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Review

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.
Methods: We review scientific data concerning BUP-induced changes in μOR availability and their relationship to clinical efficacy.
Results: Withdrawal suppression appears to require $\leq$50% μOR availability, associated with BUP trough plasma concentrations $\geq$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 $\geq$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.

Contents

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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 drugs (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).

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