The feasibility of abrupt methadone-buprenorphine transfer in British opiate addicts in an outpatient setting

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Abstract

A study of 13 male opiate addicts was undertaken to investigate the feasibility of transferring abruptly from methadone maintenance treatment to buprenorphine in an outpatient setting. The mean age of subjects was 30 years (range 18-45) and all fulfilled DSM-III-R criteria for opioid dependence. All were maintained on a methadone dose of 20-30 mg mixture daily and were transferred for 3 days to 4 mg buprenorphine sublingually 24-26 hours after their last dose of methadone. On day 1 repeated measures of drug effects were performed, including agonist and withdrawal effects, and this was complemented by saccadic eye movements, a potential new measure of central opioid effects. These recordings were repeated once on days 2 and 3 and the subjects returned to their previous dose of methadone on day 4. Buprenorphine caused no detectable agonist effects or drug "high", but had "good" effects, was "liked" and well tolerated, suggesting that subjects would comply with buprenorphine treatment despite the lack of reinforcing effects. A mild increase in subjective withdrawal symptoms, which was not clinically significant, was seen in association with an increase in saccadic peak velocity on day 2 of the study but no withdrawal occurred on the other days, indicating that the abrupt transfer technique was acceptable.

Introduction

Buprenorphine was introduced into the United Kingdom as an analgesic in 1978. It is a partial agonist at the mu-opioid receptor and an antagonist at the kappa receptor, and therefore has advantages over other opioid analgesics. The lack of κ agonism may explain why it has no significant dysphoric and psychotomimetic effects and since it is a partial μ agonist, it has reduced abuse potential and is much safer in overdose (Lewis, 1995), with a ceiling on its respiratory depressant effects (Walsh *et al.,* 1994). It was recognized as a potential agent for treating opiate addiction early on (Jasinski, Pevnick & Griffiths, 1978) and the drug was subsequently evaluated for its abuse potential and its role in the treatment of addiction. Buprenorphine was found to be 15-50 times more potent than morphine, was perceived as being morphine-like and able to retain patients in treatment, showed cross-tolerance with other full p-agonists blocking the drug high during "on-top" use and, due to its long duration of action and slow dissociation from the opioid receptors, it produced low levels of withdrawal symptomatology (Lewis, 1995).

Buprenorphine has been extensively studied both in nondependent opioid users and in users dependent on morphine or methadone. In the former, dose-ranging studies have been performed (Jasinski *et al.,* 1978, 1982, 1989; Walsh *et al.,* 1992, 1993, 1994). At high doses, acutely, buprenorphine produced significantly less respiratory depression than full agonists, caused no marked cardiovascular effects and no excessive sedation or other signs of intoxication. These studies, as well as chronic dosing studies (Jasinski *et al.,* 1978, Mello, Mendelson & Kuelmle, 1982, Bickel *et al.,* 1988a,b, Kosten, Morgan & Kosten, 1990), have suggested that buprenorphine does have morphine-like subjective, behavioural and physiological effects. Bickel & Amass (1995) have recently reviewed the clinical use of buprenorphine in addiction, both for maintenance and withdrawal. Its long duration of action means it can be given daily or on alternate days at high doses (doses above 8 mg buprenorphine may prolong the half-life rather than increase the agonist activity). It is less reinforcing because it does not cause a drug high itself due to its slow onset of action. It shows cross-tolerance with other p-receptor agonists and thus can reduce the proportion of urines positive for illicit opioids to the same degree as methadone. It produces only limited withdrawal symptoms on abrupt termination and may allow a direct transition to naltrexone without the need for an opioid free period.

The ability to transfer between methadone and buprenorphine without causing withdrawal is of particular practical and theoretical importance. Several studies in opioid dependent subjects have substituted buprenorphine for methadone or heroin (Jasinski *et al.,* 1983, 1984; Johnson *et al.,* 1989; Strain *et al.,* 1995) to assess its propensity to precipitate withdrawal. Withdrawal may be caused by the buprenorphine dose being too low to substitute for the methadone, and also

because buprenorphine is a partial μ -agonist which may have insufficient efficacy to substitute for the full agonist methadone (Johnson *et al.,* 1989). Thus, within the range of buprenorphine's efficacy withdrawal may be caused by the buprenorphine displacing methadone from the p-receptors, but in addition withdrawal may also be caused precisely because the degree of agonism required is above the range of buprenorphine's efficacy. The relative doses of buprenorphine and methadone and the time interval between the two is critical to avoid precipitating withdrawal. Only two other studies have examined the transfer from methadone to buprenorphine 20 hours or more after the last methadone dose, both of which were single dose studies with small numbers of inpatients in a research ward. In the first study six male methadone-dependent subjects on 30 mg methadone were given 0.5, 1, 2, 4 and 8 mg intramuscular buprenorphine 20 hours after the last methadone dose in ascending dose order. No significant positive or withdrawal effects were found except an increase in "good" effects after the 1 mg buprenorphine dose (Strain *et al.,* 1992). However, the length of time (48 hours) between testing sessions may have been insufficient in view of the long biological half-life of buprenorphine. In the second study male methadone-dependent subjects on 30 mg *(n* = 7) and 60 mg *(n* = 6) methadone were given 2, 4 and 8 mg sublingual buprenorphine in random order 40 hours after the last methadone dose with 1 week between the different doses. No positive or agonist effects were found but dose-dependent increases in "bad" effects and withdrawal scores occurred which did not reach significance in the 30 mg group, but which were significant in the 60 mg group (June *et al.,* 1993; Walsh *et al.,* 1995).

Both these studies have limitations which we felt it would be important to remedy before the acceptability and effectiveness of methadone-buprenorphine transfer in a clinical setting could be determined. First, subjects would be likely to find it more acceptable if the transition occurred around 24 hours after their last methadone dose (rather than at 40 hours), as this would be when their next dose of methadone would normally be received. Secondly, single dose studies are unable to assess changes when steady state levels are approached, which takes five drug half-lives, so we decided to give buprenorphine for 3 consecutive days. Thirdly, rather than using an in-patient setting as in the US studies, we felt the typical UK outpatient setting would provide tougher test of the tolerability of the transfer Fourthly, we felt abrupt transfer would be preferable in a clinical setting because of its simplicity, rather than the accepted procedure in heroin-buprenorphine transfer of making the transition to the full buprenorphine dose over 2 or more days (Johnson *et al.,* 1989). Finally, in view of the uncertainty over what are equivalent doses of buprenorphine and methadone at the higher dose levels, we chose to replicate the US work at the lower methadone dose level. Buprenorphine 4 mg was chosen as equivalent to 20-30 mg methadone, as buprenorphine 2 mg resulted in more withdrawal and less tolerance than 30 mg methadone (Bickel *et al,* 1988b, reviewed in Jasinski & Preston, 1995). Our primary hypothesis was therefore that the subjects would find the transfer acceptable and that the withdrawal symptoms on abrupt methadone-buprenorphine transfer would not be clinically significant.

We also introduced a new technique into research in opioid addiction: saccadic eye movements (SEMs). SEMs are rapid, step-like conjugate changes of gaze, the purpose of which is to centralize objects of interest on the fovea (the most sensitive area at the back of the eye). SEMs are used extensively in psychopharmacological research and have proved to be a sensitive measure of central drug effects. For example, SEMs have been particularly useful for pharmacodynamic-pharmacokinetic modelling for benzodiazepines (Ball *et al.,* 1991) and demonstrate sensitivity to a_2-adrenoceptor ligands such as clonidine (Glue *et al.,* 1991) and ethoxyidazoxan (Coupland *et al.,* 1994). SEMs have potential advantages over pupillometry as they are affected by relatively few confounding variables, are re-liable, provide a superior measure of performance impairment than, for instance, critical flicker fusion or digit-symbol substitution tests (Glue, 1991), can be repeated regularly and, once initiated, the movement is thought to be without cognitive or conscious input (Coupland *et al.,* 1995). SEMs are known to be affected particularly by arousal level and some drugs, particularly those active at the GABA receptors (alcohol, benzodiazepines, barbiturates), whereas pupil diameter is affected by ambient light conditions, accommodation, arousal level, degree of sensory stimulation, emotional state and cognitive thoughts (Murray, Adler & Korczyn, 1983). Single dose studies in non-dependent non-tolerant individuals have shown that some opioid ligands given acutely slow SEM velocity (Richens *et al.,* 1983, Griffiths, Marshall & Richens, 1984), and increase the latency or reaction time (Rothenberg *et al.,* 1980). Of particular relevance is the study using the partial opioid agonist (at the pi receptor) meptazinol which reported an acute reduction in peak saccade velocity (Richens *et al.,* 1983). SEM velocity changes are thought to be due to an effect on opioid receptors influencing the motor component and latency changes an effect on opioid receptors influencing the sensory component of neural pathways controlling saccadic eye movements (Rothenberg *et al.,* 1980; Griffiths *et aL,* 1984). Thus our secondary hypothesis was that the partial agonist buprenorphine would cause slowing of SEM velocity in association with its agonist effect, which would recover as the buprenorphine was washed out.

Methods

Subjects

Thirteen male opiate addicts stabilized on 20-30 mg/day methadone for at least 2 weeks were recruited by the investigators from the clientele of the Avon Drug Problem Team. The mean age was 30 years (range 18-45) and mean weight was 61.5 kg (range 55.3-80.2 kg). They were typically long-standing opiate users with their first opiate use being on average 15 years 8 months ago (range 14 months-24 years), and they had on average been on methadone continuously for 18 months (range 1-61 months). All underwent a medical examination for physical and mental health, which included a medical history, physical examination, mental state examination, electrocardiogram and blood tests and subjects were excluded if there were clinically significant abnormalities. All fulfilled DSM-III-R criteria (APA, 1987) for opioid dependence as judged by the examining clinician, urine tests and case note review. Subjects were clear of other drugs of abuse as demonstrated by clean urines on initial screening, with the exception of cannabinoids (as the urine can remain positive for 1 month or more after use). During the study period a urine sample was taken daily for analysis of drugs of abuse, and analysed by EMIT (Syva Co, San Jose, CA, USA) followed by thin layer chromatography performed at the biochemistry department of Frenchay Hospital in Bristol. Drugs screened for included methadone, opiates, cocaine, amphetamines, benzodiazepines, barbiturates and cannabis, but these results were only avail-able after the subject had completed the study. Breath alcohol measures were recorded every morning of the study using a Lion Alcolmeter.

All subjects were given a 4 mg dose of buprenorphine sublingually for 3 consecutive days, beginning 24-26 hours after the last methadone dose. In the first two subjects this was given in liquid (4 mg/1 ml) form (supplied by the National Institute on Drug Abuse, Rockville, MD), but because subjects found it difficult to hold under their tongue for several minutes without swallowing, and became anxious about how much they swallowed, the change to two 2 mg sublingual tablets was made, a formulation which the subjects found more acceptable. These were supplied by the manufacturers (Reckitt and Colman, Hull, England) and taken under supervision with observation of the subject until the tablets had completely dissolved (1-5 minutes).

Measurements were performed in a quiet clinical testing room over 7 hours on day 1 and hour on subsequent days. Between tests subjects were made comfortable in a quiet sitting room with a television and video, had free access to soft drinks and snacks, and were allowed to smoke tobacco. Informed consent was obtained and a voucher from the shop of their choice for £45 was given and subjects recommenced methadone on completion of the study. The study was approved by the Research Ethics Committee of the United Bristol Healthcare Trust.

Measures

Subjective measures included the Adjective checklist (Frazer *et al.,* 1961; Jasinski, 1977) which measures agonist (16 items) and withdrawal (21 items) effects, and the Addiction Research Centre Inventory (ARCI) 49-item short form (Haertzen, 1970; Jasinski, 1977) which is an empirically developed scale scored for the MBG ("euphoria"), LSD ("dysphoria") and PCAG ("sedation") scales. Both measures were completed at - 60, 90 and 180 minutes on day 1 and once on days 2 and 3. Six visual analogue scales (VAS) from the Single Dose Opiate Questionnaire ("high", "drug effects", "good" effects, "bad" effects, "like" and "sick"), with instructions to indicate how the test drug (i.e. buprenorphine) made them feel "at this moment", with ends labelled "not at all" and "extremely" (Frazer *et al.,* 1961). These were completed at 30, 90, 180, 240 and 330 minutes on day 1 and once on days 2 and 3. On day 4, using the same VAS, subjects were asked for a global rating of how the test drug made them feel "over the past 3 days". Subjects were also asked the question "If in the future you were offered buprenorphine in place of your usual methadone, how likely would you be to accept it?" with ends labelled "not at all likely" and "most likely ever". Finally the drug class questionnaire (adapted from Strain *et al.,* 1992) was used on study day 4 to assess subjects' perceived similarity to known drugs.

Objective evidence of withdrawal was measured using an adaptation of the Kolb & Himmelsbach (1938) point system for the presence or absence of six signs of opiate withdrawal at - 60, 90 and 180 minutes on day 1 and once on days 2 and 3. Blood pressure and heart rate were measured by automated sphygmomanometer (Dinamap, Critikon) after rest at - 90, - 60, 60, 120, 180, 240 and 330 minutes on day 1 and once after rest on days 2 and 3.

Saccadic eye movement testing was performed using the Cardiff Saccade Generation and Analysis System and this method has been previously described in detail (Glue, 1991; Coupland *et al.,* 1995). Briefly, subjects are placed centrally 67 cm from a display of light-emitting diodes and are instructed to follow a light sequence of fixed order with their eyes. The light sequence changes at 1.5-second intervals and spans angles of 10-40 degrees from the central point, producing 24 analysable saccades. Two sequences of 24 saccades were measured at each testing time. Saccadic parameters measured and analysed were peak velocity, peak acceleration, peak deceleration, acceleration/deceleration

ratio, saccade latency and saccade error. Data are re-ported as a value derived from a saccade displacement of *35°* (Coupland *et al.,* 1995). Recordings were made at the same time points as the vital signs. Pupil diameter was measured at the same time points using a static polaroid close-up system (Marquardt, Martin & Jasinski, 1967). The Polaroid Image camera with close-up lens and electronic flash was used to take photo-graphs at 25 cm in front of the right eye giving half-times magnification. A room with blackout blinds that was lit only by a lamp giving indirect light was used while subjects were fixing on a point 6 feet away. The pupil measurements were made from the colour photographs using dial callipers (Batt' International) sensitive to 0.1 mm.

Data analysis

This was an exploratory study with the main emphasis being univariate descriptive statistics. Comparisons were made between pre- and post-buprenorphine on day 1 and also between peak (3-6 hours post-drug on day 1) and nadir levels (pre-drug on days 2 and 3). Pairwise comparisons between data points using two-tailed paired t-tests and ANOVA tests as appropriate were used, with significance set at $p < 0.05$.

Results

Clinical effects

All but two subjects completed all test days. One complained of withdrawal symptoms on the second day and the other complained of dysphoria but did not withdraw until day 3 of the study. As far as the other subjects are concerned, no clini-cally significant withdrawal effects were noted on days 1 and 3, but a mild withdrawal was clinically detectable on day 2, which in no case resulted in the subjects reporting a desire to seek opioid drugs. The objective signs of withdrawal scale did not detect any increase on day 2 (even in the subject that withdrew due to withdrawal effects), and indeed the mean score was less than 2 (maximum score 18) and no statistically significant changes were observed. When asked "If in the future you were offered buprenorphine in place of your usual methadone, how likely would you be to accept it?", the mean rating was a 77% likelihood with over half of subjects scoring 95%.

Agonist effects

No significant difference occurred in the agonist scale of the Adjective check list or the "high" VAS (Fig. 1 a) over the study period. This was consistent with a non-significant decrease in the MBG ("euphoria") scale of the ARCI short form (Fig. 2). There was also no change on the "sick" VAS confirming that the buprenorphine was well tolerated. There were, however, significant in creases in drug "like" $p = 0.04$ (Fig. lb) and "good" effects, $p = 0.05$ (Fig. lc) as well as "drug effects" ($p = 0.02$) on the VAS.

Withdrawal effects

The withdrawal scale of the Adjective check list showed a non-significant decrease during day 1 and a significant increase from day 1 to day 2 ($p = 0.006$), which nearly returned to baseline on day 3. This was consistent with similar significant changes ($p < 0.001$) in the PCAG ("sedation") and LSD ("dysphoria") groups of the ARCI short form. There was also a significant increase in "bad" effects ($p = 0.02$) on day 2 (Fig. 1d), which rather than returning to baseline remained significantly elevated on day 3.

Saccadic eye movements

A significant increase in saccadic peak velocity ($p = 0.02$) of 37 degrees/second was demonstrated on day 2 (Fig. 3). A similar non-significant trend was also seen for peak acceleration and deceleration. A significant reduction in saccadic latency of 45 milliseconds was demonstrated during day 1 ($F = 4.35$, $p = 0.003$).

Pupillometry

There were no changes in the average pupil diameter at any point during the study.

Cardiovascular measures

A significant increase of 12 mm Hg above base-line in mean systolic blood pressure was seen within 2 hours of buprenorphine which was sustained on day 1 ($p = 0.002$), and which was also seen on day 2 ($p = 0.001$); ANOVA over

time F = 8.28, p = 0.0003), but had vanished by day 3. A similar trend was seen for diastolic BP, although this did not reach significance. A transient decrease in mean heart rate of 6 beats/min occurred within an hour of the administration of the buprenorphine (p = 0.03) and a significant increase in heart rate of 8 beats/min above the day 1 level occurred pre-drug on days 2 and 3 (p = 0.02), consistent with withdrawal effects.

Other measures

Global ratings (VAS) taken on day 4 closely resembled the average VAS ratings for the 3 days, except "good" effects and "bad" effects global scores were well above the average scores. The Drug Class Questionnaire revealed that subjects felt buprenorphine was most like opiates (n = 8), benzodiazepines (n = 2), placebo (n = 1), stimulants (n = 1), and half the subjects also made a second choice despite being asked for only one. The analysis of urine for drugs of abuse revealed that only 3 of 13 subjects had clean urines (i.e. methadone and cannabinoids only) for the duration of the study. There were six opiate-positive urines on each of the 3 days of the study. Seven subjects showed morphine or other opiates (of whom three were also positive for alcohol and one for benzodiazepines), two showed cocaine and one showed amphetamine. Seven subjects were also positive for cannabis throughout the study.

Discussion

This study demonstrates the acceptability of transferring from methadone to buprenorphine in UK opiate addicts in a typical outpatient setting. At the doses used abrupt transfer was possible without any undue discomfort or withdrawal effects in the large majority of subjects confirming our primary hypothesis and indicating that gradual transfer is not necessary. The period of peak withdrawal effects is consistent with the buprenorphine plasma levels being lowest pre-drug on day 2 before steady state had been reached. Withdrawal effects were just detectable clinically at the nadir of the drug effect (pre-drug on day 2), but subjects described these as insufficient to cause them to seek other drugs and this was not apparent by day 3 of the study. The objective withdrawal scale was insufficiently sensitive to detect these changes, but the subjective measures did confirm the clinical findings. Opiate withdrawal typically causes a high PCAG, an increase in LSD and a reduction in MBG, but no reduction in MBG ("sedation") occurred with buprenorphine. Both "good" and "bad" drug effects were significantly elevated simultaneously, indicating that they are independent. The continued elevation of "bad" effects and heart rate on day 3 suggests that these may be more sensitive measures of withdrawal or that they change at a different rate from the other effects, and" it may therefore be of benefit in future transfer studies with buprenorphine to extend the time of the study beyond a 3-day period. Abrupt transfer may not be so acceptable at higher methadone doses as indicated by the findings of other workers (June et al., 1993; Walsh et al., 1995), where in order to minimize withdrawal symptoms it would presumably be necessary to build up the dose of buprenorphine over 2 or 3 days as suggested for heroinbuprenorphine transfer (Johnson et al., 1989).

Subjects reported a high acceptability of buprenorphine treatment. Subjectively no unpleasant effects were seen on day 1 and indeed a gradual increase in "good" effects and "like" occurred in association with no change in "high" or agonist effects. Our study suggests a differentiation between positive effects ("like" and "good" effects) and euphoric ("high" and agonist effects) effects-findings that are in contrast to previous studies which used identical measures, but found no significant increase in "like" or "good" effects at these dose levels. This may be because our study had twice as many subjects as the US studies, because of a placebo effect in our study, our subjects had typically been long-term methadone users, because of lingering effects of previous buprenorphine doses in the US studies or because our subjects were research naive, whereas there is a tendency for US subjects to be frequent participators in studies (possibly becoming less sensitive to smaller changes). Buprenorphine, unlike full opiate agonists, did not result in an increase in MBG ("euphoria") and PCAG ("sedation"). Thus our findings suggests that using buprenorphine to substitute for methadone could result in compliance similar to that seen with full opiate agonists, and at the same time it could avoid the psychologically reinforcing effects that occur with drugs with a more rapid onset of action.

This study successfully demonstrated the acceptability and effectiveness of a methadone to buprenorphine transfer in a clinically relevant situation. This was not an efficacy study but our results may be to some extent confounded by the subject's use of alcohol and illicit drugs. Illicit drug use is obviously a hazard of outpatient studies, and eight of the 10 subjects who were found to have dirty urines had used prior to the study beginning, indicating that it was not the buprenorphine that was responsible. The other two subjects had both definitely used between days 1 and 2 of the study (one heroin, one alcohol). The subject that left the study due to withdrawal effects had clean urines throughout the study, indicating that the withdrawal was not due to an interaction with illicit opiates. The small difference (five scale units) detected on the subjective withdrawal scales tends to confirm that the degree of withdrawal detected would have been insufficient to produce drug seeking, and that drug use was therefore driven by other factors.

Our study confirms that SEMs are a potential new measure of central opioid effects. SEM measures were shown to be acceptable to opioid dependent subjects, who were able to learn the technique without difficulty. Our secondary hypothesis was, however, not confirmed, as no agonist effects were detected, and indeed the SEM velocity changes may

be a withdrawal effect. SEMs typically operate near maximal velocity (Coupland *a al.*, 1994), and the increase in velocity associated with withdrawal suggests the velocity was being reduced by the opioid drugs, initially methadone and subsequently the buprenorphine. Single dose studies with small numbers of non-tolerant non-dependent subjects have demonstrated a significant reduction of SEM peak velocity with papaveretum (Richens *et al.*, 1983), dextropropoxyphene (Griffiths *et al.*, 1984), a significant slowing (by 70 degrees/ second) with i.m. meptazinol (Richens *et al.*, 1983) but not oral meptazinol (Tedeschi, Smith & Richens, 1984, Ali *et al.*, 1985), and a non-significant slowing (by 50 degrees/second) with methadone (Rothenberg *et al.*, 1980). Methadone was associated with a significant increase in latency (Rothenberg *et al.*, 1980), but latency was only measured in one other study which found no change in latency for dextropropoxyphene (Griffiths *et al.*, 1984), a relatively weak agonist. Our study failed to find a decrease in peak velocity during the agonist phase (day 1), probably because we used tolerant subjects and were substituting equivalent doses, but we did find an increase in latency or reaction time on day 1, a variable that is under voluntary control. We did, however, find an increase in peak velocity during the withdrawal phase (day 2) which has not been demonstrated before, no doubt in part as there have been no other studies of SEMs during opioid withdrawal. The lack of change in the pupillometry tends to confirm that withdrawal effects were minor and that no significant agonist effects occurred. As buprenorphine is known to have pupillary effects similar to full opiate agonists in non-dependent subjects (Pick-worth, Lee & Fudala, 1990), SEMs may be a more sensitive measure of opioid effects than pupillometry during the withdrawal phase, or at least while the level of receptor stimulation is changing rapidly. SEMs have the additional ad-vantage that once initiated, they are out of conscious and cognitive control. Further studies in opioid dependent subjects during peak and nadir, and during precipitated withdrawal are needed to demonstrate that SEMs are responding to central opioid receptor stimulation rather than some other confounding factor.

In conclusion, achieving a smooth transfer from methadone to buprenorphine is of both scientific and clinical importance. This study has extended the findings of US studies by showing that it is possible to conduct such studies on an outpatient basis in UK addicts without any significant withdrawal problems and to make the ansfer abruptly. Buprenorphine was found to be acceptable and well tolerated, which confirms its potential as an alternative to methadone in the treatment of opioid dependence. Further studies with buprenorphine should explore whether abrupt transfer is possible at higher dose levels of methadone at other time intervals, the possible causes of the increase in "bad" effects, and the further application of buprenorphine in the clinical arena to maintenance treatment and withdrawal.

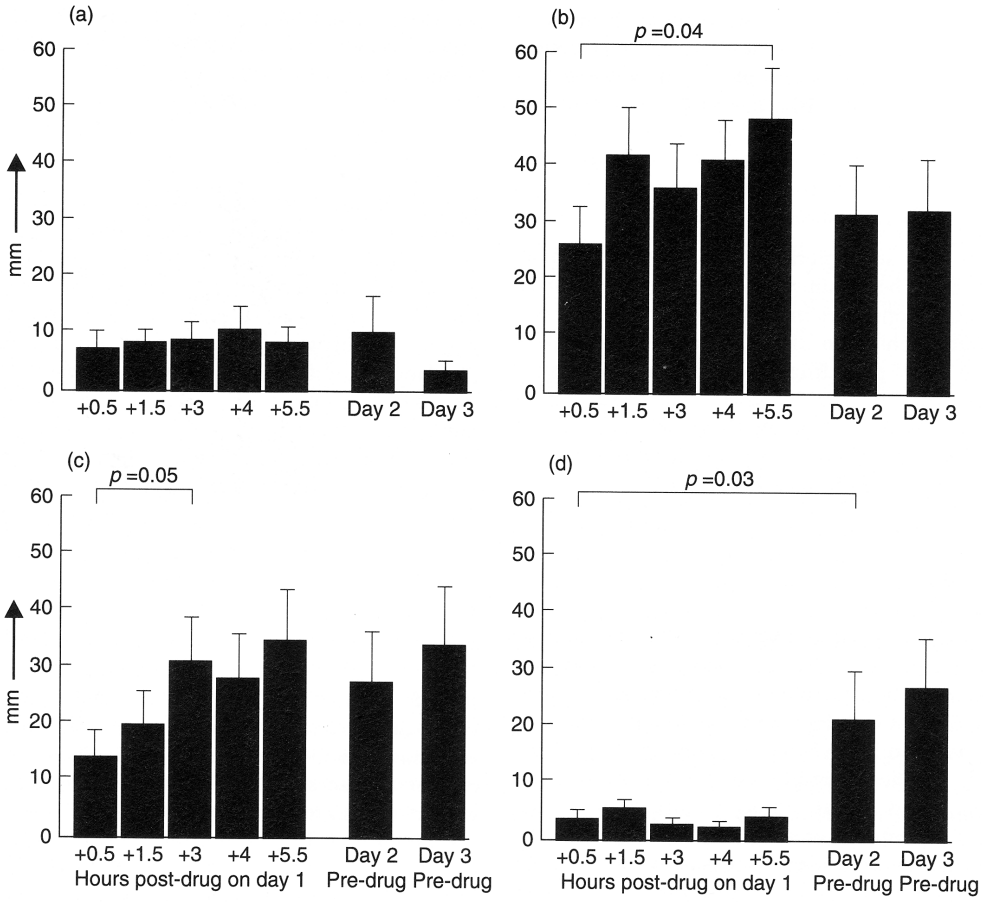

Figure 1. *Visual analogue scales, mean ± sem* (n = *13) using paired t-tests. No significant changes occurred with drug "high" (a). A significant increase in drug "like"* (p = *0.04) (b) and "good effects"* (p = *0.05) (c) occurred to the peak of the expected drug effect of buprenorphine (3–5.5 hours post-drug). A significant increase in "bad effects"* (p = *0.03) occurred pre-drug on day 2 which was sustained on day 3 (d).

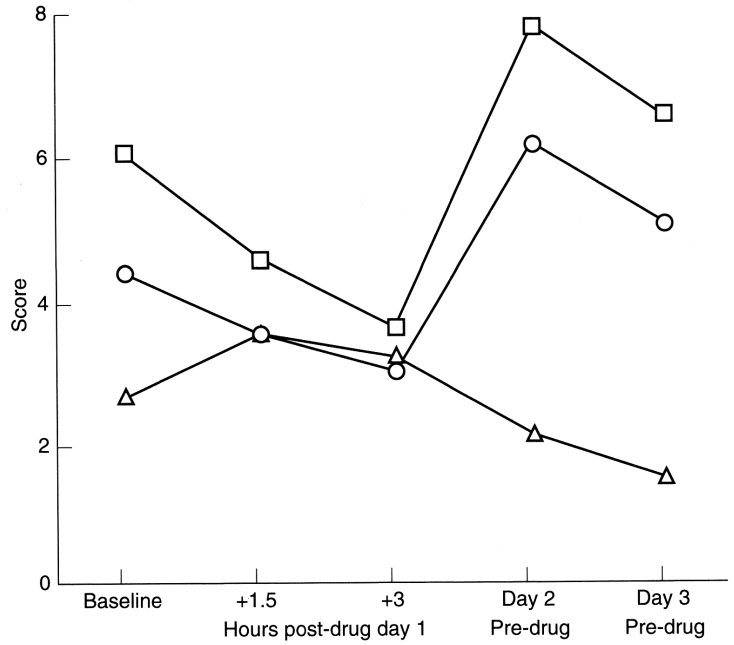

Figure 2. *ARCI Short Form, mean score ± sem* (n = *13) of MBG △ (euphoria), PCAG □ (sedation) and LSD ○ (dysphoria) groups. No significant change for MBG, but* p < *0.001 (paired* t*-test) from expected peak buprenorphine effect (+ 3 hours day 1) and nadir (pre-drug day 2) for PCAG and LSD.*

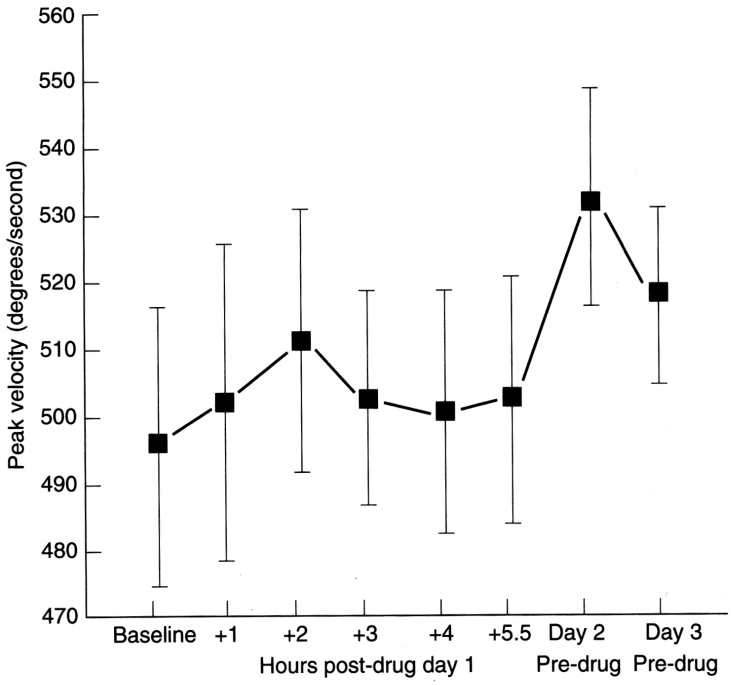

Figure 3. *Saccadic eye movement peak velocity, mean ± sem* (n = *12). From baseline to pre-drug on day 2,* p = *0.02 (paired* t*-test).*

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