin: a review of its pharmacology and therapeutic use in horses. J Vet Intern Med 1994;8(1):26–35.

73. Ingle-Fehr JE, Baxter GM. The effect of oral isoxsuprine and pentoxifylline on digital and laminar blood flow in healthy horses. Vet Surg 1999;28(3):154–60.
74. Wattle O, Ekfalck A, Funkquist B, et al. Behavioural studies in healthy ponies subjected to short-term forced recumbency aiming at an adjunctive treatment in an acute attack of laminitis. Zentralbl Veterinärmed A 1995;42(1):62–8.
75. Gilhooly MH, Eades SC, Stokes AM, et al. Effects of topical nitroglycerine patches and ointment on digital venous plasma nitric oxide concentrations and digital blood flow in healthy conscious horses. Vet Surg 2005;34(6):604–9.
76. van Eps AW, Pollitt CC. Equine laminitis: cryotherapy reduces the severity of the acute lesion. Equine Vet J 2004;36(3):255–60.
77. Baker WR Jr. Treating laminitis: beyond the mechanics of trimming and shoeing. Vet Clin North Am Equine Pract 2012;28(2):441–55.
78. McGuigan MP, Walsh TC, Pardoe CH, et al. Deep digital flexor tendon force and digital mechanics in normal ponies and ponies with rotation of the distal phalanx as a sequel to laminitis. Equine Vet J 2005;37(2):161–5.
79. Eastman TG, Honnas CM, Hague BA, et al. Deep digital flexor tenotomy as a treatment for chronic laminitis in horses: 35 cases (1988-1997). J Am Vet Med Assoc 1999;214(4):517–9.
80. Hardeman LC, van der Meij BR, Oosterlinck M, et al. Effect of Clostridium botulinum toxin type A injections into the deep digital flexor muscle on the range of motion of the metacarpus and carpus, and the force distribution underneath the hooves, of sound horses at the walk. Vet J 2013;198(Suppl 1):e152–6.
81. Wijnberg ID, Hardeman LC, van der Meij BR, et al. The effect of Clostridium botulinum toxin type A injections on motor unit activity of the deep digital flexor muscle in healthy sound Royal Dutch sport horses. Vet J 2013;198(Suppl 1):e147–51.
82. Eustace RA, Caldwell MN. The construction of the heart bar shoe and the technique of dorsal wall resection. Equine Vet J 1989;21(5):367–9.
83. Eustace RA, Caldwell MN. Treatment of solar prolapse using the heart bar shoe and dorsal hoof wall resection technique. Equine Vet J 1989;21(5):370–2.
84. Ritmeester AM, Blevins WE, Ferguson DW, et al. Digital perfusion, evaluated scintigraphically, and hoof wall growth in horses with chronic laminitis treated with egg bar-heart bar shoeing and coronary grooving. Equine Vet J Suppl 1998;26:111–8.
85. Taylor D, Hood DM, Wagner IP. Short-term effect of therapeutic shoeing on severity of lameness in horses with chronic laminitis. Am J Vet Res 2002;63(12):1629–33.
86. Olivier A, Wannenburg J, Gottschalk RD, et al. The effect of frog pressure and downward vertical load on hoof wall weight-bearing and third phalanx displacement in the horse–an in vitro study. J S Afr Vet Assoc 2001;72(4):217–27.