Unobserved "Home" Induction Onto Buprenorphine

Joshua D. Lee, MD, MSc, Frank Vocci, PhD, and David A. Fiellin, MD

Background: Unobserved, or "home" buprenorphine induction is common in some clinical practices. Patients take the initial and subsequent doses of buprenorphine after, rather than during, an office visit. This review summarizes the literature on the feasibility and acceptability, safety, effectiveness, and prevalence of unobserved induction.

Methods: We searched the English language literature for studies describing unobserved buprenorphine induction and associated outcomes. Clinical studies were assessed by strength of design, bias, and internal and external validity. Surveys of provider practices and unobserved induction adoption were reviewed for prevalence data and key findings. We also examined previous review papers and international buprenorphine treatment guidelines.

Results: N = 10 clinical studies describing unobserved induction were identified: 1 randomized controlled trial, 3 prospective cohort studies, and 6 retrospective cohort studies. The evidence supports the feasibility of unobserved induction, particularly in office-based primary care practices. Evidence is weak to moderate in support of no differences in adverse event rates between unobserved and observed inductions. There is insufficient or weak evidence in terms of any or no differences in overall effectiveness (treatment retention, medication adherence, illicit opioid abstinence, other drug use). N = 9 provider surveys assessed unobserved induction: observed induction logistics are seen as barriers to buprenorphine prescribing; unobserved induction appears widespread in specific locations. International guidelines reviewed emphasize clinician or pharmacist observed induction (the United States, the United Kingdom, France, Australia); only one (Denmark) explicitly endorses unobserved induction.

Conclusions: There is insufficient evidence supporting unobserved induction as more, less, or as effective as observed induction. However, the predominantly observational and naturalistic studies of unobserved induction reviewed, all of which have significant sources of bias and limited external validity, document feasibility and low rates of adverse events. Unobserved induction seems to be widely adopted in US and French regional provider surveys. Prescribers, policy makers, and patients should balance the benefits of observed induction such as maximum clinical supervision with the ease-of-use and comparable safety profile of unobserved induction.

Key Words: buprenorphine, induction, medication adherence, opioid-related disorders, patient compliance, unobserved induction

(*J Addict Med* 2014;8: 299–308)

From the Department of Population Health (JDL), Division of General Internal Medicine, New York University School of Medicine, New York; Friends Research Institute (FV), Baltimore, MD; and Department of Internal Medicine (DAF), Yale University School of Medicine, New Haven, CT.

Received for publication November 3, 2013; accepted May 19, 2014.

Dr. Lee is a Co-Lead Investigator of the National Institute of Drug Abuse Clinical Trial Network Study 0051, Extended-Release Naltrexone vs. Buprenorphine Opioid Treatment, which is receiving free study drug from Reckitt Benckiser. Dr. Lee is the principal investigator of an investigator-initiated trial funded by Alkermes, Inc. Dr. Vocci is a member of an External Advisory Board that advises Buprenorphine Products Manufacturers. Dr. Vocci has provided consultation on medications development projects for the following companies: Alkermes, Braeburn, Catalyst Pharmaceutical Partners, Demerx, GW Pharmaceuticals, Intrratabs, Pinney Associates, Reckitt Benckiser, Titan, Transcept and Teva Pharmaceuticals. Dr. Vocci has also worked on grant collaborations with Catalyst Pharmaceutical Partners, Kingston Pharmaceuticals, and Reckitt Benckiser Pharmaceuticals. Dr. Vocci has also been on the speaker's. bureau for Reckitt Benckiser Pharmaceuticals. Dr. Vocci is currently an investigator for Alkermes, Intratabs, and Braeburn Pharmaceuticals. All financial compensation for all the above activities is paid to Friends Research Institute, Dr. Vocci's employer. David A. Fiellin, MD, has received honoraria from Pinney Associates for serving on an external advisory committee monitoring the diversion and abuse of buprenorphine.

Send correspondence and reprint requests to Joshua D. Lee, MD, MSc, 227 E 30th St 712, New York, NY 10016. E-mail: joshua.lee@nyumc.org.

ISSN: 1932-0620/14/0805-0299
DOI: 10.1097/ADM.0000000000000059

Unobserved, or "home" buprenorphine induction, in which patients take the initial doses of buprenorphine after, rather than during, an office visit, seems to be common in some clinical practices (*this report uses the term "buprenorphine" to represent the general category of all buprenorphine and buprenorphine-naloxone products approved for office-based opioid treatment*) (Walley et al., 2008). However, current US national prescribing guidelines published by the Center for Substance Abuse Treatment (CSAT) of the Substance Abuse and Mental Health Service Administration (SAMHSA) addressing buprenorphine induction describe observed induction as standard practice (CSAT, 2004; Fiellin et al., 2004). The Food and Drug Administration buprenorphine labeling also specifies supervised induction, as well as initiating treatment with the buprenorphine mono tablet product at a maximum day 1 dose of 8 mg (Reckitt Benckiser, 2011a, 2011b). A recent label revision for Suboxone buprenorphine-naloxone film adds the supervised induction indication (Reckitt Benckiser, 2014). The discrepancy between guideline protocols and clinical practice supports the need to evaluate the existing literature and compare the feasibility and acceptability, safety, effectiveness, and prevalence of the 2 induction approaches, and consider updates to national guidelines.

The number of total US individual patients treated with buprenorphine has steadily risen in the last decade after US

approval for opioid dependence treatment in 2002, from approximately 100,000 in 2005 to more than 800,000 in 2009 (SAMHSA, 2013). Concurrently, nonmedical (nonprescribed) buprenorphine-related ED visits have risen, from 4440 in 2006 to 15,788 in 2010, raising concerns regarding safe prescribing and diversion (SAMHSA, 2013). In this context, it is likely that the merits of "more intensive" versus "less intensive" approaches to buprenorphine dispensing will continue to be of interest to patients, providers, and policy makers.

Directly observed buprenorphine induction dosing of patients in opioid abstinence syndrome (withdrawal) is an important element of the Center for Substance Abuse Treatment and Veterans Administration guidelines (CSAT, 2004; Department of Veterans Affairs, 2013). Buprenorphine has higher μ-opioid receptor binding affinity than other opioids, yet, as a partial μ agonist, may precipitate acute opioid withdrawal symptoms in tolerant patients who have recently used opioids. Patients must refrain from use and enter a state of opioid withdrawal before buprenorphine induction. US and other countries' guidelines describe protocols in which clinicians document withdrawal symptoms before induction dosing and then monitor patients over a 1- to 2-hour period. At least 1 follow-up visit during the first week of treatment is encouraged. It is important to note that these guidelines were based on the best available evidence at the time and designed for providers and patients for whom buprenorphine induction was new. The guidelines prioritize minimizing induction complications and ensuring a successful transition onto buprenorphine maintenance.

Observed induction, however, can present significant challenges to many practice settings. Staffing, medication availability, regulations governing dispensing of controlled substance, and practice environments may not readily accommodate patients in active opioid withdrawal being given buprenorphine and subsequent assessments over 1 or more hours. Primary care and general psychiatry settings typically do not require consecutive observed induction or consecutive daily visits to begin other chronic care treatments or when prescribing other controlled substances, although few other prescription medications have the potential of causing a syndrome such as acute precipitated opioid withdrawal. Induction issues were among the top issue for contacts to the Physician Clinical Support System for Buprenorphine (PCSS-B), a Substance Abuse and Mental Health Service Administration (SAMHSA)–sponsored national mentoring network for buprenorphine prescribers (Egan et al., 2010).

Unobserved, off-site, or "home," induction is a potentially less resource intensive approach to buprenorphine induction. A patient is evaluated to determine their appropriateness for buprenorphine treatment before beginning treatment, typically while still using opioids and not experiencing opioid withdrawal. If deemed appropriate for buprenorphine treatment, the patient then receives self-induction instructions, a prescription for buprenorphine, and decides themselves, based on instructions, when to discontinue opioid misuse, initiate withdrawal, and self-administer the first and all subsequent doses of buprenorphine. This sequence is consistent with most ambulatory prescribing. It offers potential time- and resource-saving advantages and may be more comfortable for the patient, provided the unobserved induction experience is otherwise as safe and uncomplicated as observed induction.

To further address the gap between the earlier guidelines and what seems to now be common practice, we reviewed the literature for published studies that examine the feasibility and acceptability, safety, and effectiveness of unobserved buprenorphine induction. Of particular interest were induction outcomes, including rates of precipitated withdrawal, adverse events, and postinduction treatment retention. We also reviewed studies examining provider attitudes and detailing the prevalence of unobserved induction prescribing, and guidelines commenting on current best practices, to assess the practical adoption of unobserved induction.

METHODS

Eligibility, Information Sources, and Search Strategy

We conducted a systematic review of the English-language literature on unobserved buprenorphine induction after an adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) approach (Moher et al., 2009). We targeted human opioid treatment clinical studies presenting data on the feasibility and acceptability, safety, and effectiveness of unobserved buprenorphine induction, and provider and practice surveys, reviews, letters, and published guidelines pertinent to unobserved induction. We performed MEDLINE (PubMed.gov) searches with no date restrictions using terms related to unobserved buprenorphine induction and treatment ("buprenorphine," "buprenorphine/naloxone," "induction," "treatment," "buprenorphine/therapeutic use," "unobserved induction," "home induction," "at-home induction") and Google searches for international buprenorphine treatment guidelines.

Study Selection, Data Collection, Data Items, and Synthesis of Results

All clinical trials and observational studies that described an unobserved induction cohort and interpretable outcome data, including naturalistic, practice-based retrospective studies, were identified and reviewed by the 3 authors. This included buprenorphine treatment cohort studies not primarily designed to assess differences between unobserved or observed induction outcomes. Primary outcomes of interest were rates and methods of unobserved induction, induction-related adverse events, treatment retention at 1 week, longer-term retention, and other clinical outcomes (ie, negative opioid urine toxicologies during maintenance treatment). Study characteristics and outcomes were tabulated: study design, sample size, practice setting, method of unobserved induction assignment (ie, random assignment, patient preference, unobserved induction only), and key descriptive findings and other sources of bias. As described previously, studies and results were considered individually rather than synthesized and pooled because of a limited number of published studies, including a single small pilot randomized control trial, the otherwise nonrandom and unbalanced assignment of observed induction controls, and the heterogeneity of study designs, aims, and lack of blinded

primary outcomes. Data were extracted by the primary author (J.D.L.), and the strength of evidence was determined and adjudicated by the 3 authors. Review results were organized by strength of internal validity (study design, power, biases, outcome assessment) and external validity (generalizability, relevance of outcomes) after a US Preventive Services Task Force (USPSTF, 2008) critical appraisal methodology. Provider surveys were assessed for reported rates of adoption of unobserved induction (prevalence), provider attitudes, and barriers and facilitators of unobserved/observed induction. Finally, we summarized review articles, letters, and published national treatment guidelines for endorsements or specific recommendations against unobserved induction and relevant comments regarding feasibility, safety, and effectiveness.

RESULTS

Randomized Clinical Trials and Observational Studies

Ten studies comprised the published English-language literature on clinical studies of unobserved buprenorphine induction: 1 randomized controlled trial (RCT), 3 prospective cohort studies, and 6 retrospective cohort studies (Table 1). No studies describing an unobserved induction approach were excluded. Seven of the 10 compared outcomes between unobserved and observed induction; 4 of which (1 RCT, 1 prospective, 2 retrospective) were designed a priori to focus on and analyze differences in unobserved versus observed induction outcomes. Notably, none are large randomized trials powered to focus on or detect small but possibly clinically significant differences between induction approaches in terms of adverse events or retention. The studies were predominantly conducted among safety net populations in primary care settings.

The sole RCT of observed versus unobserved buprenorphine induction was a single-site pilot that randomized 20 opioid-dependent adults to unobserved induction with patient pamphlet and phone support versus a multiday office-based observed induction, both after 2 screening and diagnostic visits (Gunderson et al., 2010). Patients were primarily heroin-only users (75%) and many (45%) had prior treatment with buprenorphine. Primary outcomes were nonblinded rates of induction-related safety events, including precipitated withdrawal, successful induction at 1 week defined as remaining in treatment, withdrawal free, and taking buprenorphine, and retention at weeks 4 and 12. Findings indicated no differences in rates of induction-related safety events, including one case of precipitated withdrawal in an unobserved induction participant. There were no differences in successful induction, treatment retention, buprenorphine maintenance dose, or opioid misuse. While a small pilot study was conducted at a single center without blinding, this is the only reviewed trial that employed a randomized design.

Three reports on overlapping buprenorphine patient cohorts at a Federally Qualified Health Center (FQHC) in Bronx, New York, by researchers at Montefiore Medical Center specifically focused on observed versus unobserved induction (Sohler et al., 2010; Whitley et al., 2010; Cunningham et al., 2011). Unobserved induction emphasized self-management of opioid withdrawal and buprenorphine induction using a "patient-centered toolkit" and provider telephone support. Sohler et al. retrospectively reviewed and analyzed a combined unobserved/observed cohort (N = 115; n = 51 observed, n = 64 unobserved). Participants underwent observed induction during the first 2 years of the program; later participants (n = 87) were given a choice, with physician agreement, of observed versus unobserved. A majority of patients (n = 51; 59%) elected unobserved induction. Nonblinded analysis of safety and retention found no differences between groups in rates of induction-related adverse events (17%, both groups) or day 30 retention (78%, both groups).

Whitley et al. (2010) then examined cohorts who underwent unobserved (n = 47) or observed (n = 60) induction from the same center for factors associated with "difficult inductions," including acute precipitated (9% of all inductions) and protracted withdrawal (7%), defined as typical opioid withdrawal symptoms persisting for 24 hours or more despite initial buprenorphine induction doses. Similar to the earlier Sohler study (the 2 studies examined many of the same subjects; sample sizes differed slightly), rates of adverse induction events did not differ between the 2 induction groups. Factors independently associated with complicated inductions included recent use of methadone, recent benzodiazepine use, no prior patient experience with buprenorphine (prescribed or unprescribed), and low induction doses of buprenorphine. The occurrence of induction adverse events was associated with lower rates of retention at day 30 (56% among those with adverse events vs 88% with uncomplicated inductions; $P = 0.001$), with most of this dropout occurring by the seventh day of treatment.

Cunningham et al. (2011) prospectively analyzed differences in drug misuse and treatment retention after buprenorphine maintenance initiation, again comparing participants undergoing observed (n = 13) with participants choosing the same patient-centered, toolkit-based unobserved (n = 66) induction at the same Bronx, New York, FQHC. The authors state, "[a]fter recognizing the barriers associated with standard-of-care inductions, we developed a patient-centered unobserved home-based induction strategy and introduced it into clinical practice." Barriers described were "employed patients had difficulties missing work, patients felt uncomfortable experiencing opioid withdrawal symptoms in a busy waiting room, and physicians struggled with time demands." This study began recruiting HIV-infected patients to observed induction and later recruited patients with any HIV status while also incorporating unobserved induction; early participants were, therefore, more likely to have been HIV-infected and to have undergone observed induction. Once the unobserved induction protocol was in place, most (95%) participants in this study cohort chose unobserved induction. Except for higher rates of HIV infection among those who underwent observed inductions, no baseline differences were found between the 2 groups. Unobserved induction participants had no significant differences in opioid use (adjusted odds ratio = 0.63, 95% confidence interval = 0.13-2.97) but greater reductions in any drug use (adjusted odds ratio = 0.05, 95% confidence interval = 0.01-0.37) during the first 6 months of treatment, as determined by urine toxicology tests. Declines in opioid and other drug use seen in the first month of treatment were sustained through 6 months. These 3 studies are the largest comparative

TABLE 1. Unobserved Buprenorphine Induction Studies, 2007–2012 (N = 10): Study Characteristics, Sorted by Sample Size

Author	Year	Study Design	N	Unobserved Induction, %	Unobserved Induction Assignment	Site	Discussion
Soeffing JM	2009	Retrospective cohort	255	Not specified	Preference	Academic center, primary care	Feasibility of unobserved induction was implied (% unobserved induction not available); overall cohort with usual rates of good clinical outcomes
Doolittle B	2011	Retrospective cohort	228	228 (100%)	Unobserved	Academic-affiliated, community hospital primary care	Feasibility of unobserved induction appeared high; very low rate of "clinically significant" precipitated withdrawal (1 case in 228 inductions)
Lee JD	2012	Prospective cohort	142	120 (85%)	Jail-induced (observed) vs community-induced (unobserved)	Academic center, public hospital primary care	No differences in drug misuse and retention of office-based buprenorphine between jail (observed induction) and community (unobserved) referrals; no specific analysis by induction
Sohler NL	2010	Retrospective cohort	115	51 (44%)	Observed only, then preference	Academic center, FQHC primary care	Unobserved induction was highly feasible; no difference vs observed induction in AEs and retention; unobserved induction preferred by 59% of patients
Whitley SD	2010	Retrospective cohort	107	47 (44%)	Observed only, then preference	Academic center, FQHC primary care	No difference vs observed induction in AEs; prolonged withdrawal symptoms more likely with methadone-to-buprenorphine
Lee JD	2008	Prospective cohort	103	103 (100%)	Unobserved only	Academic center, public hospital primary care	Unobserved induction highly feasible; low rates of induction-related AEs; retention and drug misuse outcomes similar to other public sector naturalistic studies
Mintzer IL	2007	Retrospective cohort	99	54 (55%)	Hospital clinic (observed) vs FQHC (unobserved)	Academic center, hospital and FQHC primary care	No difference by primary care site and observed/unobserved induction in treatment retention and opioid misuse
Alford DP	2007	Retrospective cohort	85	41 (48%)	Homeless (observed) vs nonhomeless (unobserved)	Academic center, primary care	No difference by housed/homeless status and observed/unobserved induction in treatment retention or opioid misuse
Cunningham CO	2011	Prospective cohort	79	66 (84%)	Preference	Academic center, FQHC primary care	No difference in drug misuse at week 24; unobserved induction preferred by 95% of patients
Gunderson EW	2010	Randomized controlled trial	20	10 (50%)	Randomization	Academic center, primary care	Pilot randomized controlled trial; no difference in safety and effectiveness outcomes

analyses explicitly focused on differences between induction methods and are limited by lack of randomization, potential selection bias (unobserved induction reflected patient preference), unbalanced HIV status, and size of comparison arms in Cunningham et al., nonblinded outcome determination, and retrospective assessments of main outcomes. As such they provide limited observational evidence that induction adverse event rates, buprenorphine maintenance retention, and in-treatment opioid and drug misuse, are similar regardless of induction approach.

One prospective, nonblinded, single-arm cohort study in a NYC public hospital primary care clinic provided adverse event and retention rates at 1 week among 103 consecutive participants offered unobserved induction only (Lee et al., 2009). Similar to the Bronx FQHC, this center used a patient home induction pamphlet and physician telephone support. This study collected detailed information on induction-related adverse events, and reported no cases of severe precipitated withdrawal or adverse events among the 92 of 103 patients with available data (adverse events among the 11 patients lost-to-follow-up could not be ruled out). Mild-to-moderate precipitated withdrawal (5%), defined as any new buprenorphine-triggered withdrawal symptom rated by the patient as mild or moderate (vs severe) and protracted withdrawal (5%), defined similarly to Whitley et al., were not associated with dropout at 1 week of treatment. Protracted withdrawal symptoms were associated with baseline methadone use, as in the Whitley study. In addition, an important contributor to week 1 dropout was participants' failure to fill buprenorphine prescriptions due to insurance issues or out-of-pocket costs.

Lacking a comparison observed induction arm and using non-blinded assessments, the Lee et al. practice-based study prospectively estimated rates of unobserved induction adverse events, yielding findings very similar to the Gunderson, Sohler, and Whitley studies. All of these consolidated around a rate of serious adverse events of less than 1%, rates of precipitated withdrawal of less that 9%, and rates of any difficult induction including protracted withdrawal of less than 30%. Recent methadone use was a risk factor for difficult inductions, and difficult induction were, along with lacking health insurance, associated with early treatment dropout across the Sohler, Whitley, and Lee studies.

Three additional clinical studies provided an unobserved versus observed comparison nested within a primary comparison of 2 cohorts defined by clinic site, housing status, and jail release status, respectively. Mintzer et al. retrospectively analyzed treatment retention and a composite "opiate sobriety" primary outcome, defined as a physician's "global assessment" at 6 months of treatment goals and urine toxicology tests, among adults treated with buprenorphine at 2 Boston sites, a hospital clinic (observed) and a neighborhood health center (unobserved) (Mintzer et al., 2007). Because of a lack of on-site pharmacy services, the health center provided unobserved induction with phone support. This study found no differences between the 2 settings in terms of treatment retention or the opiate sobriety outcome at 6 months: 51% neighborhood health center, 58% hospital clinic ($P = 0.50$). The authors cited as a clinical challenge, "[t]he multiple visits required during the induction phase of treatment result[ing] in scheduling problems, particularly at the hospital-based clinic, where patients were observed on-site for 4 hours after the induction dose of buprenorphine was administered." Alford et al. (2007) described a collaborative nurse-physician model of care among both homeless and domiciled patients treated at Boston Medical Center. Domiciled patients were offered unobserved induction; homeless patients were offered observed induction. Both groups retrospectively demonstrated comparable outcomes in terms of treatment retention and opioid abstinence. A second prospective study from NYU/Bellevue compared referrals from NYC jails (n = 32), 22 of whom had completed observed buprenorphine induction before jail release, to community-referred buprenorphine patients (n = 110, which included the n = 103 unobserved inductions previously described) offered only unobserved induction (Lee et al., 2012). Rates of longitudinal retention and opioid misuse were similar between groups. As described previously, the primary foci of these 3 studies were feasibility and longitudinal outcomes within primary care, homeless, and criminal justice populations. They were not focused on differences between the 2 induction approaches and did not report rates of immediate postinduction outcomes, including induction-related adverse events.

Doolittle and Becker, retrospectively and in a non-blinded fashion, reviewed community hospital primary care office-based buprenorphine treatment outcomes after unobserved induction only (Doolittle and Becker, 2011). One case of "clinically significant" precipitated withdrawal requiring hospitalization was described out of 228 inductions over a 4-year period, yielding a crude event rate of 1% or less. Soeffing et al. (2009) describe a cohort receiving both unobserved and observed inductions. Both induction strategies are reported as feasible; however, the report does not specify the number of patients treated with each method or present induction-related outcomes, including adverse events. Neither study allows for comparison of observed versus unobserved induction cohorts.

Provider and Practice Surveys

Nine physician and practice cross-sectional surveys pertinent to unobserved induction and buprenorphine prescribing barriers were identified and reviewed (Table 2). Observed induction logistics and complexity (provider and patient time, on-site medication storage, addiction expert back-up) are identified as barriers to buprenorphine prescribing, particularly among new prescribers with less addiction treatment experience (Turner et al., 2005; Cunningham et al., 2007; Gunderson et al., 2006; Kissin et al., 2006; Thomas et al., 2008; Netherland et al., 2009; Albright et al., 2010). However, these surveys examined buprenorphine prescribing generally and did not focus on unobserved versus observed induction differences or specifics. Similarly but not included in Table 2 as it was not a formal provider survey and instead a description of a mentoring program, the Egan et al. report on PCSS-B reported buprenorphine induction dosing and timing issues as 2 of the 3 most frequent topics discussed between PCSS-B mentors and community providers (Egan et al., 2010). Based on a 2007 US state (Massachusetts) and a 2001 French regional sample, the practice of unobserved induction was common: the Massachusetts survey indicated that many physicians (43%) had adopted unobserved induction as regular practice (Walley et al., 2008); the French survey documented that 29% of pharmacy-based inductions were unobserved, and none were supervised by prescribing general practitioners or conducted in a medical office setting (Vignau et al., 2001).

Reviews, Letters, and National Guidelines

No general or systematic reviews regarding unobserved induction were identified. One scientific letter provides a summary of unobserved induction (Gunderson, 2011). The

TABLE 2. Cross-Sectional Surveys Pertinent to Unobserved Induction Practices, 2001–2013 (N = 8): Study Characteristics, Sorted by Publication Date

Author	Year	N	Population	Discussion
Vignau J	2001	142 patients, 280 GPs, 110 pharmacies	French regional patient, physician, and pharmacist sample	29% of buprenorphine inductions not supervised by pharmacists or other health personnel; no supervised dosing by prescribing physicians; during the first 61 wks of buprenorphine national approval in France, 28% of physicians and 51% of pharmacists were buprenorphine providers
Turner BJ	2005	249	New York State Medicaid-accepting public sector clinic directors	Ability to store narcotics on site was associated with greater willingness to prescribe buprenorphine
Cunningham CO	2007	99	Attending and resident primary care physicians, single academic site	The most frequent reasons for not prescribing buprenorphine were lack of knowledge or training (48%) and lack of time (25%); physicians involved in primary care-oriented programs (vs nonprimary care) were more likely to have positive attitudes regarding buprenorphine.
Gunderson E	2006	53	Practicing (73%) and in-training (23%) buprenorphine-novice physicians (57%, psychiatry)	Posttest following online and in-person American Psychiatric Association office-based buprenorphine training; among the respondents who were hesitant to begin prescribing buprenorphine after the training, the primary barriers were a lack of experience (41%), concern that induction is difficult and time consuming (24%), and inadequate reimbursement (24%).
Kissin W	2006	545	US buprenorphine-waivered physicians	Prescribers identified prescribing challenges: induction logistics (27% of prescribers), record-keeping requirements, the previous 30-patient limit, DEA involvement, limited patient compliance; induction logistics was not associated with stopping prescribing
Walley AY	2008	235	Massachusetts buprenorphine-waivered physicians	Observed induction practices reported by 57% of prescribers
Thomas CP	2008	495	General and addiction psychiatrists	Among top barriers for both groups of prescribers: "[buprenorphine] does not fit in with my practice," "it would change the patient mix undesirably," "prescribing is too complex"
Netherland J	2009	172	Buprenorphine-waivered HIV providers	Compared with other physicians, experienced prescribers were less concerned with induction logistics
Albright J	2010	294	Buprenorphine-waivered psychiatrists in a managed care network	5 factors that were endorsed by the greatest number of psychiatrists as adversely affecting decisions to use buprenorphine or increase the number of buprenorphine patients: urine testing requirements and logistical issues, possibility of patients selling their buprenorphine or taking more than prescribed, attracting more opioid-dependent patients to their practice, concern about DEA intrusion, belief of greater time commitment for treating buprenorphine patients

letter considered many of the current review's sources and supported the overall approach of unobserved induction for reasons of feasibility, patient preference, and comparable safety and effectiveness versus observed induction. These recommendations aligned with the rationale and aims of the author's unobserved induction randomized trial (Gunderson, 2011). A 2009 PCSS-Medication Assisted Treatment (PCSS-MAT) document, "Buprenorphine Induction," updated in

2013, rated the evidence supporting unobserved induction as "Low/Moderate," stating, "Unobserved induction remains outside the TIP Guidelines, remains under investigation, and there is no evidence to support its use by inexperienced clinicians or with unstable patients" (Casadonte and Sullivan, 2013). This 2013 update referenced 3 of the 10 clinical studies included in the current review.

English-, French-, and German-language guidelines from the United Kingdom (2005), Australia (2006), Denmark (2008), Germany (2010), and France (2011) were reviewed and summarized using the European Monitoring Centre for Drugs and Drug Addiction index (EMCDDA, 2013) and a previous review (Carrieri et al., 2006). Overall, these guidelines do not consistently focus on specific unobserved versus observed induction differences. Only one, Denmark, explicitly endorses both observed and unobserved inductions (National Board of Health, 2008). Australian guidelines specifically recommend supervised (observed) dosing (typically through pharmacies) not only during induction, but during the early months of buprenorphine maintenance phase as well, and as such are not wholly applicable to typical US office-based prescribing (Lintzeris et al., 2006). UK guidelines specify supervised induction; however, they also seem to allow for unobserved dosing, depending on "social factors," including employment and child-care considerations (National Institute for Health and Clinical Excellence, 2005). German guidelines mandate supervised treatment for the initial 6 months of treatment (Bundesaerztekammer, 2010). French guidelines recommend that physicians coordinate treatment closely with an area pharmacist, and that the pharmacist directly administer observed buprenorphine day 1 to 14 doses "when possible" (Agence Francaise de Sécurité Sanitaire des Produits de Santé, 2011). This may reflect the fact that observed dosing by the pharmacist is not always possible or necessary and may proceed unobserved. Notably, French office-based buprenorphine treatment relies entirely on community pharmacists for dispensing and supervised dosing; general practitioners or other office-based staff do not themselves administer or observe induction (Carrieri et al., 2006). In summary, it seems that Danish, French, and UK guidelines allow for a range of induction approaches, including unobserved induction, with only Denmark explicitly discussing and endorsing unobserved induction. Australian and German guidelines directly recommend observed induction and directly observed maintenance treatment. Pharmacist-observed induction in Australia and France is presumably less time-consuming and not as carefully documented as recommended by US observed induction guidelines, which include pre/post–Clinical Opioid Withdrawal Scales and in-office counseling.

DISCUSSION

A growing body of evidence reveals that unobserved or home induction with buprenorphine is feasible and prevalent. Considering well-described implementation models, practice data, and patient preference reports, there is weak to moderate evidence to support the feasibility of unobserved induction. In terms of rates of adverse events and safety outcomes, the data reviewed are of weak to moderate strength in support of no differences between induction approaches. In terms of induction effectiveness, which we defined as a clinically successful induction week 1, there is insufficient evidence to comment on unobserved induction as less, equal, or more effective versus observed induction. Provider attitudinal data consistently cite observed induction logistics as barriers to adoption across multiple provider surveys, although it seems that unobserved induction has been relatively widely adopted in the Massachusetts and French regional surveys. Observed induction remains the recommended induction approach in Australian, French, German, UK, and US national treatment guidelines. Denmark's explicit endorsement of unobserved induction is a notable exception. These guidelines were largely published after the unobserved induction literature included in this review appeared in press. Allowing for unobserved induction in Danish, French, and UK guidelines, the French and Australian emphasis on community pharmacist, not in-office provider, observed dosing, as well the 2013 Casadonte and Sullivan PCSS-MAT induction update, may reflect a consensus to minimize barriers to access.

Feasibility and Acceptability

The 2 regional provider surveys with prevalence data (Vignau et al., 2001; Walley et al., 2008) and the 10 clinical studies reviewed provide weak to moderate support for the feasibility of unobserved buprenorphine induction among interested patients. Although acceptability to patients is more difficult to infer if sites offered only unobserved induction, the 3 analyses from investigators at Albert Einstein College of Medicine and Montefiore Medical Center (Sohler et al., 2010; Whitley et al., 2010; Cunningham et al., 2011), in which unobserved induction was the physician-supported preference of a large majority of patients (59% and 95% in consecutive cohorts), and the RCT by Gunderson (Gunderson et al., 2010), which randomized patients to the unobserved versus observed induction arms, are the clearest signals that some patients either prefer or at least willingly accept unobserved induction when offered. The data supporting feasibility of unobserved induction have been generated largely from academic and community primary care settings, rather than specialty drug treatment programs, supporting the translation of these findings to office-based buprenorphine treatment. However, these studies characterize a limited number of individuals receiving treatment in a restricted range of largely academic and public sector treatment settings, where detailed patient educational materials were provided and follow-up care was perhaps more closely observed than would be routine in other office-based practices. This may not yet reflect the realities of smaller or solo practices.

Safety

In the 4 comparative unobserved versus observed induction studies, rates of adverse events and serious adverse events were low in both arms, with no differences between arms detected (Gunderson et al., 2010; Sohler et al., 2010; Whitley et al., 2010; Cunningham et al., 2011). Given the lack of a priori noninferiority or equivalence designs focused explicitly on adverse event outcomes, a single small pilot randomized trial, and selection and measurement bias across the remaining comparative analyses, the evidence was weak to moderate

in support of no significant differences between induction approaches in terms of safety. Interestingly, direct comparisons to expected observed induction-related adverse event rates are not available across a broad range of studies. In the largest and most rigorously designed buprenorphine treatment trials using observed induction methods, acute precipitated withdrawal was not a common adverse event, compared to headache, nausea, and insomnia, and is typically not listed as occurring with any regularity (Ling et al., 1996, 1998; Fudala et al., 2003, Weiss et al., 2011). One Australian trial observed precipitated withdrawal in 10% (11 of 115) subjects undergoing observed induction in specialty versus primary care settings (Gibson et al., 2003); another a rate of 12% during a 5-day outpatient buprenorphine detoxification taper for heroin dependence (Lintzeris et al., 2002). This principal safety concern surrounding buprenorphine induction seems to occur in about 10% or fewer inductions, regardless of whether observed or unobserved induction methods are used. Furthermore, mild or moderate precipitated or protracted withdrawal symptoms are treated with additional doses of buprenorphine over several hours to several days and seem not to merit inpatient admissions. Thus, regardless of induction approaches or the frequency of postinduction clinic visit schedules, management of induction-related adverse events is largely accomplished with provider support by the patient themselves outside of a clinical setting.

Diversion of buprenorphine is another important safety concern. Strategies promoted to minimize diversion include avoiding excessive daily doses, prescription of buprenorphine/naloxone rather than the buprenorphine mono product when feasible, patient education regarding storage, urine testing for opioids, including buprenorphine, observed ingestion, and pill counts (Martin, 2010). No identified studies analyzed diversion as an induction-related outcome. As there are no available data comparing the two approaches in terms of diversion, providers and practices must weigh a higher theoretical possibility of diversion associated with unobserved induction, where patients receive an initial prescribed quantity of buprenorphine but may not return for close follow-up. A mitigation strategy would be to shorten the duration and quantity of the initial unobserved prescription. Otherwise, given most US office-based buprenorphine diversion likely takes place during maintenance, when dosing is unobserved and dropout likely involves much larger quantities of buprenorphine, the contribution of induction-related diversion to the overall supply of illicit buprenorphine is unknown but likely modest.

Effectiveness

Patients seem to successfully induce onto buprenorphine at high rates independent of unobserved versus observed approaches. In general, induction completion rates in recent randomized clinical trials and naturalistic studies employing observed buprenorphine induction clustered around 84% (range, 83%-85%) (Stein et al., 2005; Fiellin et al., 2006; Moore et al., 2007; Lucas et al., 2010), proportions that did not include additional preinduction dropout of 10% to 15% of screened eligible patients not returning for observed induction. In the observational studies comparing unobserved versus observed induction, ranges for successful unobserved induction were 60% to 93% (Alford et al., 2007; Mintzer et al., 2007; Gunderson et al., 2010; Cunningham et al., 2011; Lee et al., 2012). When retention data were available, dropout rates at 1, 4, 12, and 14 weeks were similar between the 2 induction approaches, as were rates of continued opioid misuse over time. However, given the heterogeneity of effectiveness outcomes and the lack of large randomized comparative effectiveness trials, the degree to which different induction strategies impact postinduction and longer-term buprenorphine effectiveness is unknown. More than likely, factors, including social support and stable health insurance, other drug and alcohol use disorders, and serious psychiatric and medical comorbidities, contribute more to good clinical outcomes than do unobserved versus observed induction protocols.

Program Characteristics and Methodological Limitations

Considering the 10 clinical studies reviewed, it is clear that large safety net buprenorphine primary care practices affiliated with academic medical centers in Baltimore, New York City, Connecticut, and Boston have adopted unobserved buprenorphine induction approaches as standard of care. These sites used team-based collaborative care models and emphasized patient-centered chronic disease management, patient handouts, and telephone support. The extent to which these characteristics are replicated in other office-based buprenorphine treatment settings is not known. The US survey data that show a high rate of unobserved induction adoption (43%) are restricted to a single state (Massachusetts) and time (2007). It would be useful to have more recent information reflecting national practice.

CONCLUSIONS

Unobserved buprenorphine induction seems to have been adopted by some large US academic centers, community primary care sites, and Massachusetts providers, and seems common in France. Compared with observed induction, unobserved induction does not seem to be associated with disproportionate adverse events or lower treatment retention rates in the small number of studies that have reported on this practice. It would appear either manner of induction onto buprenorphrine provides a reasonable strategy to allow access to the beneficial health and treatment outcomes associated with the buprenorphrine maintenance. Prescribers should weigh the benefits of observed induction and supervised dosing with the potentially increased ease of use and comparable safety of unobserved induction. Continued optimization and dissemination of effective buprenorphine induction and maintenance strategies remain an important area for clinical and research effort.

REFERENCES

Agence Francaise de Sécurité Sanitaire des Produits de Santé. Initiation et suivi du traitement substitutif de la pharmacodépendance majeure aux opiacés par buprénorphine haut dosage. 2011. Available at http://www.emcdda.europa.eu/attachements.cfm/att_185066_FR_FR07_buprenorphine%20ANSM_2011.pdf. Accessed March 3, 2014.

Albright J, Ciaverelli R, Essex A, et al. Psychiatrist characteristics that influence use of buprenorphine medication-assisted treatment. *J Addict Med* 2010;4:197–203.

Alford DP, LaBelle CT, Richardson JM, et al. Treating homeless opioid dependent patients with buprenorphine in an office-based setting. *J Gen Intern Med* 2007;22:171–176.

Bundesaerztekammer, Germany. Richtlinien der Bundesaerztekammer zur Durchfuehrung der substitutionsgestuetzten Behandlung Opiatabhaengiger. 2010. Available at http://www.emcdda.europa.eu/attachements.cfm/att_115796_DE_6.&20BÄK&20(2010)&20Substitutionsrichtlinien-1.pdf. Accessed March 3, 2014.

Carrieri MP, Amass L, Lucas GM, et al. Buprenorphine use: the international experience. *Clin Infect Dis* 2006;15(43)(suppl 4):S197–S215.

Casadonte PP, Sullivan MA. Buprenorphine induction. Providers' clinical support system for medication assisted treatment, PCSS guidance. 2013. August 9, 2006 (Updated November 27, 2013). Available at http://pcssmat.org/wp-site/wp-content/uploads/2014/02/PCSS-MATGuidanceBuprenorphineInduction.Casadonte.pdf. Accessed March 3, 2014.

Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction: A Treatment Improvement Protocol (TIP) Series 40. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2004.

Cunningham CO, Giovanniello A, Li X, et al. A comparison of buprenorphine induction strategies: patient-centered home-based inductions versus standard-of-care office-based inductions. *J Subst Abuse Treat* 2011;40:349–356.

Cunningham CO, Kunins HV, Roose RJ, et al. Barriers to obtaining waivers to prescribe buprenorphine for opioid addiction treatment among HIV physicians. *J Gen Intern Med* 2007;22:1325–1329.

Department of Veterans Affairs, Pharmacy Benefits Management Services. Clinical guidance—Buprenorphine sublingual, criteria for use. April 2013. Available at http://www.pbm.va.gov. Accessed March 3, 2014.

Doolittle B, Becker W. A case series of buprenorphine/naloxone treatment in a primary care practice. *Subst Abus* 2011;32:262–265.

Egan JE, Casadonte P, Gartenmann T, et al. The physician clinical support system-buprenorphine (PCSS-B): a novel project to expand/improve buprenorphine treatment. *J Gen Intern Med* 2010;25:936–941.

European Monitoring Centre for Drugs and Drug Addiction. Standards and guidelines for practices. 2013. Available at http://www.emcdda.europa.eu/best-practice/standards/treatment. Accessed March 3, 2014.

Fiellin DA, Kleber H, Trumble-Hejduk JG, et al. Consensus statement on office-based treatment of opioid dependence using buprenorphine. *J Subst Abuse Treat* 2004;27:153–159.

Fiellin DA, Pantalon MV, Chawarski MC, et al. Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. *N Engl J Med* 2006;355:365–374.

Fudala PJ, Bridge TP, Herbert S, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med* 2003;349:949–958.

Gibson AE, Doran CM, Bell JR, et al. A comparison of buprenorphrine treatment in clinic and primary care settings: a randomised trial. *Med J Aust* 2003;179:38–42.

Gunderson EW. Buprenorphine induction: a major barrier for physician adoption of office-based opioid dependence treatment. *J Addict Med* 2011;5:304–305.

Gunderson EW, Fiellin DA, Levin FR, et al. Evaluation of a combined online and in person training in the use of buprenorphine. *Subst Abus* 2006;27:39–45.

Gunderson EW, Wang XQ, Fiellin DA, et al. Unobserved versus observed office buprenorphine/naloxone induction: a pilot randomized clinical trial. *Addict Behav* 2010;35:537–540.

Kissin W, McLeod C, Sonnefeld J, et al. Experiences of a national sample of qualified addiction specialists who have and have not prescribed buprenorphine for opioid dependence. *J Addict Dis* 2006;25:91–103.

Lee JD, Grossman E, DiRocco D, et al. Home buprenorphine/naloxone induction in primary care. *J Gen Intern Med* 2009;24:226–232.

Lee JD, Grossman E, Truncali A, et al. Buprenorphine-naloxone maintenance following release from jail. *Subst Abus* 2012;33:40–47.

Ling W, Charuvastra C, Collins JF, et al. Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. *Addiction* 1998;93:475–486.

Ling W, Wesson DR, Charuvastra C, et al. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. *Arch Gen Psychiatr*. 1996;53:401–407.

Lintzeris N, Bell J, Bammer G, et al. A randomized controlled trial of buprenorphine in the management of short-term ambulatory heroin withdrawal. *Addiction* 2002;97:1395–1404.

Lintzeris N, Clark N, Winstock A. Commonwealth of Australia, National Clinical Guidelines and Procedures for the use of Buprenorphine in the Treatment of Opioid Dependence. 2006. Available at http://www.nationaldrugstrategy.gov.au/internet/drugstrategy/publishing.nsf/content/9011C92D2F6E1FC5CA2575B4001353B6/$File/bupren.pdf. Accessed March 3, 2013.

Lucas GM, Chaudhry A, Hsu J, et al. Clinic-based treatment of opioid-dependent HIV-infected patients versus referral to an opioid treatment program: a randomized trial. *Ann Intern Med* 2010;152:704–711.

Martin J. Adherence, diversion and misuse of sublingual buprenorphine. In: Physicians' Clinical Support System—Buprenorphine. 2010. Available at http://pcssb.org/wp-content/uploads/2010/09/PCSS-B-Adherence-diversion-and-misuse-of-sublingual-buprenorphine1.pdf. Accessed March 3, 2014.

Mintzer IL, Eisenberg M, Terra M, et al. Treating opioid addiction with buprenorphine-naloxone in community-based primary care settings. *Ann Fam Med* 2007;5:146–150.

Moher D, Liberati A, Tetzlaff J, et al. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006–1012.

Moore BA, Fiellin DA, Barry DT, et al. Primary care office-based buprenorphine treatment: comparison of heroin and prescription opioid dependent patients. *J Gen Intern Med* 2007;22:527–530.

National Board of Health, Denmark. Guidance no. 42 on medical treatment of drug abusers in substitution treatment for opioid dependence. 2008. Available at http://www.emcdda.europa.eu/attachements.cfm/att_101843_EN_1.%20DK04_Guidance_Opioid_10nov08-1.pdf. Accessed March 3, 2014.

National Institute for Health and Clinical Excellence (NICE), National Health Service, UK. Methadone and buprenorphine for the management of opioid dependence, NICE technology appraisal guidance 114. 2005. Available at http://www.nice.org.uk/TA114. Accessed March 3, 2014.

Netherland J, Botsko M, Egan J, et al. Factors affecting willingness to provide buprenorphine treatment. *J Subst Abuse Treat* 2009;36:244–251.

Reckitt Benckiser. Suboxone full prescribing information. 2011a. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020733s007s008lbl.pdf. Accessed March 3, 2014.

Reckitt Benckiser. Subutex full prescribing information. 2011b. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020732s006s007lbl.pdf. Accessed March 3, 2014.

Reckitt Benckiser. Labeling Revision: Suboxone. April 28, 2014. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022410s004s017s018lbl.pdf. Accessed May 19, 2014.

Soeffing JM, Martin LD, Fingerhood MI, et al. Buprenorphine maintenance treatment in a primary care setting: outcomes at 1 year. *J Subst Abuse Treat* 2009;37:426–430.

Sohler NL, Li X, Kunins HV, et al. Home- versus office-based buprenorphine inductions for opioid-dependent patients. *J Subst Abuse Treat* 2010;38:153–159.

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

Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. The DAWN Report: Emergency Department Visits Involving Buprenorphine. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2013.

Thomas CP, Reif S, Haq S, et al. Use of buprenorphine for addiction treatment: perspectives of addiction specialists and general psychiatrists. *Psychiatr Serv* 2008;59:909–916.

Turner BJ, Laine C, Lin YT, et al. Barriers and facilitators to primary care or human immunodeficiency virus clinics providing methadone or buprenorphine for the management of opioid dependence. *Arch Intern Med* 2005;165:1769–1776.

US Preventive Services Task Force. Critical Appraisal Methodology, U.S. Preventive Services Task Force Procedure Manual. 2008. Available at http://www.uspreventiveservicestaskforce.org/uspstf08/methods/procmanual.html. Accessed March 3, 2014.

Vignau J, Duhamel A, Catteau J, et al. Practice-based buprenorphine maintenance treatment (BMT): how do French healthcare providers manage the opiate-addicted patients? *J Subst Abuse Treat* 2001;21:135–144.

Walley AY, Alperen JK, Cheng DM, et al. Office-based management of opioid dependence with buprenorphine: clinical practices and barriers. *J Gen Intern Med* 2008;23:1393–1398.

Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. *Arch Gen Psychiatr* 2011;68:1238–1246.

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