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Discontinuation of Buprenorphine Maintenance Therapy: Perspectives and Outcomes ☆

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ABSTRACT

Buprenorphine maintenance therapy (BMT) is increasingly the preferred opioid maintenance agent due to its reduced toxicity and availability in an office-based setting in the United States. Although BMT has been shown to be highly efficacious, it is often discontinued soon after initiation. No current systematic review has yet investigated providers' or patients' reasons for BMT discontinuation or the outcomes that follow. Hence, provider and patient perspectives associated with BMT discontinuation after a period of stable buprenorphine maintenance and the resultant outcomes were systematically reviewed with specific emphasis on pre-buprenorphine-taper parameters predictive of relapse following BMT discontinuation. Few identified studies address provider or patient perspectives associated with buprenorphine discontinuation. Within the studies reviewed providers with residency training in BMT were more likely to favor long term BMT instead of detoxification, and providers were likely to consider BMT discontinuation in the face of medication misuse. Patients often desired to remain on BMT because of fear of relapse to illicit opioid use if they were to discontinue BMT. The majority of patients who discontinued BMT did so involuntarily, often due to failure to follow strict program requirements, and 1 month following discontinuation, rates of relapse to illicit opioid use exceeded 50% in every study reviewed. Only lower buprenorphine maintenance dose, which may be a marker for attenuated addiction severity, predicted better outcomes across studies. Relaxed BMT program requirements and frequent counsel on the high probability of relapse if BMT is discontinued may improve retention in treatment and prevent the relapse to illicit opioid use that is likely to follow BMT discontinuation.

1. Introduction

Opioid maintenance therapy (OMT) with methadone or buprenorphine is the current gold standard treatment for opioid use disorders (Mattick, Breen, Kimber, & Davoli, 2009; Mattick, Kimber, Breen, & Davoli, 2008; Thomas et al., 2014). In addition to reducing illicit opioid use (Mattick et al., 2008, 2009), OMT can be associated with reductions in mortality (Clausen, Anchersen, & Waal, 2008; Degenhardt et al., 2011), criminal activity (Bates & Pemberton, 1996; Dolan et al., 2005; Mattick et al., 2009), and high-risk behavior associated with transmission of human immunodeficiency virus (Gowing, Farrell, Bornemann, Sullivan, & Ali, 2011). Further, OMT increases quality of life (Giacomuzzi et al., 2003; Nosyk et al., 2011; Ponizovsky & Grinshpoon, 2007; Winklbaur, Jagsch, Ebner, Thau, & Fischer, 2008), and adherence to OMT significantly reduces overall healthcare costs (Tkacz, Volpicelli, Un, & Ruetsch, 2013).

Despite known efficacy of OMT, the majority of opioid-dependent patients in the United States are not currently being treated with OMT (Kleber, 2008; SAMHSA, 2011). Financial barriers, restrictive legislation, patient preference, physician ambivalence and non-evidence-based approaches to addiction treatment all contribute to low rates of OMT (Appel, Ellison, Jansky, & Oldak, 2004; Gryczynski et al., 2013; Nosyk et al., 2013), and these rates persist despite the significantly enhanced availability of OMT afforded through the Drug Addiction Treatment Act of 2000, which allows for buprenorphine to be prescribed in a less restrictive office-based setting (Jaffe & O'Keeffe, 2003).

Buprenorphine OMT (BMT), because of its blunted toxicity (Walsh, Preston, Bigelow, & Stitzer, 1995; Walsh, Preston, Stitzer, Cone, & Bigelow, 1994) and increased accessibility (Jaffe & O'Keeffe, 2003), offers some advantages to methadone OMT. Buprenorphine's unique partial mu agonist pharmacology and extended receptor occupation time lend to a comparatively less severe withdrawal syndrome (Tompkins, Smith, Mintzer, Campbell, & Strain, 2013; Westermeyer & McCance-Katz, 2012). A less severe withdrawal syndrome could potentially reduce relapse propensity, a hypothesis supported by the observation that longer OMT tapering procedures result in better outcomes (Dunn, Sigmon, Strain, Heil, & Higgins, 2011; Nosyk et al., 2012; Sigmon et al., 2013). Although, this is not always the case (Ling et al., 2009). In light of this less severe withdrawal syndrome, the approval of

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buprenorphine was heralded by enthusiasm for improved outcomes following detoxification (National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction, 1998) apropos of the high relapse rates known to accompany discontinuation of methadone OMT (Amato et al., 2013). Unfortunately, buprenorphine detoxification has not lead to increased rates of abstinence following withdrawal (Dunn et al., 2011; Horspool, Seivewright, Armitage, & Mathers, 2008), and as such, the practice of BMT discontinuation may be perpetuated by the provider expectation that abstinence is likely to follow (Newman, 2009). Furthermore, some providers may feel that abiding by program rules is necessary for BMT success to the extent that BMT is discontinued for rule infractions; however, patients often find benefit in remaining in programs despite failure to achieve program-imposed criteria (Mitchell et al., 2011).

In addition to factors associated with BMT treatment providers, patient preference is also a major factor in the discontinuation of BMT. Although patient satisfaction with buprenorphine treatment is high (Barry et al., 2007; Ling, Hillhouse, Ang, Jenkins, & Fahey, 2013), many patients ask to discontinue BMT after several months of treatment (Kleber, 2007), a preference that could be driven in part by perceived low probability of relapse (Bailey, Herman, & Stein, 2013). Hence, it is essential that both physician and patient harbor realistic, evidence-based expectations of outcomes following discontinuation of BMT; however, current systematic reviews of BMT discontinuation have focused on its use in detoxification protocols (Dunn et al., 2011; Horspool et al., 2008) and no current reports could be found that link perspectives of patients or providers with outcomes. Here we bridge patient and provider perspectives of BMT with rates of abstinence following discontinuation of BMT by systematically reviewing patient and provider perspectives that may lead to BMT discontinuation after a period of stable BMT and the outcomes that follow.

2. Methods

2.1. Search strategy and inclusion criteria

Potential studies were identified using Boolean search strings within the Pubmed database. All searches were limited to articles available in English. Studies that included patient perspectives on buprenorphine were identified using the following string: buprenorphine AND patients AND (preference* OR perspective* OR attitude* OR satisfaction OR reason*) where * denotes a wildcard. This search was most recently conducted on September 24, 2014. Studies of patient perspectives on buprenorphine were included if they quantitatively assessed patients' subjective evaluations of buprenorphine as a treatment for opioid dependence. Further, only studies that linked these subjective evaluations with decisions to continue or discontinue BMT were included. Citations within identified articles were screened for identification of additional references.

Studies that included provider perspectives on buprenorphine were identified using the following string: buprenorphine AND (physician* OR provider* OR counselor* OR psychiatrist*) AND (preference* OR perspective* OR attitude* OR satisfaction OR reason*). This search was most recently conducted on September 27, 2014. Studies of provider perspectives on buprenorphine were included if they quantitatively assessed providers' subjective evaluations of buprenorphine as a treatment for opioid dependence. Further, only studies that linked these subjective evaluations with decisions to continue or discontinue BMT were included. Citations within identified articles were screened for identification of additional references.

Studies of cessation of buprenorphine maintenance were identified using the following search string: buprenorphine AND (detoxification OR taper OR discontinue OR cessation OR withdrawal). Search results were then limited to clinical trials. References of identified articles were also searched for additional reports that met review criteria. This search was most recently conducted on September 24, 2014. Articles were included if participants were opioid-dependent and maintained on a buprenorphine-containing medication for at least 14 days before starting medication taper. Notably, 14 days does not reflect what most providers/investigators would consider to be a maintenance period. We chose this time period for 2 reasons: (1) It is the typical time frame required to titrate a patient to a stable maintenance dose (Chiang & Hawks, 2003); thus, shorter time periods would not allow us to consider the pre-taper maintenance dose. (2) Our goal was to determine typical outcomes after cessation of buprenorphine maintenance therapy and relate these outcomes to pre-taper variables. However, very few studies have maintained patients on buprenorphine and studied outcomes following cessation. Thus, to include enough studies to consider pre-taper associations with outcomes, we required a very broad quantitative definition of maintenance period. In addition to the requirement of a minimum 14 day maintenance period, only studies that reported urine drug screens for opioids at least 1 month following completion of the taper were included, ensuring final outcome measures occurred outside of the withdrawal epoch.

2.2. Analysis

Study outcomes were analyzed as intention-to-treat with the initial patient sample size defined as the number of patients retained at the start of the taper. Primary outcome was defined as the proportion of participants retained in the study at the start of the tapering procedure who tested negative for opioids via urinalysis at least 1 month after buprenorphine taper cessation. One study reported a urinalysis-based outcome, and study authors indicated that it approximated a simple urinalysis outcome (Weiss et al., 2011). Hence, we included reported outcomes of Weiss et al. as if they were simple urinalysis outcomes; a recent buprenorphine-focused review made a similar approximation for this study (Thomas et al., 2014). All missing urinalysis data were assumed to be opioid-positive. Pre-taper parameters reported to predict opioid urinalysis 1 month or more after taper cessation within included studies were compared across studies. Statistical analyses were performed using IBM SPSS Statistics (Version 19). Weighted-least-squares regression with weights determined by study sample size was used to relate potential predictors to outcome. Because of the low number of studies included, multivariate comparisons were not performed.

3. Results

3.1. Patient perspectives of buprenorphine

The search for studies that quantitatively assessed patient perspectives associated with BMT discontinuation most recently (September 24, 2014) returned 203 possible studies. After screening all article titles and abstracts for relevancy, 11 articles were screened in their entirety. One of these articles was excluded, because although it quantified patients' reasons for ceasing maintenance therapy, 90% of these patients were maintained on methadone and no comparison was performed to determine if the distribution of reasons was similar for both buprenorphine and methadone (Awgu, Magura, & Rosenblum, 2010). One article was excluded on the grounds that it did not quantify reasons patients discontinued treatment (Guichard, Lert, Brodeur, & Richard, 2007). Seven of these articles were excluded on the basis that they did not include patients' reasons for discontinuing BMT. Two studies of patient perspectives on buprenorphine met all criteria (Gryczynski et al., 2013; Winstock, Lintzeris, & Lea, 2011). Screening citations within these 2 articles did not result in identification of additional relevant references. These studies are summarized here in chronological order with emphasis on reasons patients decided to discontinue BMT as well as the limitations present in each study.

Winstock et al. (2011) surveyed 145 patients from public clinics in Sydney, Australia who were maintained on either buprenorphine ($n = 56$) or methadone ($n = 89$). The purpose of the survey was to