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## Journal of Addictive Diseases

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/wjad20>

### Effect of Buprenorphine Dose on Treatment Outcome

Ayman Fareed MD<sup>a</sup>, Sreedevi Vayalapalli MD<sup>a</sup>, Jennifer Casarella MD<sup>a</sup> & Karen Drexler MD<sup>a</sup>

<sup>a</sup> Emory University, School of Medicine, Atlanta VA Medical Center, Decatur, Georgia, USA

Available online: 05 Dec 2011

To cite this article: Ayman Fareed MD, Sreedevi Vayalapalli MD, Jennifer Casarella MD & Karen Drexler MD (2012): Effect of Buprenorphine Dose on Treatment Outcome, *Journal of Addictive Diseases*, 31:1, 8-18

To link to this article: <http://dx.doi.org/10.1080/10550887.2011.642758>

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## ARTICLES

### EFFECT OF BUPRENORPHINE DOSE ON TREATMENT OUTCOME

Ayman Fareed, MD, Sreedevi Vayalapalli, MD, Jennifer Casarella, MD, Karen Drexler, MD

Emory University, School of Medicine, Atlanta VA Medical Center, Decatur, Georgia, USA

The goal of this meta-analysis is to provide evidence based information about proper dosing for buprenorphine maintenance treatment to improve treatment outcome. To be selected for the review and inclusion in the meta-analysis, articles had to be randomized, controlled, or double-blind clinical trials, with buprenorphine as the study drug; the length of buprenorphine maintenance treatment had to be 3 weeks or longer; doses of buprenorphine had to be clearly stated; outcome measures had to include retention rates in buprenorphine treatment; outcome measures had to include illicit opioid use based on analytical determination of drugs of abuse in urine samples as outcome variables; and outcome measures had to include illicit cocaine use based on analytical determination of drugs of abuse in urine samples as outcome variables. Twenty-nine articles were excluded because they did not meet the inclusion criteria. The authors present the results of 21 articles that met inclusion criteria. The higher buprenorphine dose (16–32 mg per day) predicted better retention in treatment compared with the lower dose (less than 16 mg per day) ( $P = .009$ ,  $R^2$  adjusted = 0.40), and the positive urine drug screens for opiates predicted dropping out of treatment ( $P = .019$ ,  $R^2$  Adjusted = 0.40). Retention in treatment predicted less illicit opioid use ( $P = .033$ ,  $R^2$  Adjusted = 0.36), and the positive urine drug screens for cocaine predicted more illicit opioid use ( $P = .021$ ,  $R^2$  Adjusted = 0.36). Strong evidence exists based on 21 randomized clinical trials that the higher buprenorphine dose may improve retention in buprenorphine maintenance treatment.

**KEYWORDS.** Buprenorphine, dose, treatment outcome

## INTRODUCTION

Buprenorphine has many qualities that make it an effective treatment for opioid dependence. It is a partial mu receptor agonist that can hinder priming for opioids and is safer compared with other full opioid receptor agonists.<sup>1</sup> It has kappa receptor antagonistic properties that may improve dysphoric mood in this population.<sup>2</sup> Buprenorphine is a promising and practical option for managing opioid addiction in patients receiving long-term opioid maintenance treatment, particularly for those who may not qualify for or desire methadone

maintenance treatment. A recent multicenter study reported promising results for using buprenorphine in treatment of opioid dependent pregnant women.<sup>3</sup> However, methadone is still the standard treatment for this population.<sup>3</sup> Buprenorphine induction is easy—even for physicians with limited experience with opioid maintenance treatment.<sup>4</sup>

Several studies reported that buprenorphine is a safe and effective medication for office-based treatment of opiate dependence.<sup>5–8</sup> Most of the initial studies reported that lower doses of buprenorphine<sup>9–12</sup> (8 mg or

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Address correspondence to Ayman Fareed, MD, Department of Psychiatry, Emory University, School of Medicine, Atlanta VA Medical Center 116A, 1670 Clairmont Road, Decatur, GA 30033. E-mail: ayman.fareed@va.gov

less per day) were not as effective as higher buprenorphine doses (8–16 mg per day) or methadone.<sup>13–16</sup> Illicit opiate use, as measured by urine drug screens and dropping out of treatment, were higher for the participants who received lower doses of buprenorphine in those studies. These data have led to studying the safety and efficacy of higher doses of buprenorphine. More recent studies reported that a buprenorphine dosage ranging from 16 to 32 mg per day is safer and more effective than lower doses in reducing illicit use and craving for opioids.<sup>17–19</sup> Despite the current agreement that higher doses of buprenorphine may offer better treatment outcome compared with lower doses, limited information exists about the treatment outcome for the higher dose range (16 to 32 mg per day) compared with the lower dose range (less than 16 mg per day). The buprenorphine's insert reports that a dose between 12–16 mg per day is the target for buprenorphine maintenance treatment.<sup>20</sup> This dose may block the opioid withdrawal syndrome, but some patients may continue to use illicit opioids in this range. The severity and duration of opioid addiction may reflect the need for a higher or lower buprenorphine dose to achieve an adequate mu receptor blockade, reduce the subjective opioid craving, and prevent relapse on opioids. Comorbid chronic pain may also explain the need to be on a higher buprenorphine dose. A recent multicenter study done by the National Institute of Drug Abuse clinical trial network reported that the presence of pain predicts buprenorphine dose levels in opioid-dependent patients. They added that patients with pain have opioid use outcomes comparable with those without pain but require higher buprenorphine doses.<sup>21</sup>

Buprenorphine has a ceiling effect, i.e., the linear relationship between the dose and the effect disappears at doses greater than 24 mg per day.<sup>1</sup> The ceiling effect reduces the risk for overdose. Therefore, doses greater than 24 to 32 mg per day would not add to its respiratory depressant effect.<sup>22–24</sup> Some studies reported an increased risk for respiratory depression and death due to mixing buprenorphine with other central nervous system depressants such as ben-

zodiazepines and alcohol.<sup>25,26</sup> Therefore, patients on the high dose range should be monitored for the increased risk of overdose due to the drug-drug interaction with other central nervous system depressants. Achieving the best treatment outcome without jeopardizing safety should be the goal for office-based buprenorphine treatment.

We conducted a literature review and meta-analysis to compare the treatment outcome for the higher dose range of buprenorphine (16 mg or greater per day) to the lower dose range (less than 16 mg per day). Our goal was to provide evidence-based information about proper dosing for buprenorphine maintenance treatment to improve treatment outcome.

## METHODS

### Literature Search

Studies eligible for inclusion in the review were retrieved through a computer-based MEDLINE and PsycINFO search from 1960 to December 2010 using the major medical subject headings *buprenorphine* (all fields). Articles in English language only were included. Additional reports were identified from the references lists of retrieved articles, as well as by manual review of the tables of contents of journals on drug of abuse included in the psychiatry and substance abuse subject category listing 2010 of the Journal Citation Reports. Abstracts of medical meetings were excluded.

### Selection, Extraction, and Collection of Data

More than 2120 abstracts were reviewed for selection of studies included in the analysis (Figure 1). Fifty studies were selected for the review, and three investigators performed the review. We (AF, SV, and JC) created a data extraction form to collect data from each study and to reduce interrater selection bias. The form included information about the author and year of publication, type of the study, number of participants, buprenorphine dose, duration of the study, percentage of retention for

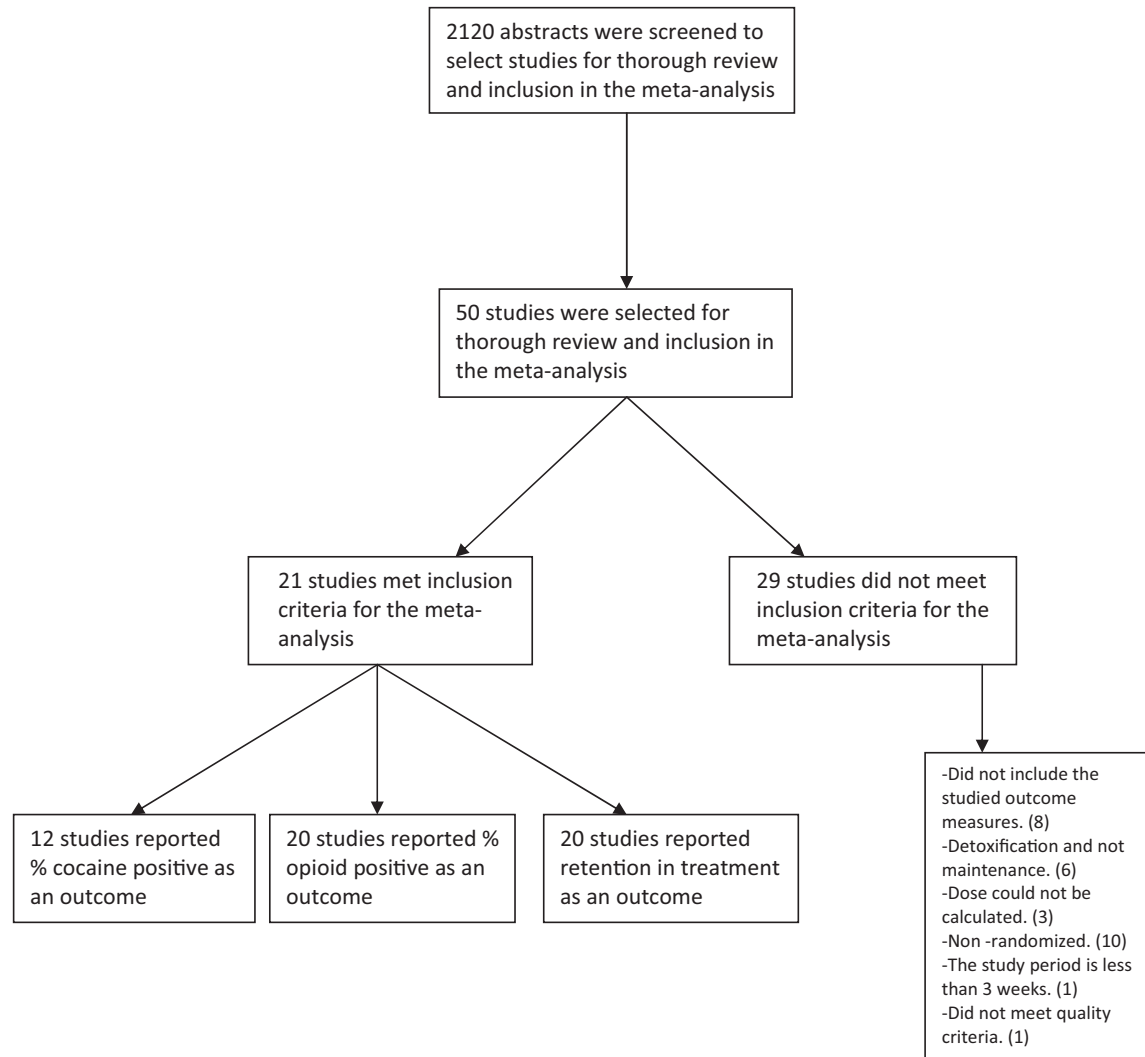


FIGURE 1. Scheme of the selection of the studies included in the meta-analysis.

participants in the study, percentage of positive urine drug screens for opioids and cocaine, summary, and conclusions of the study. One investigator (AF) performed a second review for the selected studies to ensure accuracy of the retrieved information.

To be selected for the study, articles had to fulfill and provide the following information:

1. Randomized, controlled, or double-blind clinical trials with buprenorphine as the study drug. We used the Jadad's scale to evaluate the quality of the selected studies.<sup>27</sup> The scale is widely used to assess the quality of clinical trials. It is a five-question scale

to assess randomization, blindness, and description of participant withdrawals. Studies with a score of 3 or more were included in the meta-analysis.

2. Length of buprenorphine maintenance treatment for 3 weeks or longer.
3. Doses of buprenorphine were clearly stated. For flexible dosing studies, we used the average dose stated, or if there was a range, we used the upper limit of the range for inclusion in the analysis.
4. Outcome measures include retention rates in buprenorphine treatment. Percentage of completers was retrieved or calculated from text, tables or graphs.

5. Outcome measures included illicit opioid use based on analytical determination of drugs of abuse (natural and synthetic opioids) in urine samples as outcome variables. Percentage of positive urine opioid screens was retrieved or calculated from text, tables, or graphs.
6. Outcome measures include illicit cocaine use based on analytical determination of drugs of abuse in urine samples as outcome variables. Percentage of positive urine cocaine screens was retrieved or calculated from text, tables, or graphs.
7. Studies in which opioid detoxification was a main objective were excluded.

### Main Outcome Measure

1. Effect of buprenorphine dose, duration of treatment, illicit opioid use, and cocaine use as measured by urine drug screens on retention in treatment.
2. Effect of buprenorphine dose, duration of treatment, retention in treatment, and cocaine use on illicit opioid use.

### Statistical Analyses

We used the Student's *t* test to compare the characteristics of participants who received higher dose (16 mg or greater per day) to those who received lower dose (less than 16 mg per day). For the first outcome measure, we performed a univariate logistic regression analysis to determine whether any of the following factors could be used to predict retention in treatment. These factors include buprenorphine dose, duration in treatment, opioid use, and cocaine use. Factors that showed a significant prediction of retention in treatment were then included in a multivariate analysis to determine whether they will continue to show significant prediction of retention.

For the second outcome measure, we performed a univariate logistic regression analysis to determine whether any of the following factors could be used to predict retention in treatment. These factors include buprenorphine dose, duration in treatment, retention in treatment, and cocaine use. Factors that

showed significant prediction of illicit opiate use were then included in a multivariate analysis to determine whether they will continue to show significant prediction of illicit opiate use. A *P* value < .05 was considered statistically significant. We used the SPSS version 16.0 (SPSS, Inc, Chicago, IL) software for statistical analysis.

## RESULTS

A total of 50 articles were included in the review, and 21 articles were eligible for inclusion in the meta-analysis. Table 1 presents the studies that were included in the meta-analysis. A total of 2703 participants were included in our study. We categorized the studies into two groups. The higher dose group is used a buprenorphine dose of 16 mg or more per day. The lower dose group used a buprenorphine dose of less than 16 mg per day. Table 2 presents the *t* test comparison between the higher and lower dose groups. We compared daily buprenorphine dose used, duration of the study in weeks, retention in treatment (percentage of participants completed the study), percentage of positive urine opioid, and cocaine drug screens. The higher dose group showed significantly better retention in treatment compared with the lower dose group (69% vs. 51%,  $t = 3.06$ ,  $df = 19$ ,  $P = .006$ ).

### Effect of Buprenorphine Dose, Duration of Treatment, Illicit Opiate Use, and Cocaine Use on Retention in Treatment

The univariate analysis of predictor variables for retention in treatment showed that the buprenorphine dose ( $P < .00001$ ,  $R^2 = 0.44$ ) and urine drug screens for opiates ( $P = .0003$ ,  $R^2 = 0.39$ ) were significant predictors for retention status. The higher buprenorphine dose predicted better retention in treatment compared with the lower dose, and the positive urine drug screens for opioids predicted dropping out of treatment.

The variables that showed significant prediction of retention status (buprenorphine dose and urine drug screens for opioids) were

**TABLE 1.** Randomized Studies Included in the Analysis

Author & Year	Number of subjects	Buprenorphine daily dose	Duration in weeks	Retention (% completed)	UDS-opiates (% positive)	UDS-cocaine (% positive)
Springer et al. 2010 <sup>46</sup>	23	9.5	12	74%	25%	29%
Chakrabarti et al. 2010 <sup>21</sup>	69	16	12	72%	17%	
Lucas et al. 2010 <sup>53</sup>	41	16	48	74%	44%	51%
Woody et al. 2008 <sup>49</sup>	74	24	12	70%	46%	
Kakko et al. 2007 <sup>19</sup>	17	29.6	24	77%	20%	
Fiellin et al. 2006 <sup>52</sup>	166	16–24	24	43%	59%	27%
Sullivan et al. 2006 <sup>47</sup>	16	16–24	12	81%	23%	33%
Marsch et al. 2005 <sup>54</sup>	134	12–16	24	69%	28%	
Montoya et al. 2004 <sup>55</sup>	46	16	10	61%	52%	60%
	43	8	10	45%	52%	66%
	44	8	10	43%	52%	64%
	46	2	10	45%	62%	70%
Mattick et al. 2003 <sup>12</sup>	200	11.2	13	50%	52%	
Fudala et al. 2003 <sup>17</sup>	472	16–24	24	48%		
Ahmadi 2003 <sup>50</sup>	41	1	18	29%		
		3	18	46%		
		8	18	68%		
Amass et al. 2001 <sup>51</sup>	46	8	3	28%	43%	17%
Amass et al. 2000 <sup>5</sup>	26	8	3	54%	56%	36%
Johnson et al. 2000 <sup>18</sup>	55	8–16	17	58%	62%	70%
Schottenfeld et al. 2000 <sup>56</sup>	92	16	12	74%	58%	47%
Ling et al. 1998 <sup>16</sup>	181	16	16	61%	62%	
Schottenfeld et al. 1997 <sup>44</sup>	29	12	24	55%	58%	66%
	29	4	24	34%	77%	79%
	188	8	16	52%	67%	
	182	4	16	51%	71%	
	185	1	16	40%	81%	
Ling et al. 1996 <sup>11</sup>	75	8	26	35%	55%	
Strain et al. 1996 <sup>48</sup>	84	9	16	51%	39%	61%
Johnson et al. 1995 <sup>7</sup>	99	8	11	57%	64%	45%

included in a multivariate analysis. Table 3 shows the results of the multivariate analysis for retention in treatment. Buprenorphine dose ( $P = .009$ ) and urine drug screens for opiates ( $P = .019$ ) continued to show significant correlation with retention in treatment ( $R^2$  adjusted = 0.40).

### Effect of Buprenorphine Dose, Duration of Treatment, Retention in Treatment, and Cocaine Use on Illicit Opioid Use

The univariate analysis of predictor variables for illicit opiate use showed that the buprenorphine dose ( $P = .0019$ ,  $R^2 = 0.29$ ), retention in treatment ( $P = .0003$ ,  $R^2 = 0.34$ ), and urine drug

**TABLE 2.** Student's *t* Test Comparison of Studies that Used Buprenorphine Higher Dose versus Lower Dose

Characteristics of high dose and low dose groups	Higher dose (16 mg daily and above)	Lower dose (below 16 mg daily)	<i>t</i> (df)	<i>P</i>
Number of studies	12	10		
Average buprenorphine dose (SD)	21 (5.1)	7.4 (3.3)	7.62 (20)	<b>&lt; .0001</b>
Average duration, wks (SD)	19.8 (12.2)	12.8 (6)	1.79 (20)	.088
Average retention,% completed (SD)	69% (12)	51% (14)	3.06 (19)	<b>.006</b>
Average UDS-opiates,% positive (SD)	41% (16)	47% (13)	0.96 (17)	.35
Average UDS-cocaine,% positive (SD)	44% (13)	49% (20)	0.49 (11)	.64

UDS = urine drug screens; SD = standard deviation. Bolded data indicate statistical significance.

**TABLE 3.** Multiple Regression Analysis of Predictor Variables for Retention in Treatment

Variables	Coefficient	Standard error	<i>t</i>	<i>P</i>	R <sup>2</sup>	R <sup>2</sup> adjusted for degrees of freedom
Buprenorphine dose	0.89	0.35	2.54	<b>.009</b>	0.47	0.40
UDS-opiates	-0.33	0.15	2.20	<b>.019</b>		

UDS = urine drug screens. Bolded data indicate statistical significance.

screens for cocaine ( $P = .014$ ,  $R^2 = 0.30$ ) were significant predictors for illicit opioid use. The higher buprenorphine dose predicted less illicit opioid use compared with the lower dose; retention in treatment also predicted less illicit opioid use, and the positive urine drug screens for cocaine predicted more illicit opioid use.

The variables that showed significant prediction of illicit opioid use status (buprenorphine dose, retention in treatment, and urine drug screens for cocaine) were included in a multivariate analysis. Table 4 shows the results of the multivariate analysis for illicit opioid use. Buprenorphine dose ( $P = .32$ ) did not continue to show significant correlation with illicit opioid use. Retention in treatment ( $P = .033$ ) and urine drug screens for cocaine ( $P = .021$ ) continued to show significant correlation with illicit opioid use ( $R^2$  adjusted = 0.36).

## DISCUSSION

In this metaanalysis, the illicit opioid use as evidenced by the percentage of positive urine drug screens predicted dropping out of treatment and retention in treatment predicted reduction in illicit opioid use. Several studies confirmed the relationship between the retention in treatment and reduction of illicit drug use in general. Retention in buprenorphine maintenance treatment is associated with better treatment outcomes and dropping out is asso-

ciated with poor treatment outcomes. Some studies reported that retention in buprenorphine maintenance treatment was associated with reduced risk for overdose mortality, and dropping out increases that risk.<sup>28,29</sup> Other studies reported that retention in buprenorphine maintenance treatment could improve other outcomes, such as the spread of HIV and hepatitis, criminal activities, and employment.<sup>30-35</sup> Our metaanalysis reported that the buprenorphine dose range of 16 mg or more per day is associated with significantly improved retention in buprenorphine maintenance treatment compared with lower doses. Therefore, buprenorphine dose may play an important role in improving treatment outcomes for buprenorphine maintenance treatment. Clinicians need to consider using the higher dose range (more than 16 mg per day) for patients who would not respond to the lower dose range, especially if they express intense opioid craving.

Craving is a subjective phenomenon. Some clinicians may be reluctant to consider dose titration based on a subjective symptom due to the risk of buprenorphine diversion.<sup>36,37</sup> Diversion could be associated with the higher dose range, especially for an office-based model of buprenorphine maintenance treatment. Some patients, who are on the higher dose range, may need to be monitored for diversion. A urine confirmation test for

**TABLE 4.** Multiple Regression Analysis of Predictor Variables for Illicit Opiate Use

Variables	Coefficient	Standard error	<i>t</i>	<i>P</i>	R <sup>2</sup>	R <sup>2</sup> adjusted for degrees of freedom
Buprenorphine dose	-0.27	0.58	0.47	.32	0.49	0.36
Retention in treatment	-0.46	0.23	2.02	<b>.033</b>		
UDS-cocaine	0.39	0.17	2.26	<b>.021</b>		

UDS = urine drug screens. Bolded data indicate statistical significance.

buprenorphine/norbuprenorphine could be ordered if there is a suspicion of diversion or to confirm patient's compliance with treatment before considering dose titration. The cost and lack of availability of this test in some laboratories might be barriers for some patients and treatment providers. Medication cost could also be a barrier for some patients, which deters clinicians from considering the higher dose range. This practice may increase the risk for relapse and dropping out of treatment, which may increase the overall cost. Clinicians need to consider the pros and cons of the higher dose range to help them make a good clinical decision about buprenorphine dosing.

Maintenance treatment for illicit opioid addicts was originally studied, and most of the earlier studies performed have had illicit opioid (i.e., heroin) addicts as study participants. However, the treatment has expanded over the years to include prescribed opioids addicts. In United States, a typical patient in an office-based buprenorphine maintenance treatment is not a hardcore, heavy street drug (i.e., heroin) addict, but rather an illicit prescribed opioid user. This will most certainly blur the picture of what is a high dose. Although a typical buprenorphine dose in the United States is 16 mg per day, the doses are higher in countries that exclusively treat illicit heroin addicts. For instance, in Sweden the mean buprenorphine dose is approximately 24 mg per day; in one of the studies included in this meta-analysis, the study participants were hardcore heroin addicts in urban Sweden, with a history of 10 years of intravenous heroin use; the mean buprenorphine dose in this specific population reached approximately 30 mg of buprenorphine per day.<sup>19</sup>

While the earlier meta-analyses have come to the same conclusion as this one, it may not be accurate to write, as for instance in the latest Cochrane review<sup>38</sup>, that 16 mg of buprenorphine is a high dose. Defining a dose as high or low might be arbitrary. For example, 16 mg may be considered high for certain patients but low for others. Defining a dose range as higher or lower may reflect more accurate description of the patient's dose. Patient with long history of intravenous heroin use or patients with

comorbid chronic pain may need to be on the higher dose range (i.e., 16 mg or more per day) to achieve good treatment outcomes. Patients with less addiction severity (e.g., prescribed opioids abusers) may need to be on the lower dose range (i.e., less than 16 mg per day).

Concerns about safety may have led to buprenorphine induction being introduced to the field in a methadone way, which is to go slow and stay low. Several authors have pointed out that this has contributed to problems with attrition during induction and poor treatment outcomes.<sup>11,12,39-41</sup> The dose titration during buprenorphine induction needs to be individualized to improve treatment outcome without jeopardizing safety. Rapid dose titration may be warranted for some patients who are in acute withdrawal and at risk of relapse on illicit opioids. Slow titration may be needed for patients who are not in acute withdrawal but still at risk of relapse, e.g., being discharged from prisons or abstinent-based residential treatment programs.

The meta-analysis also reported that illicit cocaine use predicted illicit opioid use. Comorbid cocaine disorders may be associated with poor outcomes, such as illicit opioid use, if they were not addressed early in treatment. Therefore, it is important to address the cocaine and other drug comorbidities early in treatment. Offering a referral to evidence-based psychotherapeutic intervention designed for treatment of drug addiction (e.g., cognitive behavior therapy or contingency management) might be appropriate for this patient population.<sup>42-45</sup> Moreover, a higher level of care such as intensive outpatient or residential treatment may be needed for some patients with comorbid drug addiction. Buprenorphine maintenance treatment programs may vary in offering ancillary services such as evidence-based psychotherapy and resources to refer patients to a higher level of care if needed. Some programs may lack human and financial resources that contribute to their inability to meet care standards. Therefore, retention in treatment may vary across buprenorphine maintenance treatment programs.

Some of the outcome measures investigated are dependent on the dose, but this may be



confounded by speed in the induction and different patient populations. These factors were not mentioned or were difficult to analyze in most of the studies we reviewed for inclusion in the meta-analysis. Therefore, our results might be biased because we did not include other confounding factors in the analysis.

The higher buprenorphine dose predicted better retention in treatment compared with the lower buprenorphine dose, and the positive urine drug screens for opioids predicted dropping out of treatment. Retention in treatment predicted less illicit opioid use, and the positive urine drug screens for cocaine predicted more illicit opioid use. There is strong evidence based on 21 randomized clinical trials that the higher buprenorphine dose may improve retention in buprenorphine maintenance treatment.

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