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

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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Trials and the World Health Organization International Clinical Trials Registry Platform were used to identify unpublished trial results. Records 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

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Opioid 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

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complicated process of transferring patients from methadone to buprenorphine.[6,9,18,19] 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.[10] 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.[20] 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.[21–39] 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 Table B-2, http://links.lww.com/JAM/A275).

One small case series used a microdosing procedure.[39] 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 $r \geq 0.50$, 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*

	ASAM (United States) 2015[5]	Common-wealth of Australia 2014[6]	British Columbia (Canada) Ministry of Health 2017[9]	CCBHO (Pittsburgh, PA) 2013[40]	New Zealand Ministry of Health 2014[19]	NHS (United Kingdom) Fife 2011[41]	WHO 2009[18]	SAMHSA (United States) 2018[42]
Before BUP administration								
METH dose and taper guidance	NA; patients on 30–40 mg will be less comfortable	Gradual dose reductions to ≤60 mg/d	Taper to <60 mg, ideally ≤30 mg/d, for 6–7 d	Gradual taper to ≤30 mg/d for 5–7 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	24–72 h	NA	≥24 h, preferably 48–72 h	48–72 h	≥24 h	≥24 h, preferably 36 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 > 12	COWS 13–24	"Ideally when withdrawal signs are evident"	COWS ≥ 12
BUP administration: day 1								
Initial dose	2–4 mg	2 mg	BUP/NLX 4 mg/1 mg†	2 mg	2 mg	2 mg if equivocal objective signs of withdrawal, 4 mg if clear signs of moderate withdrawal	NA	BUP/NLX 2/0.5 mg–4/1 mg
Additional dosing guidance	Prescribe increments of 2–4 mg if no withdrawal symptoms evident after 60–90 minutes	If initial dose does not cause precipitated withdrawal after 1 h, may give additional 6 mg Supplementary doses: COWS <6: no additional BUP; COWS 6–12: additional 4 mg; COWS ≥13: additional 8 mg	Increments of 2 mg/0.5 mg BUP/NLX up to a maximum of 12 mg/3 mg If need for additional dose uncertain, consider prescribing one or two 2 mg/0.5 mg BUP/NLX tablets as take-home doses	2 mg every 2 h as needed; maximum 8 mg	Additional 6 mg after 1 h if the initial dose does not precipitate withdrawal Supplementary doses (every 1–3 h): COWS < 6 = no BUP; COWS 6–12 = additional 4 mg; COWS ≥ 13 = additional 8 mg	Additional 2–4 mg depending on COWS (cut-offs not specified) score and pupil size; maximum 8 mg	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 +: COWS 0–5, SOWS <8: +4 mg COWS 6–12, SOWS 8–15: +4 mg COWS ≥13, SOWS ≥16: +8 mg Maximum 32 mg	If no withdrawal symptoms since last BUP, continue once-daily dose of the total amount of BUP/NLX administered on day 1, titrating as needed in subsequent days, aiming for target dose ≥16 mg/4 mg	Start with day one total dose +4 mg BUP; if still symptomatic after 2 h, give 4 mg to a total of 16 mg on day 2	Dosing on days 2–4: total amount from day 1 +: COWS 0–5: +4 mg COWS 6–11: +4 mg COWS > 12: +8 mg Maximum 32 mg	Total day one dose + 2–4 mg if obvious withdrawal features present, otherwise repeat day 1 dose	NA	Maximum 16 mg, otherwise document rationale for higher dose
Dose range	Generally 8–16 mg; maximum 24 mg/d	Most patients require 12–24 mg; some as little as 4–8 mg, others as much as 32 mg/d (maximum)	Target dose of BUP/NLX ≥16 mg/4 mg; maximum 24 mg/6 mg/d	8–24 mg	Generally 12–24 mg; maximum 32 mg/d	NA	Generally 8–24 mg/d; maximum 32 mg/d	BUP/NLX 2 mg/0.5 mg–4 mg/1 mg; 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; CCBOH, Community Care Behavioral Health Organization; COWS, Clinical Opiate Withdrawal Scale; METH, methadone; mg, milligrams; NA, not addressed; NHS, National Health Service; NLX, naloxone; SAMHSA, Substance Abuse and Mental Health Services Administration; SOWS, Subjective Opiate Withdrawal Scale; WHO, World Health Organization.

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
Interventions and Comparisons	Transfer from BUP (or BUP/NLX) to METH	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
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*)	Non-serious adverse events
Study Designs	Randomized and non-randomized controlled trials; Non-comparative and uncontrolled trials; Prospective and retrospective cohort studies; Case series	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
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/ucm053087.htm.
BUP indicates buprenorphine; METH, methadone; NA, not applicable; NLX, naloxone; OUD, opioid use disorder.

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]; 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.[29] 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).

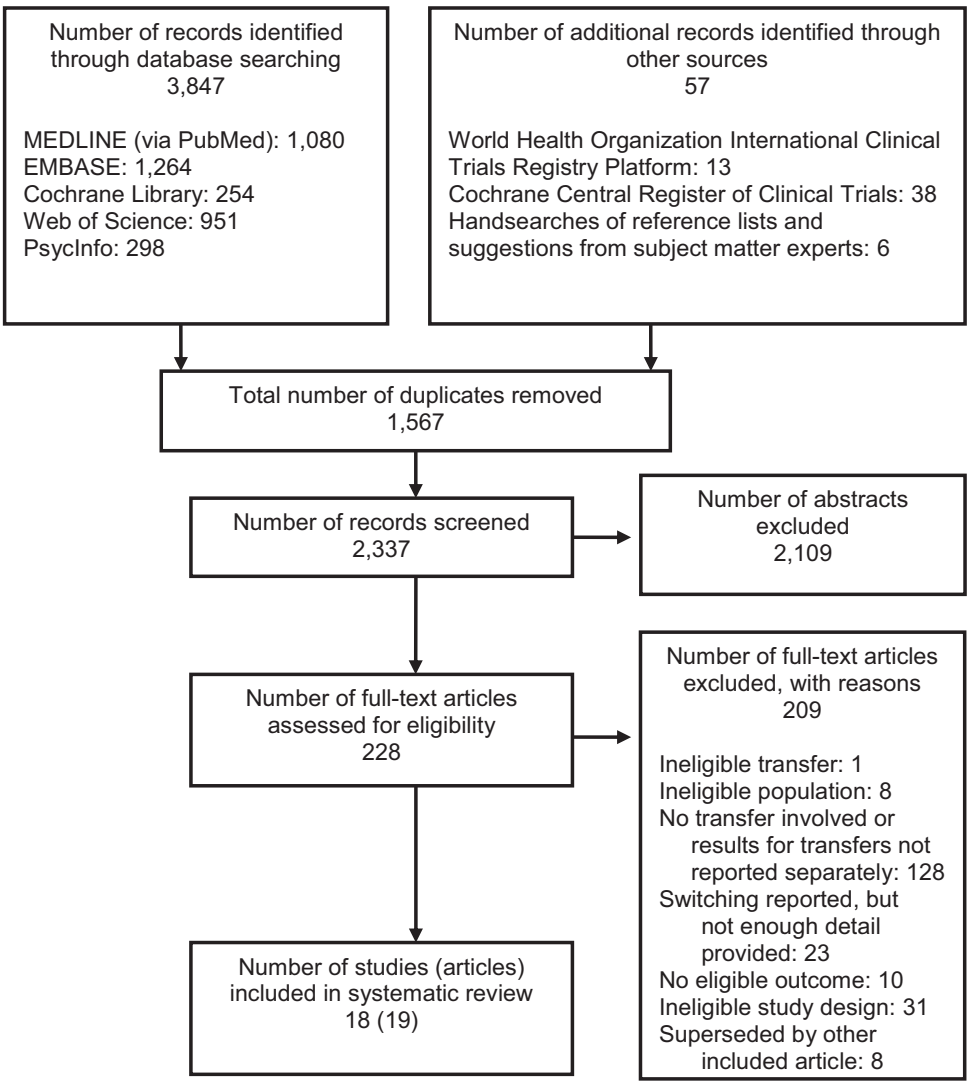

FIGURE 1. Article Flow Diagram.

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.

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	Completion rate
		0.95	0.50	0.08	0.41	0.57	0.10	0.74	Stable METH
			0.51	0.11	0.49	0.54	0.09	0.76	Last 5D METH
				0.00	0.27	0.52	−0.16	0.53	Min wait
					0.65	0.50	0.25	0.14	Initial D1 dose
						0.90	−0.30	0.46	Total D1 BUP
							−0.19	0.67	Total D2 BUP
								0.29	Escalation
									Stable BUP

5D 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 studies[21–23,26,30,32] 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 over 2 to 7 days.[23,26,29,32,36]

In 3 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.[34] 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 the following 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.[21,24,26,29,33,35,38,39] However, the definitions and timing of "precipitated withdrawal" were often not well-described. Only 1 study[38] 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 dose[23]; 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 withdrawal[35–38]; development of withdrawal symptoms that were not severe but caused sufficient discomfort that the patient chose to reinitiate methadone[27,29]; side effects of buprenorphine[38]; failure to "stabilize" on buprenorphine[25]; consumption of prohibited medications (eg, benzodiazepines, amphetamines)[27,36]; return to opioid use[29,38]; alcohol intoxication on transfer day[36]; and incarceration.[36]

TABLE 4. Transfer Completion Rate* by Transfer Component

Variable	Transfer Completion Rate (Unweighted)	*F* or *t* Statistic and Corresponding *P*
Setting		
Inpatient	125/138 (90.6%)	$t = -1.41$
Outpatient	154/163 (94.5%)	$P = 0.18$
Pretransfer METH dose†		
<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‡		
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

*Defined as achieving and maintaining a stable dose of BUP, unless defined otherwise by individual study.

†Transfer completion rates were identical for starting METH dose and METH dose averaged over final 5 days.

‡Does not include the study that administered a 35 μg/hr 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.

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 complicate 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

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.

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