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## The Association between Outpatient Buprenorphine Detoxification Duration and Clinical Treatment Outcomes: A Review

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### Abstract

**Background**—The association between buprenorphine taper duration and treatment outcomes is not well understood. This review evaluated whether duration of outpatient buprenorphine taper is significantly associated with treatment outcomes.

**Methods**—Studies that were published in peer-reviewed journals, administered buprenorphine as an outpatient taper to opioid-dependent participants, and provided data on at least one of three primary treatment outcome measures (opioid abstinence, retention, peak withdrawal severity) were reviewed. Primary treatment outcomes were evaluated as a function of taper duration using hierarchical linear regressions using pre-taper maintenance as a cofactor.

**Results**—Twenty-eight studies were reviewed. Taper duration significantly predicted percent of opioid-negative samples provided during treatment, however pre-taper maintenance period predicted percent participants abstinent on the final day of treatment. High rates of relapse were reported. No significant association between taper duration and retention in treatment or peak withdrawal severity was observed.

**Conclusion**—The data reviewed here suggest taper duration is associated with opioid abstinence achieved during detoxification but not with other markers of treatment outcome. The reviewed studies varied widely on several parameters (e.g., frequency of urinalysis testing, provision of

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ancillary medications) that may influence treatment outcome and thus could have interfered with the ability to identify relationships between taper duration and outcomes. Future studies evaluating opioid detoxification should utilize rigorous experimental methods and report a wider range of outcome measures in order to help advance our understanding of the association between taper duration and treatment outcomes.

## Keywords

opioid; buprenorphine; taper; detoxification; withdrawal; outpatient

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## 1. Introduction

Abuse of opioids (e.g., heroin; prescription opioids) is a significant national and international public health problem (European Monitoring Centre for Drugs and Drug Addiction, 2010; Substance Abuse and Mental Health Administration, 2010a). Illicit use of opioids has been associated with considerable societal costs, including increased rates of emergency department visits, drug overdoses, criminal activity, lost work days and general medical and psychiatric consequences (Becker et al., 2008; Clausen et al., 2009; Shah et al., 2008; Wisniewski et al., 2008). Treatment admissions for opioid abuse and dependence in the U.S. and across Europe have increased dramatically in recent years (European Monitoring Centre for Drugs and Drug Addiction, 2010). For example, in the U.S. between 1992 and 2008, treatment admissions for heroin and prescription opioid (e.g., Oxycontin, Vicodin, Percocet) dependence increased by 57% and 717% respectively (Substance Abuse and Mental Health Administration, 2010b). More than one million people in the U.S. sought treatment for opioid abuse or dependence in 2009 (Substance Abuse and Mental Health Administration, 2010a), and need for treatment has increased in Europe as well (European Monitoring Centre for Drugs and Drug Addiction, 2010).

Buprenorphine-naloxone (Suboxone<sup>®</sup>) is prescribed in the U.S. and internationally as a treatment for opioid dependence (European Monitoring Centre for Drugs and Drug Addiction, 2010). Buprenorphine is approved in the U.S. as a Schedule-III drug, and is the first opioid agonist that can be prescribed to treat opioid dependence from a primary care setting (Johnson et al., 2003). The importance of prescribing buprenorphine directly from a primary care setting cannot be understated. Up to 50% of patients visiting a primary care provider are believed to require some form of substance abuse treatment; therefore, office-based buprenorphine treatment may represent an important first point of contact for opioid-dependent patients in need of treatment (Miller and Gold, 1998; Prater et al., 1999). The number of prescriptions for buprenorphine has increased steadily since its approval and office-based buprenorphine has been associated with bringing new users into treatment. Buprenorphine may appeal to patients who are unwilling or unable to access methadone treatment, particularly those residing in rural areas where access to methadone treatment may be limited (Apple et al., 2004; Becker and Fiellin, 2005; Cicero et al., 2005; Havens et al., 2007; Fiellin, 2007; Korthius et al., 2010; Pinto et al., 2010; Rosenblum et al., 2007; Schnoll, 2001; Schwartz et al., 2008; Sullivan et al., 2005; Winstock et al., 2009; Zacny et al., 2003).

Maintenance on methadone or buprenorphine is the most common form of treatment for opioid-dependence, however detoxification (i.e., medically supervised withdrawal) is a common treatment option that is an important alternative to maintenance for several reasons (Amato et al., 2005; Drug and Alcohol Services Information System, 2006; Gruber et al., 2008; Substance Abuse and Mental Health Administration, 2008). First, some opioid users prefer detoxification to maintenance (Apple et al., 2004; Luty, 2004; Pinot et al., 2010; Zacny et al., 2003). Second, the advent of prescription opioid abuse has resulted in a

subgroup of opioid-dependent patients who are younger and have briefer and less severe opioid use histories compared to traditional heroin-dependent patients, which could make them good candidates for detoxification, or even ineligible for agonist maintenance (Fiellin, 2007; Kissin et al., 2006; Sullivan et al., 2005). Finally, when maintenance availability is limited, a circumstance that is likely to occur in rural areas that are struggling with high rates of prescription opioid dependence, detoxification is a valuable and necessary treatment option (Booth and McLaughlin, 2000; Cicero et al., 2007; Cunningham et al., 2007; Fortney and Booth, 2001; Havens et al., 2007; Kissin et al., 2006; Lenardson and Gale, 2008; O'Connor et al., 1997; Rounsaville and Kosten, 2000).

Buprenorphine may be well-suited for use in opioid detoxification settings for several reasons. First, data indicates that buprenorphine produces a more limited withdrawal syndrome when compared to other full opioid agonists like methadone (Bickel et al., 1988a; Fudala et al., 1990; Jasinski et al., 1978). This may be related to buprenorphine's long plasma half-life and slow dissociation from the receptor (Bickel et al., 1988a; Bullingham et al., 1980; Fudala et al., 1990; Hambrook and Rance, 1976; Jasinski et al., 1978). Second, buprenorphine blocks the effects of exogenously-administered opioids, and can potentially slow or prevent relapse to illicit opioids from occurring (Jasinski et al., 1978; Mello et al., 1982; Rosen et al., 1994; Walsh et al., 1995). Third, buprenorphine has a ceiling on its agonist effects that reduces the risk for buprenorphine-related overdose, making it a good candidate for use in outpatient settings (Banks, 1979; Jasinski et al., 1978; Lewis, 1985; Mello and Mendelson, 1980; Walsh et al., 1994; Walsh et al., 1995). Recent preliminary evidence has confirmed an advantage of buprenorphine over methadone in detoxification settings (Gowing et al., 2009).

The use of buprenorphine for opioid detoxification is increasing (Gowing and Ali, 2006; Helm et al., 2008; Horspool et al., 2008; Ridge et al., 2008), yet there is little standardization of buprenorphine detoxification designs. As a result, detoxifications vary widely and limited scientific attention has been paid to the role that various treatment components may have on treatment outcomes. The duration of a buprenorphine detoxification and its association with treatment outcomes is one important component that warrants further empirical consideration. Methadone detoxification studies have reported significant associations between detoxification duration and treatment outcome (Fudala et al., 1990; Gossop et al., 1989; Senay et al., 1977), however it remains unclear whether these results will generalize to buprenorphine given its unique pharmacological profile. Although there have been some scientific efforts to parametrically compare different buprenorphine taper durations (Amass et al., 1994; Katz et al., 2009; Ling et al., 2009; Woody et al., 2008), the results of these studies have been mixed and the majority of studies on this topic are uncontrolled reports of a single taper duration. Therefore, the aim of this report is to review the current literature on outpatient buprenorphine detoxification and examine whether taper duration is associated with three commonly reported measures of treatment outcome: biochemically-verified opioid abstinence, treatment retention and opioid withdrawal severity. This review also highlights the heterogeneity of the scientific literature on this topic and makes recommendations for future research considerations.

## 2. Methods

### 2.1 Search strategy

Studies meeting inclusion criteria (see below) were identified by searching PsychInfo, Pubmed and MEDLINE (1973-September 2010) using a combination of keywords: buprenorphine, buprenorphine detoxification, buprenorphine taper, opiate treatment, opioid treatment, opiate detoxification, opioid detoxification, opiate taper and opioid taper. The

reference sections of identified articles were also searched for additional reports that met the review criteria.

## 2.2 Inclusion criteria

Peer-reviewed journal articles were selected for inclusion if they specified buprenorphine as a primary pharmacological agent, sought to detoxify participants with a primary end goal of opioid abstinence and took place in an outpatient setting for the duration of treatment. Studies that compared buprenorphine to other medications were included in this review; however, only data related to buprenorphine administration are reported here. Studies that parametrically compared multiple buprenorphine taper durations (Amass et al., 1988; Katz et al., 2009; Ling et al., 2009; Woody et al., 2008) were divided such that individual taper durations were included in the analyses as independent observations. Studies varied widely with respect to design, primary outcomes and other treatment components that may have influenced treatment outcome, including the duration of the pre-taper maintenance period (Table 1). Only studies that reported one or more of the three primary outcomes measures reviewed here (i.e., biochemically-verified abstinence, treatment retention, peak withdrawal severity) were included in this review.

Twenty-eight studies, including 4 parametric comparisons of taper duration (resulting in 32 total observations), met criteria and are reviewed here. Overall, the above search terms resulted in 16 randomized trials (Amass et al., 1988; Bickel et al., 1988b; Blondell et al., 2010; Breen et al., 2003; Cameron et al., 2001; Gandhi et al., 2003; Gibson et al., 2003; Ling et al., 2005; Ling et al., 2009; Lintzeris et al., 2002; Marsch et al., 2005; O'Connor et al., 1997; Raistrick et al., 2005; Resnick et al., 1992; Woody et al., 2008; Wright et al., 2007), 10 unrandomized evaluations (Becker et al., 2001; Diamont et al., 1998; Galanter et al., 2003; Katz et al., 2009; Lintzeris, 2002; Quigley et al., 1987; Resnick et al., 2001; Sigmon et al., 2009; Summers and Stone, 2002; Williams et al., 2002) and 2 retrospective comparisons with other treatment medications (Fingerhood et al., 2001; White et al., 2001).

## 2.3 Data analysis

Studies were categorized by taper duration, defined here as the number of days during which the buprenorphine dose was reduced (excluding the initial induction onto buprenorphine or any maintenance period that preceded the taper). Due to the potential for duration of pre-taper maintenance period to impact treatment outcomes, hierarchical linear regressions that held maintenance period constant were conducted to determine whether taper duration contributed unique variance to the regression model. Opioid abstinence, retention and self-reported withdrawal were evaluated as dependent variables. Opioid abstinence was generally reported in one of two ways: mean percent opioid-negative samples collected during treatment (n=16) and percent participants opioid-negative on the final day of treatment (n=9). Both abstinence outcomes are evaluated here. Withdrawal was measured with several different assessment tools (see Table 2). To facilitate comparison across different measures and studies, withdrawal scores were converted to peak withdrawal severity (represented as percent of the maximum possible scale value) and evaluated using hierarchical linear regressions. Data were generally skewed towards briefer taper durations so measures of central tendency are presented as median (range). All statistical analyses were conducted using SPSS 19.0 (Chicago, IL). A p-value of <0.05 was considered significant.

## 3. Results

### 3.1 Taper duration

Taper duration varied substantially across the studies reviewed, ranging from abrupt discontinuation of buprenorphine (e.g., 0 taper days) to a 120-day taper. The median (range)

number of taper days was 17 (0–132). The duration of the pre-taper maintenance period was specified for 29 (91%) of the studies and also varied substantially (*Median*: 5 days, range: 0–56). Additional study characteristics are presented in Table 1.

### 3.2 Biochemically-verified opioid abstinence

Twenty-six (81%) of the studies reported results of urine toxicology testing. The median percent opioid-negative samples provided during treatment was 41% (range: 1%–94%) and the median percent participants who were opioid-negative on the final day of treatment was 30% (range: 22%–41%). A hierarchical regression model revealed that taper duration was a significant predictor of percent opioid-negative samples collected during treatment when maintenance period was held constant (Table 3), however the duration of maintenance period was a better predictor of the percent of participants negative on the final day of treatment than was taper duration (Table 3).

Three studies used contingency management (CM), a behavioral intervention that provides monetary-based incentives for urinalysis-verified drug abstinence, to increase opioid abstinence (Amass et al., 1994; Becker et al., 2001; Marsch et al., 2005). Percent opioid abstinence among participants who earned monetary rewards in exchange for providing opioid-negative urine samples were generally higher (*Median*: 64%; range: 39%–78%) when compared to studies that did not use CM (*Median*: 23%; range: 1%–94%).

Eleven (34%) studies included a post-taper follow-up assessment, ranging from 8–365 days after the taper (Table 1), and 8 (25%) of those reported urinalysis results from these visits. Median opioid-negative samples collected at the first post-taper follow-up visit (e.g., samples that occurred in closest proximity to the final taper day, marked by an asterisk in Table 1) were 23% (range: 8.4% – 52%). Regression analyses revealed no significant relationship between maintenance period and/or taper duration at the first post-detoxification follow-up (Table 3). Follow-up abstinence was further examined among only those studies that reported urinalysis outcomes on the final day of treatment and a follow-up visit (n=5). Among these studies, median percent participants opioid-negative on the final day of treatment and at the first follow-up assessment were 30% (range: 25%–44%) and 29% (range: 17.6% – 52%), respectively.

### 3.3. Retention

Twenty-nine (91%) of the studies reported treatment retention as an outcome variable. Median percent participants retained at the end of treatment was 65.5% (range: 4%–100%). In contrast to data regarding opioid abstinence achieved during treatment, neither maintenance nor taper duration significantly predicted the number of participants retained at the end of treatment (Table 3).

### 3.4. Withdrawal severity

The studies employed a wide variety of self-report and observer-rated measures to assess opioid withdrawal (Table 2). Of the studies reviewed, 17 (53%) reported using at least one withdrawal assessment during detoxification. With the exception of 4 studies that measured withdrawal but did not provide specific data (Amass et al., 1994; Bickel et al., 1988a; Quigley et al., 1987; Resnick et al., 1992), data from peak withdrawal severity are presented in Figure 1. Overall, withdrawal from buprenorphine was relatively mild (e.g., represented a small percentage of the maximum possible score), with median peak self-reported and observer ratings of withdrawal at 18.5% (range: 5%–47%) and 13% (range: 6%–31%) of maximum scale values, respectively. Neither maintenance period or taper duration were significantly predictive of peak self-reported withdrawal severity (Table 3).

Interestingly, several of the reviewed studies indicated that peak buprenorphine withdrawal occurred at the very end of the detoxification or even after the final buprenorphine dose had been administered. Five studies reported that withdrawal severity peaked after the buprenorphine dose decreased below 2 mg (Cameron et al., 2001; Quigley et al., 1987; Resnick et al., 1992; Resnick et al., 2001; White et al., 2001), and 7 studies reported that withdrawal severity peaked 3 to 15 days after the last dose was administered (Amass et al., 1994; Becker et al., 2001; Cameron et al., 2001; Lintzeris, 2002; Raistrick et al., 2002; Sigmon et al., 2009; White et al., 2001).

#### 4. Discussion

This review evaluated the association between taper duration and treatment outcome following outpatient detoxification using buprenorphine. Twenty-seven studies that administered buprenorphine as a primary pharmacological agent for opioid detoxification in an outpatient setting were reviewed.

Analysis of abstinence outcomes revealed interesting results. First, taper duration was associated with the amount of opioid abstinence achieved during the taper and this association was not influenced by the preceding duration of buprenorphine maintenance. An association between taper duration and percent negative samples provided during treatment has also been observed following detoxification using methadone (Senay et al., 1977). Second, duration of pre-taper buprenorphine maintenance was a better predictor than taper duration of the percent participants who were opioid-negative on the final day. Buprenorphine maintenance has been associated with reductions in illicit drug use, which has itself been associated with better inpatient detoxification outcomes (Franken and Hendriks, 1999; Mattick et al., 2008). Thus, it is possible that longer maintenance periods may provide more opportunities to become stable in treatment, thus making participants good candidates for a detoxification; however, more research on the relationship between maintenance duration and detoxification outcomes is needed.

None of the studies reviewed here reported results for both of the urinalysis outcomes reviewed (i.e., percent negative samples collected during treatment and percent participants who were opioid-negative on the final day of treatment); therefore, it is not possible from this review to evaluate whether an association between these outcome measures exists. However, the fact that duration of taper is significantly predictive of one urinalysis outcome (i.e., percent negative samples collected during treatment) but not another (i.e., percent participants who were opioid-negative on the final day of treatment) may help explain, in part, the lack of consensus in the literature regarding the optimal duration for outpatient buprenorphine detoxification. For example, of the 4 parametric comparisons of buprenorphine taper duration, the two studies that defined abstinence as percent negative samples during treatment reported an advantage of longer duration detoxifications (Amass et al., 1994; Katz et al., 2009), while the two studies that defined abstinence as the percent of participants opioid-negative on the final day of treatment reported no advantage of longer duration detoxifications (Ling et al., 2009; Woody et al., 2008). Since no study reported both abstinence outcomes, it is not possible to determine which outcome is more clinically significant, therefore future studies are encouraged to report outcomes to enable this comparison (Table 4).

Only 34% of the reviewed studies reported urinalysis-testing outcomes from follow-up assessments, and the median opioid abstinence rate at follow-up was 23%. It is important to evaluate whether participants who completed the detoxification without relapse remained abstinent at the first post-detoxification follow-up assessment to help judge the efficacy of an intervention. Among studies that reported both percent abstinence on the final day of

treatment and at the first follow-up assessment (n=5), median abstinence rates were 30% and 29% respectively. These data are encouraging and suggest abstinence may have persisted among those participants who completed the detoxification without relapse. It will be important for future studies to report the percent abstinence at follow-up as a function of those participants who completed the treatment successfully, to help evaluate whether those participants continued to abstain from opioids (Table 4).

Nevertheless, the high rate of relapse observed here is consistent with the larger literature that suggests only a minority (41% and 20%) of patients leaving a residential detoxification remain abstinent from illicit opioid use at 7 and 30 days post-detoxification, respectively (Smyth et al., 2010). Similar relapse rates have been reported following detoxification from methadone maintenance, wherein approximately 17–37% of patients who complete detoxification remain abstinent from opioids 2 – 6 years later (Cushman, 1978; Gossop et al., 1986; Stimmel and Rabin, 1974; Stimmel et al., 1977). In order for opioid detoxification to be successful, additional research is needed to evaluate strategies for maintaining opioid abstinence following detoxification. Use of the opioid antagonist naltrexone, which has recently been approved for use in a sustained release formulation, represents one promising method for reducing relapse that warrants additional research consideration (Comer et al., 2002; Comer et al., 2006; Foster et al., 2003).

Neither taper duration nor maintenance period significantly predicted the percent of participants retained at the end of treatment. Longer taper durations can provide more opportunities for participants to drop out of treatment, whereas shorter taper durations require more limited engagement and may result in higher, albeit limited, retention. However, this was not supported by results from the four parametric studies reviewed here, in which 63% and 35% of participants in long vs. short taper durations completed the intervention, respectively. The type or intensity of ancillary services provided during treatment has also been shown associated with better retention outcomes during opioid detoxification treatment (Bickel et al., 1997). Yet, the lack of information on treatment services in the reviewed studies prevents any firm conclusions from being drawn. Therefore, to facilitate a better understanding of the relationship between taper duration and retention, it would be helpful for future studies to report retention outcomes as both percent of scheduled days attended and percent of participants retained at the end of treatment (Table 4). It would also be important to evaluate retention in the context of withdrawal severity and buprenorphine dose, to determine whether study attrition is most likely to occur once a specific withdrawal threshold is crossed. This information can be used to help target effectively ancillary services that could increase retention and completion of the detoxification.

Withdrawal during buprenorphine detoxification was assessed by 53% of studies. Peak withdrawal severity was generally mild and no significant association between taper duration and peak withdrawal severity was observed. However, withdrawal reports may have been confounded by continued illicit opioid use, study attrition that may be complicated by differential group dropout (e.g., patients with high withdrawal severity) or provision of ancillary medications to treat withdrawal symptoms. To better evaluate withdrawal during outpatient buprenorphine detoxifications, it will be important to know the manner in which ancillary medications are administered (e.g., according to protocol guidelines such as reaching a numerical threshold on a withdrawal self-report or observer-rated inventory, or by participant request; Table 4).

Interpretation of withdrawal is further complicated by the wide range of self-report and observer-rated measures used (Table 2), which limits sensitive comparisons of withdrawal across studies. In general, buprenorphine appeared to produce a relatively mild withdrawal

syndrome compared to the withdrawal expected following detoxification using methadone or clonidine. This is consistent with the literature on buprenorphine withdrawal (Bickel et al., 1988a; Bullingham et al., 1980; Fudala et al., 1990; Hambrook and Rance, 1976; Jasinski et al., 1978). Review of these studies suggests several potential areas for future research. First, in several studies, peak withdrawal symptoms emerged once the dose dropped below 2mg, and withdrawal symptom severity peaked 3–15 days *after* the final dose was administered. This suggests patients may be experiencing the most severe withdrawal in the days following a detoxification, presumably when treatment resources may no longer be available to help manage the withdrawal, and therefore may benefit most from ancillary medications and other resources when they are provided at the end of the detoxification. This information can be useful for designing efficient and cost-effective detoxification treatments. Second, it was not possible to determine from the studies reviewed here whether the magnitude of the buprenorphine dose decrease was associated with withdrawal syndrome severity and/or duration. Magnitude decrease has been associated with differential outcomes following methadone detoxification, yet it is not clear this finding will generalize given buprenorphine's unique pharmacological profile (Strang and Gossop, 1990). The relationship between magnitude decrease and withdrawal is an important factor to consider when designing tapering schedules. Third, studies reviewed here administered a wide variety of buprenorphine formulations that may have different absorption and excretion patterns (Table 1; Chawarski et al., 2005). The degree to which buprenorphine formulation influenced treatment outcomes was not evaluated. Although the majority of buprenorphine products being administered for opioid dependence today are in sublingual tablet form (e.g., Suboxone, Subutex), new abuse-deterrent (e.g., Suboxone soluble film strip) and sustained-release products are becoming available that may have unique excretion patterns (Ling et al., 2010; Strain et al., 2011; White et al., 2009). Ultimately, additional research is needed to more rigorously evaluate buprenorphine withdrawal, including the relationship between buprenorphine dose and withdrawal severity, the duration of the withdrawal syndrome, the severity of withdrawal that persists after the final buprenorphine dose has been administered, the severity of withdrawal following detoxification with alternative formulations of buprenorphine and the association between withdrawal and other treatment outcomes, including abstinence and retention.

Review of these studies suggested several areas that warrant additional research consideration. First, do specific characteristics of opioid-dependent patients exist (e.g., amount of opioids used per day, primary route of administration) that predict success in outpatient buprenorphine detoxification? This information could help match patients to appropriate treatments and reduce the potential that an individual will not complete a detoxification. Second, what additional contribution will concomitant therapies (including CM) have on abstinence rates during and after detoxification? CM produced promising outcomes in the studies reviewed here, consistent with studies that have used CM with opioid-dependent patients (Bickel et al., 1997; Gross et al., 2006; Kosten et al., 2003), and that have addressed other drug use more broadly (Lussier et al., 2006). Third, is it more advantageous to use a fixed or a flexible dosing schedules, or are results comparable? Fixed dosing schedules use guidelines to determine the frequency and magnitude of a dose decrease and are common among research interventions. Flexible dosing schedules allow participants to dictate the frequency and magnitude of the dose decreases and are common in “real-world” practice (Connock et al., 2007; Mattick et al., 2008). Though we know of no studies that have experimentally evaluated opioid abstinence outcomes following fixed vs. flexible buprenorphine detoxification schedules, flexible dosing has been associated with poorer retention in treatment following methadone detoxification (Dawe et al., 1991). Five of the studies reviewed here (Breen et al., 2003; Resnick et al., 2001; Summers and Stone, 2002; White et al., 2001; Williams et al., 2002) utilized a flexible dosing strategy, yet only 1 reported the percent of samples that were opioid abstinent (23%; Williams et al., 2002).



Additional research that evaluates whether an advantage exists for fixed vs. flexible dosing schedules will help guide clinical decisions about detoxification.

In conclusion, opioid abuse and dependence continue to be serious national and international public health problems. Administration of buprenorphine in outpatient settings is an important treatment option. The data reviewed here suggest the duration of an outpatient buprenorphine detoxification is positively associated with opioid abstinence achieved during treatment, and the duration of the preceding maintenance period is positively associated with the percent of participants who were opioid-negative on the final day of treatment. There was high concordance between participants who were negative on the final day of treatment and at the first follow-up visit, suggesting a persisting effect of the intervention, however this observation is based on a small sample size and warrants further research consideration. Although these data have important scientific and clinical implications, this review was based on several uncontrolled observations of a single taper duration that employed a wide range of study designs and reported a diverse array of outcome measures, which ultimately restricted sensitive comparisons across studies. Therefore, this review should be considered a first evaluation into the association between taper duration and clinical treatment outcomes and additional research is needed to further investigate these results. Report more standardized outcome measures will facilitate better comparisons across studies (Table 4), permit meta-analytic reviews and promote development of recommendations for clinical practice.

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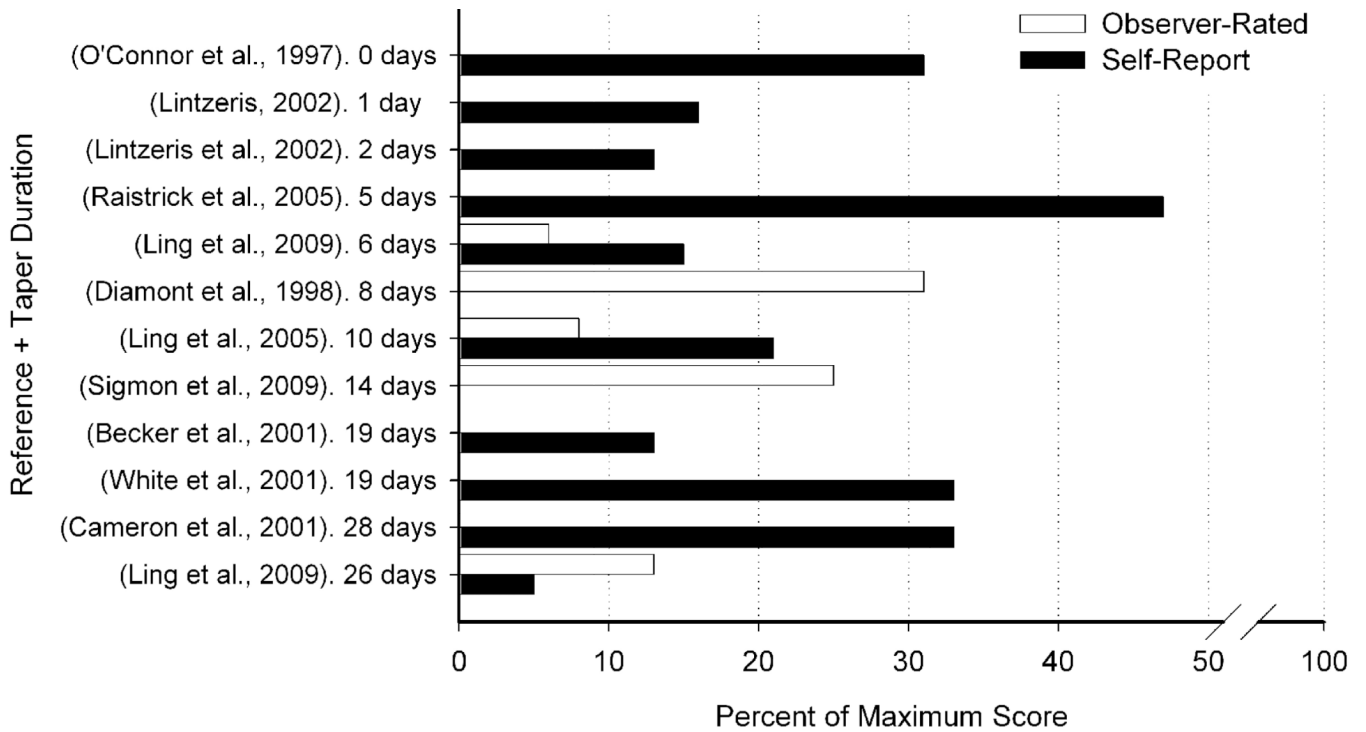
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**Fig 1.** Peak buprenorphine withdrawal during taper, presented as percent of maximum scale value. Only studies from which peak withdrawal severity could be calculated are presented here. Black bars represent self-report measures and open bars represent observer-rated measures. Studies are organized by taper durations on the y-axis and percent peak withdrawal is presented on the x-axis.

Table 1

of Reviewed Studies

	Participants (#)	Opioid <sup>a</sup>	Buprenorphine Type	Buprenorphine Maintenance Period prior to Taper (days)	Mean Taper Duration (days)	Mean Starting Buprenorphine Dose (mgs) <sup>b</sup>	Urinalysis testing	Approximate # urine samples collected during taper	Counseling	Withdrawal Assessment	Ancillary Medications	Naltrexone encouraged	Follow-up Assessment (days)
et al.,	5	Opioid	SL Liquid	28	12	8	Y	4	Y	Y	NS	NS	NS
	3	Opioid	SL Liquid	28	36	8	Y	12	Y	Y	NS	NS	NS
et al.,	17	Heroin	SL Liquid	7	19	8	Y	6	NS	Y	NS	NS	NS
et al.,	45	Opioid	SL Liquid	21	28	2	Y	11	NS	Y	NS	NS	NS
et al.,	6	Prescription	Suboxone	2	120	9.8	Y	4	Y	NS	NS	NS	NS
et al.,	55	Methadone	NS	19	77	8.8	NS	NS	Y	Y	Y	Y	30*
et al.,	13	Opioid	NS	7	28	8	Y	5	NS	Y	NS	NS	NS
et al.,	50	Opioid	SL (Temgesic)	0	8	2.58	Y	3	NS	Y	Y	NS	NS
et al.,	65	Opioid	Buprenex	0	4	0.3	NS	NS	Y	Y	Y	NS	NS
et al.,	52	Heroin	Suboxone	35	52	16.4	Y	15	Y	Y	Y	Y	NS
et al.,	119	Heroin	SL Tablet or IM	3	0	4 or 0.6	Y	1	Y	Y	Y	NS	30*, 60, 90
et al.,	115	Heroin	SI Tablet	3	2	12	Y	1	NS	NS	NS	Y	8*
et al.,	364	Heroin	Suboxone	5	0	2	Y	1	Y	NS	NS	NS	NS
et al.,	146	Heroin	Suboxone	22	7	14.6	Y	4	Y	NS	NS	NS	NS
et al.,	157	Opioid	Suboxone	3	10	16	Y	10	Y	Y	Y	NS	NS
et al.,	255	Opioid	Suboxone	29	6	24	Y	1	Y	Y	Y	NS	30*, 90
et al.,	261	Opioid	Suboxone	30	26	24	Y	4	Y	Y	Y	NS	30*, 90

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Participants (#)	Opioid <sup>a</sup>	Buprenorphine Type	Buprenorphine Maintenance Period prior to Taper (days)	Mean Taper Duration (days)	Mean Starting Buprenorphine Dose (mgs) <sup>b</sup>	Urinalysis testing	Approximate # urine samples collected during taper	Counseling	Withdrawal Assessment	Ancillary Medications	Naltrexone encouraged	Follow-up Assessment (days)
18	Heroin	Subutex	4	1	10.1	Y	1	NS	Y	NS	Y	NS
58	Heroin	Subutex	3	2	9.6	Y	1	NS	Y	NS	NS	35
18	Opioid	Subutex	0	28	8	Y	12	Y	Y	Y	Y	NS
53	Heroin	NS	3	0	3	NS	NS	NS	Y	Y	Y	NS
15	Heroin	SL Liquid	28	30	4	Y	10	NS	Y	Y	NS	NS
107	Heroin	Subutex	2	5	8	Y	1	NS	Y	NS	Y	30
51	Heroin	SL Liquid	12 – 365	35	8	Y	3	Y	Y	Y	NS	NS
40	Heroin	Buprenex	NS	18	16	NS	NS	NS	NS	NS	Y	90*, 365
14	Prescription	Suboxone	12	14	9	Y	6	Y	Y	Y	Y	NS
>35	Opioid	Subutex	5	15	21.3	NS	NS	NS	NS	Y	Y	90
38	Opioid	Subutex	NS	19	8	Y	NS	NS	Y	Y	NS	NS
60	Heroin	NS	5	17	10	Y	NS	NS	NS	NS	NS	NS
78	Opioid	Suboxone	3	11	8	Y	1	Y	NS	NS	NS	30*, 60, 90, 180, 270, 365
74	Opioid	Suboxone	56	28	14	Y	3	Y	NS	NS	NS	180*, 270, 365
28	Opioid	NS	3	12	24	Y	1	NS	NS	NS	NS	NS

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at did not specify heroin vs. prescription opioids are considered to have addressed general opioid dependence

multiple dose values were available, mean highest maintenance dose was provided.

Y = Yes, N= No, NS= Not specified,

astineness at this follow-up visit was included in analysis

**Table 2**

## Questionnaire utilization among studies assessing withdrawal

	<b>% used</b>
Self-Report	35
Adjective Rating Scale	44
Short Opiate Withdrawal Scale (SOWS)	25
Subjective Opiate Withdrawal Scale (SOWS)	25
Visual Analog Scales (VAS)	44
Craving	13
Withdrawal Severity	19
Drug effects	13
Observer-Rated	10
Clinical Institute Narcotic Assessment (CINA)	18
Clinical Opiate Withdrawal Scale (COWS)	6
Opiate Objective Withdrawal Scale (OOWS)	18
Physiological Measures (e.g. blood pressure, pupil)	6
Wang Scale	6
Unspecified observer-report	13

Table 3

## Hierarchical Regression Analyses

Outcome	Variable	B	SE B	Beta	R <sup>2</sup>	ΔR <sup>2</sup>	p-value
Percent Opioid-negative Samples Provided During Treatment							
Step 1	Maintenance Duration	0.608	0.569	0.275	0.076	0.076	0.303
Step 2	Maintenance Duration	0.467	0.511	0.211	0.318	0.243	0.377
	Taper Duration	0.442	0.205	0.497			<b>0.051</b>
Percent Participants Opioid-negative on the Final Day							
Step 1	Maintenance Duration	0.230	0.105	0.640	0.409	0.409	0.063
Step 2	Maintenance Duration	0.491	0.108	1.362	0.776	0.366	<b>0.004</b>
	Taper Duration	-0.733	0.234	-9.420			<b>0.020</b>
Percent Participants Opioid-negative at Follow-up							
Step 1	Maintenance Duration	0.347	0.287	0.476	0.226	0.226	0.281
Step 2	Maintenance Duration	0.314	0.328	0.431	0.251	0.024	0.392
	Taper Duration	0.079	0.219	0.162			0.737
Percent Participants Retained on the Final Day							
Step 1	Maintenance Duration	-0.049	0.350	-0.029	0.001	0.001	0.889
Step 2	Maintenance Duration	0.031	0.356	0.018	0.055	0.054	0.932
	Taper Duration	-0.213	0.189	-0.238			0.273
Peak Self-reported Withdrawal							
Step 1	Maintenance Duration	-0.619	0.355	-0.550	0.302	0.302	0.125
Step 2	Maintenance Duration	-0.644	0.422	-0.571	0.305	0.002	0.178
	Taper Duration	0.062	0.452	0.052			0.895

**Table 4****Recommendations for Outcome Measures and Methodology**

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**Outcome Measure Recommendations**

## Abstinence Outcomes

Percent opioid abstinence achieved during treatment

Percent of participants opioid-negative on the final day of treatment

Percent opioid abstinence at follow-up among participants who completed the detoxification without relapse

## Retention Outcomes

Percent of scheduled treatment days attended

Percent of participants retained on the final day of treatment

## Withdrawal Outcomes

Dose at which withdrawal severity peaked.

**Methodological Recommendations**

## Withdrawal Methods

Describe dose tapering schedule

Indicate whether tapering schedule was fixed or flexible

Evaluate withdrawal after completion of the taper

## Ancillary Medications and Counseling

Indicate manner in which medications are provided (e.g., protocol-driven vs. patient request)

Indicate presence of ancillary counseling procedures

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