Drugs for behavior modification in stallions and geldings*

Sue M. McDonnell
Section of Reproduction, Department of Clinical Studies, School of Veterinary Medicine, University of Pennsylvania, New Bolton Center, Kennett Square, PA, USA

A common request of horse owners, trainers, and breeders is for veterinary assistance with pharmacological aids to behavior modification in male horses, including quieting of stallion-like sexual or aggressive behavior in stallions or geldings and enhancement of libido and copulatory efficiency in breeding stallions. Where skilled personnel and adequate facilities are available, in most instances management and handling changes are recommended as the most effective primary approach to behavior modification. A number of drug treatment protocols can be recommended as an aid to behavior modification. In certain situations where the handling challenge goes beyond the skills of available personnel or options for management changes, use of drugs as the primary approach to behavior modification may be recommended. This presentation summarizes the principal approaches and drugs we employ with stallions and geldings presented to our reproduction and behavior clinic at New Bolton Center.

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Quieting sexual and aggressive behavior

The most common drug approaches to quieting aggressive and sexual behavior of stallions for general handling, training, work, or performance situations, or even in rare instances for handling for breeding, include attempts to disrupt pituitary-gonadal endocrinology, nutritional supplements to modify general temperament, and sedation. For geldings with problematic residual stallion-like behavior in training, show, or for group housing situations, the main treatment approaches include administration of progesterone for its general calming effects, nutritional supplements to modify general temperament, and sedation.

Endocrine suppression

Progesterone administration. In the United States, progesterone administration has been fairly commonly used for the purpose of quieting aggression and sexual behavior in training or performance situations where such behavior is problematic, either for intact stallions or for geldings showing residual stallion-like behavior. Oral altrenogest is the form of progesterone most widely available to the horse industry in North America and is likely the most commonly used and best tolerated form of progesterone for this purpose. In a 2002 survey of 200 Quarter Horse farms in which owners and trainers were asked specifically about oral altrenogest use in stallions, about one third of 63 respondents reported using altrenogest in one or more stallions within that year, either for young colts or mature stallions in training, work or breeding.

In organized studies, with stallions of various ages, and with treatment regimens ranging from 0.044 to 0.088 mg/kg oral altrenogest daily for eight weeks or longer, there has been consistent evidence of expected down-regulation of the pituitary-gonadal axis hormones and consequent reduction in testicular size and sperm production. While reduction in sexual and aggressive behavior have been demonstrated, it is important to note that in general the changes in behavior, measured primarily in semen collection protocols, have been relatively modest.

Semen collection protocols in a breeding farm environment may not directly reflect the behavior changes sought or achieved for performance horses in training or work environments. So, as with many other treatments, without field efficacy studies it is difficult to judge the value of

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progesterone treatment other than by repeated use requested by astute and frugal trainers. It is important to advise owners of stallions that in studies to date, a treatment regimen has not been identified at which sexual and aggressive behavior are effectively modified without potentially fertility-limiting side effects on semen. Any adverse effects of progesterone treatment on spermatogenesis are expected to be temporary, at least in mature stallions, but this has not been adequately addressed.

GnRH vaccines, antagonists or agonists. A second endocrine approach to modification of reproductive behavior and fertility in horses involves attempts to temporarily disrupt pituitary-gonadal hormone production by suppressing GnRH production, using GnRH antagonists or agonists, and more recently, GnRH immunization. In summary, the most promising means for suppression of stallion behavior are immunization and agonists, as stallions appear resistant to down-regulation by administration of agonists. A GnRH vaccine is not yet available for stallions.

Dietary “calming” supplements

A number of dietary supplements are commercially available for calming horses. Horse calming products are typically a formulation of two or more compounds, each with purported behavioral effects. While there are almost no published data on efficacy of particular dietary supplements for horses, some of the specific compounds included in horse calming formulations have been used with horses for decades and judged helpful in many horses for improving general temperament and tractability. Some of the common ingredients, while not specifically tested in horses, do have basis for efficacy in theory or from research in other species. While most horse “calming” supplements are not marketed specifically for male-type behavior, improved general temperament can be quite beneficial to overcoming common handling and management challenges of stallion behavior. For example, l-tryptophan, a common ingredient in commercial calming supplements, is the precursor of the behaviorally important neurotransmitter serotonin. L-tryptophan supplementation has been found to induce calm and fatigue-like behavior in a number of species. In horses, we have blindly evaluated 24-hour time budgets with and without l-tryptophan supplementation given for a variety of behavior problems, including stereotypies, social hyperactivity in confined horses, as well as mild handling challenges in mares, geldings, and stallions (McDonnell, unpublished clinical case studies). We have found that supplementation with l-tryptophan at a rate of 1 to 2 grams once to twice daily typically has a mild calming effect on stalled horses, evident in less problem behavior and greater standing rest as well as more normal cycles of eating and resting behavior beginning within two to four weeks after start of treatment.

Sedation

In rare instances it may be judged necessary and useful for a stallion to be lightly sedated for safe handling for breeding. In such a circumstance, xylazine or detomedine may be recommended. At sedative doses, these compounds have been found to facilitate rather than inhibit ejaculation. When sedation is necessary for any reason for stallions, xylazine or detomidine are recommended over acepromazine, due to greater risk of penile paralysis in horses with the phenothiazine derivative compounds.

A note on calming pheromone approach

In recent years, a synthetic preparation based on an appeasing pheromone identified in peri-mammary gland secretions of lactating females has been commercially available in Europe and North America as a behavior modification aid for a number of domestic species, including horses (Pherocalm® in France and Germany; Modipher EQ® in USA, Veterinary Products Laboratory, Phoenix, AZ). The target applications for the equine product have been general handling challenges that may involve fear, anxiety or stress, such as transportation, feet trimming, veterinary procedures, changes in work or environment, or stressful performance situations.
While a pheromone approach to behavior modification is widely appealing and perhaps quite promising, unfortunately efficacy of currently available products remains somewhat controversial in domestic species. For horses in particular, the sparsely available data on efficacy of current formulations in horses have been formally refuted.\textsuperscript{10,11} In our clinical research setting we have conducted over 200 controlled random switchback trials with mares, foals, stallions, and geldings as an aid to traditional behavior modification in a variety of common management and handling situations, using various application protocols and pheromone preparations provided by the product developer (McDonnell and co-workers, unpublished). So far in that controlled blind study, no statistically significant benefit of treatment has been evident. The developers of the pheromone product have not proposed application to stallion behavior modification, and no data are available specifically for effects of a calming pheromone on problematic male-typical sexual behavior or aggression. Though often unrecognized by handlers, there is typically an element of fear and anxiety to stallion handling problems, either as the primary cause of colt or stallion “misbehavior” or secondary to attempts to discipline the horse. Further investigation of a calming pheromone approach for use with stallion behavior modification would be worthwhile.

Enhancing stallion sexual arousal and response

The principal approaches to drug therapy for enhancing sexual arousal and response in stallions include analgesics to relieve musculoskeletal discomfort that may be impeding or distracting the stallion, anxiolytics to relieve psychosocial or handling inhibitions inherent to domestic breeding environments, and endocrine approaches aimed at increasing gonadal steroids to maintain required levels of arousal and stamina with minimal increase in undesirable or counterproductive aggressive behavior and with minimal down-regulation of sperm production. Additional drug therapy that is useful for certain breeding stallions includes genital smooth muscle active agents to enhance ejaculatory function \textit{in copula} or to pharmacologically induce ejaculation \textit{ex copula}. For more detailed description of evaluation and therapy of sexual behavior dysfunction see McDonnell, 2009.\textsuperscript{12}

Analgesics

\textit{Phenylbutazone}. Specific musculoskeletal breeding behavior problems and treatment strategies including drug protocols have been detailed.\textsuperscript{11} In summary, phenylbutazone orally has been recommended and has in our experience been the most useful of equine analgesics for improving comfort for breeding. We recommend 2.2 mg/kg orally twice daily as tolerated. Although fertility trials have not been done, clinical experience suggests no adverse effects of chronic treatment with phenylbutazone at levels tolerated by a stallion. For stallions that tend to develop problems during a busy breeding schedule, we recommend keeping the stallion on daily treatment throughout the breeding season to maintain comfort and efficient ejaculation so as to avoid a potential downward spiral of delayed ejaculation, additional effort, and exacerbated lameness that often occurs in such stallions.

\textit{Gabapentin}. In recent years, we have used oral gabapentin for certain stallions in combination with phenylbutazone in an attempt to help breeding stallions with possible neurogenic as well as musculoskeletal discomfort (McDonnell and Turner, unpublished clinical observations). Recent studies indicate that oral bioavailability of gabapentin is low compared to intravenous administration, but is well-tolerated at 20 mg/kg.\textsuperscript{12-14}

\textit{Firocoxib}. In recent years firocoxib formulations for horses have become commercially available. Although not yet tested in breeding stallions, in greater than 250 horses with osteoarthritis lameness, the proportion of patients with improved lameness scores at two weeks was similar for firocoxib treatment at 0.1 mg/kg orally once daily as for phenylbutazone treatment at 4.4 mg/kg orally once daily.\textsuperscript{15} For additional measures of pain on manipulation or palpation, joint circumference, and range of motion score, the proportion of horses improved at two weeks into treatment was greater for firocoxib-treated horses.
Anxiolytic therapy

For slow starting novice breeders or for stallions with failure to respond in a novel environment or following known negative experience, such as rough handling, a painful event associated with breeding, or a breeding accident, we recommend trying treatment with diazepam during breeding sessions. We recommend 0.05 mg/kg, not to exceed 20 mg, injected IV slowly just before exposure to the mare. The maximum effectiveness appears to be at about 5 to 10 minutes after injection. Our rule of thumb has been to expect about one third of stallions that we judge would be good candidates for such therapy to respond well immediately, about one third to have no change with treatment, and about one third to become quieter and less responsive. For horses that are quieted by a full dose, a lower dose may be helpful.

Endocrine enhancement

For most stallions, sexual arousal, response, and stamina can be enhanced by increasing circulating testosterone. Gonadotropin-releasing hormone can be used to induce a release of endogenous gonadotropins and testicular hormones. Independent of gonadal androgens, GnRH treatment has been shown to promote sexual behavior. We continue to find a regimen of 50 µg of the simple decapeptide GnRH SC one and two hours before each breeding to be helpful in many cases. Should GnRH treatment not yield sufficient rise in testosterone or improvement in behavior, we may consider administering testosterone in addition to GnRH, with careful consideration to baseline endocrinology, the cost of potential down-regulation and adverse effects on sperm production in light of the stallion’s breeding obligations, how dire the stallion’s breeding career situation has become, and the ability to manage a potential increase in problematic aggressive behavior. Endocrinology is monitored with the goal of increasing serum or plasma testosterone levels to remain within the range of 2 to 4 ng/ml. Traditionally, we have used a variety of preparations of testosterone and the longer-stored esterified forms in aqueous and oil preparations for injection as available. More recently we have used transdermal preparations of testosterone in oil applied to hairless perineal skin or directly to the penis for added benefit of improved genital sensitivity. For the typical stallion with baseline endogenous levels of 0.5 to 1 ng/ml testosterone, our starting dose for a light horse stallion is 80 to 100 mg testosterone every other day for injectable preparations, and daily or twice daily for transdermal application to achieve testosterone levels within the target range of 2 to 4 ng/ml. Improvement in sexual response typically lags as much as five to eight days behind increased blood levels of testosterone. Aggressive behavior often increases before sexual arousal and response.

Enhancing/inducing ejaculation

For a variety of physical and behavioral problems in breeding stallions, it is often helpful to pharmacologically lower the ejaculatory threshold to enable breeding with less musculoskeletal effort, or to simply induce ejaculation ex copula. Protocols that have been developed over the years have been reviewed in detail elsewhere and should be carefully reviewed before recommending such therapies. The compounds used have dose-dependent inhibitory and facilitatory effects, and there is wide variation among individuals in effective dose. Imipramine hydrochloride remains our first choice for lowering ejaculatory threshold for breeding or semen collection in copula. We recommend 2.2 mg/kg orally two hours before breeding.

Pharmacologically-induced ex copula ejaculation protocols developed to date remain fairly unreliable, but can be useful in certain cases. Among several protocols that have been evaluated for pharmacologically inducing ejaculation ex copula, our first choice is 2.2 mg/kg imipramine PO, followed two hours later by xylazine at 0.4 to 0.6 mg/kg IV. The level of sedation associated with greatest success involves a smooth induction to a comfortably deep standing sedation over the course of the first three minutes.
A note on self-mutilation in stallions or geldings

A relatively uncommon, but often fertility- and life-threatening behavior problem of stallions, is self-mutilation. We have come to appreciate that the most common cause of self-mutilative behavior in horses is physical discomfort. Unfortunately, when a physical cause of discomfort is not readily identified, it is quite common for the behavior to be attributed to psychological causes and for owners to seek behavior modification including veterinary assistance with drugs. Many horses with painful physical conditions will show some improvement with training or behavior modification approaches, further delaying diagnosis and treatment of the underlying physical problem. Our current recommendation in cases of self-mutilation in which a physical cause has not been identified is to have a detailed veterinary behavior evaluation to aid in judging whether the problem is physical or psychological and to provide guidance in localizing the discomfort to suggest further veterinary diagnostics. Videotaped samples of self-mutilation episodes as well as longer samples of the horse at rest are most helpful toward this goal.

References