Strategies for Transfer From Methadone to Buprenorphine for Treatment of Opioid Use Disorders and Associated Outcomes: A Systematic Review

Nicholas Lintzeris, BMedSci, MBBS, PhD, FAcChAM, Baher Mankabady, MD, Carlos Rojas-Fernandez, PharmD, and Halle Amick, MSPH

Objectives: To review the currently available evidence on transfer strategies from methadone to sublingual buprenorphine used in clinical trials and observational studies of medication for opioid use disorder treatment, and to consider whether any strategies yield better clinical outcomes than others.

Methods: Six medical and public health databases were searched for articles and conference abstracts. The Cochrane Central Register of Controlled Trials and the World Health Organization International Clinical Trials Registry Platform were used to identify unpublished trial results. Results were dually screened, and data were extracted and checked independently. Results were summarized qualitatively and, when possible, analyzed quantitatively.

Results: Eighteen studies described transfer from methadone to buprenorphine. Transfer protocols were extremely varied. Most studies reported successful rates of transfer, even among studies involving transfer from high methadone doses, although lower pretransfer methadone dose was significantly associated with higher rate of successful transfer. Precipitated withdrawal was not reported frequently. A range of innovative approaches to transfer from methadone to buprenorphine remains untested.

Conclusions: Few studies have used designs that enable comparison of different approaches to transfer patients from methadone to buprenorphine. Most international clinical guidelines provide recommendations consistent with the available evidence. However, clinical guidelines should be perceived as providing “guidance” rather than “protocols,” and clinicians and patients need to exercise judgment when attempting transfers.

Key Words: buprenorphine, methadone, opioids, transfer

(J Addict Med 2022;16: 143–151)

Opoid use disorder, arising from the use of pharmaceutical and illicit opioids, is a global public health crisis.1–4 The mainstay of medication for opioid use disorder (MOUD) treatment includes use of primarily buprenorphine (a partial opioid agonist) or methadone (a full opioid agonist), in conjunction with psychosocial interventions.5,6 When used as directed, buprenorphine, alone or in combination with the opioid antagonist naloxone, and methadone are effective and safe.5,6 There are medical, practical, and patient preference reasons a provider may initiate treatment with buprenorphine or methadone. During the course of treatment, however, a medication change may be warranted.

Efficacy and/or safety factors are the main reasons for initiating a change in medication.5–17 Logistics of treatment provision may also warrant a change in medication.5,8 For example, in some countries, including the United States, methadone is available only at substance use disorder treatment centers, which can pose a logistical burden and carry social stigma. In some settings, patients have greater access to unsupervised dosing with buprenorphine than with methadone, such that patients may wish to transition to buprenorphine to receive care in a less restrictive setting. The recent introduction of long-acting depot buprenorphine formulations may also drive patient demand to transfer from methadone to buprenorphine.

Various guidelines suggest that transferring from transmucosal buprenorphine to methadone is relatively straightforward. For this reason, this review focuses on the more...
complicated process of transferring patients from methadone to buprenorphine. Buprenorphine is a partial agonist with higher affinity for the mu opioid receptor; hence, it can precipitate withdrawal symptoms when switching from full opioid agonists such as methadone. Various factors can affect the patient experience of precipitated withdrawal and successful transfer from methadone to buprenorphine, including the size of the last methadone dose; the interval between methadone and buprenorphine dosing; the induction regimen of buprenorphine; patient expectations; the use of other substances; or psychiatric comorbidities. Several organizations have published guidelines for transferring patients from methadone to buprenorphine, but with variations in some parts of the process (Table 1).

A 2012 review of studies that transferred patients from methadone to buprenorphine included many studies that used buprenorphine as a brief intermediate treatment in the process of ceasing MOUD entirely, or in laboratory studies in which patients were immediately returned to methadone. The purpose of this paper is to update and review the currently available evidence on transfer strategies used in clinical trials and observational studies of longer-term treatment with buprenorphine or methadone and to consider whether any strategies yield better clinical outcomes than others.

**METHODS**

**Protocol Registration**

The protocol for this review was registered with the PROSPERO international prospective register of systematic reviews (CRD42017076133). A brief description of methods follows; additional details are available in Supplementary Digital Content A, http://links.lww.com/JAM/A275.

**Terminology**

In this review, the term “transfer” refers to the entire process of switching from one medication to another. “Taper” refers to the reduction of a medication dose before it is discontinued, “induction” refers to the start of a medication, and “escalation” refers to increasing a medication’s frequency, dose, or both. “Stabilization” refers to the point at which adjustment of a medication’s frequency and dose ceases, and “maintenance” is the period beyond stabilization.

**Data Sources and Searches**

MEDLINE (via PubMed), EMBASE, the Cochrane Library, Web of Science, and PsycINFO were searched for articles and conference abstracts published through August 31, 2017. The Cochrane Central Register of Controlled Trials and the World Health Organization International Clinical Trials Registry Platform were used to identify unpublished results of trials. Updated searches of the aforementioned sources were performed on August 3, 2019. The search strategies are detailed in Supplementary Digital Content B, http://links.lww.com/JAM/A275. To supplement electronic searches, the reference lists of pertinent articles and all studies suggested by subject matter experts were reviewed.

**Study Selection**

Two investigators independently reviewed titles, abstracts, and full-text articles to determine eligibility using prespecified criteria (Table 2). Disagreements were resolved by discussion.

**Data Extraction and Risk of Bias (ROB) Assessment**

For each included study, 1 investigator extracted information about the populations, tests or treatments, comparators, outcomes, settings, and designs, and a second investigator reviewed for completeness and accuracy. Two reviewers independently assessed each included study’s ROB using measures appropriate for each study’s design (Supplementary Digital Content A, http://links.lww.com/JAM/A275); disagreements were resolved by discussion.

**Data Synthesis and Analysis**

Findings were summarized in tabular and narrative forms, and basic statistics were calculated when the data permitted. Individual study means or medians were used when possible; midpoints of ranges were used when neither was given. For comparisons, t tests with two-tailed distributions were used to compare 2 groups and one-way analyses of variance were used to compare more than 2 means. A P-value less than 0.05 was considered statistically significant.

**RESULTS**

After review of 2337 titles and abstracts and 228 articles, 19 articles reporting on 18 studies were included (Fig. 1). Study characteristics, detailed descriptions of the transfer strategies, and study outcomes are provided in Supplementary Digital Content Tables B-1, B-2, and B-3, http://links.lww.com/JAM/A275, respectively. Both randomized controlled trials (RCTs) were rated “fair” quality, and most (10/17, 59%) of the observational studies were rated “medium” ROB (3 were rated “high”).

**Description of Included Studies and Their Transfer Strategies**

Eighteen studies (reported in 19 articles) transferred patients from methadone to buprenorphine, with a total of 382 patients enrolled. Eight studies were conducted in the United States, 6 in Europe, and 4 in Australasia. There were 2 RCTs, 8 noncomparative trials, 5 cohort studies, 1 crossover trial, and 2 case series. Transfers occurred in outpatient settings in 8 studies, inpatient settings in 7 studies, and the setting was mixed or not described in 3 studies. There was little consistency across studies in the transfer strategies used (Supplementary Digital Content B-2, http://links.lww.com/JAM/A275).

One small case series used a microdosing procedure. Because microdosing procedures differ significantly from other transfer strategies, results from that case series are not included in the quantitative analyses; however, the study procedures and outcomes are included descriptively.

Several transfer strategy components were at least moderately correlated with each other (Pearson r ≥ 0.50, Table 3). Methadone dose before transfer was positively correlated with minimum wait time between ceasing methadone and starting buprenorphine, dose of buprenorphine on day 2 of transfer, and total stable dose of buprenorphine.
### TABLE 1. Published Guidelines for Transfer of Patients From Methadone to Buprenorphine

| Before BUP administration | ASAM (United States) 2015 | Common-wealth of Australia 2014 | British Columbia (Canada) Ministry of Health 2017 | CCBHOF (Pittsburgh, PA) 2013 | New Zealand Ministry of Health 2014 | NHS (United Kingdom) 2011 | WHO 2009 | SAMHSA (United States) 2018 |
|---------------------------|---------------------------|-------------------------------|---------------------------------|-------------------|---------------------------------|-------------------|--------|---------------------------|
| METH dose and taper guidance | NA; patients on 30–40 mg will be less comfortable | 24–72 h | Taper to ≤60 mg, ideally ≤30 mg/d for 6–7 d | NA | Reduce to ≤30 mg | Taper to 30 mg | Taper to 30–40 mg/d for ≥7 d |
| Time between last METH dose and first BUP dose | NA | ≥24 h, preferably 48–72 h | 48–72 h | ≥24 h | 24 h | 24 h, preferably ≥36 h |
| Withdrawal symptoms before BUP administration | Mild-moderate withdrawal (COWS 11 to ≥12) | Moderate withdrawal (COWS ≥13, SOWS ≥16) | COWS > 12 | “Clear objective signs of withdrawal” | Moderate withdrawal | COWS 13–24 | “Ideally when withdrawal signs are evident” |
| BUP administration: day 1 | Initial dose | 2–4 mg | 2 mg | BUP/NLX 4 mg/1 mg | 2 mg | 2 mg | NA | BUP/NLX 20.5 mg–4/1 mg |
| Additional dosing guidance | Prescribe increments of 2–4 mg if no withdrawal symptoms evident after 60–90 minutes | BUP/NLX up to a maximum of 12 mg/5 mg | If initial dose does not precipitate withdrawal, consider prescribing one or two 2 mg/0.5 mg BUP/NLX tablets as take-home doses | Increments of 2 mg/0.5 mg BUP/NLX up to a maximum of 24 mg/10 mg | additional 2–4 mg/day, depending on COWS (cut-offs not specified) | NA | Additional dosing in increments of BUP/NLX either 2 mg/0.5 mg or 4 mg/1 mg every 2 h as needed; maximum 8 mg |
| BUP day 2 and beyond | Starting dose | Not addressed | Total dose of day 1 + 2 mg every 2 h as needed; maximum 8 mg | Taper to <60 mg, ideally ≤30 mg/d for 6–7 d | Additional 6 mg after 1 h if the initial dose does not precipitate withdrawal | Maximum 32 mg | Maximum 16 mg, otherwise document rationale for higher dose |
| Dose range | Generally 8–16 mg; maximum 24 mg | 8–24 mg | 16 mg on day 2 | NA | 24 mg | NA | 8–24 mg | BUP/NLX mg/d; maximum 0.5 mg/4 mg/1 mg/d; maximum 8 mg/2 mg |

*If separate guidelines existed for BUP and METH, they were incorporated into one column.**If high risk of precipitated withdrawal or if patient is currently abstinent from opioid use, starting dose may be lowered to one 2 mg/0.5 mg BUP/NLX tablet. If severe withdrawal symptoms at the time of induction (COWS > 24), starting dose may be increased to three 2 mg/0.5 mg BUP/NLX tablets.

ASAM, American Society of Addiction Medicine; BUP, buprenorphine; CCBHOF, Community Care Behavioral Health Organization; COWS, Clinical Opiate Withdrawal Scale; METH, methadone; mg, milligrams; NA, not addressed; NLX, naloxone; SAMHSA, Substance Abuse and Mental Health Services Administration; SOWS, Subjective Opiate Withdrawal Scale; WHO, World Health Organization.
Minimum wait time between ceasing methadone and starting buprenorphine was positively correlated with day 2 and stable buprenorphine doses.

**Stable Methadone Dose**

The weighted mean daily methadone dose at which patients were maintained before commencing the transfer process was approximately 52 mg for patients taking between 30 and 100 mg/d of methadone. Four studies allowed enrollment of patients taking more than 100 mg methadone/d.35–38

**Methadone Taper**

The mean final dose of methadone 5 days before transfer to buprenorphine, ranged from 19 mg to 78 mg, with an overall weighted mean of 46 mg. Methadone was discontinued with no apparent dose reduction in 9 studies,21,22,24,28,29,33–35,37 including 2 of the 4 studies that included patients taking relatively high doses of methadone.35,37

Seven studies used a fixed or flexible methadone dose taper.23,25–27,30,32,36 In one of these studies, taper was offered to patients, but it is not reported whether any patients chose that strategy.32 In another study, one of 3 groups was randomized to taper.25

**Concomitant Medications**

Many studies allowed adjunctive medications to relieve withdrawal symptoms during the transfer. These included lofexidine, clonidine, benzodiazepines, analgesics (nonsteroidal anti-inflammatory drugs), and loperamide (Supplementary Digital Content Table B-2, http://links.lww.com/JAM/A275).

**Presence of Withdrawal Features and Timing of the Initial Dose of Buprenorphine**

Most studies required patients to exhibit features of opiate withdrawal before initiating buprenorphine, though many did not objectively describe the severity of withdrawal. Four studies required patients to reach a threshold on the Clinical Opiate Withdrawal Scale (COWS) before induction of buprenorphine treatment.32,33,37,38 Thresholds were COWS scores >10,37 ≥10,33 >12,38 and ≥13.32 Buprenorphine was given no sooner than 42 hours after the last methadone dose in 2 studies,32,37 and no sooner than 24 hours in a third,38,33 the interval duration was not reported in the fourth study.33

In 4 studies, patients were provided an initial dose of buprenorphine at a set time since the last methadone dose, potentially regardless of the presence of withdrawal symptoms.21,23,26,34

**Buprenorphine Induction**

Only 1 study tested different buprenorphine induction protocols.26 Patients were randomized to a slow, moderate, or rapid transfer after methadone discontinuation (no taper; details in Supplementary Digital Content Table B-2, http://links.lww.com/JAM/A275).

---

**TABLE 2. Inclusion and Exclusion Criteria**

| Include | Exclude |
|---------|---------|
| Populations | Humans undergoing treatment for OUD (including pregnant women) | Patients undergoing treatment for detoxification only or acute withdrawal without post-detoxification follow-up; Patients undergoing treatment for pain with no concomitant OUD; Animal studies Any other medication interventions or comparisons; Studies that did not describe the transfer strategy for at least the first day; Studies that did not transfer directly from one to the other (e.g., exclude if morphine used between METH and BUP); Studies that included transfers and non-transfers but did not report stratified results Non-serious adverse events |

| Interventions and Comparisons | Transfer from BUP (or BUP/NLX) to METH Pharmacokinetic and pharmacodynamic studies; Single case reports; Cost-effectiveness studies; Articles that did not contain original data (e.g., editorials, non-research letters, narrative reviews); Systematic reviews |
|-----------------------------|---------------------|

| Outcomes | Precipitated withdrawal; Transfer completion; Post-transfer retention in treatment; Treatment adherence; Abstinence; Relapse; Mortality; Major clinical morbidity attributable to BUP or METH (overdose or serious adverse events’*) |

| Study Designs | Randomized and non-randomized controlled trials; Non-comparative and uncontrolled trials; Prospective and retrospective cohort studies; Case series |

| Geography | No limit NA |
| Study Duration | No minimum NA |
| Languages | Any NA |

*As determined by FDA guidance at https://www.fda.gov/safety/medwatch/howtoreport/acmn053087.htm. BUP indicates buprenorphine; METH, methadone; NA, not applicable; NLX, naloxone; OUD, opioid use disorder.
Buprenorphine Product

Almost all studies used single-ingredient buprenorphine, but 6 28,32,33,35,38,39 used buprenorphine combined with naloxone. One study used the single-ingredient product in the first part of the study but switched to the combination product when it became available.37 Various routes of administration were used, but in most of the studies, buprenorphine was administered sublingually (Supplementary Digital Content Table B-2, http://links.lww.com/JAM/A275).

Details about each study’s dosing strategies are provided in Supplementary Digital Content Table B-2, http://links.lww.com/JAM/A275; the general strategies are summarized here.

FIGURE 1. Article Flow Diagram.

TABLE 3. Correlation Between Transfer Components (Pearson r)

| Completion Rate | Stable METH | Last 5D METH | Min Wait | Initial D1 dose | Total D1 BUP | Total D2 BUP | Escalation | Stable BUP |
|-----------------|-------------|--------------|----------|-----------------|--------------|--------------|------------|------------|
|                 | −0.63       | −0.54        | −0.25    | 0.12            | 0.06         | −0.17        | −0.14      | −0.38      |
|                 | 0.95        | 0.50         | 0.08     | 0.11            | 0.41         | 0.57         | 0.10       | 0.74       |
|                 | 0.51        | 0.11         | 0.00     | 0.27            | 0.09         | 0.54         | 0.09       | 0.76       |
|                 |             |              |          | 0.65            | 0.52         | 0.52         | −0.16      | 0.53       |
|                 |             |              |          |                 | 0.50         | 0.50         | 0.25       | 0.14       |
|                 |             |              |          |                 | 0.09         | 0.90         | −0.30      | 0.46       |
|                 |             |              |          |                 |              |              | −0.19      | 0.67       |
|                 |             |              |          |                 |              |              |           | 0.29       |

SD indicates 5 days; BUP, buprenorphine; D1, Day 1; D2, Day 2; METH, methadone.
Initial Buprenorphine Dose on First Day

The weighted mean initial buprenorphine dose on the first day was 3.3 mg. In 10 studies, the initial buprenorphine dose on the first day was fixed.21,23,25–29,35,37,38 In another study, the initial buprenorphine dose was administered via a transdermal patch that delivered 35 µg/h.34 The remaining studies allowed the initial dose on the first day to vary.22,24,30,32,33,36

Most studies assessed response to the initial dose of buprenorphine and administered at least 1 additional dose later on the first day if response was insufficient. However, in 6 studies21–25,26,30,32 and 1 arm of a seventh,24 patients received only a single first-day buprenorphine dose.

Total First-Day Dose of Buprenorphine

The crude and weighted mean total buprenorphine doses on the first day were 8.6 and 7.8 mg, respectively. The lowest total first-day fixed dose was 2 mg,21 and the lowest possible total first-day flexible-dose was 1 mg.30 The highest initial fixed or flexible total daily dose on the first day was 32 mg.29,37

Buprenorphine Dose Stabilization

The weighted mean stable buprenorphine dose was 14 mg per day. The difference between the initial buprenorphine dose on day 1 and the stable dose ranged from 0.0 to 31.2 mg, with a crude mean of 11.7 mg. The difference between the total dose on the first day and the stable dose ranged from 0.0 to 28.8 mg with a crude mean of 6 mg.

Individual studies’ progression from the first buprenorphine dose to stabilization varied widely (Supplementary Digital Content Table B-3, http://links.lww.com/JAM/A275). For example, a stable dose of buprenorphine was reached in a single day in some studies.21,29,35,37 Other studies used various fixed, multiple-day schedules that were designed to reach target doses anywhere between 8 mg and 32 mg.23,25,26,29,32,36

In studies, buprenorphine dosing was determined by the patient’s response to the previous buprenorphine doses.25,27,38 A single study used transdermal buprenorphine for the transition.32 The remaining studies were vague in their descriptions of the stabilization process.22,28,30,33

The microdosing procedure used in the case series is described in detail in Supplementary Digital Content Table B-2, http://links.lww.com/JAM/A275.39 Briefly, the intended process was to administer the patient’s full dose of methadone for 7 days concurrently with an increasing dose of sublingual buprenorphine/naloxone. The protocol used in the case series was intended to begin with a single 0.5-mg dose once on the first day and then escalate to an 8-mg dose following the morning and a 4-mg dose in the evening on day 7 (which was also the last day of methadone—still at the full dose). On day 8, the patient began taking a single daily 12-mg dose of buprenorphine. Two of 3 patients whose outcomes were described in the case series ultimately deviated from the treatment protocol (Supplementary Digital Content Table B-2, http://links.lww.com/JAM/A275).

Outcomes

Precipitated Withdrawal

Precipitated withdrawal not attributable to a protocol violation was reported in 8 studies.21,24,26,29,33,35,38 The definitions and timing of “precipitated withdrawal” were often not well-described. Only 1 study38 operationally defined precipitated withdrawal: an increase in COWS score of 6 or more points, occurring within 6 hours of the first dose of sublingual buprenorphine. In this study, the proportion of patients experiencing precipitated withdrawal was 3/33 (9%) overall, with 3 cases reported in the high-dose group (3/15 [20%]) and none in low and moderate dose groups (between-groups P = not significant). Two of 3 cases noted above involved deviations from the study protocol.

Transfer Completion

Fifteen studies reported the number of patients who completed the transfer process, generally defined as achieving and maintaining a stable dose of buprenorphine, though the definition varied across individual studies.21–23,25–27,29,31,32,34–39 Transfer completion rates were generally high (Table 3; range 67%–100%; weighted mean 92%), with no trend by publication year.

Meta-analysis and meta-regression were considered but were deemed inadvisable due to several factors including (a) considerable heterogeneity among the included studies’ designs, populations, and treatments; (b) the inherent interrelatedness of several of the transfer components; (c) the small number of patients in several studies; (d) the overall high level of transfer completion; and (e) the lack of any significant findings in one-way analyses of variance (see next paragraph).

Although some of the individual components of the transfer process were correlated at least moderately with transfer completion rate (Table 3), only 1 statistically significant association was found (Table 4). Stable (pretaper) methadone dose was negatively correlated with completion rate (Pearson r = −0.63), and the completion rate decreased from 98% at methadone doses less than 40 mg to 82% at methadone doses greater than 60 mg (P = 0.03). No other differences were statistically significant. In addition to the aforementioned results, both patients in the microdosing study completed the transfer.

Reasons for Discontinuation of Transfer

Patients across studies discontinued the transfer for several reasons including intolerable withdrawal symptoms before the first buprenorphine dose23; failure to show signs of withdrawal, even after 5 days of methadone abstinence (thus buprenorphine was not given)36; severe precipitated withdrawal secondary to administration of buprenorphine without ensuring that the patient was in withdrawal35–38; development of withdrawal symptoms that were not severe but caused sufficient discomfort that the patient chose to reinitiate methadone27,29; side effects of buprenorphine28; failure to “stabilize” on buprenorphine28; consumption of prohibited medications (eg, benzodiazepines, amphetamines)27,36; return to opioid use29,38; alcohol intoxication on transfer day36; and incarceration.36
Methadone to Buprenorphine Transfer Strategies

### DISCUSSION

There have been few well-conducted, adequately powered, randomized studies that enable firm conclusions to be drawn regarding optimal transfer strategies. Most identified studies were observational case series with little harmonization between studies on how study populations, procedures, and outcomes were defined or reported, complicating comparisons across studies. Nonetheless, we identified a number of key variables previously documented as being important in understanding the transfer process and outcomes. Those factors are commonly described in clinical practice guidelines, and an aim of this review was to identify whether the available evidence can provide greater clarity in transfer recommendations.

Our review identified high correlations between many of these factors, highlighting that they are not independent of each other and complicating the interpretation of each variable in isolation, particularly as no studies have used proper study designs (eg, randomization) or had sufficient patient numbers to enable these factors to be assessed independently. Another difficulty in comparing strategies was the high rates of successful completion of transfers reported: most approaches reported achieved positive outcomes a majority of the time.

Although there is limited clinical utility in examining single transfer components because they are by design part of an interconnected process, the extreme heterogeneity of the included studies’ designs, populations, drug formulations, and outcome measurements made it unfeasible to group and examine “transfer strategies.”

Our findings suggest that, while no “best” or “optimal” method of transfer can be identified from the available studies, some conclusions can be drawn. Successful transfer (defined loosely as having reached and maintained a stable dose of buprenorphine) was statistically significantly associated with lower pretransfer methadone dose, particularly below methadone doses of 60 mg. Although many of the included studies found that pretransfer methadone reduction did not affect transfer completion, it may remain good clinical practice to do so when attempting to transition patients. However, where dose reduction is difficult to achieve, the evidence does not preclude the transfer of patients from higher methadone doses up to 100 mg – most studies at such dose levels reported favorable outcomes, which indicates that higher dose transfer are possible although may be somewhat more difficult to achieve.

Although the approaches documented in most of these studies yielded high rates of transfer completion and generally mirrored the procedures recommended in most clinical guidelines, there remains a poor understanding of how to address transfer when recommended strategies cannot be followed or when complications arise. For example, though the recommendation to reduce the methadone dose gradually to a low dose (less than 40 or 60 mg) can be followed under most circumstances, the available evidence does not provide concrete guidance to the clinician who needs to discontinue high-dose methadone (eg, 180 mg) rapidly in a hospitalized patient with high-risk QT interval corrected (QTc) prolongation (eg, QTc = 540 ms). Another issue poorly addressed in the available literature is the clinical management of the patient

| Variable | Transfer Completion Rate (Unweighted) | F or t Statistic and P |
|----------|--------------------------------------|-----------------------|
| Setting  |                                      |                       |
| Inpatient| 125/138 (90.6%)                       | \(t = -1.41\)          |
| Outpatient| 154/163 (94.5%)                      | \(P = 0.18\)          |
| Pretransfer METH dose\(^1\) |                        |                       |
| < 40 mg | 108/110 (98.2%)                       |                       |
| 40–60 mg | 86/93 (92.5%)                        | \(F = 4.23\)          |
| > 60 mg | 66/81 (81.5%)                        | \(P = 0.03\)          |
| Minimum wait time before initial BUP dose |                   |                       |
| \(< 24 h\) | 121/129 (93.8%)                    | \(t = 1.12\)          |
| \(> 24 h\) | 176/194 (90.7%)                    | \(P = 0.28\)          |
| Degree of withdrawal at initial BUP dose |                       |                       |
| Mild | 81/86 (94.2%)                        | \(t = 0.44\)          |
| Moderate | 107/121 (88.4%)                     | \(P = 0.66\)          |
| BUP product |                                  |                       |
| BUP monotherapy | 211/230 (91.7%)     | \(t = 0.09\)          |
| BUP + NLX | 90/97 (92.8%)                     | \(P = 0.93\)          |
| Initial first-day BUP strategy |                      |                       |
| Fixed dose | 202/220 (91.8%)                  | \(t = -0.17\)         |
| Flexible dose | 105/114 (92.1%)     | \(P = 0.87\)          |
| Total first-day BUP strategy\(^2\) |                  |                       |
| Single dose | 105/111 (94.6%)              | \(F = 0.49\)          |
| Split dose | 114/128 (89.1%)                 | \(P = 0.62\)          |
| Mixed or flexible strategy | 78/84 (92.9%) |                       |
| Overall | 307/334 (91.9%)                     | NA                    |

\(^1\)Defined as achieving and maintaining a stable dose of BUP, unless defined otherwise by individual study.

\(^2\)Transfer completion rates were identical for starting METH dose and METH dose averaged over final 5 days.

\(^3\)Does not include the study that administered a 35 mg/h BUP patch at 12 hours after last METH dose.

BUP indicates buprenorphine; METH, methadone; NA, not applicable; NLX, naloxone.

### Treatment Retention

Seven studies reported retention in treatment for at least 2 months after transfer.\(^28–32,34,39\) Retention rates ranged from 40% to 73% during follow-up periods ranging from 2 to 30 months. Reasons for not remaining in the study treatment programs included completion of treatment, return to methadone, removal for disciplinary reasons, transfer of treatment outside to other providers, return to opioid use, and death.

### Mortality and Morbidity

One death was reported, specifically a case of hepatic failure secondary to long-standing chronic hepatitis C infection occurring 42 months after transfer to buprenorphine, which was not considered related to transfer procedures.\(^32\) No studies reported overdose, and a serious adverse event was reported in one study.\(^29\) A patient in the “slow transfer” arm of the RCT of 3 buprenorphine induction protocols left treatment on day 4 after receiving 16 mg of buprenorphine and with a prescription for 32 mg daily thereafter. One week postdischarge, he was admitted involuntarily to a hospital psychiatric ward for an apparent psychotic reaction that was thought to be possibly attributable to buprenorphine; however, after discharge, the patient recommenced buprenorphine 8 mg and then 16 mg, without recurrence of psychosis.
experiencing severe precipitated withdrawal. Various guidelines suggest symptomatic medications, additional buprenorphine, or resumption of full MOUD, but there is little documented evidence from clinical settings to support these recommendations. Whilst there is increasing interest in a number of “less conventional” transfer procedures (eg, microdosing, transfer using a short-acting opioid as a bridging medication [eg, oxycodone, morphine], or initiation direct from methadone to depot buprenorphine formulations), there is insufficient documented evidence to support these approaches at this time.

Several recommendations for future research can be made. First, studies should be carefully designed and sufficiently powered to measure, compare, and statistically analyze the key components of the transfer strategy or clinical guideline. Greater attention must be given to how key variables are defined and measured. For example, few studies operationalized how precipitated withdrawal was identified or used a clearly stated withdrawal threshold for initiating buprenorphine dosing. Additionally, the motivation for transfer (eg, as an attempt to withdraw from MOUD or due to medication side effects) can have significant clinical implications for the approach used, yet few studies have documented patient experience and motivation in this context.7,38

Finally, patient education and its effect on patient behavior and outcomes should be examined.

CONCLUSIONS

Despite more than 20 years of research, our evidence base for informing optimal approaches to transfer from methadone to buprenorphine remains limited. Few studies have used designs that enable comparison of different approaches; thus, only general recommendations can be reached. Most international clinical guidelines provide recommendations consistent with the available evidence. However, clinical guidelines should be seen as providing “guidance” rather than “protocols” to be adhered to, and clinicians and patients need to exercise judgment in attempting transfers.

ACKNOWLEDGMENTS

The authors wish to thank Barbara Zedler, MD, Chris Chapleo, BSc (Hons) PhD, Lenn Murrelle, MSPH, PhD, and Bret Ryder, B Pharm MPH, for their support in the article review process. This work was funded by Indivior Inc.

REFERENCES

1. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study, 2017. Lancet (London England). 2018;392(10159):1789–1858.

2. United Nations Office on Drugs and Crime. World Drug Report 2019. Vienna, Austria: United Nations; 2019.

3. Overdose death rates, 2019. Available at: https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates. Accessed January 27, 2020.

4. The Council of Economic Advisors. The underestimated cost of the opioid crisis. 2017. Available at: https://www.whitehouse.gov/sites/whitehouse.gov/files/images/The%20Council%20underestimated%20The%20Cost%20of%20the%20Opioid%20Crisis.pdf. Accessed March 9, 2020.

5. Board of ASAM Directors. The ASAM National Practice Guideline for the use of medications in the treatment of addiction involving opioid use. Chevy Chase, MD: American Society of Addiction Medicine; 2015.

6. Gowing L, Ali R, Dunlop A, Farrell M, Lintzeris N. National guidelines for medication-assisted treatment of opioid dependence. 2014. Available at: https://www.health.gov.au/sites/default/files/national-guidelines-for-medication-assisted-treatment-of-opioid-dependence.pdf. Accessed March 9, 2020.

7. Winstock AR, Lintzeris N, Lea T. Why do patients report transferring between methadone and buprenorphine? Drug Alcohol Rev. 2009;28(6):686–687.

8. Casadonte PP, Sullivan MA. Transfer from Methadone to Buprenorphine. 2013. Available at: https://ccssnow.org/wp-content/uploads/2014/03/PCSS-MATGuidanceTransferMethadonetoBup.Casadonte.pdf. Accessed March 9, 2020.

9. British Columbia Centre on Substance Use. A guideline for the clinical management of opioid use disorder. 2017. Available at https://www.bccsu.ca/wp-content/uploads/2017/06/BC-OUDD-Guidelines_June2017.pdf. Accessed March 9, 2020.

10. Walsh SL, June HL, Schuh KJ, Preston KL, Bigelow GE, Stitzer ML. Effects of buprenorphine and methadone in methadone-maintained subjects. Psychopharmacology. 1995;119(3):268–276.

11. Ehret GB, Desmeules JA, Broers B. Methadone-associated long QT syndrome: improving pharmacotherapy for dependence on illegal opioids and lessons learned for pharmacology. Expert Opin Drug Saf. 2007;6(3):289–303.

12. Gupta A, Lawrence AT, Krishnan K, Kvinsky CJ, Trohan RG. Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de points. Am Heart J. 2007;153(6):891–899.

13. Martell BA, Arnsten JH, Krantz MJ, Gourevitch MN. Impact of methadone treatment on cardiac repolarization and conduction in opioid users. Am J Cardiol. 2005;95(7):915–918.

14. Yee A, Danaee M, Loh HS, Sulaiman AH, Ng CG. Sexual dysfunction in heroin dependents: A comparison between methadone and buprenorphine maintenance treatment. PLoS One. 2016;11(11):e0147852.

15. Yee A, Loh HS, Hisham Hashim HM, Ng CG. The prevalence of sexual dysfunction among male patients on methadone and buprenorphine treatments: A meta-analysis study. J Sex Med. 2014;11(1):22–32.

16. Fanoe S, Hvidt C, Ege P, Jensen GB. Syncope and QT prolongation among patients treated with methadone for heroin dependence in the city of Copenhagen. Heart. 2007;93(9):1051–1055.

17. Wedman EF, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MC. QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. Arch Intern Med. 2007;167(22):2469–2475.

18. World Health Organization. Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence. Geneva, Switzerland: World Health Organization; 2009.

19. New Zealand practice guidelines for opioid substitution treatment. 2014. Available at https://www.health.govt.nz/system/files/documents/publications/nz-practice-guidelines-opioid-substitution-treatment-apr14-v2.pdf. Accessed March 10, 2020.

20. Mannelli P, Peindl KS, Lee T, Bhatia KS, Wu LT. Buprenorphine-mediated transition from opioid agonist to antagonist treatment: State of the art and new perspectives. Curr Drug Abuse Rev. 2012;5(1):52–63.

21. Lukas SE, Jasinski DR, Johnson RE. Electroencephalographic and behavioral correlates of buprenorphine administration. Clin Pharmacol Ther. 1984;36(1):127–132.

22. Rosen M, Kosten TR. Detoxification and Induction onto Naltrexone. In: Cowan A, Lewis JW, eds. Buprenorphine: Combating Drug Abuse with a Unique Opioid. New York, NY: Wiley-Liss; 1995:289-305.

23. Levin FR, Fischman MW, Connerney I, Foltin RW. A protocol to switch high-dose, methadone-maintained subjects to buprenorphine. Am J Addict. 1997;6(2):105–116.

24. Bouchez J, Beauverie P, Touzeau D. Substitution with buprenorphine in methadone- and morphine sulfate-dependent patients. Preliminary results. Eur Addict Res. 1998;4(Suppl 1):8–12.
25. Breen CL, Harris SJ, Lintzeris N, et al. Cessation of methadone maintenance treatment using buprenorphine: transfer from methadone to buprenorphine and subsequent buprenorphine reductions. *Drug Alcohol Depend.* 2003;71(1):49–55.

26. Greenwald MK, Schuh KJ, Stine SM. Transferring methadone-maintained outpatients to the buprenorphine sublingual tablet: a preliminary study. *Am J Addict.* 2003;12(4):365–374.

27. Glasper A, Reed LJ, de Wet CJ, Gossop M, Bearn J. Induction of patients with moderately severe methadone dependence onto buprenorphine. *Addict Biol.* 2005;10(2):149–155.

28. Stein MD, Cioe P, Friedmann PD. Buprenorphine retention in primary care. *J Gen Intern Med.* 2005;20(11):1038–1041.

29. Clark NC. Transferring from high doses of methadone to buprenorphine. Expanding the options for the treatment of heroin dependence with oral supervised opioid substitution therapy: LAAM, buprenorphine and slow release oral morphine as alternatives to methadone. *Melbourne, Australia: University of Melbourne; 2006:103–188.

30. Gonzalez-Saiz F, Gutierrez Ortega J, Bilbao Acedos I, Ballesta Gomez R, Lozano Rojas O. Induction from methadone to sublingual buprenorphine: A descriptive clinical trial in a methadone patients sample treated in therapeutic communities. *Trastor Adict.* 2008;10(1):49–64.

31. Gonzalez-Saiz F, Gomez RB, Acedos IB, Rojas OL, Ortega JG. Methadone-treated patients after switching to buprenorphine in residential therapeutic communities: An addiction-specific assessment of quality of life. *Heroin Addict Relat Clin Probl.* 2009;11(2):9–20.

32. Salsitz EA, Holden CC, Tross S, Nugent A. Transitioning stable methadone maintenance patients to buprenorphine maintenance. *J Addict Med.* 2010;4(2):88–92.

33. Whitley SD, Sohler NL, Kunins HV, et al. Factors associated with complicated buprenorphine inductions. *J Subst Abuse Treat.* 2010;39(1):51–57.

34. Hess M, Boesch L, Leisinger R, Stohler R. Transdermal buprenorphine to switch patients from higher dose methadone to buprenorphine without severe withdrawal symptoms. *Am J Addict.* 2011;20(5):480–481.

35. Conroy S, Hill D. Transfer to buprenorphine from daily doses of methadone greater than 30 mg - Initial review of transfers. *Heroin Addict Relat Clin Probl.* 2013;15(3):19–28.

36. Naumovski B, Batey RG. High-dose methadone transfer to buprenorphine in outpatient settings. *Int J Ment Health Addict.* 2015;13(2):194–203.

37. Oretti R. A retrospective evaluation of inpatient transfer from high-dose methadone to buprenorphine substitution therapy. *J Subst Abuse Treat.* 2015;57:102–105.

38. Lintzeris N, Monds LA, Rivas C, et al. Transferring patients from methadone to buprenorphine: The feasibility and evaluation of practice guidelines. *J Addict Med.* 2018;12(3):234–240.

39. Terasaki D, Smith C, Calcaterra SL. Transitioning hospitalized patients with opioid use disorder from methadone to buprenorphine without a period of opioid abstinence using a microdosing protocol. *Pharmacotherapy.* 2019;39(10):1023–1029.

40. Supporting recovery from opioid addiction: community care best practice guidelines for buprenorphine and suboxone. 2013. Available at: http://www.williamwhitepapers.com/pr/Community%20Care%20Best%20Practice%20Guidelines%20for%20Buprenorphine%20and%20Suboxone%202014.pdf. Accessed March 9, 2020.

41. Cockayne L. Guidelines for titration onto buprenorphine in opioid dependence. 2011. Available at: https://www.fifeadtc.scot.nhs.uk/media/12771/a7-guidelines-for-the-titration-on-to-buprenorphine-for-opioid-dependence-final-april-2011.pdf. Accessed March 9, 2020.

42. Treatment Improvement Protocol 63: Medications for Opioid Use Disorder. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2018.