# Drugs and Equine Performance: A Review

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One of the fundamental questions which veterinarians and researchers on equine performance are asked concerns whether or not a given drug or medication will improve the racing performance of a horse. The question is most commonly asked about central nervous system (CNS) stimulants, which are known from experience in human medicine to produce a certain spectrum of stimulant effects. Based on this experience, these drugs are then 'tried' in horses. Both the people using these drugs in horses and the people regulating the use of drugs in horses have considerable interest in knowing whether or not these agents will actually enhance performance (Tobin 1981). Researchers have made numerous attempts to answer this question experimentally with varying degrees of success.

TABLE 1. Experimental approaches to the effect of drugs on equine performance.

1. 'Horseman's Experiment': run horses ± drug at top speed for one mile.
2. 'Quasi-Horseman's Experiment': trot or canter horses ± drug for short distances.
3. 'Pharmacologist's Experiment': study the effects of drugs on simple behavioural models.
4. 'Statistician's Experiment': retrospective study of times ± drug in large numbers of horses.

The experimental approaches to this problem can be divided into four separate headings (Table 1). The simplest approach, which we call the 'Horseman's Experiment', is to run a small number of horses at top speed for about one mile, with and without drug. Results are then analyzed for effects on performance. This approach has been tried by a number of workers with relatively little success. Studies of this type were carried out at Ohio State University and at the University of Kentucky. In the Kentucky studies, horses were intravenously dosed with 0.5 mg/kg of furosemide or an equivalent volume of normal saline 30 minutes prior to the trial. They were then paced at their best speed for one mile and their times compared. Analysis of the data (Table 2) showed no significant difference between their times with and without furosemide. The basic conclusion from this experiment, and from broadly similar experiments carried out by Professor Gabel and his colleagues at Ohio State University (reported in this Proceedings), was that furosemide had no effect on equine performance.

Similar experiments with amphetamine, thiamine and acepromazine were carried out in Australia (Stewart 1972). Stewart treated three Thoroughbred horses with

TABLE 2. Effect of furosemide on time trials in Standardbred horses.

| Trial | Horse | Saline | Furosemide | Δ |
|---|---|---|---|---|
| 1 | Noelle | 131 | 141 | +10 |
| 2 | | 135 | 134 | −1 |
| 3 | | 135 | 129 | −6 |
| 4 | Doc Stultz | 134 | 135 | +1 |
| 5 | | 134 | 132 | −2 |
| 6 | Beau | 142 | 136 | −6 |
| 7 | | 139 | 141 | +2 |
| 8 | Ballards Love Bug | 143 | 142 | −1 |
| 9 | Wilson | 134 | 134 | 0 |
| All horses | | 136.33 | 136.00 | −0.33 |

All values represent times in seconds required for these horses to pace one mile. The Δ symbol refers to the change from the matched control associated with furosemide administration. Applying a t test to all data points, t = 0.2, less than one-tenth the value required for significance at the 0.05 level.

amphetamine, thiamine and acepromazine pre race, and then galloped them for distances of between 800 and 1600 metres 30 minutes later. While he found that the gallop speed was improved in each of five trials, he did not consider the improvement to be statistically significant. Stewart's problem, and the general problem with this type of study, is that the experimental baseline is large, the experimental variable is small and, in general, the number of horses in the experiment is too small (Fig. 1).

The experimental baseline is large because the horse is being galloped or paced for about a mile at as high a speed as he can go. For a Standardbred horse, the baseline will be at least two minutes, and for a Thoroughbred, about one minute and 40 seconds. A drug-induced improvement of one second, an enormous improvement in terms of a horse race, is only about a 1% improvement and is readily lost in the 'noise' or inherent variability of equine performance (Fig. 1). There are two principal ways of getting around this problem. One is to reduce the baseline such that drug effects show up readily. The other, and more difficult, approach is to increase the number of animals in the experimental system until very small improvements in performance can be detected. Different workers have used both of these strategies under differing circumstances with varying degrees of success.

There are two basic experimental approaches to reducing the level of the baseline. A number of workers have chosen to trot or canter horses over shorter distances and therefore study the effects of drugs on trot, canter and gallop tests. Under these circumstances, Sanford (1971, 1973) (Table 3) was able to show effects of a variety of drugs on times to trot and/or canter a certain distance. However, it is not at all clear whether these experiments measured effects on performance or simply central stimulant or locomotor stimulant actions of these drugs. Sanford, therefore, has been very cautious about interpreting his results in terms of effects on performance. Broadly similar experiments have also been carried out by Fujii *et al.* (1970, 1974) in Japan. Since the above

experiments are a variation of the 'Horseman's Experiment', we have chosen to call them the 'Quasi-Horseman's Experiment'.

FIGURE 1. 'Performance tests' are unsatisfactory experimental models because the objective is to run the horse as close to his maximum speed as possible, then administer a drug and look for an improvement. On this model, indicated to the right side of the illustration, the baseline constitutes about 99% of the measured response, and the drug effect is very difficult to distinguish. If, however, the experiment starts with a standing horse, both baseline and the random variation of the baseline called noise are very small compared with the maximal response. Under these circumstances, it is relatively easy to measure a drug effect, as the experimental variable is large. Experiments are thus best set up with a large variable to measure, rather than with a miniscule variable and massive baselines. Reproduced from "Drugs and the Performance Horse", by Thomas Tobin. Charles C. Thomas Ltd, Springfield, Illinois 62717.

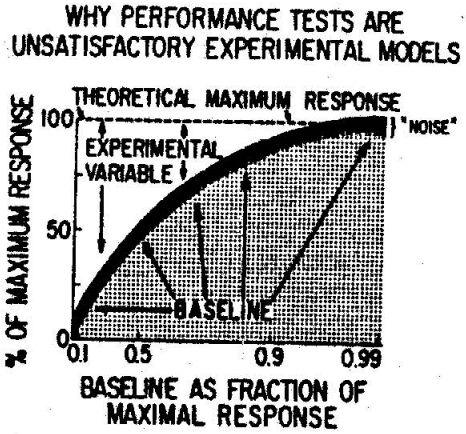



TABLE 3. Performance test effect of CNS stimulants on speed at trot and canter.

| Compound | Dose (mg/kg) | Route | No. tested | Effect on speed at trot and canter |
|---|---|---|---|---|
| Methylamphetamine | 0.05 | IM | 4 | + in 2/4 at extended trot |
| | 0.01 | IM | 4 | + in 2/4 at collected trot |
| | | | | + in 4/4 at extended trot |
| | | | | + in 2/4 at canter |
| Methylphenidate | 0.25 | SC | 4 | + in 4/4 at all paces |
| | 0.5 | SC | 4 | + in 4/4 at all paces |
| Pemoline | 4.0 | Oral | 3 | + in 3/3 at all paces |
| | 8.0 | Oral | 3 | + in 3/3 at all paces |
| Caffeine | 2.0 | Oral | 3 | No consistent effect |
| | 4.0 | Oral | 3 | No consistent effect |

+ = increased speed

Source: Sanford, J. (1983). Drugs affecting equine performance. *In Pharmacological Basis of Large Animal Medicine*. Bogan, J. A., Lees, P. and Yoxall, A. T. (eds.). Blackwell Scientific Publications, Oxford. pp. 495–510.

A logical extension of the reduction of the baseline approach is to start with a zero baseline, i.e. a standing horse, and to see what different stimulant drugs will do. This particular behavioural model works very well for drugs with a dopaminergic component of action, such as the narcotic analgesics, and with pure dopaminergic stimulants, such as apomorphine. Because these methods enable clear characterization of both dose and time response to these drugs, we have chosen to call them the 'Pharmacologist's Experiment'.

FIGURE 2. Horses trot faster after increased doses of fentanyl. The lower panel shows the normal activity of a horse at rest in his stall, about four steps in two minutes. The top panel shows the trotting response produced in horses by injection of about 0.5, 2, 4 and 8 mg of fentanyl/1000 lb by rapid IV injection. Note the short, sharp time course of the fentanyl stimulation of trotting activity. Reproduced from "Drugs and the Performance Horse", by Thomas Tobin. Charles C. Thomas Ltd, Springfield, Illinois 62717.

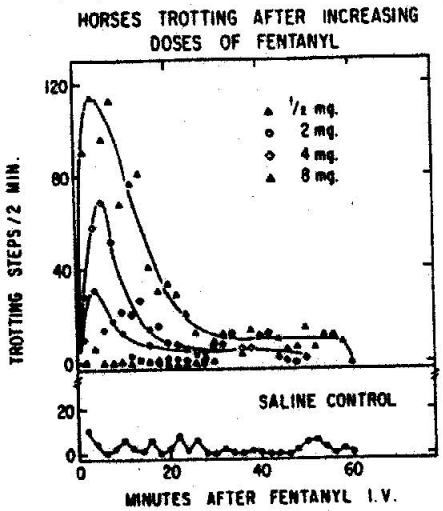
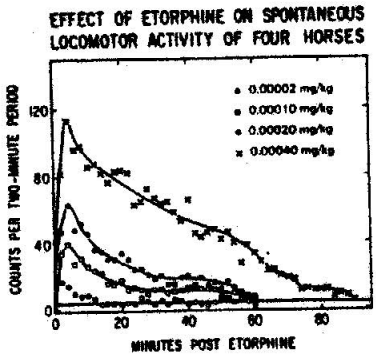


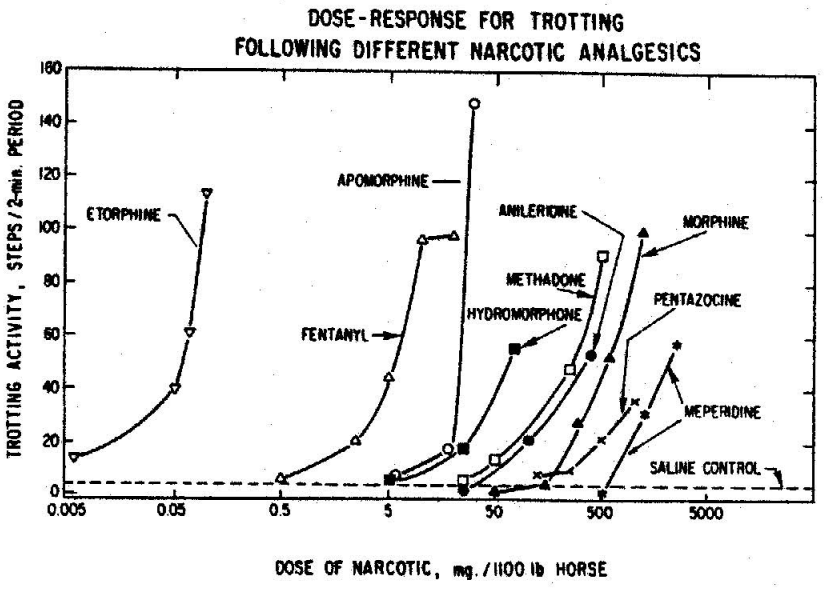

FIGURE 3. Four horses were injected IV with saline and then increasing doses of etorphine. The locomotor response to 0.00002 mg/kg etorphine is shown by the open circles (○—○), 0.00010 mg/kg by open squares (□—□), to 0.00020 mg/kg by closed circles (●—●), and to 0.00040 mg/kg by crosses (×–×). The straight line at 4 counts/2-minute period represents the average response to saline. Reproduced from "Drugs and the Performance Horse", by Thomas Tobin. Charles C. Thomas Ltd, Springfield, Illinois 62717.



We stumbled upon this method early on in our kinetic studies on fentanyl in the horse (Tobin 1981). If a horse is placed in a box stall and allowed a period of acclimation, the horse will walk around the stall at about four steps/2-minute period (Tobin and Miller, 1979; Tobin and Woods, 1979; Tobin *et al.*, 1979a, 1979b, 1979c). If the horse is given increasing doses of fentanyl, he exhibits a short sharp locomotor response, as shown in Fig. 2. At 0.02 mg/kg, which is about the maximum dose of fentanyl that can be safely administered to a horse, a locomotor response is observed which peaks at about 100 steps/2 minutes and occurs about five minutes after intravenous administration of the drug. The response then decays rapidly to control levels between 45 and 60 minutes after drug administration.

This locomotor response is a characteristic response of horses to narcotic analgesics. Etorphine, which is about 100 times more potent than fentanyl, produces a broadly similar response (Fig. 3), as do hydromorphone, methadone, anileridine, morphine, pentazocine and meperidine (Combie 1979; Combie *et al.*, 1979). When the peak locomotor responses to different doses of these agents are plotted, a classic family of parallel dose response curves is obtained covering a 10000-fold range of concentrations (Fig. 4). These data suggest that locomotor stimulation is a characteristic dose-related effect of narcotic analgesics in the horse.

FIGURE 4. Horses were dosed with increasing amounts of the indicated drugs, and the average number of steps taken during the peak 2-minute period was plotted for etorphine, fentanyl and apomorphine. For all other drugs, average counts per 2-minute period were determined for the 16-minute interval of peak activity. Three to ten horses were used in the experiments on etorphine, fentanyl, apomorphine, methadone, morphine and pentazocine. One horse was used to determine each dose response curve for hydromorphone, anileridine and meperidine. The average counts per 2-minute period for the saline control are shown by the dashed line near the bottom of the graph. Reproduced from "Drugs and the Performance Horse", by Thomas Tobin. Charles C. Thomas Ltd, Springfield, Illinois 62717.



The locomotor response to fentanyl is also highly reproducible in the horse. As shown in Fig. 5, horses can be dosed with fentanyl every 90 minutes, and essentially the same locomotor response results. The time course of the locomotor response to fentanyl is probably dependent on the rate of entry and exit of fentanyl from the CNS.

All in all, the response to the narcotic analgesics, and particularly to fentanyl, has been reproducible. Fentanyl is therefore a good drug for performance work since its responses are predictable and highly reliable.

An example of a drug which can give a dramatic locomotor response but whose action is unreliable is apomorphine. Apomorphine is a dopaminergic agonist, and at the right dose, in the right horse, on the right day, it can produce a dramatic locomotor response (Fig. 6). However, for reasons which we have not been able to determine, this response is quite unreliable. The dose response curves to apomorphine are quite scattered, in contrast to the response curves of fentanyl which are quite consistent (Fig. 7). Apomorphine would therefore be a very poor choice for performance work because of the uncertainty of obtaining the desired stimulant effect of the drug during performance trials.

Other drugs, while categorized as narcotic analgesics, produce a poor locomotor response. One such drug is butorphanol (stadol) which was used occasionally in American racing in the early 1980s. This drug produced a very poor locomotor response in horses (Fig. 8) and thus would not be a drug of choice for performance work.

FIGURE 5. Horses were dosed IV with 0.1 mg/kg acepromazine or 0.015 mg/kg Narcan® at 15 and 5 minutes, respectively, before a series of four doses of 0.020 mg/kg fentanyl. The open circles (O—O) represent the locomotor response of horses dosed with fentanyl at 0, 90, 180 and 360 minutes. The crosses (x—x) show the response to fentanyl following pretreatment with acepromazine, and the solid squares (■—■) show the response after pretreatment with naloxone. All points are the means of experiments on three horses. Reproduced from "Drugs and the Performance Horse", by Thomas Tobin. Charles C. Thomas Ltd, Springfield, Illinois 62717.

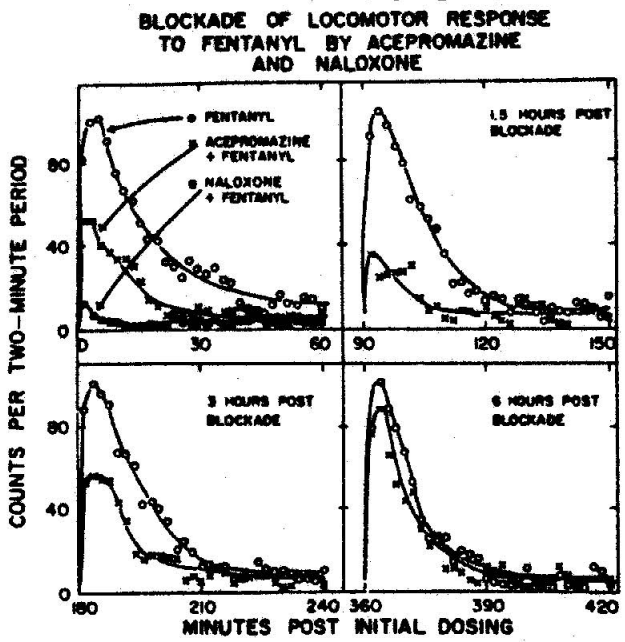


FIGURE 6. A horse was injected IV with either 6 mg (△– △), 18 mg (○—○), 30 mg (□—□) or 60 mg (●—●) of apomorphine. The symbols represent the number of steps taken per 2-minute period post injection. Reproduced from "Drugs and the Performance Horse", by Thomas Tobin. Charles C. Thomas Ltd, Springfield, Illinois 62717.

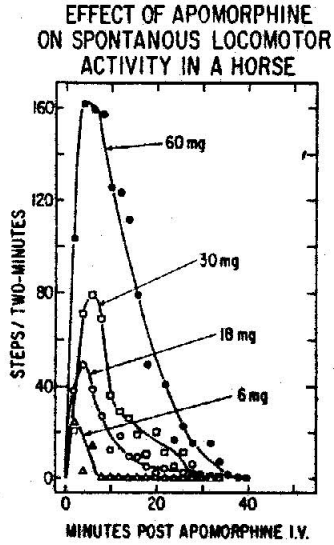



FIGURE 7. Individual dose response curves to fentanyl and apomorphone in the horse. The left-hand panel shows four individual dose response curves to fentanyl obtained in a sequence of experiments. The consistent nature of the response to fentanyl is indicated by the dashed window. The right-hand panel shows all the dose response data obtained with apomorphine, demonstrating the wide scatter in responses and the often very steep dose response curves obtained with apomorphine. Reproduced from "Drugs and the Performance Horse", by Thomas Tobin. Charles C. Thomas Ltd, Springfield, Illinois 62717.

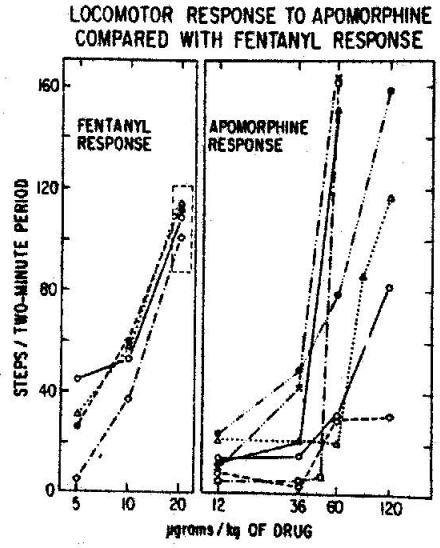
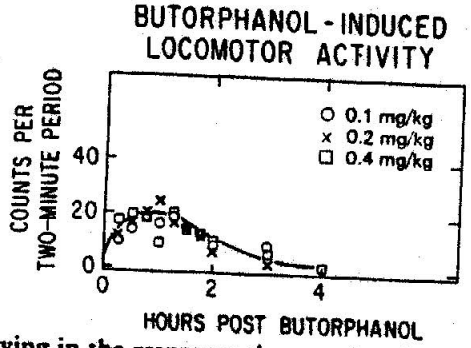


FIGURE 8. One horse was dosed IV with butorphanol increasing from 0.1 mg/kg shown by the open circles (O—O) to 0.2 mg/kg shown by the crosses (×—×) and 0.4 mg/kg shown by the open squares (□—□). There was no significant difference ($p < 0.01$) among the number of counts obtained following injection of these three doses. Reproduced from "Drugs and the Performance Horse", by Thomas Tobin. Charles C. Thomas Ltd, Springfield, Illinois 62717.




As well as drugs varying in the responses they produce in horses, horses will also vary in their responses to individual drugs. Using a behavioural responding apparatus which measures work for food reinforcement, we have shown that the responses of horses to cocaine vary dramatically (Shults 1980; Shults *et al.*, 1982). In our hands, some horses responded to as little as 4 mg cocaine/horse, while others required up to 100 times this dose for maximal responding (Fig. 9). These experiments suggest that with some drugs the sensitivity of individual horses to the agent selected for performance testing needs to be determined.

The fourth approach to this problem was suggested by Mr Carl Larsen of the Kentucky Harness Racing Commission who pointed out that the only legal medication for harness horses racing in Kentucky was furosemide. He therefore suggested that a retrospective statistical analysis of track times of horses racing with and without furosemide in Kentucky be carried out. Because the principal skills involved are statistical, we called this the 'Statistician's Experiment'. The results of this experiment are shown in Table 4. Fifty-eight horses which ran in the Louisville Downs summer meet of 1977 with and without furosemide were identified. One hundred and sixty times for those horses running without furosemide and 232 times for those running on furosemide were obtained. It turned out that the mean time of these horses to pace one mile was about 0.14 seconds slower on furosemide than without it. This difference, however, was far too small to be statistically significant, and the basic conclusion from these experiments was that the horsemen at Louisville Downs in the summer of 1977 were essentially unable to improve the performance of their horses by the use of furosemide.

In summary, performance trials are difficult, time-consuming and expensive experiments to conduct. Using the 'Horseman's Experiment' with small numbers of animals, it is very difficult to demonstrate statistically significant effects. By reducing the output demanded of the animal, one can produce statistically significant effects, but these results should not be interpreted as indicative of effects on performance.

Simple behavioural experiments can be used to determine the suitability of drugs for performance work and to determine the optimal dose of a drug and time post dosing for performance experiments to be carried out. Simple behavioural experiments may also be

FIGURE 9. Acute effects of cocaine on variable interval responding.
Each symbol shows the change from control response rate caused by the administration of the indicated doses for cocaine to a single horse. A control response rate was established for each horse before each drug administration. The control rate is the average of three consecutively run sessions in which saline was administered. Reproduced from "Drugs and the Performance Horse", by Thomas Tobin. Charles C. Thomas Ltd, Springfield, Illinois 62717.

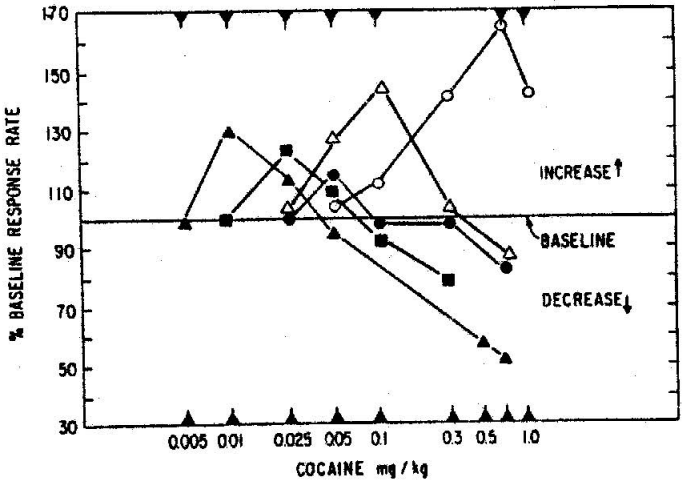



TABLE 4. Effect of medication with furosemide on the performance of horses racing at Louisville Downs, summer 1977.

| | No. of horses | No. of trials | Mean times | SEM |
|---|---|---|---|---|
| Pre furosemide | 58 | 160 | 128 5925 | 0.2031 F = < 0.00 |
| With furosemide | 58 | 232 | 128 7366 | 0.1594 (F for significance should be > 3.0) |

At this meet, furosemide was the only permitted medication, and its use was monitored by urinalysis. Horsemen could elect to put their horses on furosemide. Once begun, furosemide treatment was obligatorily maintained throughout the meet. Performance times for horses pre-furosemide and post-furosemide treatment were obtained from the meet programmes and compared. Only times on good or fast tracks were taken. For the 58 horses selected, 160 pre-furosemide times and 232 post-furosemide times were available. A randomized block design was used, where each horse represented a block. After adjusting for blocks (i.e. difference between horses) there was no significant difference between treatments (i.e. times on and off furosemide).

used to determine the responsiveness of individual horses to drugs. Because of the expense of performance experiments, the use of simple behavioural experiments to characterize drug action in horses is highly advisable before experiments are carried out.

Retrospective studies of drug effects in populations of racing horses is probably the most satisfactory way of determining the effects of drugs on performance. Unfortunately, the applicability of this approach is limited by the rules of racing as well as by ethical and legal concerns.

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