# Buprenorphine maintenance and *mu*-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy

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## Abstract

**Background**—Sublingual formulations of buprenorphine (BUP) and BUP/naloxone have well-established pharmacokinetic and pharmacodynamic profiles, and are safe and effective for treating opioid use disorder. Since approvals of these formulations, their clinical use has increased. Yet, questions have arisen as to how BUP binding to *mu*-opioid receptors (µORs), the neurobiological target for this medication, relate to its clinical application. BUP produces dose- and time-related alterations of µOR availability but some clinicians express concern about whether doses higher than those needed to prevent opioid withdrawal symptoms are warranted, and policymakers consider limiting reimbursement for certain BUP dosing regimens.

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**Methods**—We review scientific data concerning BUP-induced changes in μOR availability and their relationship to clinical efficacy.

**Results**—Withdrawal suppression appears to require 50% μOR availability, associated with BUP trough plasma concentrations 1 ng/mL; for most patients, this may require single daily BUP doses of 4-mg to defend against trough levels, or lower divided doses. Blockade of the reinforcing and subjective effects of typical doses of abused opioids require <20% μOR availability, associated with BUP trough plasma concentrations 3 ng/mL; for most individuals, this may require single daily BUP doses >16-mg, or lower divided doses. For individuals attempting to surmount this blockade with higher-than-usual doses of abused opioids, even larger BUP doses and <10% μOR availability would be required.

**Conclusion**—For these reasons, and given the complexities of studies on this issue and comorbid problems, we conclude that fixed, arbitrary limits on BUP doses in clinical care or limits on reimbursement for this care are unwarranted.

## 1. INTRODUCTION

### 1.1. Background

Buprenorphine (BUP), a partial *mu*-opioid receptor (μOR) agonist, is approved in several countries for treating opioid use disorder. Since its introduction, clinicians and policymakers have made decisions that place limits on treatment dose and duration, which can impact care that patients receive (Clark et al., 2011). These decisions are sometimes implemented inflexibly and defended with certainty, citing anecdotal experience, policy constraints such as cost, and research literature. Such certainty may be unwarranted given the state of science in this field. This review is designed to inform clinicians and policymakers about empirical data underlying BUP dose-related changes in μOR availability and behavior, with emphasis on educating these individuals about evidence-based maintenance dosing practices. We will: (1) examine findings regarding the extent of BUP binding to μORs under varying experimental dosing conditions; (2) describe relationships between μOR availability and plasma concentrations of BUP toward achieving desired clinical effects including withdrawal suppression and blockade of opioid agonist effects; and (3) communicate the complexity of methods and data, and how their interpretation may affect clinical dosing and policy recommendations.

### 1.2. Basis for clinical use of buprenorphine in treating opioid use disorder

**1.2.1. Pre-FDA approval**—In animal studies, μORs have been implicated in opioid reinforcement (Bertalmio and Woods, 1989; Kreek et al., 2012; Matthes et al., 1996), discriminative stimulus effects (Bertalmio and Woods, 1987; Comer et al., 1993; Dykstra et al., 1988; Walker et al., 1994), and withdrawal effects (France and Woods, 1989; France et al., 1990; Maldonado et al., 1992; Matthes et al., 1996). Administered chronically, BUP antagonizes self-administration of *mu*-opioid agonists (Mello et al., 1983; Mello and Negus,

1998), which predicts clinical findings. BUP can precipitate withdrawal depending on the level of opioid dependence, agonist on which the subject is dependent, and time since last agonist dose (Kosten and Kleber, 1988; Sell et al., 2003; Walsh et al., 1995a; Woods and Gmerek, 1985; Woods et al., 1992). In humans, BUP precipitates moderate to severe opioid withdrawal in subjects maintained on moderate-dose methadone (60 mg/day), but less withdrawal in participants taking lower doses of methadone (25–30 mg/day) or heroin (Kosten and Kleber, 1988; Kosten et al., 1991; Strain et al., 1992; Walsh et al., 1995a).

Human laboratory studies that incorporate supervised inpatient stays, urine testing, and placebo control enable assessment of the impact of BUP on opioid reinforcing, subjective and physiological effects. Opioid reinforcement is measured using operant drug self-administration procedures whereby participants work on a computer task to earn drug (e.g., Comer et al., 2001; Greenwald et al., 2013; Mello et al., 1982). Subjective drug-effect assessments include adjective ratings that reflect abuse potential (e.g., "liking", "good effect"). Multi-item measures of opioid agonist and withdrawal effects are usually assessed. Measures of craving are often included. Physiological indices commonly recorded are pupil diameter, respiratory rate, oxygen saturation, heart rate, and blood pressure.

Sublingual BUP has been shown to dose-dependently decrease the reinforcing effects of heroin (Comer et al., 2001, 2005; Mello and Mendelson, 1980; Mello et al., 1982) and hydromorphone (Greenwald et al., 2002), consistent with reductions of opioid use in outpatient clinical trials (Johnson et al., 1995; Ling et al., 1998; Schottenfeld et al., 1993). Furthermore, many studies have reported BUP dose-dependent attenuation of the subjective effects of opioids (Bickel et al., 1988; Jasinski et al., 1978; Rosen et al., 1994; Schuh et al., 1999; Teoh et al., 1994; Walsh et al., 1995b). BUP also dose-dependently suppress opioid withdrawal symptoms in human laboratory studies (e.g., Greenwald et al., 2003) and outpatient trials (Fudala et al., 1990; Kuhlman et al., 1998), although the latter may be confounded by uncontrolled opioid use.

**1.2.2. Post-FDA approval**—BUP dosing for opioid dependent patients is informed by FDA recommendations for different formulations and phases of treatment (induction, maintenance, detoxification). At present, the only SL formulations are BUP tablets, BUP/naloxone (NAL) tablets and BUP/NAL filmstrips. Dosing guidelines are comparable for tablets and film, based on their similar pharmacokinetic and pharmacodynamic properties (Lintzeris et al., 2013). In the context of FDA guidelines, patient-related factors proximally determine clinical practice. Perhaps the most important aspect is that patients with greater levels of illegal/non-medical opioid use (Hillhouse et al., 2011) or comorbid pain severity (Chakrabarti et al., 2010) generally are prescribed higher doses of BUP, which implies there may be an association between greater clinical benefit and higher doses for these patients. Thus, during BUP induction, doses are typically 2–8 mg/day but can be escalated more rapidly depending on safety and need (Amass et al., 2012; Chiang and Hawks, 1994; Whitley et al., 2010). During maintenance, effective doses are typically 8–24 mg/day (Ling et al., 1998; Ling and Smith, 2002) but can be lower or higher (Compton et al., 1996). During detoxification, BUP doses are most often tapered over one to several weeks, usually by halving the dose at each step from the maintenance level (Amass et al., 2004; Ling et al., 2009; Sigmon et al., 2013).

## 2. METHODS

### 2.1. Estimation of in vivo mu opioid receptor (µOR) availability

#### 2.1.1. [11C]-carfentanil Positron Emission Tomography (PET) imaging of µORs

—The high-affinity, µOR-specific PET radioligand, [11C]-carfentanil (Dannals et al., 1985; Frost et al., 1985; Titeler et al., 1989) offers researchers a reliable and non-invasive means to map brain regional µOR availability. To adhere to the literature, we will refer to changes in *receptor availability*, which is an indirect measure. Although receptor "occupancy" is an intuitively attractive term, it is misleading. First, "occupancy" suggests an endogenous or exogenous ligand binds to receptors and stays bound, whereas most ligands repeatedly associate and dissociate from receptors; two affinity values $K_i$ and $K_d$, respectively, reflect this variable state of affairs. Second, "occupancy" cannot be measured directly in human subjects except with extraordinary methods to obtain receptor concentration [$B_{max}$] and affinity [$K_d$]. The conservative term, "non-displaceable binding potential", $BP_{ND}$, has become nomenclature. Using this index acknowledges that [11C]-carfentanil PET involves *in vivo* µOR binding between multiple competing ligands: the tracer, one or more exogenous ligands (e.g., BUP), and physiologically circulating endogenous opioids (e.g., endorphins). If we assume that µOR affinity and endogenous ligand concentrations are constant, then a *reduction* in µOR availability is proportional to an *increase* in "occupancy".

In studies reported here, [11C]-carfentanil was synthesized to have µOR-specific activity (Dannals et al, 1985; Jewett, 2001), and administered IV in a small mass ($\approx 0.03$ µg/kg per scan) to ensure only sub-pharmacological amounts that occupy 0.3–0.6% of µORs. Half the total dose was administered as a bolus and the remainder as a continuous infusion, calibrated to offset [11C]-carfentanil elimination rate. Once tracer concentration reached steady-state level, PET scans began. Each scan involved acquiring many images over $\approx 70$ minutes to achieve full brain coverage. Image data were obtained for each voxel. Amount of radioactivity in each region of interest (ROI) with known µOR concentrations (*specific* binding) was referenced to a region with negligible µORs, the occipital cortex, to control for *non-specific* tracer binding. µOR availability in each ROI was expressed as a [11C]-carfentanil distribution volume ratio (DVR), with higher values indicating greater µOR availability. Images were adjusted for cerebral blood flow (which can alter tracer uptake) and radioactive scatter (which can alter precision), then co-registered with an anatomical MRI brain scan. In these studies, ROIs included inferior prefrontal cortex (Brodmann area 10 [BA 10]), subgenual and rostral divisions of the anterior cingulate cortex (BA 25 and BA 32), caudate nucleus, thalamus, nucleus accumbens, and amygdala.

In each study the reader should note time(s) at which scanning occurred relative to the daily BUP dose. BUP plasma concentrations peak about 1 hr after SL administration and decrease throughout the day until the next dose. Similarly, µOR availability should decrease shortly after the BUP dose and increase until the next dose. Thus, measures taken 4 hr after the daily dose (the earliest post-dose time that has been studied), likely reflect sub-maximal reductions in µOR availability. It is not feasible to conduct within-day PET time-course studies, therefore, knowledge of peak BUP *brain* concentrations must be extrapolated from *plasma* concentration data, which can be sampled more frequently.

### 2.1.2. Mathematical (simulated) estimation of in vivo µOR availability—To estimate proportional receptor binding, one can also use a pharmacological analytical model (Black and Leff, 1983; Zernig et al., 1996) to derive a measure of medication intrinsic efficacy, relative to placebo control, that corresponds to the fraction of receptors (putatively, µORs) bound by BUP when half-maximum [$ED_{50}$] heroin responses are produced. Comer et al. (2005) estimated efficacy of BUP blockade using an equation that accounts for: (1) receptor pool size under control conditions, (2) maximum attainable response, (3) opioid agonist concentration, (4) dissociation constant, and (5) transducer function that maps receptor binding to observed response. Using these inputs, computer software finds a best-fit curve to the observed data, and derives parameters from these curve fits.

## 2.2. Methodological challenges to studying and interpreting µOR availability

We first review methodological issues related to the receptor studies reviewed herein, as these influence interpretation and application of experimental findings to clinical practice settings. We advise clinicians and policymakers to be cautious in their conclusions due to these important caveats.

### 2.2.1. Definition of "opioid blockade"—There is no gold-standard operational definition for clinically meaningful opioid "blockade", i.e., the degree to which medications such as BUP (or methadone or naltrexone) attenuate exogenous opioid effects. Blockade is important in reducing opioid agonistinduced effects such as subjective ratings related to abuse (e.g., "liking"), reinforcing effects (self-administration) or medical problems (e.g., respiratory depression). Yet, we do not know the threshold of brain µOR availability required for specific clinical effects (withdrawal suppression, blockade), nor for which types of patients, abused opioids, or routes of administration. Lack of such criteria is relevant for scientists, clinicians, and policymakers (e.g., FDA, state agencies, and insurance providers). This issue has precedents in the context of methadone treatment, as there have been historical divisions amongst clinicians and policymakers regarding whether "higher-dose" or "lower-dose" methadone is preferable. The clinical trials literature offers consistent support for the policy that, when safe for the individual patient, higher maintenance doses that provide blockade in addition to withdrawal suppression generally produce better outcomes than lower doses (Siassi et al., 1977; Ling et al., 1996, 1998; Strain et al., 1993, 1999).

BUP binding to human brain µORs displaces endogenous and exogenous opioids, and thereby reduces µOR availability that, in turn, prevents withdrawal and attenuates effects of exogenous opioids. Although these features do not directly determine clinical practice, the association between greater pre-treatment opioid use and higher prescribed BUP doses suggests µOR binding may implicitly guide practice. A stronger version of this argument is that there is a *mechanistic basis for clinician judgment*, which we explicate here. Furthermore, ongoing efforts in medication development for substance use disorders emphasize CNS target-based approaches. Importantly, BUP-induced changes in µOR availability determine two distinct functions that underpin agonist therapies: preventing opioid withdrawal and craving, and attenuating effects of exogenous opioids.

**2.2.2. Participant factors**—Studies reviewed here were conducted with *heroin-dependent* volunteers *not seeking treatment* for their drug use, who typically do not remain drug-free during outpatient periods without abstinence-contingent incentives (Greenwald, 2008). Participants underwent experimental brain imaging and other procedures under *controlled inpatient conditions* to minimize confounds. Thus, generalizability of findings to individuals dependent on other opioids (e.g., oxycodone, hydrocodone) or seeking treatment is unclear. The seemingly counterintuitive approach of studying out-of-treatment individuals was based on the goals of determining whether BUP would block subjective and physiological effects of opioid challenges, and extent of BUP-induced reduction of μOR availability for achieving these clinically important blockade effects. Thus, it was not ethically permissible to administer an abused opioid to participants who were motivated to quit using opioids.

Earlier studies in healthy subjects demonstrated that μOR availability varies by gender and age (Zubieta et al., 1999). This led to restricting ages of inclusion (18–50 years) among opioid dependent volunteers in PET studies reviewed here. Although females were not excluded from the PET studies, many fewer females than males participated. Given the small sample sizes, statistical power was inadequate to address potential influence of gender or age on μOR availability during BUP dosing.

Individuals with non-opioid substance use disorders (except nicotine) were excluded from these studies of BUP and μOR availability, as these other drugs might affect the experimental measures. In particular, elevated regional μOR availability was found among individuals dependent on cocaine than controls (Zubieta et al., 1996; Gorelick et al., 2005), even during prolonged abstinence; and correlated with greater pre-abstinence cocaine craving and use (Zubieta et al., 1996; Gorelick et al., 2005), greater cocaine use during cognitive-behavioral treatment (Ghitza et al., 2010), and greater post-abstinence relapse (Gorelick et al., 2008). [$^{11}$C]-carfentanil PET studies have also demonstrated higher μOR availability among recently abstinent alcohol-dependent individuals than controls (Heinz et al., 2005; Weerts et al., 2011). The studies reviewed here also excluded individuals with psychiatric problems including depressive, psychotic, or anxiety disorders, which have been found to affect μOR availability (Naber et al., 1981; Gross-Isseroff et al., 1990; Kennedy et al., 2006; Prossin et al., 2010; Scarr et al., 2012).

Also, brain-imaging studies reviewed here excluded pregnant women and individuals with medical conditions such as active hepatitis, respiratory or neurological disease, which could alter safety, BUP pharmacokinetics (section 2.2.3), or μOR availability. Selection of relatively healthy, opioid-dependent individuals does not represent BUP patients in clinical practice, and limits generalizability of research findings. Interestingly, patients with chronic pain who are not taking opioids exhibit lower μOR availability in pain-related brain regions than controls (Harris et al., 2007; DosSantos et al., 2012), which may reflect excess endogenous opioid release during persistent nociceptive signaling. It would be informative to ascertain whether chronic pain-related variations in endogenous opioid tone alter BUP-induced changes in μOR availability and/or clinical outcomes for opioid use or pain.

**2.2.3. Buprenorphine-related factors**—Buprenorphine is a partial μOR agonist, an antagonist at *kappa* and *delta* opioid receptors (Lewis et al., 1985; Lewis and Husbands, 2004), and agonist at nociceptin/orphanin FQ (N/OFQ) receptors (Lester and Traynor, 2006; Lutfy and Cowan, 2004). However, the clinical relevance of BUP activity at *kappa*-, *delta*- and N/OFQ receptors remains unclear at this time.

In BUP-stabilized individuals, BUP plasma concentrations are dose-proportional and peak 1 hr after daily SL administration ($T_{max}$: 0.9 – 1.2 hr across doses). Plasma concentrations of the principal metabolite, norbuprenorphine (norBUP) peak 1.5 hr after daily BUP administration ($T_{max}$: 1.4 – 1.6 hr across doses) (Greenwald et al., 2003). Plasma BUP concentrations decrease in a time-since-dose dependent manner, with mean (± 1 SD) half-life ($T_{1/2}$) estimated at 21.7 ± 8.2 hr (Greenwald et al., 2007). Naloxone is not known to alter SL BUP pharmacokinetics (Harris et al., 2000); therefore, these estimates are not likely to differ for SL BUP vs. BUP/NAL products.

Clinicians should be mindful of individual differences in BUP plasma pharmacokinetics. Elkader and Sproule (2005) noted that among healthy individuals studied, during the absorption phase, $T_{max}$ after acute SL dosing ranges from 0.5 to 3.5 hr; coefficients of variation for $C_{max}$ values ranged from 31% to 84%. In a study of opioid-dependent individuals who took SL BUP for 36 days, elimination half-life varied 3-fold for BUP (24–69 hr) and 8-fold for norBUP (22–176 hr) (Kuhlman et al., 1998).

Limited evidence suggests BUP pharmacokinetics are not significantly altered by renal impairment (Elkader and Sproule, 2005; Filitz et al., 2006). Little is known about BUP pharmacokinetic variability due to hepatic impairment; however, because cytochrome P450 (CYP) 3A4 catalyzes N-dealkylation of BUP to norBUP (Iribarne et al., 1997; Kobayashi et al., 1998), and CYP3A function is compromised in hepatic disease (George et al., 1995; Yang et al., 2003), hepatic disease or genetic variation in CYP3A4 efficiency could influence BUP pharmacokinetics.

Some medications used to treat medical or psychiatric conditions that co-occur with opioid use disorder may interact with CYP3A4 and influence BUP pharmacokinetics. These include drugs that inhibit BUP metabolism such as antiretroviral therapy for HIV/AIDS (e.g., atazanavir), azole antifungals (e.g., ketoconazole), rifampin for tuberculosis, and potentially some serotonin reuptake inhibitors (e.g., fluvoxamine); whereas other drugs may induce BUP metabolism such as phenobarbital (Elkader and Sproule, 2005; McCance-Katz et al., 2010).

Given BUP's extensive biodistribution and recirculation through central and peripheral compartments, clinicians should consider the influence of disease conditions and their treatments on μOR availability. In theory, medications or conditions that *increase* plasma/ brain concentrations of BUP (decrease μOR availability) could lead to toxicity, although its partial μOR-agonist action could protect against such concerns. In contrast, medications or conditions that *decrease* plasma/brain concentrations of BUP (increase μOR availability) could engender withdrawal symptoms and undermine BUP efficacy.

All brain-imaging studies to date have employed a specific formulation of the BUP mono product tablet rather than generic BUP mono, combination BUP/NAL tablet or film, or generic BUP/NAL products. Although NAL has poor absorption via the SL route (Weinberg et al., 1988; Harris et al., 2000) and data suggest SL BUP and BUP/NAL products have similar effects (Strain et al., 2000), these neuroimaging studies used the BUP mono formulation to eliminate possible effects of NAL while measuring μOR availability during BUP maintenance.

Notably, the FDA recommends that generic formulations produce mean bioequivalence values for $C_{max}$, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ within the 90% confidence interval of the branded formulation (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm081288.htm). This implies that generics could yield values for μOR availability, plasma concentrations, and pharmacodynamic effects that are slightly larger or smaller than reported for the branded product. Relative to this confidence interval, it is helpful to understand that coefficients of variation (i.e., [standard deviation ÷ mean score] × 100) for the 16-mg/day and 32-mg/day doses (respectively) in the Greenwald et al. (2003) study were 24% and 21% for μOR availability, 39% and 54% for BUP plasma concentrations, and 129% and 109% for opioid withdrawal symptoms. In short, the degree of between-subject variability, especially for pharmacodynamic outcomes, may lessen concerns about pharmacokinetic variability due to BUP formulation. Thus, while clinicians and policymakers should exercise caution in extrapolating findings from research literature to clinical care, patient heterogeneity may exert a larger effect on treatment outcomes than differences in BUP formulation.

## 3. RESULTS

A preliminary study (Zubieta et al., 2000) used the SL BUP-mono liquid formulation (tablets have ≈70% bioavailability of liquid formulations; Chawarski et al., 2005; Compton et al., 2006), which was discontinued prior to FDA approval. Three heroin-dependent volunteers were stabilized on daily BUP doses of 2-mg, then 16-mg, then placebo (0-mg) under double-blind conditions. Four days before each PET scan (at each BUP dose), the participant was admitted to an inpatient unit with daily urine testing to ensure any recent illegal drug use had cleared. Each scan started 4 hr after the daily dose. BUP dose-dependently decreased μOR availability, relative to placebo, in all ROIs. There were variations across ROIs, with μOR availability ranging from 50% (hypothalamus) to 64% (cerebellum) at 2-mg/day, and from 5% (hypothalamus) to 21% (thalamus) at 16-mg/day. Opioid withdrawal symptom and heroin craving scores exhibited significant inverse linear relationships with BUP dose, paralleling μOR availability.

A second study (Greenwald et al., 2003) of five heroin-dependent volunteers sought to extend these findings by: (a) using the BUP tablet, (b) implementing a detoxification protocol with a wider range of daily BUP maintenance doses (32-mg, 16-mg, 2-mg, and 0-mg), and a longer 12-day period of maintenance on placebo (i.e., more stable baseline) than the first study, (c) measuring BUP and norBUP plasma levels, (d) determining whether BUP attenuated agonist effects of hydromorphone (24-mg IM), and (e) correlating biological

concentrations and pharmacodynamic effects across doses. As in Zubieta et al. (2000), each PET scan began 4-hr after the daily dose.

Figure 1A (left panel) illustrates that BUP dose-dependently reduced μOR availability, which was reliable across participants and ROIs. Notably, subjects continued their opioid use (based on urinalysis) during outpatient periods between inpatient stays when PET scans were conducted. Thus, even 32 mg/day did not fully deter opioid use among these out-of-treatment volunteers. To address physicians' questions about 8-mg and other maintenance doses that were not studied experimentally, Figure 1A and Table 1 present results (estimated from curve fits of observed data) to help readers extrapolate regional μOR availability over a 16-fold range of doses at near-peak effect (4-hr post-BUP).

Comer et al. (2005) conducted a study of heroin-dependent volunteers without brain imaging that estimated relationships between receptor availability and heroin's reinforcing and subjective effects. They examined effects of intranasal heroin (0, 12.5, 25, 50, and 100 mg) at 15 hr after daily BUP/NAL maintenance doses of 2/0.5-mg, 8/2-mg, and 32/8-mg (during different test weeks for each subject). These broad and evenly spaced maintenance doses should produce receptor and functional blockade effects with low, moderate and high efficacy. Heroin responses in 7 BUP/NAL-maintained individuals were compared to responses in a separate group of 8 heroin-detoxified, placebo-maintained subjects. Using mathematical modeling (section 2.1.2), Comer et al. found that heroin 50-mg and 100-mg self-administration modestly decreased (Figure 3) when BUP/NAL 2/0.5-mg, 8/2-mg and 32/8-mg reduced receptor availability to 21%, 11% and 6%, respectively (Table 1).

In a study that investigated BUP duration of action, Greenwald et al. (2007) stabilized 10 heroin-dependent volunteers on BUP 16-mg/day then determined multiple outcomes during double-blind placebo substitution over three days. Repeated measures of μOR availability, BUP and nor-BUP plasma levels, and subjective and physiological effects were obtained 4, 28, 52 and 76 hr after the last 16-mg/day dose. On a different week for each participant under the same BUP dosing conditions, high-dose hydromorphone was injected (24-mg IM) to assess BUP blockade efficacy. Time-course μOR availability data in this study were referenced to the placebo condition of the Greenwald et al. (2003) study. Results indicated time-dependent increases in μOR availability and decreases in BUP plasma levels, with CNS and peripheral concentrations exhibiting an inverse exponential correlation. Figure 2 illustrates this inverse relationship between BUP plasma concentrations and μOR availability in two clinically relevant ROIs: thalamus (pain processing) and nucleus accumbens (reward processing). Based on this relationship, near-zero μOR availability should be associated with BUP plasma levels of about 14 ng/mL. Subjective effects of hydromorphone challenge were significantly attenuated at 4-hr and 28-hr post-BUP (consistent with BUP attenuation of hydromorphone reinforcement during daily and alternating-day dosing; Greenwald et al., 2002), relative to 52-hr and 76-hr. Taken together, findings from this study and Greenwald et al. (2003) suggested that BUP suppression of opioid withdrawal symptoms requires brain μOR availability of 50%, and that blockade of high-dose opioid agonist effects requires even greater percentage reduction of μOR availability.

Figure 1B (right panel) shows post-BUP time-dependent increases in μOR availability. Greenwald et al. (2007) referenced these data to the placebo condition in the dose-response study (Greenwald et al., 2003). Using a between-subject control condition to estimate percent μOR availability could be misleading if absolute μOR availability values differ across studies. To address that limitation, Figure 1B adjusts μOR availability in the 4-hr post-BUP 16-mg condition of the time course study to the identical condition in the dose-response study. This yields a comparable *intercept* for μOR availability across studies, without altering *slope* of the time-course function. These data show that post-BUP (16-mg) μOR availability ranges from 13–25% (across ROIs) at 4-hr, from 19–30% at 8-hr, from 24–36% at 12-hr, from 29–41% at 16-hr, from 37–46% at 24-hr, from 56–73% at 48-hr, and 75–90% at 72-hr post- BUP. Estimates derived here from BUP 16-mg/day dosing offer a more complete frame of reference than previous studies.

Figure 3 maps relationships between μOR availability and pharmacodynamic responses, based on re-analyses of data from Greenwald et al. (2003, 2007) and Comer et al. (2005) studies. Within each panel, non-linear regression curves are plotted: X-axis values moving from left to right (low to high μOR availability) reflect decreasing BUP dose or time since BUP dose; Y-axis values are adjusted to percent maximum effect on each measure (to interpret these on a common scale). In the Greenwald et al. (2003) BUP-dose study, there are positive relationships between μOR availability and both opioid withdrawal and heroin craving responses, but effects are clinically modest (<50% maximum effect). In the Comer et al. (2005) BUP-dose study, there are positive relationships between opioid receptor availability and heroin self-administration. These data suggest nearly all receptors would need to be occupied (beyond BUP 32-mg/day) to fully suppress self-administration of naturalistically relevant heroin doses. Results from the Greenwald et al. (2007) time course study demonstrate modest time-dependent recovery of agonist symptoms (loss of blockade) in response to hydromorphone challenge.

The potential for nicotine intake/abstinence to moderate response to opioid pharmacotherapy is clinically important, given high rates of smoking among opioid-dependent patients. Greenwald et al. (2007) found that heavier smokers ( 20 cigarettes/day) exhibited significantly less μOR availability across ROIs and post-BUP discontinuation times than lighter smokers ( 15 cigarettes/day). This is consistent with findings in chronic nicotine-exposed rats (Davenport et al., 1990) and human smokers vs. non-smokers (Scott et al., 2007). All PET imaging studies described herein specified acute nicotine deprivation prior to scanning; thus, reduction in μOR availability is attributed to the effect of chronic nicotine use. As Figure 4 shows, heavier smokers reported greater opioid pharmacodynamic responses during short-term BUP discontinuation including more withdrawal symptoms, heroin craving, and agonist symptom response to hydromorphone challenge. The small sample in this study prevents firm conclusions about the interaction of nicotine and BUP on μOR availability. However, nicotine discontinuation in laboratory animals produces hyperalgesia (Wewers et al., 1999; Yang et al., 1992) and, in post-surgical patients, hospital-enforced nicotine abstinence is associated with increased opioid analgesic self-administration (Marco et al., 2005; Steinmiller et al., 2012). Thus, opioid-dependent

smokers undergoing nicotine abstinence may respond more poorly to BUP treatment due to dysregulation of μORs.

## 4. DISCUSSION

### 4.1. Pharmacological issues

BUP maintenance dose is inversely related to μOR availability in opioid-dependent volunteers; however, it is not reasonable to compare receptor availability estimates from Comer et al. (2005) and Greenwald et al. (2003) due to methodological differences. First, these studies differed in measuring receptor availability *in vivo* (Greenwald et al., 2003) versus simulation (Comer et al., 2005), which could partly explain disparate estimates for BUP 2-mg (Table 1). Second, estimates from Comer et al. (2005) are neither receptor-nor brain-region specific, in contrast to data from Greenwald et al. (2003). Third, the two studies examined receptor availability at different post-BUP times (4-hr vs. 15-hr after the daily dose).

Notably, Comer et al. (2005) tested blockade of heroin effects 15 hr after BUP/NAL, when efficacy might be lower. Patients seeking to circumvent medication blockade might use opioids at BUP trough concentrations. Given that 32-mg/day BUP/NAL did not fully block heroin effects, this raises the empirical question as to whether even higher daily doses of BUP might be more effective. Some investigators have suggested high doses of BUP administered with longer inter-dose intervals may be just as effective as lower daily doses (Bickel et al., 1999; Marsch et al., 2005). This emphasizes the importance of considering not only dose but time-since-dose, which is positively related to μOR availability, with the proviso that absolute μOR availability is region specific.

Comer et al. (2005) observed small confidence intervals for μOR availability in all BUP dose conditions. Greenwald et al. (2003) similarly observed minimal between-subject variance at higher maintenance doses (16- and 32-mg/day), but there was 3.5-fold variability in μOR availability for most ROIs at the lowest BUP dose (2-mg/day). In the latter study, μOR availability correlated most highly with opioid withdrawal symptoms at group and individual-subject levels, but individuals varied in the slope and intercept of this relationship (see Figure 4 in Greenwald, 2006). These data confirm the idea that opioid pharmacotherapy should suppress withdrawal by decreasing μOR availability, but that there is large variation in opioid-dependent individuals' sensitivity to withdrawal symptoms during dose reduction. Although we do not fully understand the clinical importance of these observations, one hypothesis (Greenwald and Steinmiller, 2009) is that individuals who exhibit less μOR availability and more suppression of withdrawal symptoms during low-dose BUP might experience better treatment outcomes.

We observed in these data sets an inverse exponential relationship between μOR availability and BUP plasma concentrations (consistent across individual subjects and brain ROIs) and between these pharmacokinetic and pharmacodynamics measures. These relationships during SL BUP dosing were recently expanded into a comprehensive model to predict dose requirements for a novel subcutaneous depot BUP formulation (Nasser et al., 2014).

### 4.2. Implications for Clinical Use and Policy

#### 4.2.1. Safety and efficacy: individual differences and clinical titration—

Scientific and clinical data suggest BUP and BUP/NAL are safe medications with dose-related efficacy (Ling et al., 1998; Fudala et al., 2003; Connock et al., 2007) and wide safety margin, most likely due to partial μOR-agonist action. Nonetheless, we realize that co-occurring medical conditions (e.g., pregnancy, chronic pain, hepatic disease), psychiatric conditions (e.g., major depression), comorbid substance use (e.g., nicotine, cocaine, alcohol), and genetic factors, might moderate BUP treatment efficacy *via* μORs. Specific recommendations are presently unwarranted due to limited data. We strongly advocate for further empirical studies, motivated by the hypothesis that conditions that undermine BUP clinical efficacy may be altering μOR availability, pharmacokinetics, and pharmacodynamic responses that, in turn, might require higher SL BUP doses and/or divided daily doses. While some clinicians may use an algorithm to judge what BUP dose(s) a patient should receive, e.g., based on conversion units from level of opioid use, we encourage clinical judgment – rather than being reflexive – to be informed by empirical factors reviewed here. Finally, it is important to recognize that factors other than receptor availability, such as conditioned behavior, affective states and coping skills, influence illicit drug use among individuals receiving BUP.

Findings from flexible-dosing studies indicate that patients who were titrated to SL BUP doses greater than 16-mg/day had greater opioid use before and during BUP induction than patients titrated to BUP doses of 8- to 16-mg/day (Hillhouse et al., 2011; Fareed et al., 2012). This is consistent with a clinical heuristic that *opioid blockade (more so than withdrawal suppression) should be the primary criterion guiding BUP maintenance dose*, especially during phases of treatment when a patient is using opioids in the absence of withdrawal (e.g., early recovery). Given that most abused opioids are μOR agonists with high intrinsic efficacy, i.e., produce their effects with few spare receptors, this argues that clinicians should generally prescribe a higher BUP dose in a patient who continues using opioids to maximize μOR blockade in addition to minimizing opioid withdrawal symptoms.

Our re-analysis of findings from Comer et al. (2005; see Figure 3) suggests that, during BUP dosing, nearly all receptors need to be occupied to *fully block* self-administration of heroin or other μOR agonists *in the majority of opioid-dependent individuals*. This inference is consistent with an earlier study by Comer et al. (2005), given that BUP 16-mg/day did not fully block the reinforcing efficacy of 12.5-mg and 25-mg IV heroin unit doses; and Greenwald et al. (2002), showing that BUP 16-mg/day and 32-mg every other day did not fully block the reinforcing efficacy of 24-mg IM hydromorphone. We wish to be very clear that "opioid blockade" – which we define as "the absence of reactivity to (physiological or abuse-related subjective drug effects) or responding for (reinforcing effects) an opioid agonist, when statistically compared to placebo" – might be achieved in *some individuals* using lower BUP doses. However, we believe most practitioners and policymakers typically intend this desired blockade effect should be evident in *most patients* to be clinically meaningful and relevant to guidelines or dosing limits. Relying on available data and principles of negligible effect size and representativeness, we are strongly inclined to

conclude that relatively high BUP doses (perhaps greater than 24 to 32 mg/day) would be required to meet this rigorous clinical threshold.

As with any opioid medication, there are legitimate concerns about diversion of SL BUP when higher daily doses are prescribed, especially among patients with active illicit opioid use. These risks must be weighed against possible benefits of higher-dose BUP treatment. One potential strategy is to initiate dosing to suppress withdrawal and restrict subsequent dose escalation to those patients who demonstrate evidence of ongoing illicit opioid use despite suppression of withdrawal symptoms. If the clinician has reason for concern regarding diversion, strategies such as directly observed dosing can be implemented.

**4.2.2. Prior authorizations on maximum BUP dose and duration**—This discussion has significant implications for deciding BUP dosing regimens that clinicians should prescribe or agencies should approve for reimbursement. First, it has come to our attention that statistically significant reduction in μOR availability during 16-mg/day maintenance has been improperly interpreted and used by some clinicians as a rationale for restricting dosing. Second, we have learned that some State Medicaid agencies and managed care organizations have begun to limit reimbursement for higher BUP doses and/or longer duration of dosing. Although such limitations are partly due to budget considerations, additional reasons are often based on the efficacy of BUP to suppress opioid withdrawal symptoms, without considering blockade effects. In light of these caveats, we believe this rationale is misguided.

We advocate that clinical prescriptive practice and prior authorization requirements for reimbursing BUP treatment should be predicated on the best available scientific data and clear clinical priorities. The primary aim of pharmacotherapy – using agonists such as BUP or methadone, or antagonists such as naltrexone – is to *promote abstinence*, not suppress opioid withdrawal discomfort. Furthermore, the μOR threshold for suppressing opioid withdrawal symptoms is lower than for opioid blockade efficacy. Thus, for patients with ongoing illicit opioid use, the clinician's goal should be to use a sufficiently high dose to achieve opioid blockade, i.e., attenuate the reinforcing, subjective and physiological effects of abused opioids. Moreover, BUP doses above 16-mg/day have been considered too high; however, data that demonstrate large reductions of of μOR availability 4 hr after 16-mg/day dosing (Greenwald et al., 2003), may not block opioid use (Comer et al., 2005), and have been wrongly extrapolated to argue that BUP maintains this same level of μOR stimulation throughout each day, despite compelling evidence that μOR availability increases over time (Greenwald et al., 2007).

**4.3. Summary**

Re-examination of published scientific data suggests SL BUP produces two clinically important pharmacodynamic effects that have differing μOR availability requirements. First, opioid withdrawal suppression appears to require 50% μOR availability, associated with BUP trough plasma concentrations 1 ng/mL; for most patients, this may require single daily BUP doses of 4-mg to defend against trough levels, or lower divided doses. Second, blockade of opioid reinforcing and subjective effects has not been reliably observed under

BUP dosing conditions studied to date. Based on preliminary modeling, blockade of typical doses of abused opioids (i.e., those used by a nonmedicated individual) probably require <20% μOR availability, associated with BUP trough plasma concentrations 3 ng/mL; for most individuals, this may require single daily BUP doses >16-mg, or lower divided doses. For individuals attempting to surmount this blockade with higher-than-usual doses of abused opioids, even larger BUP doses and <10% μOR availability would be required. For these reasons, and given the complexities of studies on this issue and comorbid problems, we conclude that fixed, arbitrary limits on BUP doses in clinical care or limits on reimbursement for this care are unwarranted.

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## Highlights

- We review data on BUP-induced changes in *mu*-opioid receptor (µOR) availability, pharmacokinetics and clinical efficacy.

- Opioid withdrawal suppression appears to require 50% µOR availability, associated with BUP plasma concentrations 1 ng/mL.

- Blocking opioid reinforcement requires <20% µOR availability, or BUP plasma levels 3 ng/mL.

- Blockade of opioid use for many patients may require total BUP daily doses 16mg, although other factors contribute.

- Data suggest that fixed limits on BUP doses in clinical care or limits on reimbursement for this care are unwarranted.
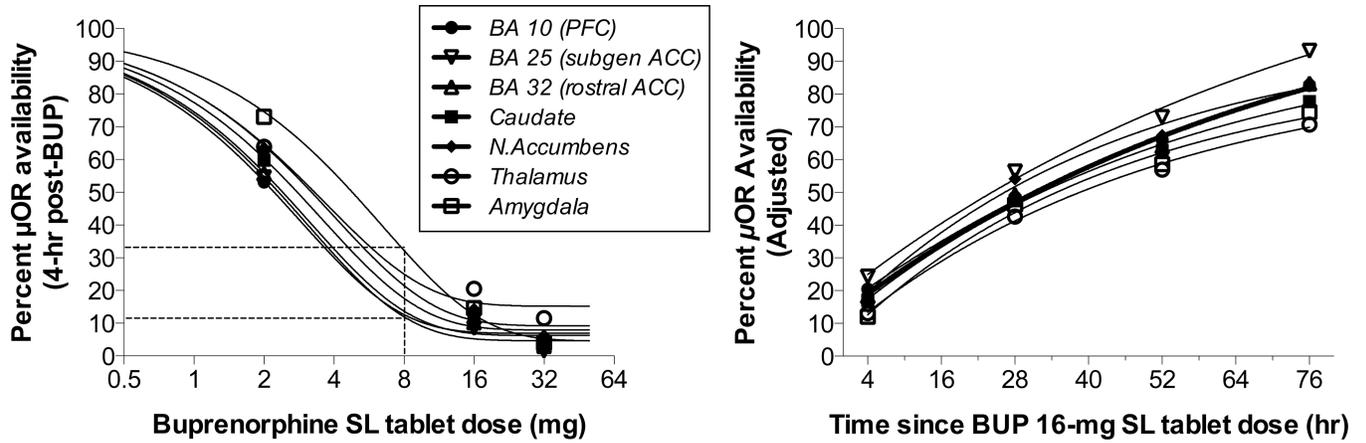
**Figure 1.**

<u>Left panel</u>: Non-linear regression curves on μOR availability (non-displaceable binding potential, $BP_{ND}$) fitted to brain region-of-interest (ROI) [$^{11}$C]-carfentanil PET data from Greenwald et al. (2003) for different buprenorphine (BUP) maintenance doses ($\log_2$ – linear plot) at 4-hr post-dose. The seven ROIs illustrated are: Brodmann area (BA) 10 in prefrontal cortex (PFC); BA 25 in subgenual anterior cingulate cortex (ACC); BA 32 in rostral ACC; caudate nucleus; nucleus accumbens; thalamus; and amygdala. Dashed lines indicate estimated range of μOR availability across ROIs for an 8-mg/day BUP dose (12 – 33%). See Table 1 for estimates of μOR availability (based on these curve fits) for BUP doses that were not experimentally studied. <u>Right panel</u>: Non-linear regression curves on regional μOR availability ($BP_{ND}$) fitted to [$^{11}$C]-carfentanil PET data from Greenwald et al. (2007) following discontinuation of BUP 16-mg/day maintenance. The Y-intercept values at the 4-hr time point for each ROI were adjusted to data for the identical condition (4 hr after BUP 16-mg) in the Greenwald et al. dose-response study (2003).

**BUP Maintenance Dose-Response**

**BUP Discontinuation Time Course**
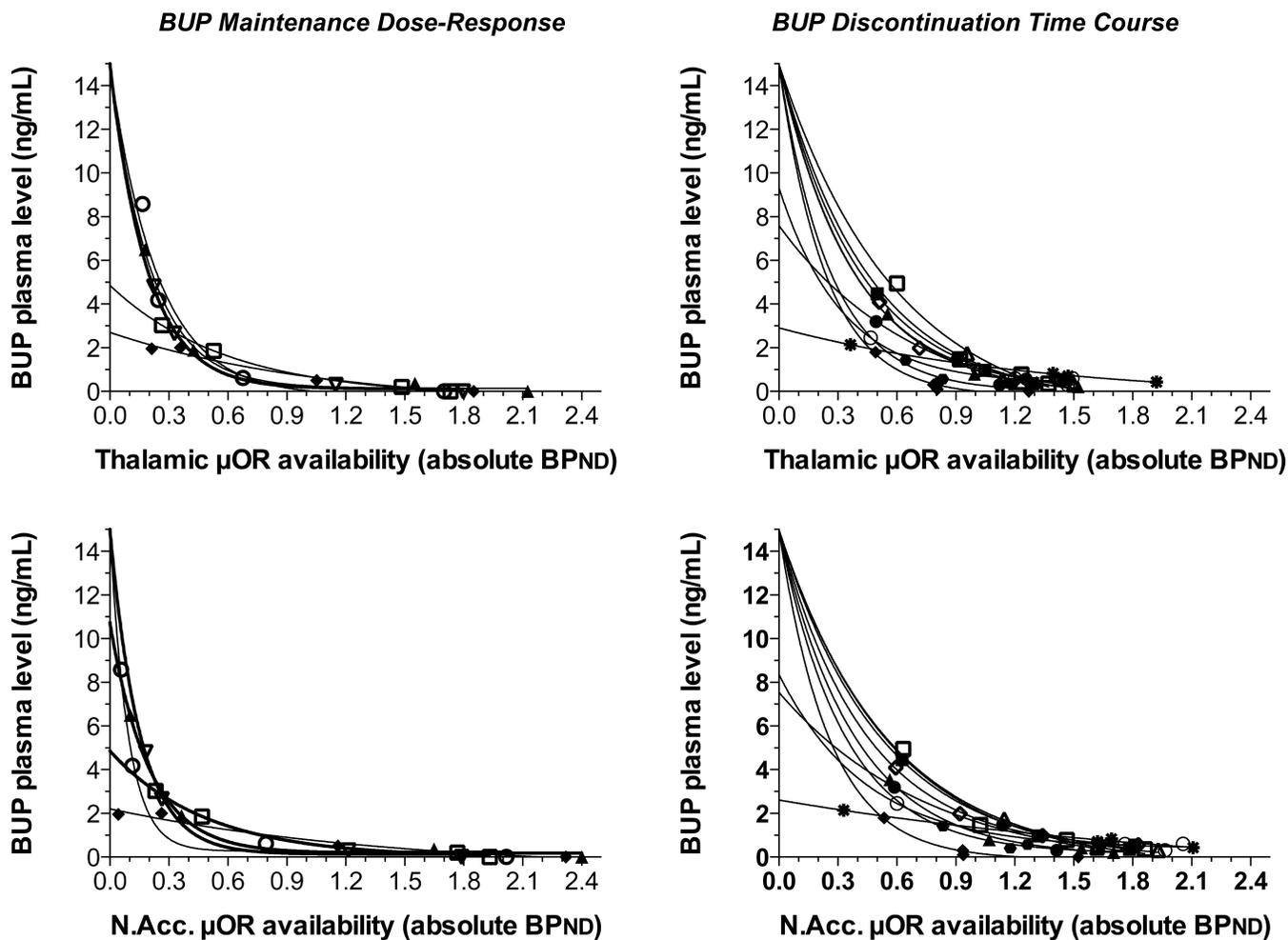


**Figure 2.**
Non-linear exponential correlations between BUP plasma concentrations and μOR availability (absolute $BP_{ND}$ values) in thalamus (upper row) and nucleus accumbens (N.Acc., lower row) across experimental conditions for all subjects in the BUP dose-response study ([Greenwald et al., 2003], left column) and the BUP discontinuation time-course study ([Greenwald et al., 2007], right column). In these plots, the maximum plasma concentration was constrained to 15 ng/mL for each subject.
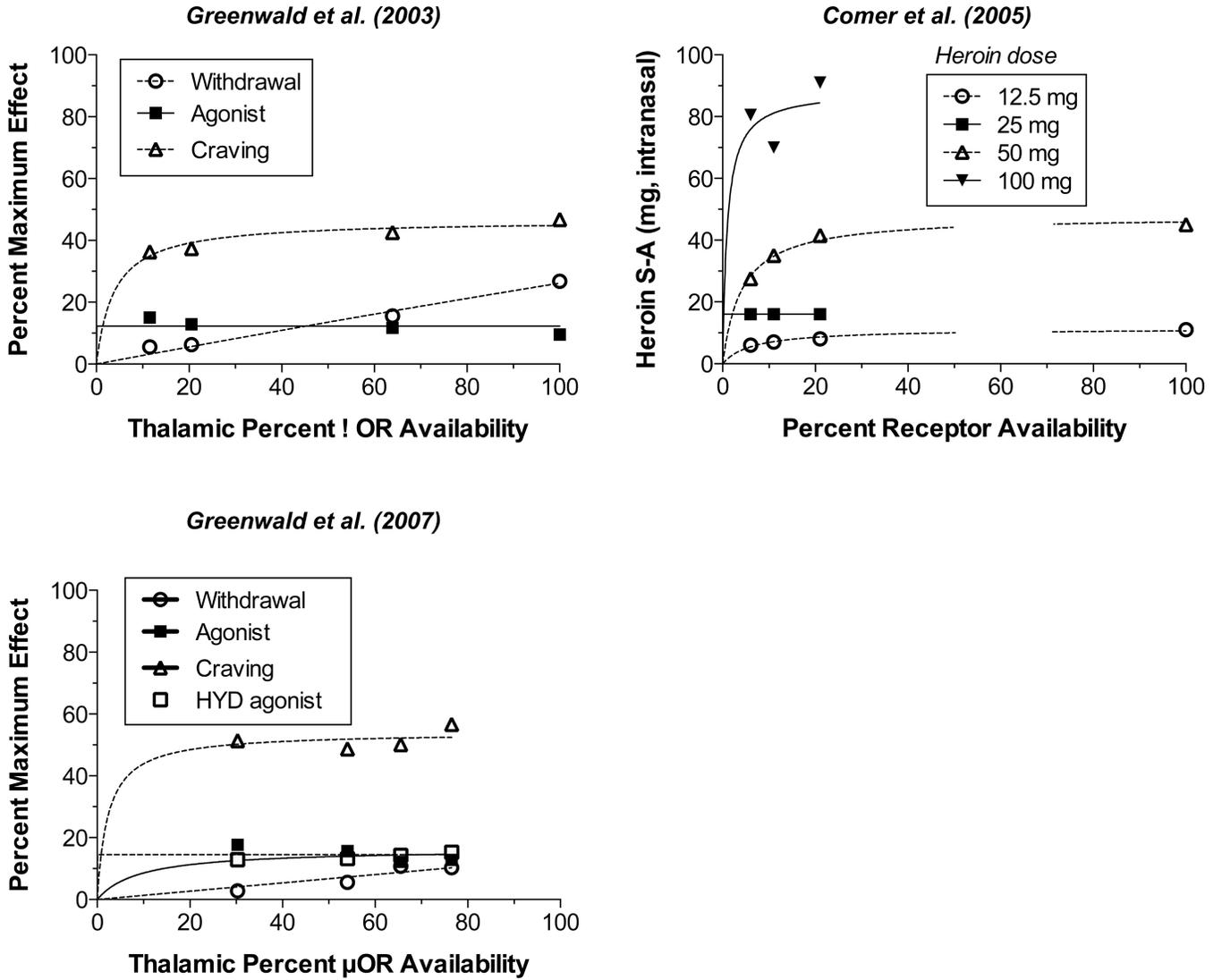
**Figure 3.**

Upper left: Non-linear hyperbolic regression curves fitted to mean µOR availability in thalamus (representative region of interest) and mean self-reported opioid withdrawal and agonist symptoms, and heroin craving (percent maximum effect on each scale) from Greenwald et al. (2003). Data points from left to right (low to high µOR availability) reflect responses at 4 hr after daily 32-mg, 16-mg, 2-mg, and 0-mg BUP maintenance doses. Upper right: Hyperbolic regression curves fitted to estimates of receptor availability (at 15 hr after BUP/NAL doses of 32-mg/8-mg, 8- mg/2-mg, and 2-mg/0.5-mg) for self-administration of various intranasal heroin doses from Comer et al. (2005). Data points to the right of the disconnected lines represent heroin self-administration (12.5 and 50 mg only) in a separate control group of opioid-detoxified volunteers, who are presumed to have nearly 100% µOR availability. Lower left: Hyperbolic regression curves fitted to mean µOR availability in thalamus (representative ROI) and self-reported opioid withdrawal and agonist symptoms, and heroin craving (percent maximum effect on each scale) during BUP maintenance, and response to cumulative hydromorphone 24-mg IM challenge, from Greenwald et al. (2007).

Data points from left to right (low to high μOR availability) reflect responses at 4 hr, 28 hr, 52 hr, and 76 hr after discontinuation of the BUP 16-mg maintenance dose.
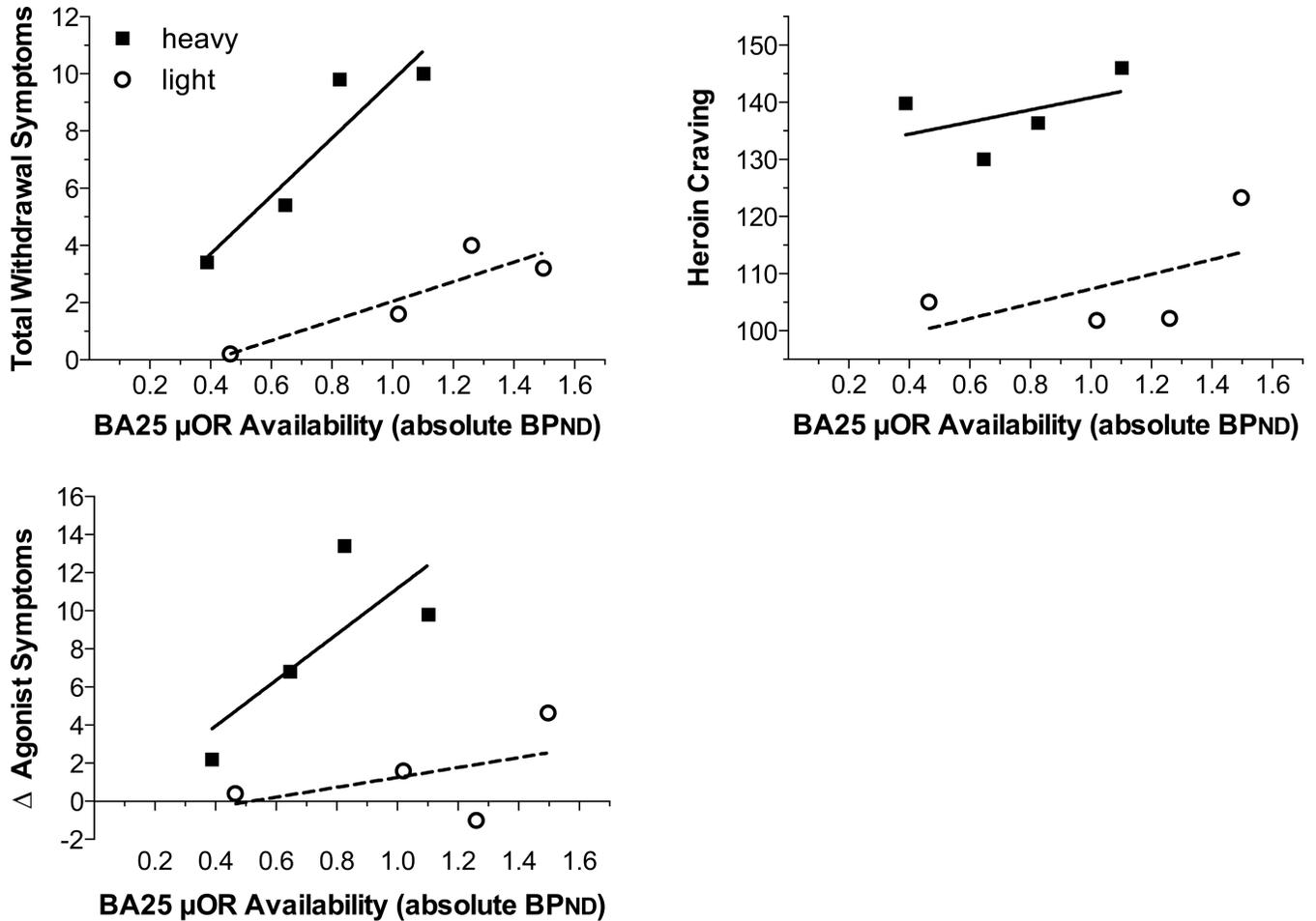
**Figure 4.**
Correlations between mean μOR availability in the subgenual anterior cingulate cortex (Brodmann area [BA] 25) and mean pharmacodynamic responses among heavier cigarette smokers ( 20 per day, *n*=5) and lighter cigarette smokers ( 15 per day, *n*=5) in the BUP time-course study (Greenwald et al., 2007). Upper left: Total opioid withdrawal symptom score. Upper right: Total heroin-craving score. Lower left: Change in total opioid agonist symptom score in response to cumulative 24-mg versus 0-mg hydromorphone injection.

**Table 1**

Estimated Percentages of Mu-Opioid Receptor Availability at Different Times Following Daily Sublingual Tablet Buprenorphine (BUP) Maintenance Doses in Heroin Dependent Volunteers

| Study Details | 1-mg | 2-mg | 4-mg | 8-mg | 12-mg | 16-mg | 24-mg | 32-mg |
|---|---|---|---|---|---|---|---|---|
| Comer et al. (2005)¶; n=7 heroin vs. n=8 controls; maintenance for 14 days at each dose, with tests at 15-hr post-BUP/NAL | | 21 – 31% | | 11 – 22% | | | | 6 – 12% |
| Greenwald et al. (2003)§; n=5; maintenance for 12 days at each dose, with tests at 4-hr post-BUP | (71 – 85%) | 53 – 72% | (36 – 55%) | (20 – 35%) | (13 – 24%) | 9 – 20% | (4 – 15%) | 2 – 12% |
| Greenwald et al. (2007)£; n=10; maintenance for 14 days minimum, with tests at: 4-hr post-BUP 28-hr post-BUP 52-hr post-BUP 76-hr post-BUP | | | | | | 27 – 31% 54 – 61% 65 – 75% 77 – 94% | | |

¶ Comer et al. reported the mean proportion of receptors (assumed to be µORs) remaining for each of four pharmacodynamic measures (intranasal heroin self-administration, and ratings of "good drug effect", "high", and "potent" following heroin). Ranges of values reflect estimated variation in mean percent receptor availability during buprenorphine/naloxone sublingual tablet dosing, relative to a different heroin-detoxified comparison group.

§ Ranges of values reflect variation in mean percent µOR availability across 7 brain regions of interest with high concentrations of µORs listed in Figure 1) during buprenorphine-mono sublingual tablet dosing, relative to the within-subject placebo control condition. Italicized µOR availability data from doses that were not directly studied reflect estimates from the non-linear curves in Figure 1.

£ Ranges of values reflect variation in mean percent µOR availability across 7 brain regions of interest in Greenwald et al. (2007), relative to the placebo condition in Greenwald et al. (2003), as a function of buprenorphine-mono sublingual tablet discontinuation time. Although the 4-hr discontinuation time in this study is identical to the Greenwald et al. study (2003) study, the percentage µOR availability differs because this study used a between-subject placebo control group whereas the earlier study used a within-subject placebo control condition. This discrepancy thus reflects differences between the two subject samples, and should lead to cautious interpretation of the absolute levels of µOR availability (but not its rate of decline).