ORIGINAL ARTICLE

Effects of buprenorphine buccal film and oral oxycodone on pupil diameter in a respiratory study

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ABSTRACT

Objective: *Evaluate the pupillary-constricting effects following administration of buprenorphine buccal film (BBF) and immediate-release (IR) oxycodone.*
Design: *A double-blind, double-dummy, six-treatment, six-period, placebo-controlled, randomized crossover study.*
Setting: *Single-center, phase 1 exploratory pharmacodynamics.*
Participants: *Healthy individuals who self-identify as recreational opioid users, confirmed via a naloxone challenge test on day 1.*
Interventions: *Placebo: BBF 300, 600, and 900 mcg and IR oxycodone 30 and 60 mg.*
Main outcome measure: *Minute ventilation (measured by the ventilatory response to hypercapnia) and pupil diameter (determined via standard pupillometry) were assessed predose and at 0.5, 1, 1.5, 2, 2.5, 3, and 4 hours post-dose.*
Results: *Change from baseline in minute ventilation was moderately correlated with change from baseline in pupil diameter during treatment with BBF (Pearson's $r = 0.38$-0.40; $p \leq 0.0011$) or oxycodone (Pearson's $r = 0.34$-0.37; $p \leq 0.005$). The initial onset of significant ($p < 0.05$) pupil constriction relative to placebo occurred at 2, 1.5, and 1 hour after dosing with BBF 300, 600, and 900 mcg, respectively, and at 0.5 hours after dosing with oxycodone 30 or 60 mg.*
Conclusions: *Although BBF and IR oxycodone achieved similar levels of pupil constriction, there was a delayed miosis seen with BBF relative to that found with oxycodone.*

INTRODUCTION

The opioid crisis and dangers associated with the use of opioids have led to increased scrutiny of prescriptions for chronic pain management.[1] Of particular concern are overdose and death, most often caused by respiratory depression,[2,3] when opioids are abused or even used as directed.[2] Opioid-related deaths are increasing during the coronavirus disease 2019 (COVID-19); in the 12 months leading up to July 2020, there were 84,000 deaths from drug overdoses, of which 61,000 involved prescription and nonprescription opioids.[4] Despite illicit opioids being the driver for this increase in deaths, prescription opioids are present in many overdose decedents.[5] Unfortunately, objective assessments of risk for abuse or an overdose are often absent from clinical assessments.[6]

Pupillometry is an objective measure of pupil constriction (miosis) and dilation (mydriasis), which are regulated by sets of antagonistic muscles in the iris (Figure 1).[7] The sphincter that constricts the pupils is controlled by parasympathetic pupilloconstrictor (Edinger–Westphal) neurons, whereas the radial muscles of the iris dilate the pupil.[8] Opioids target receptors on γ-aminobutyric acid-ergic presynaptic terminals and block transmission of an inhibitory input to the pupilloconstrictor neurons, leading to miosis.[8,9] In addition to measuring light reflexes, pupillometry has been used in research

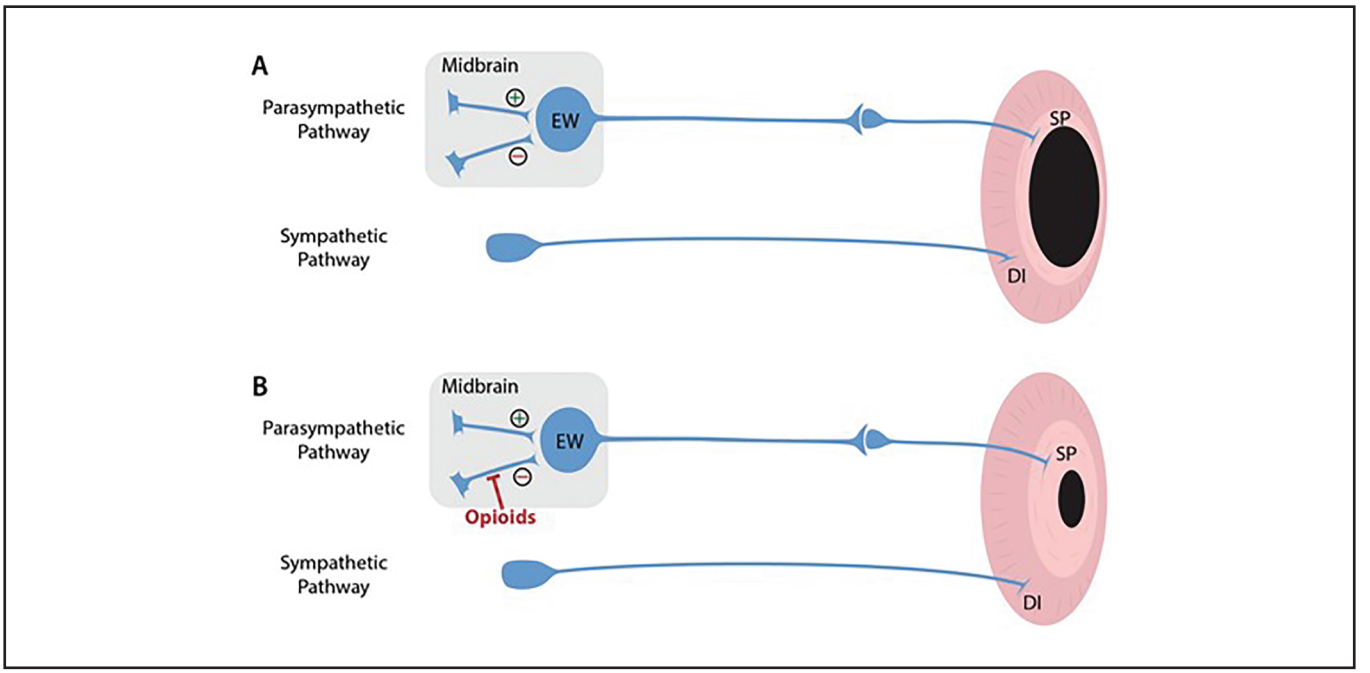

Figure 1. Anatomy of the iris and neuronal pathways controlling pupil size (A) and mechanism of pupil constriction (miosis) by opioids (B). (+) indicates excitatory; (–) inhibitory; DI, dilator iridis; EW, Edinger–Westphal; SP, sphincter pupillae.

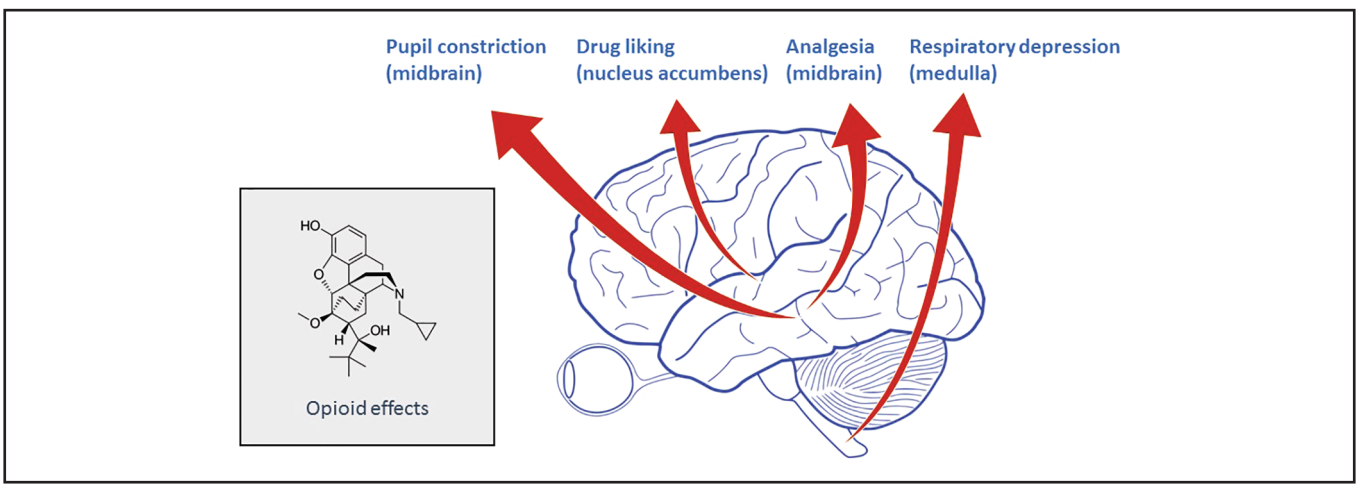

Figure 2. Key brain-mediated effects of opioids, eg, buprenorphine.[7,10-12]

settings to assess three opioid-related pharmacodynamic parameters: analgesia, respiratory depression, and drug liking (Figure 2). As a consideration in patients receiving long-term opioids, tolerance to miotic effects can develop.[13]

Pupillometry and analgesia

Pain and other noxious stimuli lead to dilation of pupils through sympathetic activation,[14] and increasing opioid-induced analgesia causes pupil constriction.[7] In a study evaluating the pupillary effects of 25 mcg of fentanyl (administered via inhalation and intravenously), the maximum decrease of approximately −1 to −1.5 mm in pupil diameter was achieved approximately 5-10 minutes after dosing, with a return to baseline at about 4-6 hours after dosing.[15] In a study of healthy volunteers, 26-66 mg of morphine was administered as an intravenous bolus, followed by continuous infusion to a target plasma

concentration of 100 ng/mL for 1.8-6.4 hours.[16] Analgesia (pain tolerance) immediately increased in a roughly linear manner, while pupil size simultaneously decreased rapidly (Appendix Figures A1 and A2).[16] The highest pain tolerance occurred slightly before the most pronounced miosis.[16] Miosis lasted much longer than analgesia in additional studies of opioids (morphine 20 or 40 mg; codeine 60 or 120 mg; oxycodone 15, 30, or 60 mg), although no correlational analyses were conducted.[17,18] Abuse potential studies confirmed the extended duration of miosis after opioid dosing.[19,20]

Pupillometry and drug liking

Pupil constriction intensifies with increases in the magnitude of drug liking, a measure used in human abuse liability studies meant to assess a component of abuse potential.[17,21,22] An increase in both pupil constriction and drug liking as measured by a visual analog scale has been reported after administration of oxycodone at 15, 30, 40, or 60 mg[17,21] and the analgesic/anesthetic remifentanil at 1 mg/kg.[22] No correlational analyses were performed between pupillometry and drug liking, but similar trends across the two measures were observed.[17,19,20,23-30]

Pupillometry and respiratory depression

Increased likelihood of respiratory depression was linked to increased pupil constriction in studies of remifentanil at ≥0.05 µg/kg/min as well as codeine at 60 or 120 mg and morphine at 20 or 40 mg.[18,31] Although no correlations were assessed between pupil diameter and respiratory depression, it was noted that associations are limited by the dynamic range of the pupil (≈3-7 mm).[31] These previous studies illustrate the potential for and limitations of utilizing pupillometry to investigate the relative safety and efficacy of opioid formulations.

Buprenorphine

Buprenorphine is a partial µ-opioid receptor agonist analgesic that has shown a ceiling effect on respiratory depression.[32,33] In contrast, full µ-opioid receptor agonists, eg, oxycodone and fentanyl, demonstrate dose-dependent effects on respiratory depression.[32,33] The pupillometry analyses presented here were conducted as part of a larger phase 1 study assessing respiratory drive. The study's primary outcome evaluated the maximum decrease in minute ventilation (E_{max}) after administration of buprenorphine buccal film (BBF; BELBUCA®, BioDelivery Sciences International, Inc.) and immediate-release (IR) oral oxycodone (commercially acquired by the clinical research site from a local vendor) by measurement of the ventilatory response to hypercapnia (VRH). Results showed that relative to placebo, oxycodone decreased respiratory drive in a dose-dependent fashion, whereas BBF did not impact respiratory drive at any of the three doses administered.[34] This report focuses on the secondary outcome of pupil diameter after administration of BBF and oxycodone.

METHODS

Population

Participants were healthy individuals who self-identified as recreational opioid users. Key inclusion and exclusion criteria are included in Table 1. Participants were not dependent on opioids, as confirmed with a naloxone challenge test on day 1, the day before treatment began.

Study design

This study utilized a double-blind, double-dummy, six-treatment, six-period, placebo-controlled, randomized crossover design (Figure 3). Study treatments were single doses of placebo: BBF 300, 600, and 900 mcg and IR oxycodone 30 and 60 mg. The dose range of 300-900 mcg for BBF is

Table 1. Key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
Age: 18-55 years	History of chronic obstructive pulmonary disease or any other lung disease that caused carbon dioxide retention
Recreational opioid user not currently dependent on opioids	Had participated in (within the last 5 years), was currently participating in, or was seeking treatment for substance-related disorders (excluding nicotine and caffeine)
Adequate ventilatory response to hypercapnia at screening	Positive result for drugs of abuse on a urine drug-screening test

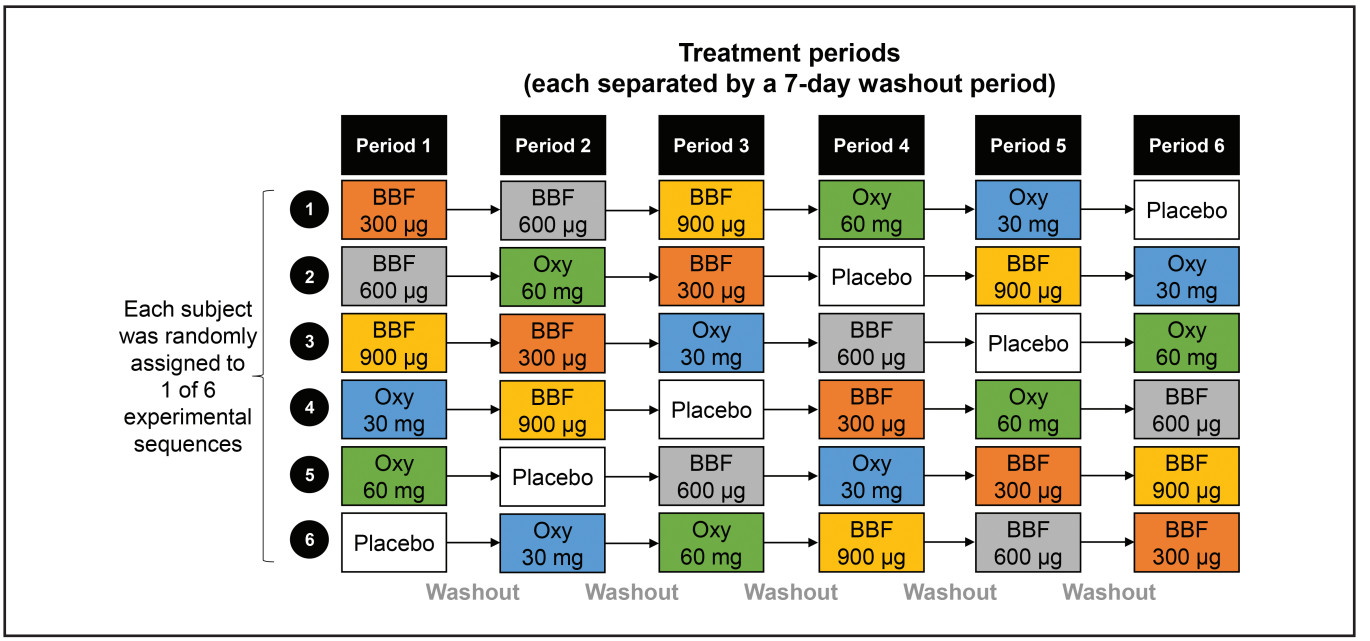

Figure 3. Randomized crossover study design. BBF, buprenorphine buccal film; Oxy, oxycodone. Reproduced with permission from Webster et al.[34]

thought to cover an equivalent range of analgesic effectiveness relative to 30-60 mg of oxycodone.[34] To maintain double-blinding, both buccal film and oral capsule were administered to each patient. Each treatment was separated by a 7-day washout period to avoid any potential carryover effects.

Each participant's number was determined with a randomization code just before dosing. On day 1, participants were assigned one of six treatment sequences in a 1:1:1:1:1:1 ratio using a computer-generated randomization scheme based on a Williams design, in which every treatment follows every other treatment at least once.

Assessments

Respiratory drive was evaluated by the VRH, which was performed while participants were recumbent or semisupine in a hospital bed. VRH was assessed once predose and at 0.5, 1, 2, 3, and 4 hours post-dose. At each time point, participants underwent an acclimation period with ambient air immediately followed by breathing a hypercapnic gas mixture (21 percent O_2, 72 percent N_2, and 7 percent CO_2) for a 5-minute capture period. If the participant reached an end-tidal CO_2 of 60 mm Hg for three consecutive breaths, the procedure was terminated.

Pupil diameter was assessed with standard pupillometry via the NeurOptics VIP® 200 pupillometer. Lighting was measured with a light sensor meter to ensure comparable values. The participant was instructed to focus on a distant object, while the pupillometer automatically detected the pupil. Pupillometry was measured predose and at 0.5, 1, 1.5, 2, 2.5, 3, and 4 hours post-dose.

Statistical analyses

Statistical analyses were performed using a mixed-effects model with treatment, period, and sequence as fixed effects and time point and treatment by time point interaction as repeated fixed effects. Pearson's r correlation coefficients were calculated for the change from baseline in minute ventilation versus the change from baseline in pupil size for each treatment. p values for correlations were obtained with a two-sided test using a null hypothesis of r = 0.

Ethics

An institutional review board (Midlands Independent Review Board, Lenexa, KS) approved the study, and informed consent was obtained from the participants.[34] This study is registered on ClinicalTrials.gov (NCT03996694).

RESULTS

Participant demographics and disposition

A total of 19 participants were enrolled, and 15 completed the study, with 16 completing at least two treatments (Table 2). There were 18 men and one woman enrolled, ranging from 27 to 41 years of age. Most (73.7 percent) of the participants were White.

Pupillometry outcomes

Change from baseline in minute ventilation was moderately correlated with change from baseline in pupil diameter during treatment with BBF (Pearson's $r = 0.38\text{-}0.40$; $p \leq 0.0011$) or oxycodone (Pearson's $r = 0.34\text{-}0.37$; $p \leq 0.005$). However, participants receiving placebo did not show a significant correlation between mean minute ventilation and mean pupil diameter, as there was little change in pupil diameter but some variability in minute ventilation in this group (Pearson's $r = -0.18$; $p = 0.12$).

Statistically, significant pupil constriction was slower to develop with BBF than with oxycodone, as expected from the difference in time to maximum concentration with the different medications. The initial onset of significant ($p < 0.05$) pupil constriction relative to placebo occurred at 2, 1.5, and 1 hour after dosing with BBF 300, 600, and 900 mcg, respectively, and at 0.5 hours after dosing with oxycodone 30 or 60 mg (Figure 4).

The magnitude of miosis appeared to be dose dependent. Pupil constriction observed with BBF 300 mcg was significantly less than that seen with oxycodone 30 mg (at all time points except 4 hours post-dose) and oxycodone 60 mg (at all time points; Figure 5A). Compared with both oxycodone doses (30 and 60 mg), administration of BBF 600 mcg resulted in significantly less pupil constriction until the 2 hours post-dose time point (Figure 5B). Similarly, BBF 900 mcg resulted in significantly less pupil constriction than both oxycodone doses up to 1.5 hours post-dose (Figure 5C).

DISCUSSION

Pupil constriction has been linked to analgesia, respiratory depression, and drug liking.[7,17,31] Analgesic efficacy of BBF has previously been demonstrated in opioid-naive[35] and opioid-experienced[36] patients with chronic pain. In this study

Table 2. Summary of demographics

	Category	Randomized and safety (n = 19)	Completer (n = 15)	Partial completer (n = 16)
Sex, n (percent)	Female	1 (5.3)	1 (6.7)	1 (6.3)
	Male	18 (94.7)	14 (93.3)	15 (93.8)
Race, n (percent)	White	14 (73.7)	12 (80.0)	13 (81.3)
	Black or African American	1 (5.3)	1 (6.7)	1 (6.3)
	Asian	1 (5.3)	1 (6.7)	1 (6.3)
	American Indian or Alaska Native	3 (15.8)	1 (6.7)	1 (6.3)
Ethnicity, n (percent)	Hispanic or Latino	5 (26.3)	3 (20.0)	3 (18.8)
	Not Hispanic or Latino	14 (73.7)	12 (80.0)	13 (81.3)
Values, mean (SD)	Age (years)	33.1 (4.5)	32.9 (4.4)	32.8 (4.3)
	Weight (kg)	78.6 (15.8)	80.6 (16.7)	79.3 (16.9)
	Height (cm)	177.1 (8.4)	177.4 (9.3)	177.0 (9.1)
	BMI (kg/m^2)	24.9 (3.7)	25.4 (3.8)	25.1 (3.9)

Abbreviation: BMI, body mass index.

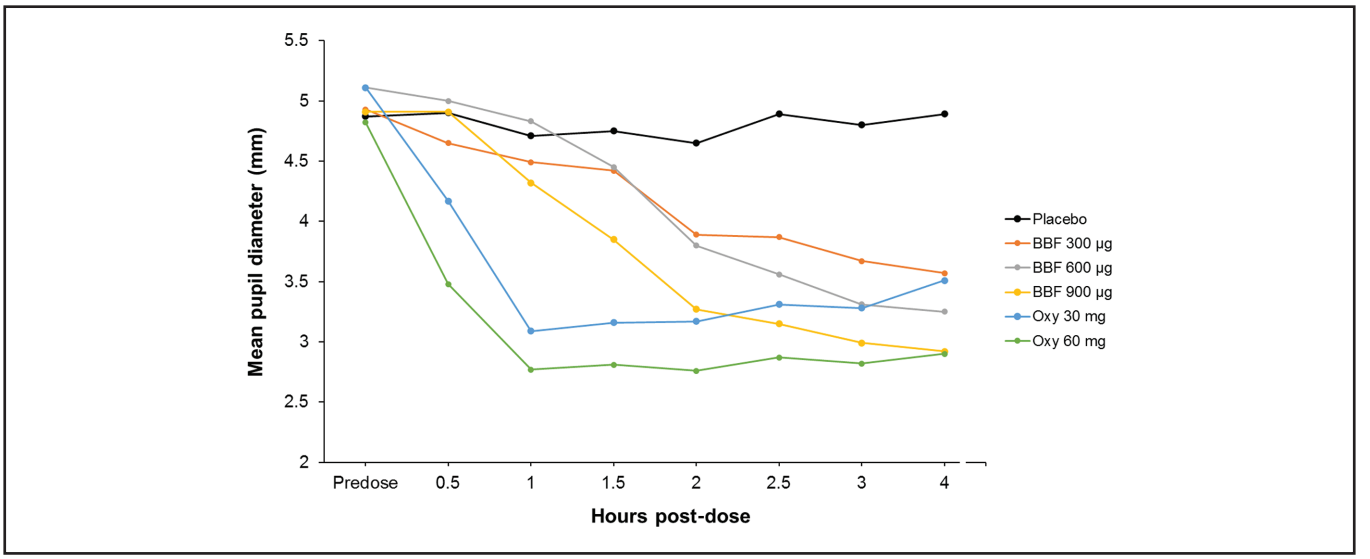

Figure 4. Mean pupil diameter in response to BBF and Oxy administration (n = 15). BBF, buprenorphine buccal film; Oxy, oxycodone.

of healthy individuals who self-identified as recreational opioid users, pupil constriction with IR oxycodone and BBF achieved similar levels, which suggests comparable analgesia. For comparison, a study of inhaled or intravenous fentanyl 25 mcg showed a similar level of miosis, with an apparent faster onset and return to baseline, although different time points were assessed than in this study.[15]

Although subcutaneous buprenorphine up to 2 mg has been shown to induce euphoria in participants who are not physically dependent on opioids,[37,38] buprenorphine is considered to have a lower abuse potential than full µ-opioid receptor agonists and is, therefore, classified as a Schedule III drug.[39,40] The more immediate pharmacokinetic and pharmacodynamic effects of the IR oxycodone formulation observed in this study could translate to higher drug liking compared with the BBF formulation, which has a more delayed time to maximum concentration.

With respiratory depression accounting for the majority of opioid-related deaths,[2,3] opioids showing fewer dose-related respiratory effects may provide some protection from this safety concern. No significant decrease in respiratory drive was observed for any BBF dose at E_{max}, whereas oxycodone produced a dose-dependent decrease in respiratory drive,[34] consistent with previous results on respiratory depression.[41] Pupillometry supported this observation; after treatment with BBF or oxycodone, change in minute ventilation and pupil diameter was moderately correlated. Results from this study suggest that BBF may have a decreased risk of drug liking and respiratory depression compared with full µ-opioid receptor agonists, such as oxycodone, at what appear to be equianalgesic doses.[42] The study results also imply that pupillometry may correlate better with analgesia and drug liking than with respiratory depression, although future research is needed.

Limitations

Limitations of the study include the small sample size (n = 16 partial completers). Analgesia was not measured in this group of healthy volunteers, and as only one dose of each medication was given to each participant, the outcomes may not be applicable to patients with chronic pain receiving long-term therapy. In addition, the influence of pharmacogenetic differences (specifically CYP2D6 deficiency) on opioid activity was not included in the scope of the study.

Another limitation for interpretation of results is that drug liking was not formally tested in this study. The formulations for BBF and IR oxycodone affect their pharmacokinetic profiles, which could influence drug liking, ie, higher drug liking with more rapid effects. Drug liking is a subjective measure and only accounts for one aspect of abuse potential. Previous studies have shown a correlation between pupillometry results and drug liking.[21,22] However, we cannot correlate the magnitude of change between buprenorphine and oxycodone for analgesia and drug liking from these results.

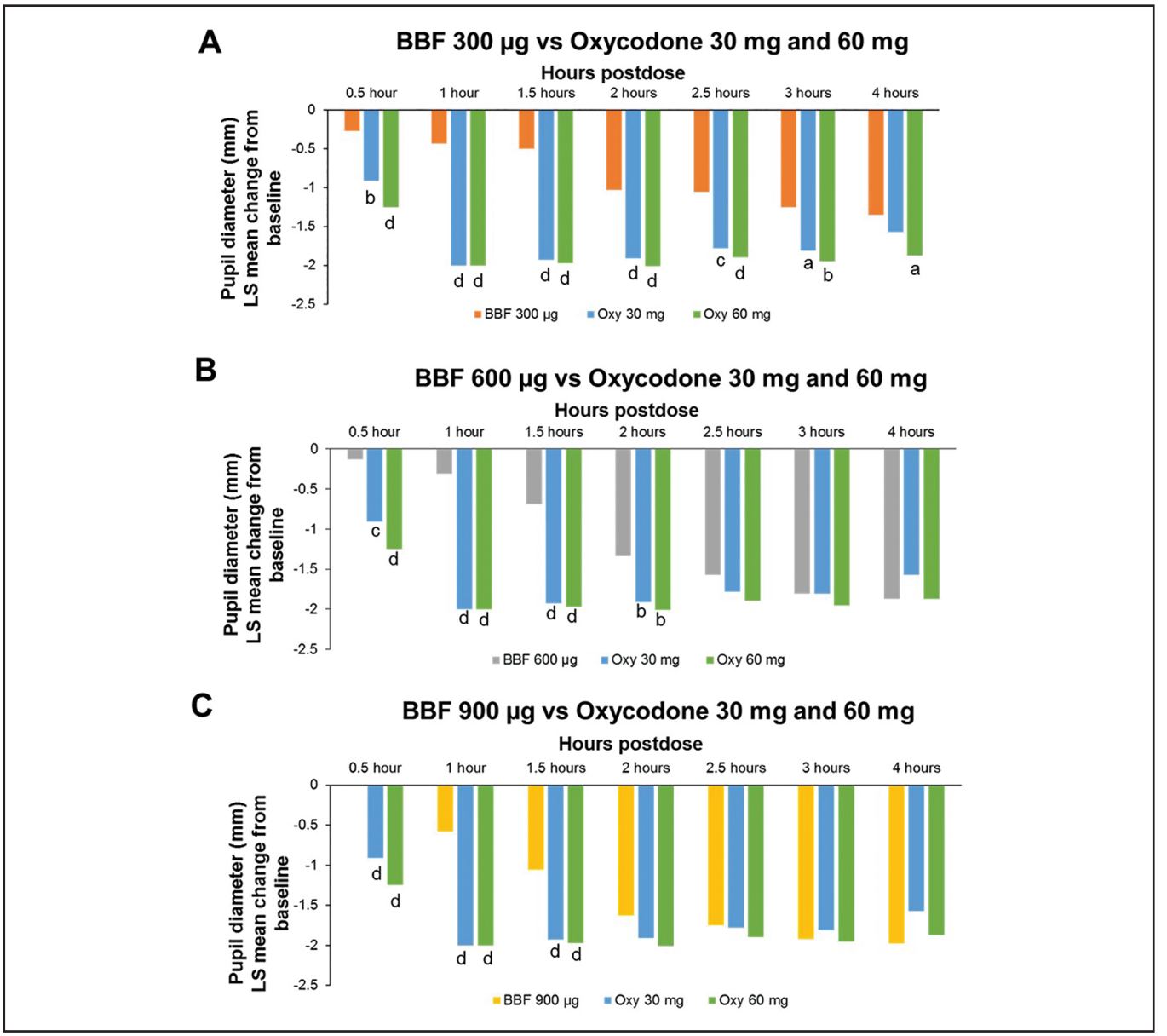

Figure 5. Effects of BBF 300 mcg (A), 600 mcg (B), and 900 mcg (C) versus Oxy 30 and 60 mg on pupil diameter (n = 16). [a]p < 0.05, [b]p < 0.01, [c]p < 0.001, and [d]p < 0.0001 (p values represent differences in LS means between BBF and Oxy). BBF, buprenorphine buccal film; LS, least squares; Oxy, oxycodone.

Future directions

Pupillometry is used primarily in research settings, but it has potential utility in clinical practice, particularly in pain management. Pupillometry can be applied to indicate opioid toxicity—eg, small pupils that are reactive to light but are not pinpoint[31]—and opioid receptor occupancy, eg, mydriasis blocked by receptor antagonists.[43] Mobile phones are emerging as tools for convenient assessment of pupillometry.[44] However, further study is needed to ensure accurate interpretation of pupillometry results, especially in patients with tolerance to opioids and for comparing among various opioids and atypical opioids.

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APPENDIX

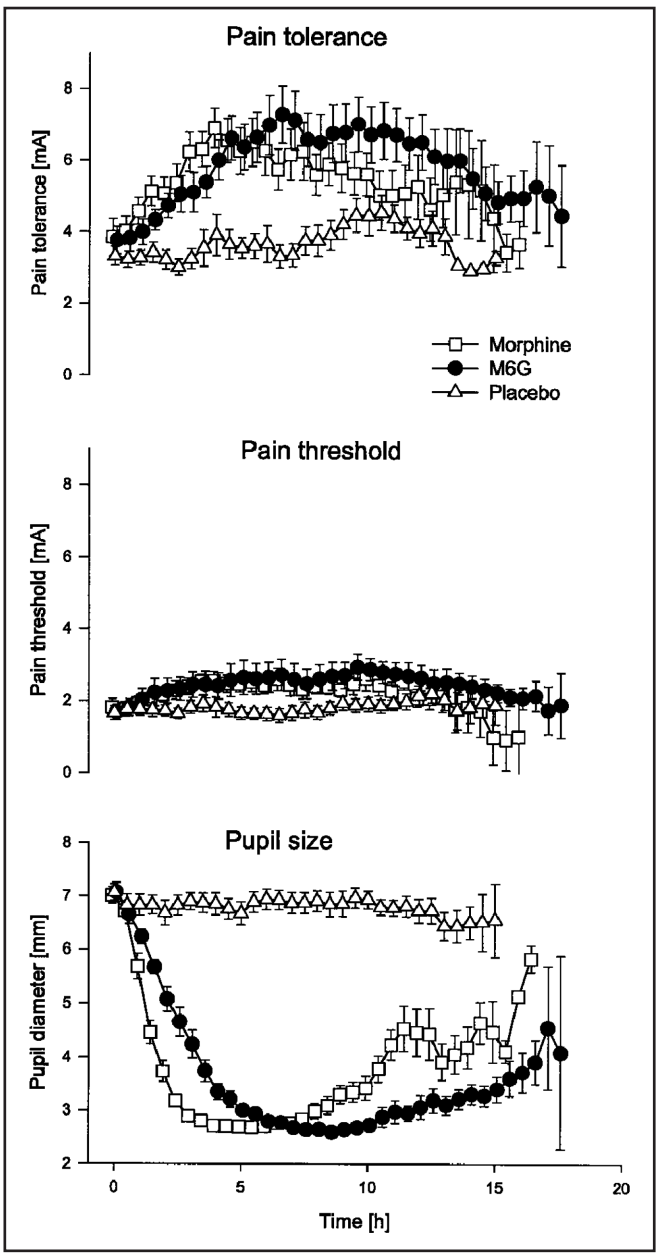

Figure A1. Pain tolerance time course (top), pain threshold (center), and pupil diameter (bottom) after intravenous administration of morphine, morphine-6-glucuronide (M6G), and placebo. Figure reproduced with permission from Skarke et al.[16]

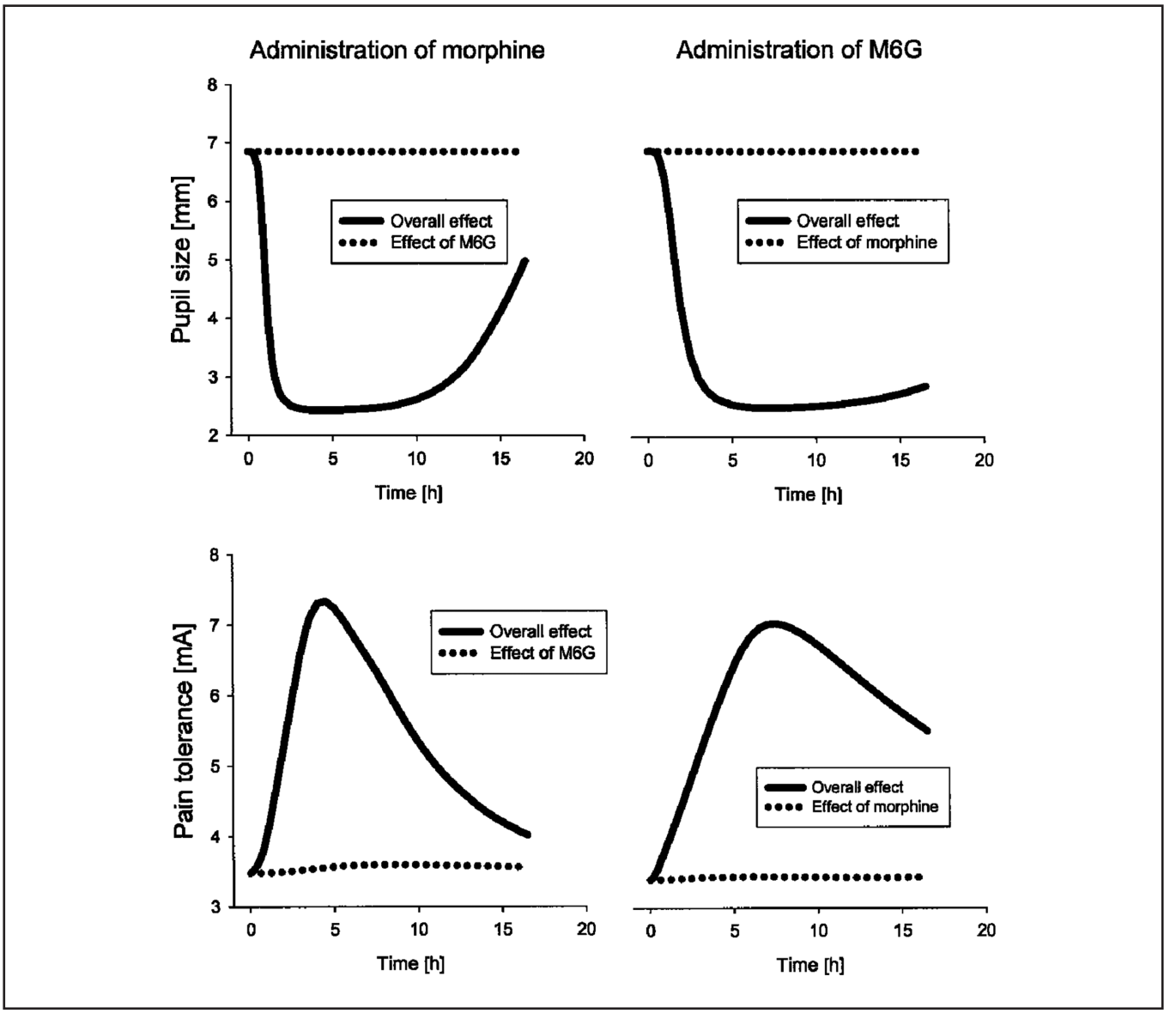

Figure A2. Time course simulations for pupil diameter (top) and pain tolerance (bottom) following infusion of morphine or morphine-6-glucuronide (M6G). The simulations are based on pharmacokinetic and pharmacodynamic models. Overall effects are shown with solid lines, while dotted lines reflect changes produced by M6G following morphine administration and by morphine following the administration of M6G. These data indicate that M6G did not contribute significantly to the effects of morphine, after morphine administration, and the small amounts of morphine formed after the administration of M6G did not impact the overall effects. Figure reproduced with permission from Skarke et al.[16]