

Eric C. Strain · Sharon L. Walsh · George E. Bigelow

## Blockade of hydromorphone effects by buprenorphine/naloxone and buprenorphine

Received: 5 February 2001 / Accepted: 13 August 2001 / Published online: 12 October 2001  
© Springer-Verlag 2001

**Abstract Rationale:** Buprenorphine is an opioid agonist–antagonist used in the treatment of opioid dependence. Naloxone has been combined with buprenorphine to decrease the parenteral abuse potential of buprenorphine. This addition of naloxone may also confer further opioid blockade efficacy. **Objectives:** To test the opioid blockade efficacy of sublingual buprenorphine/naloxone versus buprenorphine alone and determine whether: (1) the blockade efficacy of buprenorphine/naloxone varies between the time of expected maximal and minimal effects of naloxone, (2) the blockade efficacy of buprenorphine/naloxone and buprenorphine varies as a function of maintenance dose level, and (3) there are adaptive changes over time associated with repeated daily dosing of buprenorphine/naloxone and buprenorphine. **Methods:** Residential subjects ( $n=6$ ) were maintained on different double-blind dose levels of buprenorphine/naloxone (4/1, 8/2, 16/4, 32/8 mg) and buprenorphine (32 mg) for 6-day periods and challenged with parenteral doses of hydromorphone (12 mg) in laboratory sessions. **Results:** There was no evidence of additional opioid blockade efficacy conferred by combining naloxone with buprenorphine. Higher doses of buprenorphine/naloxone provided greater blockade of hydromorphone effects. Changes over time associated with repeated daily dosing of buprenorphine/naloxone and buprenorphine were minimal. **Conclusions:** The addition of naloxone to buprenorphine may deter the parenteral abuse of buprenorphine/naloxone, but it does not enhance the therapeutic efficacy of buprenorphine. The blockade efficacy of buprenorphine/naloxone is dose related; however, doses up to 32/8 mg buprenorphine/naloxone provide only partial blockade when subjects receive a high dose of an opioid agonist.

**Keywords** Agonist–antagonist · Buprenorphine · Buprenorphine/naloxone · Hydromorphone · Naloxone · Opioid abuse

### Introduction

Buprenorphine is an opioid agonist–antagonist initially developed and marketed as an analgesic. However, nearly 25 years ago, buprenorphine was identified as potentially useful for the treatment of opioid dependence (Jasinski et al. 1978), and, since the late 1990s, it has been marketed in several European countries for this latter indication. Buprenorphine is a partial  $\mu$  agonist, and this accounts for its suppression of opioid self-administration (Mello and Mendelson 1980) and attenuation of the effects of opioid agonist challenge (Bickel et al. 1988; Rosen et al. 1994; Walsh et al. 1995; Strain et al. 1997; Schuh et al. 1999). Opioid blockade effects of buprenorphine are dose related at the low range of tested doses, although there is a relative plateau in such effects at higher doses.

Several outpatient clinical trials have shown buprenorphine is safe and effective (Johnson et al. 1992, 2000; Strain et al. 1994; Ling et al. 1996, 1998; Schottenfeld et al. 1997). Because buprenorphine can be abused, a combination product of buprenorphine plus naloxone has been developed. The addition of naloxone should decrease the parenteral abuse potential of buprenorphine in opioid-dependent persons because injected naloxone could precipitate withdrawal. However, sublingual naloxone has poor bioavailability (Preston et al. 1990), so administration of buprenorphine combined with naloxone by the sublingual route should not result in a precipitated withdrawal syndrome. Human laboratory studies testing different dosage ratios of buprenorphine/naloxone (Preston et al. 1988; Weinhold et al. 1992; Mendelson et al. 1996, 1997, 1999; Fudala et al. 1998) have led to the conclusion that a buprenorphine/naloxone dose ratio of 4:1 should be optimal.

The addition of naloxone to buprenorphine might confer additional blockade efficacy, especially at higher

E.C. Strain (✉) · S.L. Walsh · G.E. Bigelow  
Behavioral Pharmacology Research Unit,  
Department of Psychiatry and Behavioral Sciences,  
The Johns Hopkins University School of Medicine,  
5510 Nathan Shock Drive, Baltimore, MD 21224, USA  
e-mail: ecsgrs@aol.com  
Tel.: +1-410-5501191, Fax: +1-410-5500030

doses of buprenorphine/naloxone. While naloxone has poor sublingual bioavailability, it does produce pharmacodynamic effects at higher ( $\geq 2$  mg) doses (Preston et al. 1990). Thus, the addition of naloxone might have therapeutic value beyond altering the abuse potential of buprenorphine, for example, through receptor occupancy by bioavailable naloxone (Rose and Levin 1992). The purpose of this study was to systematically assess the blockade efficacy of buprenorphine/naloxone and buprenorphine alone across a range of doses in opioid-dependent volunteers.

## Methods

### Subjects

Participants were adult volunteers with active opioid dependence. Applicants were excluded if they had significant medical or psychiatric illness; females could not participate if pregnant. Participants lived on a 14-bed research ward, as previously described (Strain et al. 1997, 2000). The study was approved by the Institutional Review Board; volunteers were paid for participation. Five subjects were African American and one was white; five were male. Average age was 31.2 years (range 29–37 years), average education was 10.8 years (range 9–12 years), and average duration of illicit opioid use was 10.0 years (range 3–19 years). Participants reported using illicit opioids an average of 4.2 (range 1.5–6.0) times per day prior to study entry.

### Study procedure

Subjects were admitted to the residential unit between Tuesday and Friday, gave written informed consent, and started on sublingual buprenorphine/naloxone. Each subject was maintained on five different double-blind doses of buprenorphine/naloxone or buprenorphine throughout his/her study duration and repeatedly challenged with hydromorphone as described below. Each subject participated in 22 challenge sessions, of which the first two occurred on the following Monday and Tuesday (after a minimum of 3 days stabilization on buprenorphine/naloxone). These two sessions were double-blind training sessions omitted from data analyses. After completion of the residential study, subjects were discharged to an outpatient treatment/research clinic.

### Maintenance medication dosing

Maintenance doses of buprenorphine/naloxone and buprenorphine tablets were administered at the same time each day. Subjects received a combination of active and placebo tablets in order to maintain the blindness. At the time of admission to the residential unit, participants were stabilized on 4/1 mg of daily buprenorphine/naloxone. Subjects remained on this dose for the week of admission, the subsequent week (the first full week of study participation), and the Monday of the second full week. On the Tuesday of the second full week, participants received a double-blind placebo substitute dose. The next day (Wednesday), a new maintenance dose of buprenorphine/naloxone (8/2 mg) began. This dose continued through the following Monday (the start of the third full week); placebo buprenorphine/naloxone was administered on that Tuesday, and dosing increased to 16/4 mg of daily buprenorphine/naloxone the next day. This pattern of dosing (6 days of active medication followed by placebo on a Tuesday) continued for two additional cycles (32/8 mg buprenorphine/naloxone, and then 32/0 mg buprenorphine alone).

Tablets for sublingual administration were supplied by the National Institute on Drug Abuse, Research Technology Branch

(Rockville, Md.), from a supply provided by Reckitt and Colman (Hull, England). Tablets were in two sizes. Small tablets weighed 100 mg and contained either placebo or 2 mg buprenorphine combined with 0.5 mg naloxone. Large tablets weighed 400 mg and contained either placebo, 8 mg buprenorphine alone, or 8 mg buprenorphine plus 2 mg naloxone. Tablets were matched for color and taste. Participants received four large tablets and two small tablets each day.

### Hydromorphone challenge sessions

Sessions were conducted at the same time each day – on Mondays, Tuesdays, Wednesdays, and Fridays – and followed similar procedures utilized in previous studies (Strain et al. 1997, 2000). Sessions lasted 3.5 h and began 30 min after the daily sublingual dose. During each experimental session, a double-blind intramuscular injection of 12 mg hydromorphone in 2 ml was administered into the deltoid muscle (timed to occur 30 min after the start of the session). A commercial preparation of hydromorphone hydrochloride (10 mg/ml; manufactured by Abbott Laboratories, North Chicago, Ill., for Knoll Pharmaceutical Company, Mount Olive, N.J.) was diluted to the appropriate volume with bacteriostatic saline.

### Physiological measures

Heart rate, blood pressure, skin temperature, respiratory rate, and oxygen saturation were monitored throughout the session following procedures similar to those utilized in previous studies (Strain et al. 1997, 2000). Data for each measure were collected and stored at 1-min intervals and averaged across 15-min intervals. Pupil diameter was determined from photographs taken before drug administration and at 15-min intervals after drug administration.

### Subject and observer measures

Subjective effect reports and observer rating questionnaires were completed 15 min before and at 15-min intervals after drug administration. These measures have been described in detail in previous studies (Strain et al. 1997, 2000). Subjects were instructed to respond describing how they felt at the time the questionnaire was being answered. Subjects completed visual analog scales, a pharmacological class questionnaire, and an adjective rating questionnaire. There were six visual analog scales: high, drug effects, good effects, bad effects, liking, and sick. The pharmacological class questionnaire asked the subject to select one of ten drug classes to which the administered drug was most similar. The adjective rating questionnaire (Fraser et al. 1961; Jasinski 1977) consisted of 37 items which the participant rated on a five-point scale from 0 (not at all) to 4 (extremely); the items constituted two scales: a 16-item opioid agonist scale (adjectives associated with morphine-like effects) and a 21-item withdrawal scale (adjectives associated with opioid withdrawal-like effects). Observer ratings included the same adjective rating scale, as well as an assessment of seven signs of opioid withdrawal (lacrimation, rhinorrhea, perspiration, piloerection, bowel sounds, yawning, and restlessness, derived from Kolb and Himmelsbach 1938). Ratings were made by a trained research technician who was present throughout the session and blind to the drug administered. Observer ratings were carried out at the same times as the subject ratings.

### Psychomotor/cognitive performance measures

In order to assess possible psychomotor or cognitive performance changes associated with buprenorphine, buprenorphine/naloxone, or hydromorphone effects, subjects completed during sessions a computerized form of the digit symbol substitution task (DSST; McLeod et al. 1982), a circular lights task (Griffiths et al. 1983),

and a computerized form of the trail-making b test (Reitan 1958; Strain et al. 2000). Each of the tasks were completed during the baseline period (15 min before drug administration) and at the same times as (immediately following) the subject ratings.

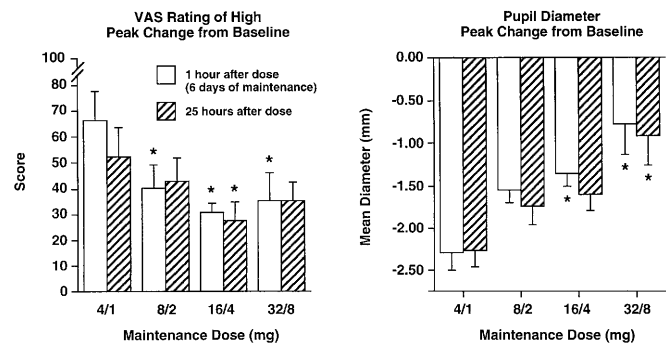
### Experimental questions

Challenge sessions were designed to answer three questions:

1. How does the blockade efficacy of buprenorphine/naloxone vary as a function of the presence versus absence of naloxone?
  - Monday sessions tested the blockade efficacy of buprenorphine/naloxone at the time of expected maximal effect of naloxone (i.e., 1 h after the daily sublingual dose). Subjects received sublingual placebo on Tuesdays, so this session measured blockade in the absence of naloxone (although diminished blockade efficacy at 25 h versus 1 h might also be attributed to declining buprenorphine concentration). Thus, Monday/Tuesday sessions for a given maintenance dose sought to answer the question of whether sublingual naloxone was conferring additional blockade efficacy. The fifth full study week replicated maintenance on 32 mg buprenorphine, but without naloxone. Comparison of responses to hydromorphone on Mondays of 32/8 mg versus 32/0 mg allowed a direct assessment of naloxone blockade effects (without the confound of a decreasing buprenorphine concentration).
2. How does the blockade efficacy of buprenorphine/naloxone and buprenorphine vary as a function of maintenance dose level?
  - Monday sessions also assessed blockade efficacy after 6 days of stabilization on each maintenance dose. Comparisons between Monday sessions assessed blockade of opioid agonist effects as a function of buprenorphine/naloxone dose.
3. Are there changes associated with repeated daily doses of the buprenorphine/naloxone and buprenorphine?
  - Within each buprenorphine/naloxone dose, sessions on Wednesdays, Fridays, and Mondays assessed the development of changes related to repeated daily dosing of buprenorphine/naloxone and buprenorphine.

### Data analysis

Results were analyzed using calculations of peak change from baseline scores. For most measures, peak change from baseline was an increase, although decreases from baseline were examined when appropriate (e.g., pupil diameter changes in response to opioid agonist challenge). This approach yielded a single value for each measure, condition, and subject. A conservative one-step procedure, Tukey's honestly significant difference (HSD), was then used to compare pairs of conditions of interest. The mean square error term needed to perform these tests was calculated using repeated-measures, two-factor analysis of variance; main effects were maintenance medication condition and day. The day varied depending on which question was addressed (blockade efficacy with versus without naloxone; blockade efficacy after 6 days of maintenance; and effects related to daily administration of buprenorphine/naloxone and buprenorphine). For the first two questions, comparisons – for which the Tukey  $q$ -value was  $>5.008$  ( $P < 0.05$ ) – are reported as statistically significant, while for the final question – comparisons for which the Tukey  $q$ -value was  $>5.001$  ( $P < 0.05$ ) – are reported as statistically significant.



**Fig. 1** Assessment of blockade efficacy of buprenorphine/naloxone: (1) at 1 h versus 25 h following the maintenance dose and (2) across different maintenance doses. Responses are to intramuscular hydromorphone. Each bar (and bracket) represents the mean peak change value (+1SEM) for six subjects. Results from pairwise, post-hoc comparisons are shown. The only significant dose differences were found in comparison with the 4/1-mg condition at the same testing time and are indicated by an asterisk above and below bars

## Results

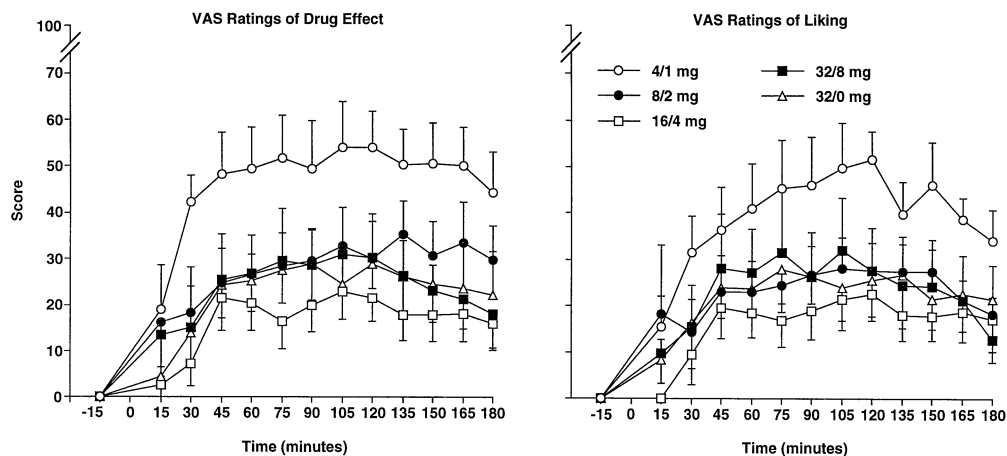
### Blockade by buprenorphine/naloxone versus blockade by buprenorphine alone

Analysis of responses to hydromorphone challenges on Mondays versus Tuesdays showed no significant difference related to time since buprenorphine/naloxone dose (1 h versus 25 h). Results from a representative subjective (visual analog scale ratings of high) and physiological measure (pupil diameter) are shown in Fig. 1 and illustrate these findings. If naloxone provided additional blockade effects, lower visual analog scale ratings of hydromorphone high would be expected 1 h (open bars in the left panel of Fig. 1) rather than 25 h after the maintenance dose (hatched bars). The magnitude of subjective responses was virtually identical for the 1-h (Monday) and 25-h (Tuesday) challenge sessions. Similarly, no difference was seen in pupillary constriction in response to hydromorphone at 1 h versus 25 h (right panel of Fig. 1).

Blockade efficacy of naloxone was further examined by comparing the responses to hydromorphone administered 1 h after the 32/8-mg and 32/0-mg conditions. There were no significant differences. Since peak change ratings might fail to capture an effect produced early in the session, the time course of measures was also examined (representative measures are shown in Fig. 2). There was no evidence that the naloxone in the 32/8-mg condition produced additional attenuation of the hydromorphone challenge effects even in the earliest portion of the session.

A review of the other outcome measures showed no evidence of significant differences between the 1-h and 25-h hydromorphone responses for a given maintenance dose of buprenorphine/naloxone, nor between Monday challenges while maintained on 32/8 mg versus 32/0 mg buprenorphine/naloxone and buprenorphine, respectively.

**Fig. 2** Time course effects for visual analog scale (VAS) ratings of drug effect and liking following acute administration of intramuscular hydromorphone. Subjects were tested after 6 days of maintenance on buprenorphine/naloxone and buprenorphine. Each point (and bracket) represents the mean peak change value ( $\pm$ SEM) for six subjects



### Blockade at different maintenance doses

Monday hydromorphone challenges provided an assessment of buprenorphine/naloxone blockade efficacy after 6 days of maintenance. These results show that the magnitude of blockade efficacy of buprenorphine/naloxone was greater for higher maintenance doses. For example, visual analog scale ratings of hydromorphone-induced high were significantly less when subjects were maintained on 8/2, 16/4, and 32/8 mg of daily sublingual buprenorphine/naloxone compared with 4/1 mg (Fig. 1). Similarly, there was significantly less hydromorphone-related pupillary constriction when maintained on 16/4 mg and 32/8 mg versus 4/1 mg buprenorphine/naloxone (right panel, Fig. 1). Similar effects were seen in response to hydromorphone administered 25 h after dosing (Fig. 1), with significantly lower ratings of high for the 16/4-mg condition and significantly less pupillary constriction for the 32/8-mg condition (each compared with the 4/1-mg condition). These effects were evident throughout the session period. Figure 2 shows the time course of two representative visual analog scales over the 3 h following hydromorphone administration. The onset of subjective responses to the challenge occurred within 30 min after injection, and maximal effects were achieved approximately 2 h after injection. Responses to hydromorphone were highest when participants were maintained on 4/1 mg buprenorphine/naloxone and lowest when maintained on 16/4 mg buprenorphine/naloxone, with little difference between the 8/2-mg and 32/8-mg maintenance dose conditions.

### Changes related to repeated dosing of buprenorphine/naloxone and buprenorphine

Results from sessions conducted on Wednesday, Friday, and Monday provide an assessment of changes related to repeated dosing of buprenorphine/naloxone and buprenorphine. These analyses showed a variable pattern of effects across measures. There were changes across time suggestive of some adaptation to a dose as subjects stabi-

lized on buprenorphine/naloxone and buprenorphine (for example, for oxygen saturation). However, these changes were not significant.

## Discussion

The purpose of this study was to examine systematically opioid blockade efficacy in subjects maintained on buprenorphine/naloxone and buprenorphine as measured by attenuation of response to a parenteral dose of hydromorphone. Naloxone has been added to buprenorphine in order to decrease the parenteral abuse potential of buprenorphine in opioid-dependent persons (Mendelson et al. 1996, 1997; Fudala et al. 1998; Stoller et al. 2001). Previous work suggests that higher doses of sublingual buprenorphine/naloxone can deliver bioactive doses of naloxone (Preston et al. 1990). However, results from this study showed no evidence that the addition of naloxone to sublingual buprenorphine produced additional blockade efficacy relative to buprenorphine alone.

The study utilized two procedures to test for possible blockade efficacy of naloxone. The first was to test blockade efficacy at 1 h versus 25 h after a sublingual dose of buprenorphine/naloxone. It was hypothesized that there would be greater attenuation of hydromorphone effects at the 1-h rather than 25-h time point; however, no significant difference was found (Fig. 1). These results also show that buprenorphine/naloxone produces stable blockade for at least 25 h, consistent with studies of buprenorphine alone (Rosen et al. 1994; Schuh et al. 1999). The second procedure compared responses to the hydromorphone challenges at the 1-h time point for the 32/8-mg versus 32/0-mg conditions and found no significant differences (Fig. 2), confirming that 8 mg sublingual naloxone did not confer any additional blockade efficacy.

This study also compared blockade effects for four different daily doses of sublingual buprenorphine/naloxone (Fig. 1 and Fig. 2). A previous study of daily buprenorphine showed dose-related blockade of hydromorphone effects by buprenorphine alone (Bickel et al.

1988), and the present study also found that higher daily doses of buprenorphine/naloxone produced greater attenuation of hydromorphone effects relative to the lowest daily dose. These results show that maintenance on a daily dose of 4/1 mg sublingual buprenorphine/naloxone is too low to block the effects of 12 mg parenteral hydromorphone, although daily doses as high as 32/8 mg also failed to completely block these effects. This may reflect, in part, the high dose of hydromorphone used in this study (equivalent to approximately 80 mg parenteral morphine).

While attenuation of hydromorphone effects was significantly larger for maintenance doses greater than 4/1 mg, there were no significant differences among the 8/2, 16/4, or 32/8-mg doses (Fig. 1). These results should not be interpreted to suggest that there is no additional value to maintenance on doses of buprenorphine/naloxone greater than 8/2 mg per day. Higher daily doses of buprenorphine/naloxone may be better at suppressing withdrawal symptoms in patients with high levels of physical dependence, and there could be greater differentiation in blockade of effects if challenges had been with lower hydromorphone doses. Differences in bioavailability between individuals might also introduce variability that could attenuate dose effects.

An additional area addressed by this study was the possible changes associated with repeated daily doses of buprenorphine/naloxone and buprenorphine. While not the primary study goal, the experimental design allowed for an evaluation of these changes because subjects were assessed regularly as they stabilized at each maintenance level. While suggestive patterns of change were seen on some measures, these were not robust or significant effects and, within a maintenance dose condition, there were no significant differences among days 1, 3, and 6 for measures of hydromorphone responses or of baseline effects. Taken together, these measures show no marked evidence of changes associated with repeated daily dosing.

Several limitations to this study should be noted. First, 6 days at each maintenance dose may have been insufficient to stabilize buprenorphine/naloxone effects. Second, while hydromorphone challenges were double blind, the absence of other challenge dose conditions (e.g., placebo, an opioid antagonist) may have led to expectancy effects as subjects progressed through the study. Third, the maintenance dose conditions in this study were not randomized for participants because of buprenorphine's long duration of effects; randomization of maintenance dose conditions could have led to carry-over effects. Subjects participated in the study sequentially, making it less likely that participants would discuss study details among themselves.

This study shows that the blockade efficacy of sublingual buprenorphine/naloxone is dose related. However, this blockade is not complete as doses up to 32/8 mg buprenorphine/naloxone provide only partial blockade when subjects receive a high dose of an opioid agonist. While these results can be interpreted to suggest bupre-

norphine/naloxone is not completely effective in blocking the effects of an opioid agonist, it is important to note that the dose of hydromorphone was high and its effects were mild. Furthermore, the duration of blockade effects lasted for at least 25 h, consistent with buprenorphine's long duration of action. There was no evidence that even higher doses of sublingual naloxone combined with buprenorphine confer additional blockade relative to buprenorphine alone or alter the efficacy of buprenorphine in any way. The study also showed that over a 6-day period minimal changes are associated with stabilization on a dose of buprenorphine/naloxone or buprenorphine. These results demonstrate buprenorphine's efficacy as a function of dose and across time.

**Acknowledgements** Supported by U.S. Public Health Service Research Scientist Award K05 DA00050 (GEB), Scientist Development Award K02 DA00332 (ECS), and R01 DA08045 from the National Institute on Drug Abuse. The authors thank Alison Terry, Tim Mudric, Linda Felch, John Yingling, and the residential nursing staff for assistance in data collection and analysis.

## References

- Bickel WK, Stitzer ML, Bigelow GE, Liebson IA, Jasinski DR, Johnson RE (1988) Buprenorphine: dose-related blockade of opioid challenge effects in opioid dependent humans. *J Pharmacol Exp Ther* 247:47-53
- Fraser HF, Van Horn GD, Martin WR, Wolbach AB, Isbell H (1961) Methods for evaluating addiction liability. (A) "attitude" of opiate addicts toward opiate-like drugs, (B) a short-term "direct" addiction test. *J Pharmacol Exp Ther* 133:371-387
- Fudala PJ, Yu E, Macfadden W, Boardman C, Chiang CN (1998) Effects of buprenorphine and naloxone in morphine-stabilized opioid addicts. *Drug Alcohol Depend* 50:1-8
- Griffiths RR, Bigelow GE, Liebson I (1983) Differential effects of diazepam and pentobarbital on mood and behavior. *Arch Gen Psychiatry* 40:865-873
- Jasinski DR (1977) Assessment of the abuse potential of morphine-like drugs (methods used in man). In: Martin WR (ed) *Drug addiction I*. Springer, Berlin Heidelberg New York, pp 197-258
- Jasinski DR, Pevnick JS, Griffith JD (1978) Human pharmacology and abuse potential of the analgesic buprenorphine: a potential agent for treating narcotic addiction. *Arch Gen Psychiatry* 35:501-516
- Johnson RE, Jaffe JH, Fudala PJ (1992) A controlled trial of buprenorphine treatment for opioid dependence (see comments). *JAMA* 267:2750-2755
- Johnson RE, Chutuape MA, Strain EC, Walsh SL, Stitzer ML, Bigelow GE (2000) A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *N Engl J Med* 343:1290-1297
- Kolb L, Himmelsbach CK (1938) Clinical studies of drug addiction. III. A critical review of the withdrawal treatments with method of evaluating abstinence syndromes. *Am J Psychiatry* 94:759-799
- Ling W, Wesson DR, Charuvastra C, Klett CJ (1996) A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. *Arch Gen Psychiatry* 53:401-407
- Ling W, Charuvastra C, Collins JF, Batki S, Brown LS Jr, Kintaudi P, Wesson DR, McNicholas L, Tusel DJ, Malkernek U, Renner JA Jr, Santos E, Casadonte P, Fye C, Stine S, Wang RI, Segal D (1998) Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. *Addiction* 93:475-486

- McLeod D, Griffiths RR, Bigelow GE, Yingling J (1982) An automated version of the digit symbol substitution test (DSST). *Behav Res Methods Instrum* 14:463–466
- Mello NK, Mendelson JH (1980) Buprenorphine suppresses heroin use by heroin addicts. *Science* 207:657–659
- Mendelson J, Jones RT, Fernandez I, Welm S, Melby AK, Baggott MJ (1996) Buprenorphine and naloxone interactions in opiate-dependent volunteers. *Clin Pharmacol Ther* 60:105–114
- Mendelson J, Jones RT, Welm S, Brown J, Batki SL (1997) Buprenorphine and naloxone interactions in methadone maintenance patients. *Biol Psychiatry* 41:1095–1101
- Mendelson J, Jones RT, Welm S, Baggott M, Fernandez I, Melby AK, Nath RP (1999) Buprenorphine and naloxone combinations: the effects of three dose ratios in morphine-stabilized, opiate-dependent volunteers. *Psychopharmacology* 141:37–46
- Preston KL, Bigelow GE, Liebson IA (1988) Buprenorphine and naloxone alone and in combination in opioid-dependent humans. *Psychopharmacology* 94:484–490
- Preston KL, Bigelow GE, Liebson IA (1990) Effects of sublingually given naloxone in opioid-dependent human volunteers. *Drug Alcohol Depend* 25:27–34
- Reitan RM (1958) Validity of the trail making test as an indicator of organic brain damage. *Perceptual Motor Skills* 8:271–276
- Rose JE, Levin ED (1992) Concurrent agonist-antagonist administration for the analysis and treatment of drug dependence. *Pharmacol Biochem Behav* 41:219–226
- Rosen MI, Wallace EA, McMahon TJ, Pearsall HR, Woods SW, Price LH, Kosten TR (1994) Buprenorphine: duration of blockade of effects of intramuscular hydromorphone. *Drug Alcohol Depend* 35:141–149
- Schottenfeld RS, Pakes JR, Oliveto A, Ziedonis D, Kosten TR (1997) Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse (see comments). *Arch Gen Psychiatry* 54:713–720
- Schuh KJ, Walsh SL, Stitzer ML (1999) Onset, magnitude and duration of opioid blockade produced by buprenorphine and naloxone in humans. *Psychopharmacology* 145:162–174
- Stoller KB, Bigelow GE, Walsh SL, Strain EC (2001) Effects of buprenorphine/naloxone in opioid-dependent humans. *Psychopharmacology* 154:230–242
- Strain EC, Stitzer ML, Liebson IA, Bigelow GE (1994) Comparison of buprenorphine and methadone in the treatment of opioid dependence. *Am J Psychiatry* 151:1025–1030
- Strain EC, Walsh SL, Preston KL, Liebson IA, Bigelow GE (1997) The effects of buprenorphine in buprenorphine-maintained volunteers. *Psychopharmacology* 129:329–338
- Strain EC, Stoller K, Walsh SL, Bigelow GE (2000) Effects of buprenorphine versus buprenorphine/naloxone tablets in non-dependent opioid abusers. *Psychopharmacology* 148:374–383
- Walsh SL, Preston KL, Bigelow GE, Stitzer ML (1995) Acute administration of buprenorphine in humans: partial agonist and blockade effects. *J Pharmacol Exp Ther* 274:361–372
- Weinhold LL, Preston KL, Farre M, Liebson IA, Bigelow GE (1992) Buprenorphine alone and in combination with naloxone in non-dependent humans. *Drug Alcohol Depend* 30:263–274