Seasonal changes can make it difficult to accurately diagnose Pituitary Pars Intermedia Dysfunction (Cushing's disease), the most common endocrine disorder in horses

An Age-Related Disease That Needs Monitoring

DIAGNOSING **CUSHING'S DISEASE/PPID** CAN BE TRICKY

By **AMANDA DUCKWORTH**

AS HORSES AGE, the list of potential medical concerns they might face changes. For equines 15 and older, one of the most common diseases owners need to be on the lookout for is Equine Pituitary Pars Intermedia Dysfunction. While the disease itself is well known, diagnosing and managing it properly continue to be highly evolving topics.

Colloquially, PPID is known as Cushing's disease. Humans and dogs can also suffer from Cushing's disease, but it differs in some very specific ways between the species. Because of that, the veterinary community prefers to refer to equine Cushing's by the acronym PPID, which stems from the location within the brain that becomes abnormal in horses.

PPID is the most common endocrine disorder in horses. The American Association of Equine Practitioners has crafted multiple papers providing an overview of PPID, including "Equine Endocrine Diseases: The Basics" by Dr. Emily Graves.

"In a normal equine pituitary gland, a specific cell type (melanotrope) receives neuronal input from the hypothalamus," explained Graves. "These neurons release dopamine. Dopamine then inhibits the intermediate lobe of the pituitary gland from making and releasing many different hormones. In the diseased gland, these hypothalamic neurons degenerate and much of that dopamine input is lost. The melanotropes become disinhibited.

"As a result, the pituitary gland's intermediate lobe undergoes hypertrophy and hyperplasia. The cells are hyperactive or present in high numbers and lead to production of abnormally high levels of many pituitary hormones."

There are a number of indicators that a horse may be affected by PPID, but the most well known involves its coat. Horses impacted by PPID will often exhibit a failure to shed fully, and they also tend to grow long, sometimes curly coats. This excessive hair growth is known as hypertrichosis.

According to the AAEP, other signs of PPID can include: chronic infections; repeated laminitis episodes, sometimes with associated hoof abscesses; excess

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or inappropriate sweating; increased water intake and urination, called polyuria/polydipsia (PU/PD); lethargy; loss of muscle mass; infertility, or lack of estrus cycles; and abnormal mammary gland development.

PPID has been on the radar for more than 90 years and how best to diagnose and manage it has changed throughout the decades. In October 2022,

Increased water intake is a symptom of PPID

Veterinary Sciences published the review "Pituitary Pars Intermedia Dysfunction (PPID) in Horses."

"Since the disease was first described in 1932, considerable research has been conducted investigating PPID pathophysiology, prevalence of clinical signs, appropriate diagnostic techniques and treatment," explained researchers. "In recent years, awareness of PPID among horse owners has grown, and veterinarians are increasingly testing for underlying endocrinopathies. An increase in awareness has led to a substantial increase in research conducted in the field of equine endocrinology."

Excessive hair growth is the most prevalent symptom of PPID, and it is one that is hard to miss. Some of the more subtle signs often require testing.

"A presumptive diagnosis of PPID can be made based on the presence of hypertrichosis in aged horses," researchers noted. "Laboratory testing is recommended in cases where treatment is financially feasible, where early or severe clinical disease is suspected, or to determine the response to treatment. Currently, testing horses for subclinical PPID is not recommended. However, the disease can have severe, life-threatening consequences and ability to diagnose subclinical or mild PPID and initiate treatment before end-stage disease may be beneficial."

One of the key reasons for increased awareness and testing is because of the apparent relationship between PPID and laminitis. Following excessive hair growth, laminitis is one of the key indicators PPID may be occurring as well.

"The cause of laminitis in horses with PPID is poorly understood," explained researchers. "Laminitis is the second most prevalent finding observed in horses and ponies with PPID and is often the first presenting complaint recognized by owners that seek veterinary attention. A systematic review reported the prevalence of laminitis in the PPID population as 48.9%."

Although PPID is common, that does not mean diagnosing it is straight forward. While there are a variety of diagnostic tests available, poor test sensitivity has been a recurring issue. Additionally, the type of tests veterinarians use continues to evolve.

Historically, an overnight dexamethasone suppression test was used. However, it became clear that it is best at diagnosing late-stage PPID. Now, ACTH level tests (measuring adrenocorticotropic hormones in the blood) as well as TRH (thyrotropin-releasing hormone) stimulation tests are preferred for earlier confirmation of the disease. In February 2024, Veterinary Journal published "Factors affecting measurement of basal adrenocorticotropic hormone in adult domestic equids: A scoping review."

"Measurement of basal adrenocorticotropic hormone (ACTH) concentration is the most commonly used diagnostic test for pituitary pars intermedia dysfunction (PPID)," researchers wrote. "Although several pre-analytical and analytical factors have been reported to affect basal ACTH concentrations in equids, the extent to which these have been evaluated in the context of PPID diagnosis is unclear. The objectives of this scoping review were to identify and systematically chart current evidence about pre-analytical and analytical factors affecting basal ACTH concentrations in adult domestic equids."

This scoping review took place June 2022 through August 2023, and ultimately 134 publications met inclusion criteria. Researchers found that time of year, exercise, breed/type,

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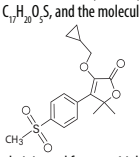

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Dosage and Administration: Always provide the Client Information Sheet with the prescription. The recommended dosage of EquiCoxib (firocoxib) for oral administration in horses is 0.045 mg/lb (0.1 mg/kg) of body weight once daily for up to 14 days. In target animal safety studies, toxicity was seen at the recommended dose when the duration of treatment exceeded 30 days. **Only administer EquiCoxib with the provided dosing syringe.**

Each 1.25 mL volume will treat 250 pounds of body weight and each additional 0.25 mL volume corresponds to approximately a 50 lb weight increment. The provided dosing syringe is calibrated so that each line corresponds to a 50 lb weight increment. To deliver the correct dose, round the horse's body weight up to the nearest 50 pound increment (if the body weight is an exact 50 pound increment, do not round up).

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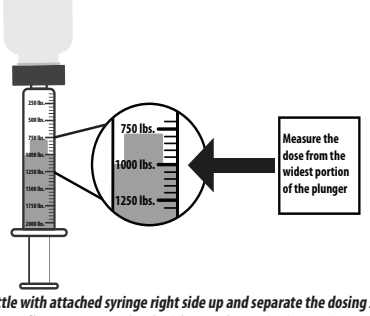
EquiCoxib Oral Dosing Guide

Body Weight (lb)	Dose Volume (mL)
250	1.25 mL
500	2.5 mL
750	3.75 mL
1000	5 mL
1250	6.25 mL

1) Remove draw-off cap. Peel off the foil-backed seal from the bottle.
2) Screw the draw-off cap tightly back on the bottle.
3) Remove the seal from the top of the cap exposing the cross-hatched opening in the center of the silicone liner.
4) Remove the provided oral dosing syringe from its plastic cover.
5) Insert the oral dosing syringe firmly into the cross-hatched opening of the cap's silicone liner.
6) Turn the bottle with attached syringe upside down. Pull back the syringe plunger until the widest portion of the plunger lines up with the line that corresponds with the animal's weight. Each line between the 250 lb increments corresponds to 50 lb.



7) Turn the bottle with attached syringe right side up and separate the dosing syringe from the bottle.
8) Give orally according to your veterinarian's instructions. DO NOT INJECT.

Contraindications: Horses with hypersensitivity to firocoxib should not receive EquiCoxib Oral Solution.

Warnings:
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Animal Safety: Clients should be advised to observe for signs of potential drug toxicity and be given a Client Information Sheet with each prescription.

Keep EquiCoxib in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Aurora Pharmaceutical at 1-888-215-1256 or www.aurorapharmaceutical.com. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

Precautions:
Horses should undergo a thorough history and physical examination before initiation of NSAID therapy. Appropriate laboratory tests should be conducted to establish hematological and serum biochemical baseline data before and periodically during administration of any NSAID. Clients should be advised to observe for signs of potential drug toxicity and be given a Client Information Sheet with each prescription. See **Information for Owner or Person Treating Horse** section of this package insert.

Treatment with EquiCoxib should be terminated if signs such as inappetance, colic, abnormal feces, or lethargy are observed. As a class, cyclooxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal, and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Horses that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Patients at greatest risk for adverse events are those that are dehydrated, on diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached or avoided. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been previously diagnosed. Since many NSAIDs possess the potential to produce gastrointestinal ulcerations and/or gastrointestinal perforation, concomitant use of EquiCoxib Oral Solution with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided. The concomitant use of protein bound drugs with EquiCoxib Oral Solution has not been studied in horses. The influence of concomitant drugs that may inhibit the metabolism of EquiCoxib Oral Solution has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy. The safe use of EquiCoxib Oral Solution in horses less than one year in age, horses used for breeding, or in pregnant or lactating mares has not been evaluated. Consider appropriate washout times when switching from one NSAID to another NSAID or corticosteroid.

Adverse Reactions: In controlled field studies, 127 horses (ages 3 to 37 years) were evaluated for safety when given firocoxib at a dose of 0.045 mg/lb (0.1 mg/kg) orally once daily for up to 14 days. The following adverse reactions were observed. Horses may have experienced more than one of the observed adverse reactions during the study.

Adverse Reactions Seen in U.S. Field Studies Firocoxib was safely used concomitantly with other therapies, including vaccines, anthelmintics, and antibiotics, during the field studies. The safety data sheet (SDS) contains more detailed occupational safety information.

To report suspected adverse drug events, for technical assistance, or to obtain a copy of the Safety Data Sheet (SDS), contact Aurora Pharmaceutical Inc. at 1-888-215-1256 or www.aurorapharmaceutical.com. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS, or online at www.fda.gov/reportanimalae.

Adverse Reactions	Firocoxib n=127	Active Control n=125
Abdominal pain	0	1
Diarrhea	2	0
Excitation	1	0
Lethargy	0	1
Loose stool	1	0
Polydipsia	0	1
Urticaria	0	1

Information for Owner or Person Treating Horse: You should give a Client Information Sheet to the person treating the horse and advise them of the potential for adverse reactions and the clinical signs associated with NSAID intolerance. Adverse reactions may include erosions and ulcers of the gums, tongue, lips and face, weight loss, colic, diarrhea, or icterus. Serious adverse reactions associated with this drug class can occur without warning and, in some situations, result in death. Clients should be advised to discontinue NSAID therapy and contact their veterinarian immediately if any of these signs of intolerance are observed. The majority of patients with drug-related adverse reactions recover when the signs are recognized, drug administration is stopped, and veterinary care is initiated.

Clinical Pharmacokinetics / Pharmacodynamics: Pharmacokinetics: When administered as a 0.045 mg/lb (0.1 mg/kg) dose in oral paste to adult horses with normal access to roughage, feed, and water, the absolute bioavailability of firocoxib from oral paste is approximately 79%. Following oral administration, drug peak concentration (Cmax) of 0.08 mcg/mL can be reached at 4 hours (Tmax) post-dosing. However, in some animals, up to 12 hours may be needed before significant plasma concentrations are observed. Little drug amount distributes into blood cells. The major metabolism mechanism of firocoxib in the horse is decyclopropylmethylation followed by glucuronidation of that metabolite. Based upon radiolabel studies, the majority of firocoxib is eliminated in the urine as the decyclopropylmethylated metabolite. Despite a high rate of plasma protein binding (98%), firocoxib exhibits a large volume of distribution (mean Vd(ss) = 1652 mL/kg). The terminal elimination half-life ($T_{1/2}$) in plasma averages 30-40 hours after IV or oral paste dosing. Therefore, drug accumulation occurs with repeated dose administrations and steady state concentrations are achieved beyond 6-8 daily oral doses in the horse. Dose linearity exists from 1X-2X of 0.1 mg/kg/day.

Mode of action: EquiCoxib (firocoxib) is a cyclooxygenase-inhibiting (coxib) class, non-narcotic, non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic activity[1] in animal models. Based on in vitro horse data, firocoxib is a selective inhibitor of prostaglandin biosynthesis through inhibition of inducible cyclooxygenase-2-isoenzyme (COX-2)[2]. Firocoxib selectivity for the constitutive isoenzyme, cyclooxygenase-1 (COX-1) is relatively low. However, the clinical significance of these in vitro selectivity findings has not been established.

Effectiveness: Two hundred fifty-three client-owned horses of various breeds, ranging in age from 2 to 37 years and weighing from 595 to 1638 lbs, were randomly administered firocoxib oral paste or an active control drug in multi-center field studies. Two hundred forty horses were evaluated for effectiveness and 252 horses were evaluated for safety. Horses were assessed for lameness, pain on manipulation, range of motion, joint swelling, and overall clinical improvement in a non-inferiority evaluation of firocoxib oral paste compared to an active control. At study's end, 84.4% of horses treated with firocoxib oral paste were judged improved on veterinarians' clinical assessment, and 73.8% were also rated improved by owners. Horses treated with firocoxib oral paste showed improvement in veterinarian-assessed lameness, pain on manipulation, range of motion, and joint swelling that was comparable to the active control.

Animal Safety: In a target animal safety study, firocoxib was administered orally to healthy adult horses (two male castrates and four females per group) at 0, 0.1, 0.3 and 0.5 mg firocoxib/kg body weight (1, 3 and 5X the recommended dose) for 30 days. Administration of firocoxib at 0.3 and 0.5 mg/kg body weight was associated with an increased incidence of oral ulcers as compared to the control group but, no oral ulcers were noted with 0.1 mg/kg. There were no other drug-related adverse findings in this study.

In another target animal safety study, firocoxib was administered orally to healthy adult horses (four males or male castrates and four females per group) at 0, 0.1, 0.3 and 0.5 mg firocoxib/kg body weight (1, 3 and 5X the recommended dose) for 42 days. Administration of firocoxib at 0.1, 0.3 and 0.5 mg/kg body weight was associated with delayed healing of pre-existing oral (lip, tongue, gingival) ulcers. In addition, the incidence of oral ulcers was higher in all treated groups as compared to the control group.

Clinical chemistry and coagulation abnormalities were seen in several horses in the 0.5 mg/kg (5X) group. One 5X male horse developed a mildly elevated BUN and creatinine over the course of the study, prolonged buccal mucosal bleeding time (BMBT), and a dilated pelvis of the right kidney. Another 5X male had a similar mild increase in creatinine during the study but did not have any gross abnormal findings. One female in the 5X group had a prolonged BMBT, bilateral tubulointerstitial nephropathy and bilateral papillary necrosis. Tubulointerstitial nephropathy occurred in one 3X female, two 3X male horses, and the 5X female horse discussed above with the prolonged BMBT. Papillary necrosis was present in one 1X male horse and the 5X female horse discussed above. Despite the gross and microscopic renal lesions, all of the horses were clinically healthy and had normal hematology, clinical chemistry and urinalysis values.

In another target animal safety study, firocoxib was administered orally to healthy adult horses (three females, two male castrates and one male per group) at 0, 0.25 mg/kg, 0.75 mg/kg and 1.25 mg/kg (2.5, 7.5 and 12.5X the recommended dose of 0.1 mg/kg) for 92 days. An additional group of three females, two male castrates and one male per group, was dosed at 1.25 mg/kg for 92 days but was monitored until Days 147-149. There were treatment-related adverse events in all treated groups. These consisted of ulcers of the lips, gingiva and tongue and erosions of the skin of the mandible and head. Gross and microscopic lesions of the kidneys consistent with tubulointerstitial nephropathy were seen in all treated groups. Papillary necrosis was seen in the 2.5X and 12.5X groups. In addition, several 12.5X horses had elevated liver enzymes (GGT, SDH, AST and ALT). One 2.5X horse had increased urine GGT and urine protein levels which was due to renal hemorrhage and nephropathy. Gastric ulcers of the margo plicatus and glandular area were more prevalent in the 2.5X and 7.5X groups, but not seen in the 12.5X group. The group of horses that were monitored until Days 147-149 showed partial to full recovery from oral and skin ulcers, but no recovery from tubulointerstitial nephropathy.

Storage Information: Store below 77°F (25°C). Brief excursions up to 104°F (40°C) are permitted.

How Supplied: EquiCoxib is available in bottles containing 90 mL of EquiCoxib Oral Solution, sufficient to treat a 1250 lb. horse for up to 14 days.

References: [1]McCann ME, Rickes EL, Hora DF, Cunningham PK et al. In vitro effects and in vivo efficacy of a novel cyclooxygenase-2 inhibitor in cats with lipopolysaccharide-induced pyrexia. Am J Vet Res. 2005 Jul;66 (7):1278-84

[2]McCann ME, Anderson DR, Brideau C et al. In vitro activity and in vivo efficacy of a novel COX-2 inhibitor in the horse. Proceedings of the Academy of Veterinary Internal Medicine. 2002. Abstract 114, p.789.

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and transportation were the factors most frequently associated with significant increases in ACTH concentration.

"Numerous factors were reported to be associated with significant changes in ACTH concentration, although findings were not always consistent between studies," researchers concluded. "Studies that did not include PPID cases predominated, therefore the relationship between many factors affecting basal ACTH concentration and diagnostic accuracy for PPID remains undefined. However, several factors were identified that could increase the frequency of false positives (such as breed, illness, exercise, and transportation) or false negatives (such as corticosteroid administration and sample handling conditions) if not accounted for when interpreting basal ACTH results.

Blood tests are used to detect the presence of adrenocorticotropic hormones, a marker for Cushing's disease

"The review provides important information about factors that should be considered as confounding variables in clinical practice and research. Furthermore, this review highlights the need for detailed reporting of preanalytical and analytical conditions in publications to facilitate translation of research evidence to practice and future systematic review."

Seasonal changes have repeatedly been noted for causing issues in terms of diagnosing PPID. In October 2023, Veterinary Journal published "Evaluation of seasonal influences on adrenocorticotropic hormone response to the thyrotropin-releasing hormone stimulation test and its accuracy for diagnosis of pituitary pars intermedia dysfunction."

"There is a need for improved endocrine tests for early disease detection, and the thyrotropin-releasing hormone (TRH) stimulation test has been recommended for diagnosis of early or mild cases," researchers remarked. "However, it is currently not recommended for year-round use due to marked seasonal variability. The aims of this cohort study were to evaluate effects of month and season on adrenocorticotropic hormone (ACTH) responses to TRH stimulation and to derive monthly cut-offs for PPID diagnosis."

For the study, 63 horses were assigned to one of three groups based on combined clinical history and examination findings with endocrine test results. In total, 17 horses were assigned to the control group, while 21 were placed in the subclinical PPID group, and 25 went into the clinical PPID group. Then, TRH stimulation tests were performed monthly for a 12-month period.

Researchers found that TRH-stimulated ACTH concentrations were lowest in February-May and highest in August-October. Additionally, TRH stimulation had higher accuracy than basal ACTH, but specificity was not significantly different between basal and TRH-stimulated ACTH.

"This study has further characterized

In clinical studies, incomplete hair coat shedding provided a high index of clinical suspicion for PPID

Lethargy is also associated with the disease

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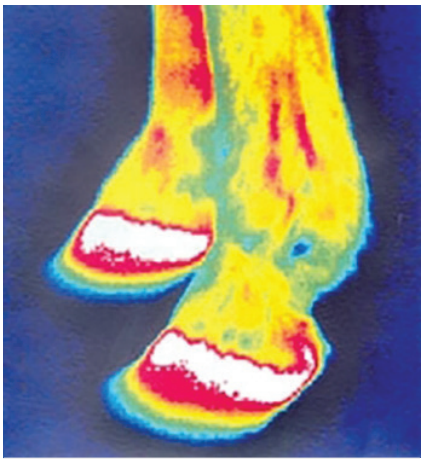
the effect of season on ACTH responses to TRH stimulation in healthy mature and aged horses and PPID cases in the Northern Hemisphere," researchers concluded. "Significant monthly differences were identified for basal and TRH-stimulated ACTH, indicating that applying seasonal DCOVs (diagnostic cutoff values) might increase the risk of misclassification at certain times of year. Accuracy of the TRH stimulation test was greater than that of basal ACTH, although specificity did not differ significantly, and sensitivity was not consistently greater year-round.

"The majority of horses with clinical signs of PPID had elevated basal ACTH, but the TRH stimulation test resulted in a greater number of positive test results in horses suspected to have subclinical PPID. Further studies to develop temporally specific DCOVs for different geographical locations are warranted; however, marked variability in ACTH responses to TRH administration during late summer to early winter is likely to make this challenging."

Beyond diagnosing PPID, understanding proper management of the disease is also critical in order to improve the horse's quality of life. In March 2024, Equine Veterinary Journal published "BEVA primary care clinical guidelines: Diagnosis and management of equine pituitary pars intermedia dysfunction."

"Diagnosis of PPID can be challenging because of its broad spectrum of clinical presentations and disparate published diagnostic criteria, and there are limited available treatment options," explained researchers. "The objective of this study was to develop evidence-based primary care guidelines for the diagnosis and treatment of equine PPID based on the available literature."

For the study, research questions were proposed by a panel of veterinarians. They were categorized into four areas: case selection for diagnostic testing, pre-test probability and diagnostic test accuracy; interpretation of test results; pharmacological treatments and other treatment/management options; and monitoring treated cases. Following this, relevant veterinary publications were identified and assessed using the GRADE (high, moderate, low, and very low) criteria.



According to the American Association of Equine Practitioners, repeated laminitis episodes have been tied to PPID

THERE IS A NEED FOR IMPROVED ENDOCRINE TESTS FOR EARLY DISEASE DETECTION, AND THE THYROTROPIN-RELEASING HORMONE (TRH) STIMULATION TEST HAS BEEN RECOMMENDED FOR DIAGNOSIS OF EARLY OR MILD CASES.

—VETERINARY JOURNAL, OCTOBER 2023

In terms of case selection, researchers concluded that the prevalence of PPID in equids aged 15 years or older is between 21% and 27% and that delayed/incomplete hair coat shedding provided a high index of clinical suspicion for PPID.

"The combination of clinical signs and age informs the index of clinical suspicion prior to diagnostic testing," explained researchers. "The estimated pre-test probability of PPID should be considered in the interpretation of diagnostic test results; the pre-test probability of PPID is low in equids aged <10 years; and both pre-test probability of disease and season of testing have strong influence on the ability to diagnose PPID using basal ACTH or ACTH after TRH stimulation."

When it comes to test results, the study found that there is a significant effect of breed on plasma ACTH concentration, particularly in the autumn, with markedly higher ACTH concentrations in some but not all 'thrifty' breeds.

"Determining diagnostic thresholds that allow for all possible contributory factors is not practical and equivocal ranges are advised," researchers concluded. "Equids with PPID and hyperinsulinemia appear to be at higher risk of laminitis, but ACTH and PPID do not appear to be insulin-independent predictors of laminitis risk."

For the third research point, pharmacologic treatments and other management options, researchers concluded that pergolide improves most clinical signs associated with PPID in the majority of affected animals.

"Pergolide treatment lowers basal ACTH concentrations and improves the ACTH response to TRH in many animals, but measures of ID are not altered," they summarized. "Chasteberry may improve some clinical signs of PPID but there is no effect on ACTH concentrations and no benefit to adding chasteberry to pergolide therapy. Combination of cyproheptadine with pergolide is not superior to pergolide alone, and there is no evidence that pergolide has adverse cardiac effects in horses or improves insulin sensitivity."

Finally, in terms of monitoring pergolide-treated cases researchers found that hormone assays provide a crude indication of pituitary control in response to pergolide therapy.

"However, it is unknown whether monitoring of ACTH concentrations and titrating of pergolide doses

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Researchers have identified several factors that could increase the frequency of false positives, including travel

accordingly is associated with improved endocrinological or clinical outcome," they added. "It is unknown whether monitoring the ACTH response to TRH or clinical signs is associated with an improved outcome. There is very weak evidence to suggest that increasing pergolide dose in autumn months may be beneficial."

Overall, researchers also emphasized that most of the recommendations are based on a small number of studies, which included small numbers of animals with PPID.

"This evidence review has highlighted the need for high-quality evidence in the veterinary literature across all areas of the diagnosis and treatment of PPID," they concluded. "The findings of this study should be incorporated into evidence-based veterinary practice and considered against each individual case to determine the optimal diagnostic tests and treatment."

Whether it is called PPID or Cushing's, aging horses are at a higher risk than their younger counterparts when it comes to this endocrine disorder. While treatment, unfortunately, rarely can achieve remission, proper diagnosis can help owners extend and improve their equine's quality of life. BH

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