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Buprenorphine maintenance subjects are hyperalgesic and have no antinociceptive response to a very high morphine dose

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Buprenorphine maintenance subjects are hyperalgesic and have no antinociceptive response to a very high morphine dose

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 Manuscripts

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5 antinociceptive response to a very high morphine dose
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53

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Abstract

Objective. Acute pain management in opioid dependent persons is complicated because of tolerance and opioid-induced-hyperalgesia. Very high doses of morphine are ineffective in overcoming opioid-induced-hyperalgesia and providing antinociception to methadone maintained patients in an experimental setting. Whether the same occurs in buprenorphine maintained subjects is unknown.

Design. Randomised double blind placebo controlled. Subjects were tested on two occasions, at least five days apart; once with intravenous morphine and once with intravenous saline. Subjects were tested at about the time of putative trough plasma buprenorphine concentrations.

Setting. Ambulatory.

Subjects. Twelve buprenorphine maintained subjects: once daily sublingual dose (range 2-22 mg); no dose change for 1.5-12 months. Ten healthy controls.

Methods. Intravenous morphine bolus and infusions administered over 2 hours to achieve two separate pseudo-steady state plasma concentrations one hour apart. Pain tolerance assessed by application of nociceptive stimuli (cold pressor (seconds) and electrical stimulation (volts)). Ten blood samples collected for assay of plasma morphine, buprenorphine and norbuprenorphine concentrations until 3 hours after the end of last infusion; pain tolerance and respiration rate measured to coincide with blood sampling times.

Results. Cold pressor responses (seconds): baseline: control 34 ± 6 versus

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3 buprenorphine 17 ± 2 ($P=0.009$); morphine infusion-end: control 52 ± 11 ($P=0.04$),
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5 buprenorphine 17 ± 2 ($P>0.5$); electrical stimulation responses (volts): baseline:
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7 control 65 ± 6 versus buprenorphine 53 ± 5 ($P=0.13$); infusion-end: control 74 ± 5
8
9 ($P=0.007$), buprenorphine 53 ± 5 ($P>0.98$). Respiratory rate (breaths per minute):
10
11 baseline: control 17 versus buprenorphine 14 ($P=0.03$); infusion-end: control 15
12
13 ($P=0.09$), buprenorphine 12 ($P<0.01$). Infusion-end plasma morphine concentrations
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15 (ng/mL): control 23 ± 1 , buprenorphine 136 ± 10 .
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20 **Conclusions.** Buprenorphine subjects, compared with controls, were: hyperalgesic
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22 (cold pressor test); did not experience antinociception, despite high plasma morphine
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24 concentrations; experienced respiratory depression. Clinical implications are
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26 discussed.
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Introduction

The prevalence of opioid dependence is growing worldwide. Dependence has traditionally been the result of illicit opioid abuse. However, it is increasingly associated with legally prescribed long-term use of opioids for the management of chronic pain [1]. Between 28 and 38.5 million people abuse opioids worldwide. In 2015, 2 million had a substance use disorder involving prescription pain relievers and 591,000 had a substance use disorder involving heroin [2]. Approximately 1% of the Australian population is opioid dependent and half of these are in opioid substitution treatment (OST) programs [3]. Of these, two-thirds receive methadone and one third buprenorphine (alone or with naloxone) but this difference is declining.

The management of acute pain in opioid dependent patients is complicated because of two major factors: tolerance, which can generally be overcome by dose increase but may be compromised by adverse effects, and the under recognized phenomenon of opioid-induced-hyperalgesia (OIH) characterized as paradoxical pain sensitization [4] which cannot be overcome by dose increase. Although there are no formal guidelines for the clinician, Macintyre et al [5] and Huxtable et al [6] advise, that in the clinical setting, the daily OST dose should be maintained and additional opioid used for acute pain management, titrated until satisfactory analgesia is achieved or an adverse effect (e.g. sedation or respiratory depression) occurs. Such an approach requires stringent observation such as admission to hospital.

Opioid-induced hyperalgesia occurs in opioid (e.g. heroin) addicted subjects prior to entry into methadone and buprenorphine treatments [7], chronic non-cancer pain

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3 patients [8], and slow release morphine, methadone and buprenorphine maintained
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5 subjects [9, 10, 11, 12]. Clinically used and very high doses of morphine are
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7 ineffective in overcoming OIH and providing antinociception to methadone
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9 maintained patients [11, 13] in an experimental setting. Whether the same occurs in
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11 buprenorphine maintained subjects is unknown.
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16 Buprenorphine, a semi-synthetic 4,5-epoxymorphinan opioid shows partial agonist
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18 properties for some responses at the mu opioid receptor and variable effects at
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20 the kappa and delta receptors [14]. Its major metabolite norbuprenorphine is also
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22 active [15], although there is conjecture whether it crosses the blood-brain barrier
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24 [16]. Opioid agonists such as morphine, over plasma concentration ranges that
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26 produce dose-related increases in analgesia, also produce concentration-
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28 dependent respiratory depression without any plateau in healthy human
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30 volunteers [17]. In contrast, buprenorphine shows dose-dependent increases in
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32 analgesia with a limited extent of respiratory depression [17, 18]. As a partial
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34 agonist, under appropriate conditions, buprenorphine may act as an agonist or
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36 antagonist at opioid receptors [19] and has shown antihyperalgesic effects in
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38 healthy subjects using a model of intradermal electric stimulation [20]. Therefore,
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40 buprenorphine may be unique in its ability to treat acute pain and possibly
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42 attenuate OIH.
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47 Previously we showed that methadone maintained subjects on doses of 2-120 mg
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49 per day, under identical experimental conditions that will be described in this study,
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51 experienced no antinociception with 55 mg of intravenous morphine but showed a
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53 significant reduction in respiratory rate [13]. To date, no studies have examined the
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55 effect of different daily buprenorphine doses on the antinociceptive and respiratory
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3 responses to morphine.
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7 The aims of the study in buprenorphine maintained subjects were to: 1. Confirm the
8 presence of OIH; 2. Ascertain whether very high intravenous morphine doses
9 produce antinociceptive and respiratory depression effects and 3. Determine any
10 relationship between buprenorphine dose and these effects. Our hypothesis is that
11 buprenorphine maintained subjects are hyperalgesic and, that in contrast to
12 methadone maintained subjects, experience antinociception with high morphine
13 doses.
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23 **Methods**

24 25 26 27 28 *Ethics*

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30 The Research Ethics Committee of the Royal Adelaide Hospital, Adelaide, South
31 Australia, Australia (RAH Protocol no: 010222) and the Institutional Review Board,
32 Friends Research Institute, Los Angeles, California, USA (FRI IRB no: 00-03-057-
33 02) approved the study. Both bodies adhere to the ethical standards set by the
34 Helsinki Declaration (2008). The study was supported by National Institutes of Drug
35 Abuse (NIDA) grant R01 DA 13706-02. This study was not registered on
36 clinicaltrials.gov as this study was carried out before the requirement for
37 registration. Subjects provided written informed consent, were paid for their
38 involvement in the study and were free to withdraw at any time.
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50 51 52 *Subjects*

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54 Twelve buprenorphine maintained subjects comprising 7 men and 5 women with
55 ages between 24 and 42 years (mean 35 years) were recruited. Their weights
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3 ranged between 49 and 97 kg (mean 71 kg). They had been receiving sublingual
4 buprenorphine (Subutex ® Reckitt Benckiser, West Ryde, New South Wales,
5 Australia) for between 1.5 and 12 months (mean 4 months) with no dose change.
6
7 They had been enrolled in a buprenorphine maintenance program for a period
8 ranging between 2 and 22 months with a mean of 10 months. The group was
9 stratified according to dose, with four subjects in each of the dose ranges of 2 to 8
10 mg, 9 to 15 mg and 16 to 22 mg per day. Subjects were recruited if they self-
11 reported intravenous heroin use at least once in the previous month. It was
12 considered more ethical to administer morphine to individuals who continued to use
13 illicit heroin, rather than to those who used no opioids, apart from their prescribed
14 buprenorphine. Ten healthy control subjects (5 men and 5 women; aged between
15 21 and 41(mean 31) years); weight 59 and 102 (mean 80) kg) were selected.
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17 These subjects were not taking any prescribed medications. They have been
18 described previously [13].
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35 *Exclusion criteria*

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40 Exclusion criteria for all subjects included pregnancy or lactation, use of
41 antiretroviral drugs, significant medical or psychiatric illness that required ongoing
42 treatment (except opioid addiction for buprenorphine subjects), daily alcohol
43 consumption exceeding 40 g for men and 20 g for women, severe liver impairment
44 (serum aspartate aminotransferase and alanine aminotransferase concentrations
45 greater than 3 times the upper limit of normal range and albumin concentrations
46 less than 33 grams per litre) or haemoglobin counts outside the normal range.
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55 Healthy control subjects were excluded if they had any personal or family history of
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3 addictive behaviours.
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8 *Study design*

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10 The study utilized a double blind placebo controlled design with four groups of
11 subjects (healthy controls, once daily buprenorphine dose of 2 to 8, 9 to 15 and,
12 16 to 22 mg). Subjects were tested on two occasions, at least five days apart;
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14 once with morphine and once with saline. The order of administration was
15
16 randomised. Buprenorphine subjects were tested at about the time of putative
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18 trough plasma concentrations of buprenorphine (approximately 20 hours after
19
20 the previous buprenorphine dose).
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25 *Procedure*

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28 Subjects were asked not to use any analgesics or illicit substances for twenty-four
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30 hours prior to testing. A urine sample was collected on each study day for the
31
32 detection of opioids, benzodiazepines, sympathomimetic amines, cannabinoids and
33
34 barbiturates. Analysis of these samples confirmed that control subjects had not taken
35
36 any of these psychoactive substances. Subjects were excluded from the study if they
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38 presented on study or screening days showing any signs of intoxication from any
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40 substance.
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46 Testing was conducted under constant ambient temperature (24°C) and constant
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48 illumination (70 lux). Each session commenced at approximately 8 am and lasted 8
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50 hours. Two indwelling catheters (Insite Autoguard, Becton Dickenson, Sandy, Utah,
51
52 USA) were inserted into peripheral veins on opposite arms. The catheter in the
53
54 dominant arm served for drug infusion; the catheter in the non-dominant arm for
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3 blood sampling. On each testing day, saline was infused at 2 ml/min for 30 min prior
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5 to morphine or saline administration for familiarisation.
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10 *Morphine administration*

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12 Morphine sulphate (David Bull Laboratories, Melbourne, Australia) infusions of 1
13
14 mg/ml were administered intravenously in two sixty-minute stages to achieve two
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16 consecutive target pseudo-steady-state plasma concentrations [11] using a
17
18 syringe driver infusion pump (3100 Graseby Syringe Pump, Watford, Hertfordshire,
19
20 UK). Buprenorphine subjects received an initial bolus of 15.2 mg of morphine
21
22 sulphate followed by a constant infusion of 8.3 mg/hr for one hour to achieve a
23
24 target pseudo steady-state plasma concentration of 80 ng/ml (Morphine 1). They
25
26 were then administered an additional bolus of 15.2 mg of morphine sulphate
27
28 followed by a constant infusion of 16.5 mg/hr for one hour to achieve the second
29
30 target pseudo steady-state plasma concentration of 180 ng/ml (Morphine 2). The
31
32 prescribed buprenorphine dose was administered 1 hour after infusions ceased.
33
34 Control subjects were administered an initial bolus of 2.2 mg morphine sulphate
35
36 followed by a constant infusion of 1.2 mg/hr for one hour to achieve a target
37
38 pseudo steady-state plasma concentration of 11 ng/ml (Morphine 1). They were
39
40 then administered 4.95 mg of morphine sulphate followed by a constant infusion of
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42 3.6 mg/hr to achieve the second target pseudo steady-state plasma concentration
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44 of 33 ng/ml (Morphine 2) [11].
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52 *Blood sampling and assessment times*

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55 Seven millilitre blood samples were taken at the following times: prior to the thirty
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3 minute saline familiarisation infusion, ten minutes prior to end of this infusion
4 (designated as baseline) and ten minutes prior to the end of each of the two
5 morphine or placebo saline infusions. Further blood samples were taken at 0.25,
6 0.5, 0.75, 1.0, 2.0, and 3 hours after the end of the last infusion. The blood samples
7 were centrifuged immediately and the plasma stored at -20°C until assay.
8
9 Respiration rate was measured and nociceptive tests (see below) were
10 administered immediately after the collection of each blood sample except at 0.25,
11 0.50 and 0.75 hours after the last infusion.
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23 *Nociceptive tests, physiological responses and safety monitoring*

24 Two nociceptive tests were administered: the cold pressor using the non-dominant
25 arm, and electrical stimulation using the earlobe. These tests have been described
26 previously [10]. Cold pressor involves the immersion of the non-dominant arm in
27 $0.5\text{--}1.5^{\circ}\text{C}$ water and the response metric is seconds. Electrical stimulation
28 involves the transmission of an electrical pulse through the earlobe and is
29 measured in volts. One nociceptive marker was used which was pain tolerance,
30 when the participant verbally indicated that they could no longer tolerate the pain
31 and removed their arm from the water or requested that the electrical stimulation
32 cease.
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47 Respiration rate was measured over one minute by observation without the
48 subjects' awareness. Safety was monitored and recorded throughout the study
49 by means of continuous pulse oximetry, continuous ECG waveform, categorical
50 nausea scale [21] and categorical sedation scale [22].
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Plasma opioid quantification

The quantification of plasma buprenorphine and norbuprenorphine was by high performance liquid chromatography coupled to mass spectrometry as previously described [23]. The assay had a limit of quantification of 0.125 ng/ml for both analytes and all variability in accuracies and precision had coefficients of variation for buprenorphine and nor-buprenorphine of less than 15%. The quantification of plasma morphine was by high-performance liquid chromatography (HPLC) with coulometric detection as previously described [11]. The assay had a lower limit of quantification of 1 ng/ml and all variability in accuracies and precision had coefficients of variation below 7%.

Data analysis

Data are presented as mean \pm SEM (with 95% confidence intervals (95% CI)). One-way ANOVA was used to compare outcome variables (cold pressor tolerance, electrical stimulation tolerance, respiration rate) between the buprenorphine dose groups. One-way ANOVA was also used to compare each outcome variable across treatments for the buprenorphine dose groups, combined buprenorphine subjects and the control subjects with 95% CI of differences. Unpaired samples t-tests were used to compare baseline values between the combined buprenorphine subjects and the control subjects. The Pearson product-moment correlation coefficient (Pearson's r) was used to measure the linear correlation between individual buprenorphine daily doses and plasma morphine concentrations. Bonferroni's and Dunnett's tests were used for post-hoc analyses as appropriate. Data for both studies were analysed using GraphPad Prism 4.2 for

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3 Windows, GraphPad Software, San Diego, California, USA and $P < 0.05$ was
4 considered significant.
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8 9 **Results**

10 11 *Nociceptive tests*

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14 There were no significant differences ($P > 0.45$) in pain tolerance responses between
15 the three buprenorphine dose groups from baseline to morphine infusion 1 or
16 morphine infusion 2. Hence, the data from the groups were combined.
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20 21 22 *Cold pressor responses*

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24
25 Pain tolerance responses at baseline and morphine infusion 2 for control subjects
26 and the buprenorphine subjects are shown in Figure 1 (upper panel) and absolute
27 values and ranges for all treatments in Table 1. Pain tolerance values for the
28 buprenorphine subjects remained unchanged between baseline and the two
29 morphine infusions. Pain tolerance values for the buprenorphine subjects were
30 significantly lower than for control subjects at baseline (ANOVA $P = 0.009$; 95% CI -
31 5 to -30). Within group comparisons revealed that pain tolerance values for control
32 subjects increased significantly ($P = 0.04$) from baseline to morphine infusion 2
33 ($P < 0.05$; 95% CI 2 to 34), but not baseline to morphine infusion 1 ($P > 0.05$; 95% CI
34 -12 to 20).
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50 51 *Electrical stimulation responses*

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53 Pain tolerance responses at baseline and morphine infusion 2 for control subjects
54 and the buprenorphine subjects are shown in Figure 1 (middle panel) and absolute
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3 values with ranges given in Table 1. Pain tolerance values for the buprenorphine
4 subjects were not significantly different to controls (ANOVA $P=0.13$) at baseline.
5
6 Within-group comparisons revealed that pain tolerance values for control subjects
7 increased significantly ($P=0.007$) from baseline to morphine infusion 2 ($P<0.01$;
8 95% CI 3 to 16), but not baseline to morphine infusion 1 ($P>0.05$; 95% CI -2.8 to
9 10 10). There was no significant change ($P=0.98$) in pain tolerance values for
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12 combined buprenorphine subjects from baseline to morphine infusion 1 or
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14 morphine infusion 2.
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23 *Respiration rates*

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25 Respiration rates (breaths per minute) relative to baseline and morphine infusion 2
26 are shown in Figure 1 (lower panel) and absolute values with ranges in Table 1.
27
28 Respiration rates for the buprenorphine subjects were significantly lower than for
29 control subjects at baseline (ANOVA $P=0.03$; 95% CI -0.25 to -4.9). Within group
30 comparisons revealed that the respiration rates for control subjects did not decrease
31 significantly ($P=0.09$) from baseline to morphine infusion 1 or morphine infusion 2.
32
33 Respiration rates for the buprenorphine subjects decreased significantly (ANOVA
34 $P=0.006$) from baseline to morphine infusion 2 ($P<0.01$; 95% CI -0.9 to -4.4) but not
35 morphine infusion 1 ($P>0.05$; 95% CI -2.8 to 10).
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47 Buprenorphine dose group comparisons demonstrated significant changes in
48 respiration rates as follows. Group 2-8 mg daily: (ANOVA $P=0.024$) from baseline to
49 morphine infusion 1 ($P<0.05$; 95% CI -0.56 to -7.4) and baseline to morphine
50 infusion 2 ($P<0.05$; 95% CI -0.56 to -7.4); group 9-15 mg daily: (ANOVA $P=0.004$)
51 between baseline and morphine infusion 2 ($P<0.01$; 95% CI -1.48 to -5.52), but not
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3 morphine infusion 1 ($P>0.05$; 95% CI -2.02 to 2.02); group 16 to 22 mg daily:
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5 (ANOVA $P=0.016$) between both baseline and morphine infusion 1 ($P<0.05$; 95% CI
6
7 -0.72 to -4.28) and baseline and morphine infusion 2 ($P<0.05$; 95% CI -0.22 to -
8
9 3.78). There were no significant differences in respiration rate between the groups
10
11 at baseline ($P=0.90$) or morphine infusion 2 ($P=0.67$). The lowest recorded
12
13 respiration rates were ten breaths per minute in the control group and nine breaths
14
15 per minute in the buprenorphine subjects.
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18 19 20 21 *Adverse events*

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23 There were no serious adverse events. Buprenorphine subjects did not experience
24
25 nausea or vomiting, but seven control subjects required one dose of intramuscular
26
27 metoclopramide hydrochloride 10 mg (Pfizer, Perth, Australia) with good effect for
28
29 mild vomiting.
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32 33 34 35 *Plasma morphine, buprenorphine and norbuprenorphine concentrations*

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37 Pseudo steady-state plasma morphine concentrations for morphine 1 and 2
38
39 infusions are shown in Table 2A. Target pseudo steady-state plasma morphine
40
41 concentration for the buprenorphine recipients were 80 ng/ml (Morphine 1) and 180
42
43 mg/ml (Morphine 2). Target pseudo steady-state plasma concentration for control
44
45 subjects were 11 ng/ml (Morphine 1) and 33 mg/ml (Morphine 2). Pseudo state
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47 plasma morphine concentrations were lower than the desired target in both groups
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49 at morphine 1 and 2. Plasma morphine concentrations are also shown for the
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51 individual daily buprenorphine dose groups 2-8, 9-15 and 16-22 mg/day. There was
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53 no significant correlation ($p=0.08$) between individual buprenorphine doses and
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3 plasma morphine concentrations at morphine infusion 1. However, there was a
4 significant inverse relationship between individual buprenorphine doses and plasma
5 morphine concentrations at morphine infusion 2 (Pearson's $r = -0.74$, $p = 0.006$; slope
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7
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9 95% CI - 0.92 to -0.28).
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14 There were no significant differences between combined mean plasma
15 buprenorphine concentrations (Table 2B), or for the three dose groups, at baseline
16 (P=0.64), morphine infusion 1 (P=0.71) or morphine infusion 2 (P=0.51). Likewise,
17 there were no significant differences between combined mean plasma
18 norbuprenorphine concentrations (Table 2C), or for the three dose groups, at
19 baseline, morphine infusion 1 or morphine infusion 2. At baseline on the saline
20 administration day, plasma buprenorphine and norbuprenorphine concentrations
21 were correlated to the buprenorphine dose ($r^2 = 0.36$ and 0.58 , respectively;
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31 Supplementary Tables 3A, 3B).
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36 Discussion

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40 To our knowledge, this is the first study to have examined the effect of added
41 morphine to buprenorphine OST subjects who were pain-free at the time of study,
42 using an experiment pain model. Buprenorphine subjects were hyperalgesic in the
43 cold pressor test in comparison with controls. Very high doses of morphine (55 mg)
44 produced high plasma concentrations (92 to 201 ng/ml) that failed to provide
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3 ng/ml), provided antinociception in both tests.
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5 Our choice of using the cold pressor response to study opioid induced-
6
7 hyperalgesia has been validated by others. Compton et al [13] examined
8
9 hyperalgesia in opioid dependent subjects and found that these subjects, prior to
10
11 induction and following stabilisation on either methadone or buprenorphine, were
12
13 similarly hyperalgesic in the cold pressor test and did not exhibit hyperalgesia in the
14
15 electrical stimulation test. Krishnan et al [12] compared the detection of
16
17 hyperalgesia in opioid-substitution subjects maintained either on methadone or
18
19 buprenorphine and healthy controls using the following pain stimuli: cold pain,
20
21 electrical stimulation, mechanical pressure, and ischemic pain. They found that cold
22
23 pain was the most suitable of the methods tested to detect opioid-induced
24
25 hyperalgesia.
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31 While the buprenorphine maintained subjects were tolerant to the antinociceptive
32
33 effects of the high doses of morphine and plasma concentrations to which they
34
35 were exposed, complete cross-tolerance to the respiratory depressant effects of
36
37 morphine did not occur. Respiration rates dropped significantly across all dose
38
39 groups, but by a limited amount (approximately 1.5 breaths per minute), which may
40
41 not be clinically significant. In healthy volunteer subjects who received a single
42
43 intravenous dose (0.2 mg/kg) of morphine, over a plasma concentration range
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45 (approximating 3-13 ng/mL) that produced a systematic increase in analgesia,
46
47 morphine produced significant respiratory depression [24]. In contrast, in healthy
48
49 adult volunteers who had experience with opioids but who were not physically
50
51 dependent on opioids, Walsh and co-workers [18] demonstrated that respiratory
52
53 depression increased with single buprenorphine single doses over a range of 1 to 4
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3 mg (approximately 4 breaths per minute decrease), but that this dose effect began
4
5 to plateau at higher doses, with no difference between a 16 and 32 mg dose. In the
6
7 present study, with subjects chronically maintained on buprenorphine, high doses
8
9 of added morphine had a limited respiratory depressant effect at all buprenorphine
10
11 doses. It is, however, possible that higher doses of morphine might produce
12
13 respiratory depression if such doses are needed to achieve anti-nociception, given
14
15 that the lowest respiratory rate recorded was nine breaths per minute. Macintyre et
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17 al [25] showed increased sedation score (a surrogate for respiratory depression) in
18
19 buprenorphine-maintained patients who received higher doses of morphine
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21 equivalents following surgery than in this study.
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28 Hyperalgesia is likely to be present, to a lesser or greater degree, in opioid
29
30 recipients for whatever indication. Non-cancer pain patients, maintained on either
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32 methadone or slow release oral morphine for the treatment of that pain, were
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34 shown to exhibit hyperalgesia in the cold pressor test [8], similar to that seen in
35
36 methadone [13] and buprenorphine subjects (this study) in opioid substitution
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38 programs. Chakrabarti et al [26] (2010) found that people with a greater reported
39
40 experience of pain prior to induction onto buprenorphine maintenance required
41
42 greater daily doses. The present study found that there was no difference in the
43
44 degree of hyperalgesia experienced at baseline between the three dose ranges.
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46 There was also no difference between the three dose ranges in terms of cross-
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48 tolerance to the antinociceptive effects of very high dose morphine.
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54 The most widely used drugs in opioid substitution programmes worldwide are
55
56 methadone and buprenorphine, with the latter gaining increasing prominence.
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3 Methadone maintained subjects were examined under conditions identical [13] to
4 those for the buprenorphine subjects in this study. The cold pressor test at
5 baseline revealed that the combined methadone subjects were similarly
6 hyperalgesic to the combined buprenorphine subjects. Furthermore, both groups
7 were cross-tolerant to the antinociceptive effects of very high plasma morphine
8 concentrations and both groups experienced similar decreases in respiration rate
9 with the addition of very high plasma morphine concentrations. While
10 buprenorphine has been used increasingly across the world because of its
11 purported limited effect on respiratory depression and greater safety profile than
12 other opioids such as morphine and methadone [17, 27, 28], our findings suggest
13 that supplementary opioids for the management of pain in subjects in opioid
14 substitution programs should be added cautiously under adequate supervision to
15 avoid clinically significant respiratory depression.
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33 Koppert et al [20], in a mechanical hyperalgesia model found that acutely,
34 buprenorphine had a pronounced antihyperalgesic effect and suggested this may
35 have clinical advantages in the management of chronic pain. In observational
36 studies of chronic pain patients who were switched from high dose full opioid
37 agonists to sublingual buprenorphine, [29, 30], the switch resulted in meaningful
38 reduction in pain scores. Buprenorphine was more effective than full opioid
39 agonists. The authors postulated that these findings may have resulted from
40 buprenorphine's antihyperalgesic action [29]. However, Ravn and coworkers [31],
41 using a multimodal testing technique, could not demonstrate any significant
42 differences between morphine and buprenorphine in the profiles of
43 antihyperalgesia and analgesia in healthy volunteers. The present study shows
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3 that buprenorphine, a partial mu opioid receptor agonist and kappa receptor
4 antagonist, when used as a maintenance agent, produces similar respiratory
5 depression and hyperalgesia to methadone (a mu opioid receptor agonist) in
6 opioid maintained subjects tested under the same experimental conditions [13].
7
8 These results suggest that, at the buprenorphine doses to which our subjects
9
10 were exposed, antihyperalgesia could not be demonstrated with the cold pressor
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20 Macintyre and colleagues [25] examined retrospectively pain relief and opioid
21 requirements in the first 24 hours after surgery in patients taking buprenorphine
22 (dose range was similar to that in the present study) and methadone as OST.
23
24 Outcomes in the two patient groups were similar. The post-operative 24-hour
25 analgesia requirement, provided as patient controlled analgesia, was defined as
26 morphine dose equivalents. Buprenorphine maintained patients required an
27 average of 200 mg; methadone maintained patients required 221 mg. Pain
28 scores were similar across both groups. Sedation scores of 2 or greater occurred
29 in 22.7% and 24.1% of buprenorphine and methadone maintained patients
30 respectively. This important clinical study was not designed to determine
31 possible mechanisms for the outcomes. Our findings, in an experimental setting
32 in OST pain-free patients, complement the findings of this clinical study: very
33 large morphine equivalent doses result in insignificant analgesia and the
34 development of respiratory depression, albeit small, given the relatively small
35 (compared to the PCA doses in the clinical study) dose of morphine provided to
36 our subjects. Our findings strongly suggest that hyperalgesia is a likely
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60 mechanism for the findings of Macintyre and colleagues [25], in addition to

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3 tolerance. It is pertinent that buprenorphine and methadone maintained patients
4 behaved almost identically, suggesting that buprenorphine had no
5 antihyperalgesic properties.
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11 We measured plasma concentrations of morphine, buprenorphine and
12 norbuprenorphine to more accurately assess the extent of exposure by the
13 subject to these analytes, rather than relying simply on the given doses. While
14 there were no significant differences between plasma buprenorphine
15 concentrations for the three dose groups at baseline, there was considerable
16 variability in the range of concentrations. Hyperalgesia occurred across the
17 whole range of plasma concentrations. The lowest individual plasma
18 buprenorphine concentration was 0.16 ng/ml (in the 2-8 mg/day dose group).
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31 Transdermal buprenorphine patches are increasingly used for the management
32 of chronic pain. In Australia, they are available in various strengths, ranging from
33 10-40 mg, which deliver 10 to 40 ug/h and are generally applied once a week,
34 likely for prolonged periods. When 10 ug/h patches were administered to healthy
35 volunteers once a week for 3 doses the average plasma concentrations were
36 between 0.155 and 0.172 ng/ml across the 3 periods [32]; 20 ug/h patches
37 administered to healthy volunteers as a single dose yielded mean maximum
38 plateau plasma concentrations of about 0.25 ng/ml between 48 and 96 hours
39 after application [33]; single applications of 35 and 70 ug/h patches yielded mean
40 maximum plasma concentrations of 0.31 and 0.62 ng/ml respectively [34]. These
41 values fall within the range of plasma concentrations described in the present
42 study that were associated with hyperalgesia. Thus, it would be reasonable to
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3 assume that some patients receiving buprenorphine for the management of
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5 chronic pain could be hyperalgesic. Kress [34] reviewed several trials/reports of
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7 the efficacy of transdermal buprenorphine (varying doses) in patients with cancer
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9 and noncancer pain with the minimum duration of observation of three months. In
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11 most of the studies, satisfactory pain relief occurred in at least 50% of subjects,
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13 suggesting that hyperalgesia may not be universal in patients suffering from pain
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15 rather than those who receive opioids as substitution treatment.
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20 There are several limitations to this study. The sample size is small and not driven
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22 by a formal power calculation. However, we based our population size on the
23
24 results of Doverty et al [11], who showed highly significant differences in cold
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26 pressor tolerance between 16 healthy controls (n=16) and 16 methadone
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28 maintenance subjects. Despite the smaller sample size in this study, significant
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30 differences were seen between buprenorphine recipients and the controls. Plasma
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32 buprenorphine concentrations were measured only at the putative peak. However,
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34 given the long half-life of buprenorphine and that the subjects would have been at
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36 steady state, we considered the sampling regimen justified.
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43 What might be the best strategy to improve pain relief in buprenorphine maintained
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45 patients who experience acute pain, such as following surgery or trauma? Reviews
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47 from Huxtable et al [6] and Schug et al [5] state that in the clinical setting, for the
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49 opioid maintained population, opioid dose should be increased until analgesia is
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51 achieved or sedation occurs and that the dose of the maintenance opioid should be
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53 continued without interruption [25]. The purpose of this study was to provide the
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55 evidence for opioid dose escalation that would provide antinociception without
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3 respiratory depression in the buprenorphine maintained population. This study
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5 demonstrates that buprenorphine maintained subjects are hyperalgesic at baseline
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7 and that very high morphine doses result in limited respiratory depression, but not
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9 antinociception. There is a need to explore alternative strategies for providing acute
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11 pain relief in buprenorphine (and methadone) maintained patients. For example,
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13 Huxtable [6] and Schug et al [5] recommend that an adjuvant analgesic alone, or in
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15 combination with morphine, may overcome the limitations of cross-tolerance and
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17 side effects to provide pain management in the buprenorphine and methadone
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19 maintained population.
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26 Figure Legend

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28 Figure 1. Cold pressor pain tolerance responses (upper panel), electrical stimulation
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30 pain tolerance responses (middle panel) and respiration rate (lower panel) mean (\pm
31
32 SEM) pain in 10 healthy control and 12 buprenorphine subjects at baseline (B) and
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34 morphine infusion 2 (M2). † $P < 0.05$; †† $P < 0.01$ between groups; * $P < 0.05$; ** $P < 0.01$
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36 between treatments. Note: different morphine concentrations between buprenorphine
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38 and control subjects.
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Table 1. Cold pressor and electrical stimulation responses, and respiration rates for 12 buprenorphine maintained and 10 control subjects on morphine administration days.

Response	Group	Baseline	Morphine 1¹	Morphine 2²
Cold Pressor (seconds)	Control	34±6†† (4 to 73)	38±7 (5 to 64)	52±11* (7 to 23)
	Combined	17±2	17±2	17±2
	Buprenorphine ³	(9 to 18)	(4 to 29)	(4 to 27)
Electrical Stimulation (volts)	Control	65±6 (38 to 100)	68±5 (48 to 100)	74±5** (60 to 100)
	Combined	53±5	53±4	53±5
	Buprenorphine ³	(24 to 92)	(24 to 72)	(34 to 96)
Respiration Rate (breaths per minute)	Control	17 (14 to 22)	16.5 (13 to 19)	15 (10 to 19)
	Combined	14†	12.5	12**
	Buprenorphine ³	(9 to 20)	(12 to 17)	(9 to 15)
	2-8 mg (P=0.024) ⁴	15.5±1.6 (13-20)	11.5±0.9* (10-13)	11.5±1.3* (9-15)

9-15 mg (P=0.004) ⁴	15±1.2	15±1.1	11.5±0.6**
	(12-17)	(12-17)	(10-13)
16-22 mg (P=0.016) ⁴	14.8±0.5	12.3±0.6*	12.8±1.3*
	(14-16)	(11-14)	(10-16)

¹ For buprenorphine maintained subjects Morphine 1 was initial 15.2 mg bolus of morphine sulphate followed by 8.3 mg/hr constant infusion for one hour. ²Morphine 2 was 15.2 mg bolus of morphine sulphate followed by 16.5 mg constant infusion for one hour. For controls Morphine 1 was initial bolus of 2.2 mg morphine sulphate followed by 1.2 mg/hr constant infusion for one hour. Morphine 2 was 4.95 bolus of morphine sulphate followed by constant infusion of 3.6 mg/hr for one hour. Data for the nociceptive responses are mean±SEM (range) and for respiration rates median (range).

³The results for the three buprenorphine dose groups are combined.

⁴ANOVA P values comparing baseline to Morphine 1 and Morphine 2.

† P<0.05, †† P<0.01 buprenorphine versus control; * P<0.05, ** P<0.01 morphine 2 versus control.

Table 2A. Plasma morphine concentrations (ng/ml) on morphine administration days in 12 buprenorphine maintained and 10 healthy control subjects.

	Morphine 1	Morphine 2
Control Subjects	7.0±0.4	23±1
All buprenorphine Subjects	62±4 (42 to 87)	136±10 (92 to 201)
Buprenorphine Subjects 2-8 mg/day	70±8 (49 to 91)	175±15 (119 to 201)
Buprenorphine Subjects 9-15 mg/day	60±4 (48 to 71)	129±9 (48 to 108)
Buprenorphine Subjects 16-22 mg/day	57±4 (52 to 71)	109±8 (92 to 129)

The infusion regimens for buprenorphine maintained subjects and healthy control subjects on Morphine 1 and Morphine 2 days are described in the methods. Data are mean±SEM (range).

Table 2B. Plasma buprenorphine concentrations (ng/ml) at baseline and on morphine administration days in 12 buprenorphine maintained subjects.

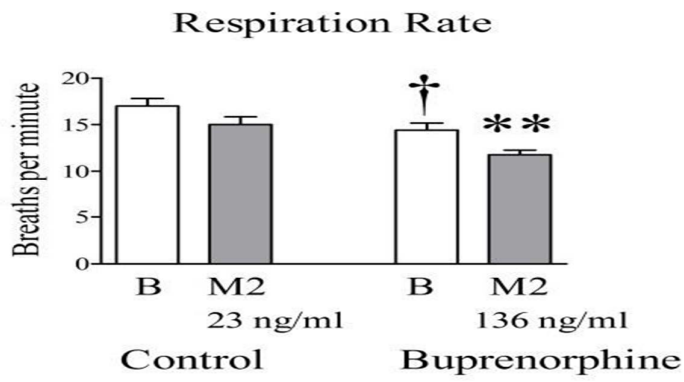
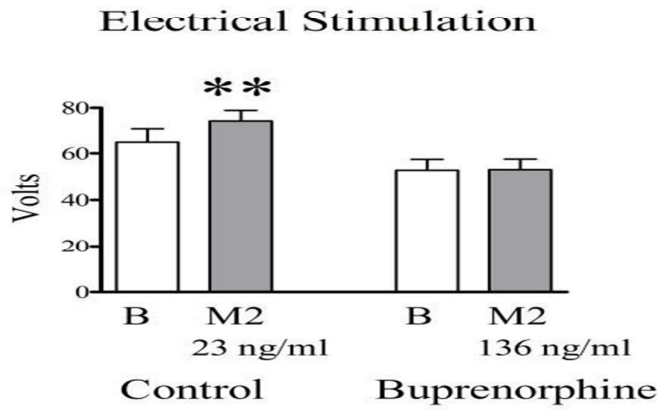
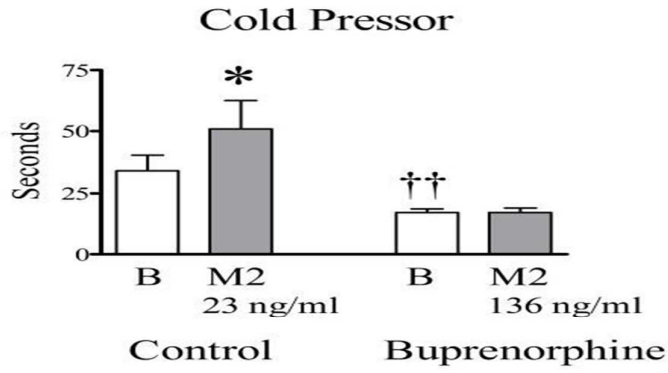
	Baseline	Morphine 1	Morphine 2
All Buprenorphine Subjects	1.2±0.3 (0.23 to 3.3)	0.95±0.19 (0.16 to 0.23)	1.03±0.23 (0.16 to 3.0)
Buprenorphine Subjects 2-8 mg/day	0.71±0.23 (0.42 to 1.17)	0.46±0.12 (0.16 to 0.76)	0.45±0.10 (0.16 to 0.58)
Buprenorphine Subjects 9-15 mg/day	1.45±0.45 (0.21 to 2.20)	1.14±0.36 (0.90 to 1.75)	1.40±0.53 (0.26 to 2.7)
Buprenorphine Subjects 16-22 mg/day	1.17±0.28 (0.8 to 1.98)	1.23±0.24 (0.79 to 1.79)	1.33±0.22 (0.79 to 1.87)

The morphine infusion regimens on Morphine 1 and Morphine 2 days are described in the methods. Data are mean±SEM (range).

Table 2C. Plasma norbuprenorphine concentrations (ng/ml) at baseline and on morphine administration days in 12 buprenorphine maintained subjects.

	Baseline	Morphine 1	Morphine 2
All Buprenorphine Subjects	1.7±0.3 (0.30-3.62)	1.61±0.33 (0.31-3.72)	1.85±0.40 (0.34-3.53)

The morphine infusion regimens on Morphine 1 and Morphine 2 days are described in the methods. Data are mean±SEM (range).



Supplementary Table. Plasma concentrations of buprenorphine (A) and norbuprenorphine (B) in 12 buprenorphine maintained subjects on saline infusion days.

A. Plasma buprenorphine (ng/ml)

	Baseline	Saline 1	Saline 2
All Buprenorphine	1.2±0.3	1.01±0.26	1.18±0.29
Subjects			
Buprenorphine	0.38±0.10	0.30±0.006	0.33±0.08
Subjects			
2-8 mg/day	(0.15 to 0.64)	(0.15 to	(0.15 to
Buprenorphine	1.59±0.68	1.16±0.46	1.3±0.6
Subjects			
9-15 mg/day	(0.23 to 3.30)	(0.24 to	(0.19 to
Buprenorphine	1.84±0.76	1.6±0.59	1.81±0.53
Subjects			
16-22 mg/day	(0.69 to 4.07)	(0.61 to	(0.63 to
		3.31)	3.03)

The infusion regimens are described in the methods. Data are mean±SEM (range).

B. Plasma Norbuprenorphine (ng/ml)

	Baseline	Saline 1	Saline 2
All Buprenorphine	1.78±0.34	1.68±0.3	1.93±0.42
Subjects	(0.29-3.9)	(0.29-3.4)	(0.24-4.7)

The infusion regimens are described in the methods. Data are mean±SEM (range).

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3 Buprenorphine maintenance subjects are hyperalgesic and have no
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5 antinociceptive response to a very high morphine dose
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10 Peter Athanasos PhD^a, Walter Ling MD^b, Felix Bochner MD^{c,e}, Jason M.
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51
52 **Disclosure/Conflict of Interest:** PA, LW, FB, JMW, AAS report No conflicts

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54 **Running Title:** Buprenorphine, hyperalgesia, antinociception, maintenance subjects
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Abstract

Objective. Acute pain management in opioid dependent persons is complicated because of tolerance and opioid-induced-hyperalgesia. Very high doses of morphine are ineffective in overcoming opioid-induced-hyperalgesia and providing antinociception to methadone maintained patients in an experimental setting. Whether the same occurs in buprenorphine maintained subjects is unknown.

Design. Randomised double blind placebo controlled. Subjects were tested on two occasions, at least five days apart; once with intravenous morphine and once with intravenous saline. Subjects were tested at about the time of putative trough plasma buprenorphine concentrations.

Setting. Ambulatory.

Subjects. Twelve buprenorphine maintained subjects: once daily sublingual dose (range 2-22 mg); no dose change for 1.5-12 months. Ten healthy controls.

Methods. Intravenous morphine bolus and infusions administered over 2 hours to achieve two separate pseudo-steady state plasma concentrations one hour apart. Pain tolerance assessed by application of nociceptive stimuli (cold pressor (seconds) and electrical stimulation (volts)). Ten blood samples collected for assay of plasma morphine, buprenorphine and norbuprenorphine concentrations until 3 hours after the end of last infusion; pain tolerance and respiration rate measured to coincide with blood sampling times.

Results. Cold pressor responses (seconds): baseline: control 34 ± 6 versus

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3 buprenorphine 17 ± 2 ($P=0.009$); morphine infusion-end: control 52 ± 11 ($P=0.04$),
4 buprenorphine 17 ± 2 ($P>0.5$); electrical stimulation responses (volts): baseline:
5 control 65 ± 6 versus buprenorphine 53 ± 5 ($P=0.13$); infusion-end: control 74 ± 5
6 ($P=0.007$), buprenorphine 53 ± 5 ($P>0.98$). Respiratory rate (breaths per minute):
7 baseline: control 17 versus buprenorphine 14 ($P=0.03$); infusion-end: control 15
8 ($P=0.09$), buprenorphine 12 ($P<0.01$). Infusion-end plasma morphine concentrations
9 (ng/mL): control 23 ± 1 , buprenorphine 136 ± 10 .

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20 **Conclusions.** Buprenorphine subjects, compared with controls, were: hyperalgesic
21 (cold pressor test); did not experience antinociception, despite high plasma morphine
22 concentrations; experienced respiratory depression. Clinical implications are
23 discussed.
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Introduction

The prevalence of opioid dependence is growing worldwide. Dependence has traditionally been the result of illicit opioid abuse. However, it is increasingly associated with legally prescribed long-term use of opioids for the management of chronic pain [1]. Between 28 and 38.5 million people abuse opioids worldwide. In 2015, 2 million had a substance use disorder involving prescription pain relievers and 591,000 had a substance use disorder involving heroin [2]. Approximately 1% of the Australian population is opioid dependent and half of these are in opioid substitution treatment (OST) programs [3]. Of these, two-thirds receive methadone and one third buprenorphine (alone or with naloxone) but this difference is declining.

The management of acute pain in opioid dependent patients is complicated because of two major factors: tolerance, which can generally be overcome by dose increase but may be compromised by adverse effects, and the under recognized phenomenon of opioid-induced-hyperalgesia (OIH) characterized as paradoxical pain sensitization [4] which cannot be overcome by dose increase. Although there are no formal guidelines for the clinician, Macintyre et al [5] and Huxtable et al [6] advise, that in the clinical setting, the daily OST dose should be maintained and additional opioid used for acute pain management, titrated until satisfactory analgesia is achieved or an adverse effect (e.g. sedation or respiratory depression) occurs. Such an approach requires stringent observation such as admission to hospital.

Opioid-induced hyperalgesia occurs in opioid (e.g. heroin) addicted subjects prior to entry into methadone and buprenorphine treatments [7], chronic non-cancer pain

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3 patients [8], and slow release morphine, methadone and buprenorphine maintained
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5 subjects [9, 10, 11, 12]. Clinically used and very high doses of morphine are
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7 ineffective in overcoming OIH and providing antinociception to methadone
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9 maintained patients [11, 13] in an experimental setting. Whether the same occurs in
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11 buprenorphine maintained subjects is unknown.
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16 Buprenorphine, a semi-synthetic 4,5-epoxymorphinan opioid shows partial agonist
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18 properties for some responses at the mu opioid receptor and variable effects at
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20 the kappa and delta receptors [14]. Its major metabolite norbuprenorphine is also
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22 active [15], although there is conjecture whether it crosses the blood-brain barrier
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24 [16]. Opioid agonists such as morphine, over plasma concentration ranges that
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26 produce dose-related increases in analgesia, also produce concentration-
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28 dependent respiratory depression without any plateau in healthy human
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30 volunteers [17]. In contrast, buprenorphine shows dose-dependent increases in
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32 analgesia with a limited extent of respiratory depression [17, 18]. As a partial
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34 agonist, under appropriate conditions, buprenorphine may act as an agonist or
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36 antagonist at opioid receptors [19] and has shown antihyperalgesic effects in
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38 healthy subjects using a model of intradermal electric stimulation [20]. Therefore,
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40 buprenorphine may be unique in its ability to treat acute pain and possibly
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42 attenuate OIH.
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47 Previously we showed that methadone maintained subjects on doses of 2-120 mg
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49 per day, under identical experimental conditions that will be described in this study,
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51 experienced no antinociception with 55 mg of intravenous morphine but showed a
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53 significant reduction in respiratory rate [13]. To date, no studies have examined the
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55 effect of different daily buprenorphine doses on the antinociceptive and respiratory
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3 responses to morphine.
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8 The aims of the study in buprenorphine maintained subjects were to: 1. Confirm the
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10 presence of OIH; 2. Ascertain whether very high intravenous morphine doses
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12 produce antinociceptive and respiratory depression effects and 3. Determine any
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14 relationship between buprenorphine dose and these effects. Our hypothesis is that
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16 buprenorphine maintained subjects are hyperalgesic and, that in contrast to
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18 methadone maintained subjects, experience antinociception with high morphine
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20 doses.
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22 23 **Methods**

24 25 26 27 28 *Ethics*

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30 The Research Ethics Committee of the Royal Adelaide Hospital, Adelaide, South
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32 Australia, Australia (RAH Protocol no: 010222) and the Institutional Review Board,
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34 Friends Research Institute, Los Angeles, California, USA (FRI IRB no: 00-03-057-
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36 02) approved the study. Both bodies adhere to the ethical standards set by the
37
38 Helsinki Declaration (2008). The study was supported by National Institutes of Drug
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40 Abuse (NIDA) grant R01 DA 13706-02. This study was not registered on
41
42 clinicaltrials.gov as this study was carried out before the requirement for
43
44 registration. Subjects provided written informed consent, were paid for their
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46 involvement in the study and were free to withdraw at any time.
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52 53 *Subjects*

54 | Twelve pain-free buprenorphine maintained subjects comprising 7 men and 5
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56 women with ages between 24 and 42 years (mean 35 years) were recruited. Their
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3 weights ranged between 49 and 97 kg (mean 71 kg). They had been receiving
4 sublingual buprenorphine (Subutex ® Reckitt Benckiser, West Ryde, New South
5 Wales, Australia) for between 1.5 and 12 months (mean 4 months) with no dose
6 change. They had been enrolled in a buprenorphine maintenance program for a
7 period ranging between 2 and 22 months with a mean of 10 months. The group
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13 was stratified according to [prescribed and efficacious maintenance](#) dose, with four
14 subjects in each of the dose ranges of 2 to 8 mg, 9 to 15 mg and 16 to 22 mg per
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17 day. Subjects were recruited if they self-reported intravenous heroin use at least
18 once in the previous month. It was considered more ethical to administer morphine
19 to individuals who continued to use illicit heroin, rather than to those who used no
20 opioids, apart from their prescribed buprenorphine. Ten healthy control subjects (5
21 men and 5 women; aged between 21 and 41(mean 31) years); weight 59 and 102
22 (mean 80) kg) were selected. These subjects were not taking any prescribed
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Exclusion criteria

40 Exclusion criteria for all subjects included pregnancy or lactation, use of
41 antiretroviral drugs, significant medical or psychiatric illness that required ongoing
42 treatment (except opioid addiction for buprenorphine subjects), daily alcohol
43 consumption exceeding 40 g for men and 20 g for women, severe liver impairment
44 (serum aspartate aminotransferase and alanine aminotransferase concentrations
45 greater than 3 times the upper limit of normal range and albumin concentrations
46 less than 33 grams per litre) or haemoglobin counts outside the normal range.

55 Healthy control subjects were excluded if they had any personal or family history of

1
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3 addictive behaviours.
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8 *Study design*

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10 The study utilized a double blind placebo controlled design with four groups of
11 subjects (healthy controls, once daily buprenorphine dose of 2 to 8, 9 to 15 and,
12 16 to 22 mg). Subjects were tested on two occasions, at least five days apart;
13
14 once with morphine and once with saline. The order of administration was
15
16 randomised. Buprenorphine subjects were tested at about the time of putative
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18 trough plasma concentrations of buprenorphine (approximately 20 hours after
19
20 the previous buprenorphine dose).
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25 *Procedure*

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28 Subjects were asked not to use any analgesics or illicit substances for twenty-four
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30 hours prior to testing. A urine sample was collected on each study day for the
31
32 detection of opioids, benzodiazepines, sympathomimetic amines, cannabinoids and
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34 barbiturates. Analysis of these samples confirmed that control subjects had not taken
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36 any of these psychoactive substances. Subjects were excluded from the study if they
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38 presented on study or screening days showing any signs of intoxication from any
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40 substance.
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46 Testing was conducted under constant ambient temperature (24°C) and constant
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48 illumination (70 lux). Each session commenced at approximately 8 am and lasted 8
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50 hours. Two indwelling catheters (Insite Autoguard, Becton Dickenson, Sandy, Utah,
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52 USA) were inserted into peripheral veins on opposite arms. The catheter in the
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54 dominant arm served for drug infusion; the catheter in the non-dominant arm for
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3 blood sampling. On each testing day, saline was infused at 2 ml/min for 30 min prior
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5 to morphine or saline administration for familiarisation.
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10 *Morphine administration*

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12 Morphine sulphate (David Bull Laboratories, Melbourne, Australia) infusions of 1
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14 mg/ml were administered intravenously in two sixty-minute stages to achieve two
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16 consecutive target pseudo-steady-state plasma concentrations [11] using a
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18 syringe driver infusion pump (3100 Graseby Syringe Pump, Watford, Hertfordshire,
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20 UK). Buprenorphine subjects received an initial bolus of 15.2 mg of morphine
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22 sulphate followed by a constant infusion of 8.3 mg/hr for one hour to achieve a
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24 target pseudo steady-state plasma concentration of 80 ng/ml (Morphine 1). They
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26 were then administered an additional bolus of 15.2 mg of morphine sulphate
27
28 followed by a constant infusion of 16.5 mg/hr for one hour to achieve the second
29
30 target pseudo steady-state plasma concentration of 180 ng/ml (Morphine 2). The
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32 prescribed buprenorphine dose was administered 1 hour after infusions ceased.
33
34 Control subjects were administered an initial bolus of 2.2 mg morphine sulphate
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36 followed by a constant infusion of 1.2 mg/hr for one hour to achieve a target
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38 pseudo steady-state plasma concentration of 11 ng/ml (Morphine 1). They were
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40 then administered 4.95 mg of morphine sulphate followed by a constant infusion of
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42 3.6 mg/hr to achieve the second target pseudo steady-state plasma concentration
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44 of 33 ng/ml (Morphine 2) [11].
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52 *Blood sampling and assessment times*

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55 Seven millilitre blood samples were taken at the following times: prior to the thirty
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3 minute saline familiarisation infusion, ten minutes prior to end of this infusion
4 (designated as baseline) and ten minutes prior to the end of each of the two
5 morphine or placebo saline infusions. Further blood samples were taken at 0.25,
6 0.5, 0.75, 1.0, 2.0, and 3 hours after the end of the last infusion. The blood samples
7 were centrifuged immediately and the plasma stored at -20°C until assay.
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9 Respiration rate was measured and nociceptive tests (see below) were
10 administered immediately after the collection of each blood sample except at 0.25,
11 0.50 and 0.75 hours after the last infusion.
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23 *Nociceptive tests, physiological responses and safety monitoring*

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25 Two nociceptive tests were administered: the cold pressor using the non-dominant
26 arm, and electrical stimulation using the earlobe. These tests have been described
27 previously [10]. Cold pressor involves the immersion of the non-dominant arm in
28 0.5–1.5 $^{\circ}\text{C}$ water and the response metric is seconds. Electrical stimulation
29 involves the transmission of an electrical pulse through the earlobe and is
30 measured in volts. One nociceptive marker was used which was pain tolerance,
31 when the participant verbally indicated that they could no longer tolerate the pain
32 and removed their arm from the water or requested that the electrical stimulation
33 cease.
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47 Respiration rate was measured over one minute by observation without the
48 subjects' awareness. Safety was monitored and recorded throughout the study
49 by means of continuous pulse oximetry, continuous ECG waveform, categorical
50 nausea scale [21] and categorical sedation scale [22].
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Plasma opioid quantification

The quantification of plasma buprenorphine and norbuprenorphine was by high performance liquid chromatography coupled to mass spectrometry as previously described [23]. The assay had a limit of quantification of 0.125 ng/ml for both analytes and all variability in accuracies and precision had coefficients of variation for buprenorphine and nor-buprenorphine of less than 15%. The quantification of plasma morphine was by high-performance liquid chromatography (HPLC) with coulometric detection as previously described [11]. The assay had a lower limit of quantification of 1 ng/ml and all variability in accuracies and precision had coefficients of variation below 7%.

Data analysis

Data are presented as mean \pm SEM (with 95% confidence intervals (95% CI)).

~~One-way ANOVA was used to compare outcome variables (cold pressor tolerance, electrical stimulation tolerance, respiration rate) between the buprenorphine dose groups.~~ One-way ANOVA was used to compare each outcome variable across treatments for the buprenorphine ~~dose groups~~, combined ~~buprenorphine~~ subjects and the control subjects with 95% CI of differences.

Unpaired samples t-tests were used to compare baseline values between the combined buprenorphine subjects and the control subjects. The Pearson product-moment correlation coefficient (Pearson's r) was used to measure the linear correlation between individual buprenorphine daily doses and plasma morphine concentrations. Bonferroni's and Dunnet's tests were used for post-hoc analyses as appropriate. Data for both studies were analysed using GraphPad Prism 4.2 for

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3 Windows, GraphPad Software, San Diego, California, USA and $P < 0.05$ was
4 considered significant.
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8 9 **Results**

10 11 *Nociceptive tests*

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14 There were no significant differences ($P > 0.45$) in pain tolerance responses between
15 the three buprenorphine dose groups from baseline to morphine infusion 1 or
16 morphine infusion 2. Hence, the data from the groups were combined.
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20 21 22 *Cold pressor responses*

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25 Pain tolerance responses at baseline and morphine infusion 2 for control subjects
26 and the buprenorphine subjects are shown in Figure 1 (upper panel) and absolute
27 values and ranges for all treatments in Table 1. Pain tolerance values for the
28 buprenorphine subjects remained unchanged between baseline and the two
29 morphine infusions. Pain tolerance values for the buprenorphine subjects were
30 significantly lower than for control subjects at baseline (ANOVA $P = 0.009$; 95% CI -
31 5 to -30). Within group comparisons revealed that pain tolerance values for control
32 subjects increased significantly ($P = 0.04$) from baseline to morphine infusion 2
33 ($P < 0.05$; 95% CI 2 to 34), but not baseline to morphine infusion 1 ($P > 0.05$; 95% CI
34 -12 to 20).
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50 51 *Electrical stimulation responses*

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53 Pain tolerance responses at baseline and morphine infusion 2 for control subjects
54 and the buprenorphine subjects are shown in Figure 1 (middle panel) and absolute
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3 values with ranges given in Table 1. Pain tolerance values for the buprenorphine
4 subjects were not significantly different to controls (ANOVA $P=0.13$) at baseline.
5
6 Within-group comparisons revealed that pain tolerance values for control subjects
7 increased significantly ($P=0.007$) from baseline to morphine infusion 2 ($P<0.01$;
8 95% CI 3 to 16), but not baseline to morphine infusion 1 ($P>0.05$; 95% CI -2.8 to
9 10 10). There was no significant change ($P=0.98$) in pain tolerance values for
11
12 combined buprenorphine subjects from baseline to morphine infusion 1 or
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14 morphine infusion 2.
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23 *Respiration rates*

24
25 Respiration rates (breaths per minute) relative to baseline and morphine infusion 2
26 are shown in Figure 1 (lower panel) and absolute values with ranges in Table 1.
27
28 Respiration rates for the buprenorphine subjects were significantly lower than for
29 control subjects at baseline (ANOVA $P=0.03$; 95% CI -0.25 to -4.9). Within group
30 comparisons revealed that the respiration rates for control subjects did not decrease
31 significantly ($P=0.09$) from baseline to morphine infusion 1 or morphine infusion 2.
32
33 Respiration rates for the buprenorphine subjects decreased significantly (ANOVA
34 $P=0.006$) from baseline to morphine infusion 2 ($P<0.01$; 95% CI -0.9 to -4.4) but not
35 morphine infusion 1 ($P>0.05$; 95% CI -2.8 to 10).
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47 Buprenorphine dose group comparisons demonstrated significant changes in
48 respiration rates as follows. Group 2-8 mg daily: (ANOVA $P=0.024$) from baseline to
49 morphine infusion 1 ($P<0.05$; 95% CI -0.56 to -7.4) and baseline to morphine
50 infusion 2 ($P<0.05$; 95% CI -0.56 to -7.4); group 9-15 mg daily: (ANOVA $P=0.004$)
51 between baseline and morphine infusion 2 ($P<0.01$; 95% CI -1.48 to -5.52), but not
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3 morphine infusion 1 ($P>0.05$; 95% CI -2.02 to 2.02); group 16 to 22 mg daily:
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5 (ANOVA $P=0.016$) between both baseline and morphine infusion 1 ($P<0.05$; 95% CI
6
7 -0.72 to -4.28) and baseline and morphine infusion 2 ($P<0.05$; 95% CI -0.22 to -
8
9 3.78). There were no significant differences in respiration rate between the groups
10
11 at baseline ($P=0.90$) or morphine infusion 2 ($P=0.67$). The lowest recorded
12
13 respiration rates were ten breaths per minute in the control group and nine breaths
14
15 per minute in the buprenorphine subjects.
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18 19 20 21 *Adverse events*

22
23 There were no serious adverse events. Buprenorphine subjects did not experience
24
25 nausea or vomiting, but seven control subjects required one dose of intramuscular
26
27 metoclopramide hydrochloride 10 mg (Pfizer, Perth, Australia) with good effect for
28
29 mild vomiting.
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32 33 34 35 *Plasma morphine, buprenorphine and norbuprenorphine concentrations*

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37 Pseudo steady-state plasma morphine concentrations for morphine 1 and 2
38
39 infusions are shown in Table 2A. Target pseudo steady-state plasma morphine
40
41 concentration for the buprenorphine recipients were 80 ng/ml (Morphine 1) and 180
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43 mg/ml (Morphine 2). Target pseudo steady-state plasma concentration for control
44
45 subjects were 11 ng/ml (Morphine 1) and 33 mg/ml (Morphine 2). Pseudo state
46
47 plasma morphine concentrations were lower than the desired target in both groups
48
49 at morphine 1 and 2. Plasma morphine concentrations are also shown for the
50
51 individual daily buprenorphine dose groups 2-8, 9-15 and 16-22 mg/day. There was
52
53 no significant correlation ($p=0.08$) between individual buprenorphine doses and
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3 plasma morphine concentrations at morphine infusion 1. However, there was a
4 significant inverse relationship between individual buprenorphine doses and plasma
5 morphine concentrations at morphine infusion 2 (Pearson's $r = -0.74$, $p = 0.006$; slope
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8
9 95% CI - 0.92 to -0.28).
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14 There were no significant differences between combined mean plasma
15 buprenorphine concentrations (Table 2B), or for the three dose groups, at baseline
16 (P=0.64), morphine infusion 1 (P=0.71) or morphine infusion 2 (P=0.51). Likewise,
17 there were no significant differences between combined mean plasma
18 norbuprenorphine concentrations (Table 2C), or for the three dose groups, at
19 baseline, morphine infusion 1 or morphine infusion 2. At baseline on the saline
20 administration day, plasma buprenorphine and norbuprenorphine concentrations
21 were correlated to the buprenorphine dose ($r^2 = 0.36$ and 0.58 , respectively;
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31 Supplementary Tables 3A, 3B).
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36 Discussion

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40 To our knowledge, this is the first study to have examined the effect of added
41 morphine to buprenorphine OST subjects who were pain-free at the time of study,
42 using an experiment pain model. Buprenorphine subjects were hyperalgesic in the
43 cold pressor test in comparison with controls. Very high doses of morphine (55 mg)
44 produced high plasma concentrations (92 to 201 ng/ml) that failed to provide
45 antinociception in either the electrical stimulation or cold pressor tests, irrespective
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49 of maintenance buprenorphine dose. In contrast, in control subjects, considerably
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55 lower morphine doses (12 mg), achieving much lower concentrations (19 to 32
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3 ng/ml), provided antinociception in both tests.
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8 Our choice of using the cold pressor response to study opioid induced-
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10 hyperalgesia has been validated by others. Compton et al [13] examined
11
12 hyperalgesia in opioid dependent subjects and found that these subjects, prior to
13
14 induction and following stabilisation on either methadone or buprenorphine, were
15
16 similarly hyperalgesic in the cold pressor test and did not exhibit hyperalgesia in the
17
18 electrical stimulation test. Krishnan et al [12] compared the detection of
19
20 hyperalgesia in opioid-substitution subjects maintained either on methadone or
21
22 buprenorphine and healthy controls using the following pain stimuli: cold pain,
23
24 buprenorphine and healthy controls using the following pain stimuli: cold pain,
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26 electrical stimulation, mechanical pressure, and ischemic pain. They found that cold
27
28 pain was the most suitable of the methods tested to detect opioid-induced
29
30 hyperalgesia.
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34 While the buprenorphine maintained subjects were tolerant to the antinociceptive
35
36 effects of the high doses of morphine and plasma concentrations to which they
37
38 were exposed, complete cross-tolerance to the respiratory depressant effects of
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40 morphine did not occur. Respiration rates dropped significantly across all dose
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42 groups, but by a limited amount (approximately 1.5 breaths per minute), which may
43
44 not be clinically significant. In healthy volunteer subjects who received a single
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46 intravenous dose (0.2 mg/kg) of morphine, over a plasma concentration range
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48 (approximating 3-13 ng/mL) that produced a systematic increase in analgesia,
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50 morphine produced significant respiratory depression [24]. In contrast, in healthy
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52 adult volunteers who had experience with opioids but who were not physically
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54 dependent on opioids, Walsh and co-workers [18] demonstrated that respiratory
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3 depression increased with single buprenorphine single doses over a range of 1 to 4
4 mg (approximately 4 breaths per minute decrease), but that this dose effect began
5 to plateau at higher doses, with no difference between a 16 and 32 mg dose. In the
6 present study, with subjects chronically maintained on buprenorphine, high doses
7 of added morphine had a limited respiratory depressant effect at all buprenorphine
8 doses. It is, however, possible that higher doses of morphine might produce
9 respiratory depression if such doses are needed to achieve anti-nociception, given
10 that the lowest respiratory rate recorded was nine breaths per minute. Macintyre et
11 al [25] showed increased sedation score (a surrogate for respiratory depression) in
12 buprenorphine-maintained patients who received higher doses of morphine
13 equivalents following surgery than in this study.
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29 Hyperalgesia is likely to be present, to a lesser or greater degree, in opioid
30 recipients for whatever indication. Non-cancer pain patients, maintained on either
31 methadone or slow release oral morphine for the treatment of that pain, were
32 shown to exhibit hyperalgesia in the cold pressor test [8], similar to that seen in
33 methadone [13] and buprenorphine subjects (this study) in opioid substitution
34 programs. Chakrabarti et al [26] (2010) found that people with a greater reported
35 experience of pain prior to induction onto buprenorphine maintenance required
36 greater daily doses. The present study found that there was no difference in the
37 degree of hyperalgesia experienced at baseline between the three dose ranges.
38 There was also no difference between the three dose ranges in terms of cross-
39 tolerance to the antinociceptive effects of very high dose morphine.
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56 The most widely used drugs in opioid substitution programmes worldwide are
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3 methadone and buprenorphine, with the latter gaining increasing prominence.
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5 Methadone maintained subjects were examined under conditions identical [13] to
6
7 those for the buprenorphine subjects in this study. The cold pressor test at
8
9 baseline revealed that the combined methadone subjects were similarly
10
11 hyperalgesic to the combined buprenorphine subjects. Furthermore, both groups
12
13 were cross-tolerant to the antinociceptive effects of very high plasma morphine
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15 concentrations and both groups experienced similar decreases in respiration rate
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17 with the addition of very high plasma morphine concentrations. While
18
19 buprenorphine has been used increasingly across the world because of its
20
21 purported limited effect on respiratory depression and greater safety profile than
22
23 other opioids such as morphine and methadone [17, 27, 28], our findings suggest
24
25 that supplementary opioids for the management of pain in subjects in opioid
26
27 substitution programs should be added cautiously under adequate supervision to
28
29 avoid clinically significant respiratory depression.
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35 Koppert et al [20], in a mechanical hyperalgesia model found that acutely,
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37 buprenorphine had a pronounced antihyperalgesic effect and suggested this may
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39 have clinical advantages in the management of chronic pain. In observational
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41 studies of chronic pain patients who were switched from high dose full opioid
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43 agonists to sublingual buprenorphine, [29, 30], the switch resulted in meaningful
44
45 reduction in pain scores. Buprenorphine was more effective than full opioid
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47 agonists. The authors postulated that these findings may have resulted from
48
49 buprenorphine's antihyperalgesic action [29]. However, Ravn and coworkers [31],
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51 using a multimodal testing technique, could not demonstrate any significant
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53 differences between morphine and buprenorphine in the profiles of
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3 antihyperalgesia and analgesia in healthy volunteers. The present study shows
4 that buprenorphine, a partial mu opioid receptor agonist and kappa receptor
5 antagonist, when used as a maintenance agent, produces similar respiratory
6 depression and hyperalgesia to methadone (a mu opioid receptor agonist) in
7 opioid maintained subjects tested under the same experimental conditions [13].
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9 These results suggest that, at the buprenorphine doses to which our subjects
10 were exposed, antihyperalgesia could not be demonstrated with the cold pressor
11 test.
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22 Macintyre and colleagues [25] examined retrospectively pain relief and opioid
23 requirements in the first 24 hours after surgery in patients taking buprenorphine
24 (dose range was similar to that in the present study) and methadone as OST.
25 Outcomes in the two patient groups were similar. The post-operative 24-hour
26 analgesia requirement, provided as patient controlled analgesia, was defined as
27 morphine dose equivalents. Buprenorphine maintained patients required an
28 average of 200 mg; methadone maintained patients required 221 mg. Pain
29 scores were similar across both groups. Sedation scores of 2 or greater occurred
30 in 22.7% and 24.1% of buprenorphine and methadone maintained patients
31 respectively. This important clinical study was not designed to determine
32 possible mechanisms for the outcomes. Our findings, in an experimental setting
33 in OST pain-free patients, complement the findings of this clinical study: very
34 large morphine equivalent doses result in insignificant analgesia and the
35 development of respiratory depression, albeit small, given the relatively small
36 (compared to the PCA doses in the clinical study) dose of morphine provided to
37 our subjects. Our findings strongly suggest that hyperalgesia is a likely
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3 mechanism for the findings of Macintyre and colleagues [25], in addition to
4 tolerance. It is pertinent that buprenorphine and methadone maintained patients
5 behaved almost identically, suggesting that buprenorphine had no
6 antihyperalgesic properties.
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13 We measured plasma concentrations of morphine, buprenorphine and
14 norbuprenorphine to more accurately assess the extent of exposure by the
15 subject to these analytes, rather than relying simply on the given doses. While
16 there were no significant differences between plasma buprenorphine
17 concentrations for the three dose groups at baseline, there was considerable
18 variability in the range of concentrations. Hyperalgesia occurred across the
19 whole range of plasma concentrations. The lowest individual plasma
20 buprenorphine concentration was 0.16 ng/ml (in the 2-8 mg/day dose group).
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33 Transdermal buprenorphine patches are increasingly used for the management
34 of chronic pain. In Australia, they are available in various strengths, ranging from
35 10-40 mg, which deliver 10 to 40 ug/h and are generally applied once a week,
36 likely for prolonged periods. When 10 ug/h patches were administered to healthy
37 volunteers once a week for 3 doses the average plasma concentrations were
38 between 0.155 and 0.172 ng/ml across the 3 periods [32]; 20 ug/h patches
39 administered to healthy volunteers as a single dose yielded mean maximum
40 plateau plasma concentrations of about 0.25 ng/ml between 48 and 96 hours
41 after application [33]; single applications of 35 and 70 ug/h patches yielded mean
42 maximum plasma concentrations of 0.31 and 0.62 ng/ml respectively [34]. These
43 values fall within the range of plasma concentrations described in the present
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3 study that were associated with hyperalgesia. Thus, it would be reasonable to
4
5 assume that some patients receiving buprenorphine for the management of
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7 chronic pain could be hyperalgesic. Kress [34] reviewed several trials/reports of
8
9 the efficacy of transdermal buprenorphine (varying doses) in patients with cancer
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11 and noncancer pain with the minimum duration of observation of three months. In
12
13 most of the studies, satisfactory pain relief occurred in at least 50% of subjects,
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15 suggesting that hyperalgesia may not be universal in patients suffering from pain
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17 rather than those who receive opioids as substitution treatment.
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23 There are several limitations to this study. The sample size is small and not driven
24
25 by a formal power calculation. However, we based our population size on the
26
27 results of Doverty et al [11], who showed highly significant differences in cold
28
29 pressor tolerance between 16 healthy controls (n=16) and 16 methadone
30
31 maintenance subjects. Despite the smaller sample size in this study, significant
32
33 differences were seen between buprenorphine recipients and the controls. Plasma
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35 buprenorphine concentrations were measured only at the putative peak. However,
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37 given the long half-life of buprenorphine and that the subjects would have been at
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39 steady state, we considered the sampling regimen justified.
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45 What might be the best strategy to improve pain relief in buprenorphine maintained
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47 patients who experience acute pain, such as following surgery or trauma? Reviews
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49 from Huxtable et al [6] and Schug et al [5] state that in the clinical setting, for the
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51 opioid maintained population, opioid dose should be increased until analgesia is
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53 achieved or sedation occurs and that the dose of the maintenance opioid should be
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55 continued without interruption [25]. The purpose of this study was to provide the
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3 evidence for opioid dose escalation that would provide antinociception without
4 respiratory depression in the buprenorphine maintained population. This study
5 demonstrates that buprenorphine maintained subjects are hyperalgesic at baseline
6 and that very high morphine doses result in limited respiratory depression, but not
7 antinociception. There is a need to explore alternative strategies for providing acute
8 pain relief in buprenorphine (and methadone) maintained patients. For example,
9 Huxtable [6] and Schug et al [5] recommend that an adjuvant analgesic alone, or in
10 combination with morphine, may overcome the limitations of cross-tolerance and
11 side effects to provide pain management in the buprenorphine and methadone
12 maintained population.
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26 Figure Legend

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28 Figure 1. Cold pressor pain tolerance responses (upper panel), electrical stimulation
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30 pain tolerance responses (middle panel) and respiration rate (lower panel) mean (\pm
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32 SEM) pain in 10 healthy control and 12 buprenorphine subjects at baseline (B) and
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34 morphine infusion 2 (M2). † $P < 0.05$; †† $P < 0.01$ between groups; * $P < 0.05$; ** $P < 0.01$
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36 between treatments. Note: different morphine concentrations between buprenorphine
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38 and control subjects.
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3 Buprenorphine maintenance subjects are hyperalgesic and have no
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5 antinociceptive response to a very high morphine dose
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51
52 **Disclosure/Conflict of Interest:** PA, LW, FB, JMW, AAS report No conflicts

53
54 **Running Title:** Buprenorphine, hyperalgesia, antinociception, maintenance subjects
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Abstract

Objective. Acute pain management in opioid dependent persons is complicated because of tolerance and opioid-induced-hyperalgesia. Very high doses of morphine are ineffective in overcoming opioid-induced-hyperalgesia and providing antinociception to methadone maintained patients in an experimental setting. Whether the same occurs in buprenorphine maintained subjects is unknown.

Design. Randomised double blind placebo controlled. Subjects were tested on two occasions, at least five days apart; once with intravenous morphine and once with intravenous saline. Subjects were tested at about the time of putative trough plasma buprenorphine concentrations.

Setting. Ambulatory.

Subjects. Twelve buprenorphine maintained subjects: once daily sublingual dose (range 2-22 mg); no dose change for 1.5-12 months. Ten healthy controls.

Methods. Intravenous morphine bolus and infusions administered over 2 hours to achieve two separate pseudo-steady state plasma concentrations one hour apart. Pain tolerance assessed by application of nociceptive stimuli (cold pressor (seconds) and electrical stimulation (volts)). Ten blood samples collected for assay of plasma morphine, buprenorphine and norbuprenorphine concentrations until 3 hours after the end of last infusion; pain tolerance and respiration rate measured to coincide with blood sampling times.

Results. Cold pressor responses (seconds): baseline: control 34 ± 6 versus

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3 buprenorphine 17 ± 2 ($P=0.009$); morphine infusion-end: control 52 ± 11 ($P=0.04$),
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5 buprenorphine 17 ± 2 ($P>0.5$); electrical stimulation responses (volts): baseline:
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7 control 65 ± 6 versus buprenorphine 53 ± 5 ($P=0.13$); infusion-end: control 74 ± 5
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9 ($P=0.007$), buprenorphine 53 ± 5 ($P>0.98$). Respiratory rate (breaths per minute):
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11 baseline: control 17 versus buprenorphine 14 ($P=0.03$); infusion-end: control 15
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13 ($P=0.09$), buprenorphine 12 ($P<0.01$). Infusion-end plasma morphine concentrations
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15 (ng/mL): control 23 ± 1 , buprenorphine 136 ± 10 .
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20 **Conclusions.** Buprenorphine subjects, compared with controls, were: hyperalgesic
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22 (cold pressor test); did not experience antinociception, despite high plasma morphine
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24 concentrations; experienced respiratory depression. Clinical implications are
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26 discussed.
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Introduction

The prevalence of opioid dependence is growing worldwide. Dependence has traditionally been the result of illicit opioid abuse. However, it is increasingly associated with legally prescribed long-term use of opioids for the management of chronic pain [1]. Between 28 and 38.5 million people abuse opioids worldwide. In 2015, 2 million had a substance use disorder involving prescription pain relievers and 591,000 had a substance use disorder involving heroin [2]. Approximately 1% of the Australian population is opioid dependent and half of these are in opioid substitution treatment (OST) programs [3]. Of these, two-thirds receive methadone and one third buprenorphine (alone or with naloxone) but this difference is declining.

The management of acute pain in opioid dependent patients is complicated because of two major factors: tolerance, which can generally be overcome by dose increase but may be compromised by adverse effects, and the under recognized phenomenon of opioid-induced-hyperalgesia (OIH) characterized as paradoxical pain sensitization [4] which cannot be overcome by dose increase. Although there are no formal guidelines for the clinician, Macintyre et al [5] and Huxtable et al [6] advise, that in the clinical setting, the daily OST dose should be maintained and additional opioid used for acute pain management, titrated until satisfactory analgesia is achieved or an adverse effect (e.g. sedation or respiratory depression) occurs. Such an approach requires stringent observation such as admission to hospital.

Opioid-induced hyperalgesia occurs in opioid (e.g. heroin) addicted subjects prior to entry into methadone and buprenorphine treatments [7], chronic non-cancer pain

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3 patients [8], and slow release morphine, methadone and buprenorphine maintained
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5 subjects [9, 10, 11, 12]. Clinically used and very high doses of morphine are
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7 ineffective in overcoming OIH and providing antinociception to methadone
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9 maintained patients [11, 13] in an experimental setting. Whether the same occurs in
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11 buprenorphine maintained subjects is unknown.
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16 Buprenorphine, a semi-synthetic 4,5-epoxymorphinan opioid shows partial agonist
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18 properties for some responses at the mu opioid receptor and variable effects at
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20 the kappa and delta receptors [14]. Its major metabolite norbuprenorphine is also
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22 active [15], although there is conjecture whether it crosses the blood-brain barrier
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24 [16]. Opioid agonists such as morphine, over plasma concentration ranges that
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26 produce dose-related increases in analgesia, also produce concentration-
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28 dependent respiratory depression without any plateau in healthy human
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30 volunteers [17]. In contrast, buprenorphine shows dose-dependent increases in
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32 analgesia with a limited extent of respiratory depression [17, 18]. As a partial
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34 agonist, under appropriate conditions, buprenorphine may act as an agonist or
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36 antagonist at opioid receptors [19] and has shown antihyperalgesic effects in
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38 healthy subjects using a model of intradermal electric stimulation [20]. Therefore,
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40 buprenorphine may be unique in its ability to treat acute pain and possibly
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42 attenuate OIH.
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47 Previously we showed that methadone maintained subjects on doses of 2-120 mg
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49 per day, under identical experimental conditions that will be described in this study,
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51 experienced no antinociception with 55 mg of intravenous morphine but showed a
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53 significant reduction in respiratory rate [13]. To date, no studies have examined the
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55 effect of different daily buprenorphine doses on the antinociceptive and respiratory
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3 responses to morphine.
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8 The aims of the study in buprenorphine maintained subjects were to: 1. Confirm the
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10 presence of OIH; 2. Ascertain whether very high intravenous morphine doses
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12 produce antinociceptive and respiratory depression effects and 3. Determine any
13
14 relationship between buprenorphine dose and these effects. Our hypothesis is that
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16 buprenorphine maintained subjects are hyperalgesic and, that in contrast to
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18 methadone maintained subjects, experience antinociception with high morphine
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20 doses.
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22 23 **Methods**

24 25 26 27 28 *Ethics*

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30 The Research Ethics Committee of the Royal Adelaide Hospital, Adelaide, South
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32 Australia, Australia (RAH Protocol no: 010222) and the Institutional Review Board,
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34 Friends Research Institute, Los Angeles, California, USA (FRI IRB no: 00-03-057-
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36 02) approved the study. Both bodies adhere to the ethical standards set by the
37
38 Helsinki Declaration (2008). The study was supported by National Institutes of Drug
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40 Abuse (NIDA) grant R01 DA 13706-02. This study was not registered on
41
42 clinicaltrials.gov as this study was carried out before the requirement for
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44 registration. Subjects provided written informed consent, were paid for their
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46 involvement in the study and were free to withdraw at any time.
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50 51 52 *Subjects*

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54 Twelve pain-free buprenorphine maintained subjects comprising 7 men and 5
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56 women with ages between 24 and 42 years (mean 35 years) were recruited. Their
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3 weights ranged between 49 and 97 kg (mean 71 kg). They had been receiving
4 sublingual buprenorphine (Subutex ® Reckitt Benckiser, West Ryde, New South
5 Wales, Australia) for between 1.5 and 12 months (mean 4 months) with no dose
6 change. They had been enrolled in a buprenorphine maintenance program for a
7 period ranging between 2 and 22 months with a mean of 10 months. The group
8 was stratified according to prescribed and efficacious maintenance dose, with four
9 subjects in each of the dose ranges of 2 to 8 mg, 9 to 15 mg and 16 to 22 mg per
10 day. Subjects were recruited if they self-reported intravenous heroin use at least
11 once in the previous month. It was considered more ethical to administer morphine
12 to individuals who continued to use illicit heroin, rather than to those who used no
13 opioids, apart from their prescribed buprenorphine. Ten healthy control subjects (5
14 men and 5 women; aged between 21 and 41(mean 31) years); weight 59 and 102
15 (mean 80) kg) were selected. These subjects were not taking any prescribed
16 medications. They have been described previously [13].
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35 *Exclusion criteria*

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40 Exclusion criteria for all subjects included pregnancy or lactation, use of
41 antiretroviral drugs, significant medical or psychiatric illness that required ongoing
42 treatment (except opioid addiction for buprenorphine subjects), daily alcohol
43 consumption exceeding 40 g for men and 20 g for women, severe liver impairment
44 (serum aspartate aminotransferase and alanine aminotransferase concentrations
45 greater than 3 times the upper limit of normal range and albumin concentrations
46 less than 33 grams per litre) or haemoglobin counts outside the normal range.
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55 Healthy control subjects were excluded if they had any personal or family history of
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3 addictive behaviours.
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8 *Study design*

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10 The study utilized a double blind placebo controlled design with four groups of
11 subjects (healthy controls, once daily buprenorphine dose of 2 to 8, 9 to 15 and,
12 16 to 22 mg). Subjects were tested on two occasions, at least five days apart;
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14 once with morphine and once with saline. The order of administration was
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16 randomised. Buprenorphine subjects were tested at about the time of putative
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18 trough plasma concentrations of buprenorphine (approximately 20 hours after
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20 the previous buprenorphine dose).
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25 *Procedure*

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28 Subjects were asked not to use any analgesics or illicit substances for twenty-four
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30 hours prior to testing. A urine sample was collected on each study day for the
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32 detection of opioids, benzodiazepines, sympathomimetic amines, cannabinoids and
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34 barbiturates. Analysis of these samples confirmed that control subjects had not taken
35
36 any of these psychoactive substances. Subjects were excluded from the study if they
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38 presented on study or screening days showing any signs of intoxication from any
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40 substance.
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46 Testing was conducted under constant ambient temperature (24°C) and constant
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48 illumination (70 lux). Each session commenced at approximately 8 am and lasted 8
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50 hours. Two indwelling catheters (Insite Autoguard, Becton Dickenson, Sandy, Utah,
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52 USA) were inserted into peripheral veins on opposite arms. The catheter in the
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54 dominant arm served for drug infusion; the catheter in the non-dominant arm for
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3 blood sampling. On each testing day, saline was infused at 2 ml/min for 30 min prior
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5 to morphine or saline administration for familiarisation.
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10 *Morphine administration*

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12 Morphine sulphate (David Bull Laboratories, Melbourne, Australia) infusions of 1
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14 mg/ml were administered intravenously in two sixty-minute stages to achieve two
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16 consecutive target pseudo-steady-state plasma concentrations [11] using a
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18 syringe driver infusion pump (3100 Graseby Syringe Pump, Watford, Hertfordshire,
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20 UK). Buprenorphine subjects received an initial bolus of 15.2 mg of morphine
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22 sulphate followed by a constant infusion of 8.3 mg/hr for one hour to achieve a
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24 target pseudo steady-state plasma concentration of 80 ng/ml (Morphine 1). They
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26 were then administered an additional bolus of 15.2 mg of morphine sulphate
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28 followed by a constant infusion of 16.5 mg/hr for one hour to achieve the second
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30 target pseudo steady-state plasma concentration of 180 ng/ml (Morphine 2). The
31
32 prescribed buprenorphine dose was administered 1 hour after infusions ceased.
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34 Control subjects were administered an initial bolus of 2.2 mg morphine sulphate
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36 followed by a constant infusion of 1.2 mg/hr for one hour to achieve a target
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38 pseudo steady-state plasma concentration of 11 ng/ml (Morphine 1). They were
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40 then administered 4.95 mg of morphine sulphate followed by a constant infusion of
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42 3.6 mg/hr to achieve the second target pseudo steady-state plasma concentration
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44 of 33 ng/ml (Morphine 2) [11].
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52 *Blood sampling and assessment times*

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55 Seven millilitre blood samples were taken at the following times: prior to the thirty
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3 minute saline familiarisation infusion, ten minutes prior to end of this infusion
4 (designated as baseline) and ten minutes prior to the end of each of the two
5 morphine or placebo saline infusions. Further blood samples were taken at 0.25,
6 0.5, 0.75, 1.0, 2.0, and 3 hours after the end of the last infusion. The blood samples
7 were centrifuged immediately and the plasma stored at -20°C until assay.
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9 Respiration rate was measured and nociceptive tests (see below) were
10 administered immediately after the collection of each blood sample except at 0.25,
11 0.50 and 0.75 hours after the last infusion.
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23 *Nociceptive tests, physiological responses and safety monitoring*

24 Two nociceptive tests were administered: the cold pressor using the non-dominant
25 arm, and electrical stimulation using the earlobe. These tests have been described
26 previously [10]. Cold pressor involves the immersion of the non-dominant arm in
27 $0.5\text{--}1.5^{\circ}\text{C}$ water and the response metric is seconds. Electrical stimulation
28 involves the transmission of an electrical pulse through the earlobe and is
29 measured in volts. One nociceptive marker was used which was pain tolerance,
30 when the participant verbally indicated that they could no longer tolerate the pain
31 and removed their arm from the water or requested that the electrical stimulation
32 cease.
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47 Respiration rate was measured over one minute by observation without the
48 subjects' awareness. Safety was monitored and recorded throughout the study
49 by means of continuous pulse oximetry, continuous ECG waveform, categorical
50 nausea scale [21] and categorical sedation scale [22].
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Plasma opioid quantification

The quantification of plasma buprenorphine and norbuprenorphine was by high performance liquid chromatography coupled to mass spectrometry as previously described [23]. The assay had a limit of quantification of 0.125 ng/ml for both analytes and all variability in accuracies and precision had coefficients of variation for buprenorphine and nor-buprenorphine of less than 15%. The quantification of plasma morphine was by high-performance liquid chromatography (HPLC) with coulometric detection as previously described [11]. The assay had a lower limit of quantification of 1 ng/ml and all variability in accuracies and precision had coefficients of variation below 7%.

Data analysis

Data are presented as mean \pm SEM (with 95% confidence intervals (95% CI)). One-way ANOVA was used to compare each outcome variable across treatments for the buprenorphine combined subjects and the control subjects with 95% CI of differences. Unpaired samples t-tests were used to compare baseline values between the combined buprenorphine subjects and the control subjects. The Pearson product-moment correlation coefficient (Pearson's r) was used to measure the linear correlation between individual buprenorphine daily doses and plasma morphine concentrations. Bonferroni's and Dunnet's tests were used for post-hoc analyses as appropriate. Data for both studies were analysed using GraphPad Prism 4.2 for Windows, GraphPad Software, San Diego, California, USA and $P < 0.05$ was considered significant.

Results

Nociceptive tests

There were no significant differences ($P>0.45$) in pain tolerance responses between the three buprenorphine dose groups from baseline to morphine infusion 1 or morphine infusion 2. Hence, the data from the groups were combined.

Cold pressor responses

Pain tolerance responses at baseline and morphine infusion 2 for control subjects and the buprenorphine subjects are shown in Figure 1 (upper panel) and absolute values and ranges for all treatments in Table 1. Pain tolerance values for the buprenorphine subjects remained unchanged between baseline and the two morphine infusions. Pain tolerance values for the buprenorphine subjects were significantly lower than for control subjects at baseline (ANOVA $P=0.009$; 95% CI -5 to -30). Within group comparisons revealed that pain tolerance values for control subjects increased significantly ($P=0.04$) from baseline to morphine infusion 2 ($P<0.05$; 95% CI 2 to 34), but not baseline to morphine infusion 1 ($P>0.05$; 95% CI -12 to 20).

Electrical stimulation responses

Pain tolerance responses at baseline and morphine infusion 2 for control subjects and the buprenorphine subjects are shown in Figure 1 (middle panel) and absolute values with ranges given in Table 1. Pain tolerance values for the buprenorphine subjects were not significantly different to controls (ANOVA $P=0.13$) at baseline. Within-group comparisons revealed that pain tolerance values for control subjects

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3 increased significantly ($P=0.007$) from baseline to morphine infusion 2 ($P<0.01$;
4 95% CI 3 to 16), but not baseline to morphine infusion 1 ($P>0.05$; 95% CI -2.8 to
5 10). There was no significant change ($P=0.98$) in pain tolerance values for
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7 combined buprenorphine subjects from baseline to morphine infusion 1 or
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9 morphine infusion 2.
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16 *Respiration rates*

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18 Respiration rates (breaths per minute) relative to baseline and morphine infusion 2
19 are shown in Figure 1 (lower panel) and absolute values with ranges in Table 1.
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21 Respiration rates for the buprenorphine subjects were significantly lower than for
22 control subjects at baseline (ANOVA $P=0.03$; 95% CI -0.25 to -4.9). Within group
23 comparisons revealed that the respiration rates for control subjects did not decrease
24 significantly ($P=0.09$) from baseline to morphine infusion 1 or morphine infusion 2.
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26 Respiration rates for the buprenorphine subjects decreased significantly (ANOVA
27 $P=0.006$) from baseline to morphine infusion 2 ($P<0.01$; 95% CI -0.9 to -4.4) but not
28 morphine infusion 1 ($P>0.05$; 95% CI -2.8 to 10).
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40 Buprenorphine dose group comparisons demonstrated significant changes in
41 respiration rates as follows. Group 2-8 mg daily: (ANOVA $P=0.024$) from baseline to
42 morphine infusion 1 ($P<0.05$; 95% CI -0.56 to -7.4) and baseline to morphine
43 infusion 2 ($P<0.05$; 95% CI -0.56 to -7.4); group 9-15 mg daily: (ANOVA $P=0.004$)
44 between baseline and morphine infusion 2 ($P<0.01$; 95% CI -1.48 to -5.52), but not
45 morphine infusion 1 ($P>0.05$; 95% CI -2.02 to 2.02); group 16 to 22 mg daily:
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47 (ANOVA $P=0.016$) between both baseline and morphine infusion 1 ($P<0.05$; 95% CI
48 -0.72 to -4.28) and baseline and morphine infusion 2 ($P<0.05$; 95% CI -0.22 to -
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3 3.78). There were no significant differences in respiration rate between the groups
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5 at baseline (P=0.90) or morphine infusion 2 (P=0.67). The lowest recorded
6
7 respiration rates were ten breaths per minute in the control group and nine breaths
8
9 per minute in the buprenorphine subjects.
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11 12 13 14 *Adverse events*

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16 There were no serious adverse events. Buprenorphine subjects did not experience
17
18 nausea or vomiting, but seven control subjects required one dose of intramuscular
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20 metoclopramide hydrochloride 10 mg (Pfizer, Perth, Australia) with good effect for
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22 mild vomiting.
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28 *Plasma morphine, buprenorphine and norbuprenorphine concentrations*

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30 Pseudo steady-state plasma morphine concentrations for morphine 1 and 2
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32 infusions are shown in Table 2A. Target pseudo steady-state plasma morphine
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34 concentration for the buprenorphine recipients were 80 ng/ml (Morphine 1) and 180
35
36 mg/ml (Morphine 2). Target pseudo steady-state plasma concentration for control
37
38 subjects were 11 ng/ml (Morphine 1) and 33 mg/ml (Morphine 2). Pseudo state
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40 plasma morphine concentrations were lower than the desired target in both groups
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42 at morphine 1 and 2. Plasma morphine concentrations are also shown for the
43
44 individual daily buprenorphine dose groups 2-8, 9-15 and 16-22 mg/day. There was
45
46 no significant correlation (p=0.08) between individual buprenorphine doses and
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48 plasma morphine concentrations at morphine infusion 1. However, there was a
49
50 significant inverse relationship between individual buprenorphine doses and plasma
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52 morphine concentrations at morphine infusion 2 (Pearson's $r = -0.74$, $p = 0.006$; slope
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3 95% CI - 0.92 to -0.28).
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7 There were no significant differences between combined mean plasma
8 buprenorphine concentrations (Table 2B), or for the three dose groups, at baseline
9 (P=0.64), morphine infusion 1 (P=0.71) or morphine infusion 2 (P=0.51). Likewise,
10 there were no significant differences between combined mean plasma
11 norbuprenorphine concentrations (Table 2C), or for the three dose groups, at
12 baseline, morphine infusion 1 or morphine infusion 2. At baseline on the saline
13 administration day, plasma buprenorphine and norbuprenorphine concentrations
14 were correlated to the buprenorphine dose ($r^2=0.36$ and 0.58 , respectively;
15 Supplementary Tables 3A, 3B).
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30 **Discussion**

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33 To our knowledge, this is the first study to have examined the effect of added
34 morphine to buprenorphine OST subjects who were pain-free at the time of study,
35 using an experiment pain model. Buprenorphine subjects were hyperalgesic in the
36 cold pressor test in comparison with controls. Very high doses of morphine (55 mg)
37 produced high plasma concentrations (92 to 201 ng/ml) that failed to provide
38 antinociception in either the electrical stimulation or cold pressor tests, irrespective
39 of maintenance buprenorphine dose. In contrast, in control subjects, considerably
40 lower morphine doses (12 mg), achieving much lower concentrations (19 to 32
41 ng/ml), provided antinociception in both tests.
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55 Our choice of using the cold pressor response to study opioid induced-
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3 hyperalgesia has been validated by others. Compton et al [13] examined
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5 hyperalgesia in opioid dependent subjects and found that these subjects, prior to
6
7 induction and following stabilisation on either methadone or buprenorphine, were
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9 similarly hyperalgesic in the cold pressor test and did not exhibit hyperalgesia in the
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11 electrical stimulation test. Krishnan et al [12] compared the detection of
12
13 hyperalgesia in opioid-substitution subjects maintained either on methadone or
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15 buprenorphine and healthy controls using the following pain stimuli: cold pain,
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17 electrical stimulation, mechanical pressure, and ischemic pain. They found that cold
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19 pain was the most suitable of the methods tested to detect opioid-induced
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21 hyperalgesia.
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27 While the buprenorphine maintained subjects were tolerant to the antinociceptive
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29 effects of the high doses of morphine and plasma concentrations to which they
30
31 were exposed, complete cross-tolerance to the respiratory depressant effects of
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33 morphine did not occur. Respiration rates dropped significantly across all dose
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35 groups, but by a limited amount (approximately 1.5 breaths per minute), which may
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37 not be clinically significant. In healthy volunteer subjects who received a single
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39 intravenous dose (0.2 mg/kg) of morphine, over a plasma concentration range
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41 (approximating 3-13 ng/mL) that produced a systematic increase in analgesia,
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43 morphine produced significant respiratory depression [24]. In contrast, in healthy
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45 adult volunteers who had experience with opioids but who were not physically
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47 dependent on opioids, Walsh and co-workers [18] demonstrated that respiratory
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49 depression increased with single buprenorphine single doses over a range of 1 to 4
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51 mg (approximately 4 breaths per minute decrease), but that this dose effect began
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53 to plateau at higher doses, with no difference between a 16 and 32 mg dose. In the
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3 present study, with subjects chronically maintained on buprenorphine, high doses
4 of added morphine had a limited respiratory depressant effect at all buprenorphine
5 doses. It is, however, possible that higher doses of morphine might produce
6 respiratory depression if such doses are needed to achieve anti-nociception, given
7 that the lowest respiratory rate recorded was nine breaths per minute. Macintyre et
8 al [25] showed increased sedation score (a surrogate for respiratory depression) in
9 buprenorphine-maintained patients who received higher doses of morphine
10 equivalents following surgery than in this study.
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23 Hyperalgesia is likely to be present, to a lesser or greater degree, in opioid
24 recipients for whatever indication. Non-cancer pain patients, maintained on either
25 methadone or slow release oral morphine for the treatment of that pain, were
26 shown to exhibit hyperalgesia in the cold pressor test [8], similar to that seen in
27 methadone [13] and buprenorphine subjects (this study) in opioid substitution
28 programs. Chakrabarti et al [26] (2010) found that people with a greater reported
29 experience of pain prior to induction onto buprenorphine maintenance required
30 greater daily doses. The present study found that there was no difference in the
31 degree of hyperalgesia experienced at baseline between the three dose ranges.
32 There was also no difference between the three dose ranges in terms of cross-
33 tolerance to the antinociceptive effects of very high dose morphine.
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49 The most widely used drugs in opioid substitution programmes worldwide are
50 methadone and buprenorphine, with the latter gaining increasing prominence.
51 Methadone maintained subjects were examined under conditions identical [13] to
52 those for the buprenorphine subjects in this study. The cold pressor test at
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3 baseline revealed that the combined methadone subjects were similarly
4 hyperalgesic to the combined buprenorphine subjects. Furthermore, both groups
5 were cross-tolerant to the antinociceptive effects of very high plasma morphine
6 concentrations and both groups experienced similar decreases in respiration rate
7 with the addition of very high plasma morphine concentrations. While
8 buprenorphine has been used increasingly across the world because of its
9 purported limited effect on respiratory depression and greater safety profile than
10 other opioids such as morphine and methadone [17, 27, 28], our findings suggest
11 that supplementary opioids for the management of pain in subjects in opioid
12 substitution programs should be added cautiously under adequate supervision to
13 avoid clinically significant respiratory depression.
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29 Koppert et al [20], in a mechanical hyperalgesia model found that acutely,
30 buprenorphine had a pronounced antihyperalgesic effect and suggested this may
31 have clinical advantages in the management of chronic pain. In observational
32 studies of chronic pain patients who were switched from high dose full opioid
33 agonists to sublingual buprenorphine, [29, 30], the switch resulted in meaningful
34 reduction in pain scores. Buprenorphine was more effective than full opioid
35 agonists. The authors postulated that these findings may have resulted from
36 buprenorphine's antihyperalgesic action [29]. However, Ravn and coworkers [31],
37 using a multimodal testing technique, could not demonstrate any significant
38 differences between morphine and buprenorphine in the profiles of
39 antihyperalgesia and analgesia in healthy volunteers. The present study shows
40 that buprenorphine, a partial mu opioid receptor agonist and kappa receptor
41 antagonist, when used as a maintenance agent, produces similar respiratory
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3 depression and hyperalgesia to methadone (a mu opioid receptor agonist) in
4 opioid maintained subjects tested under the same experimental conditions [13].
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6 These results suggest that, at the buprenorphine doses to which our subjects
7 were exposed, antihyperalgesia could not be demonstrated with the cold pressor
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11 test.
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16 Macintyre and colleagues [25] examined retrospectively pain relief and opioid
17 requirements in the first 24 hours after surgery in patients taking buprenorphine
18 (dose range was similar to that in the present study) and methadone as OST.
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20 Outcomes in the two patient groups were similar. The post-operative 24-hour
21 analgesia requirement, provided as patient controlled analgesia, was defined as
22 morphine dose equivalents. Buprenorphine maintained patients required an
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24 average of 200 mg; methadone maintained patients required 221 mg. Pain
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26 scores were similar across both groups. Sedation scores of 2 or greater occurred
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28 in 22.7% and 24.1% of buprenorphine and methadone maintained patients
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30 respectively. This important clinical study was not designed to determine
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32 possible mechanisms for the outcomes. Our findings, in an experimental setting
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34 in OST pain-free patients, complement the findings of this clinical study: very
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36 large morphine equivalent doses result in insignificant analgesia and the
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38 development of respiratory depression, albeit small, given the relatively small
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40 (compared to the PCA doses in the clinical study) dose of morphine provided to
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42 our subjects. Our findings strongly suggest that hyperalgesia is a likely
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44 mechanism for the findings of Macintyre and colleagues [25], in addition to
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46 tolerance. It is pertinent that buprenorphine and methadone maintained patients
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48 behaved almost identically, suggesting that buprenorphine had no
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3 antihyperalgesic properties.
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7 We measured plasma concentrations of morphine, buprenorphine and
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9 norbuprenorphine to more accurately assess the extent of exposure by the
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11 subject to these analytes, rather than relying simply on the given doses. While
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13 there were no significant differences between plasma buprenorphine
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15 concentrations for the three dose groups at baseline, there was considerable
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17 variability in the range of concentrations. Hyperalgesia occurred across the
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19 whole range of plasma concentrations. The lowest individual plasma
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21 buprenorphine concentration was 0.16 ng/ml (in the 2-8 mg/day dose group).
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27 Transdermal buprenorphine patches are increasingly used for the management
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29 of chronic pain. In Australia, they are available in various strengths, ranging from
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31 10-40 mg, which deliver 10 to 40 ug/h and are generally applied once a week,
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33 likely for prolonged periods. When 10 ug/h patches were administered to healthy
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35 volunteers once a week for 3 doses the average plasma concentrations were
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37 between 0.155 and 0.172 ng/ml across the 3 periods [32]; 20 ug/h patches
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39 administered to healthy volunteers as a single dose yielded mean maximum
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41 plateau plasma concentrations of about 0.25 ng/ml between 48 and 96 hours
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43 after application [33]; single applications of 35 and 70 ug/h patches yielded mean
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45 maximum plasma concentrations of 0.31 and 0.62 ng/ml respectively [34]. These
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47 values fall within the range of plasma concentrations described in the present
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49 study that were associated with hyperalgesia. Thus, it would be reasonable to
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51 assume that some patients receiving buprenorphine for the management of
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53 chronic pain could be hyperalgesic. Kress [34] reviewed several trials/reports of
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3 the efficacy of transdermal buprenorphine (varying doses) in patients with cancer
4 and noncancer pain with the minimum duration of observation of three months. In
5 most of the studies, satisfactory pain relief occurred in at least 50% of subjects,
6 suggesting that hyperalgesia may not be universal in patients suffering from pain
7 rather than those who receive opioids as substitution treatment.
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16 There are several limitations to this study. The sample size is small and not driven
17 by a formal power calculation. However, we based our population size on the
18 results of Doverty et al [11], who showed highly significant differences in cold
19 pressor tolerance between 16 healthy controls (n=16) and 16 methadone
20 maintenance subjects. Despite the smaller sample size in this study, significant
21 differences were seen between buprenorphine recipients and the controls. Plasma
22 buprenorphine concentrations were measured only at the putative peak. However,
23 given the long half-life of buprenorphine and that the subjects would have been at
24 steady state, we considered the sampling regimen justified.
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38 What might be the best strategy to improve pain relief in buprenorphine maintained
39 patients who experience acute pain, such as following surgery or trauma? Reviews
40 from Huxtable et al [6] and Schug et al [5] state that in the clinical setting, for the
41 opioid maintained population, opioid dose should be increased until analgesia is
42 achieved or sedation occurs and that the dose of the maintenance opioid should be
43 continued without interruption [25]. The purpose of this study was to provide the
44 evidence for opioid dose escalation that would provide antinociception without
45 respiratory depression in the buprenorphine maintained population. This study
46 demonstrates that buprenorphine maintained subjects are hyperalgesic at baseline
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3 and that very high morphine doses result in limited respiratory depression, but not
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5 antinociception. There is a need to explore alternative strategies for providing acute
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7 pain relief in buprenorphine (and methadone) maintained patients. For example,
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9 Huxtable [6] and Schug et al [5] recommend that an adjuvant analgesic alone, or in
10
11 combination with morphine, may overcome the limitations of cross-tolerance and
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13 side effects to provide pain management in the buprenorphine and methadone
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15 maintained population.
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26 Figure Legend

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28 Figure 1. Cold pressor pain tolerance responses (upper panel), electrical stimulation
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30 pain tolerance responses (middle panel) and respiration rate (lower panel) mean (\pm
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32 SEM) pain in 10 healthy control and 12 buprenorphine subjects at baseline (B) and
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34 morphine infusion 2 (M2). † $P < 0.05$; †† $P < 0.01$ between groups; * $P < 0.05$; ** $P < 0.01$
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36 between treatments. Note: different morphine concentrations between buprenorphine
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38 and control subjects.
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