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Short communication

Short communication: Systematic review on effectiveness of micro-induction approaches to buprenorphine initiation

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ABSTRACT

Background/objectives: Micro-induction is a novel buprenorphine induction approach that seeks to avoid withdrawal and minimize precipitated withdrawal, both barriers to standard inductions. We aimed to synthesize evidence on micro-induction effectiveness, and regimens described.

Methods: We searched scientific databases and grey literature for studies including adolescents or adults with opioid use disorder who received buprenorphine micro-induction. Study selection, data extraction and quality assessments occurred in duplicate. We narratively synthesized results.

Results: We screened 4,752 citations and included 19 case studies/series and one feasibility study (n = 57 patients; mean age 38 years [SD 12.0]; 57.9% male [33/57]).

Studies described 26 regimens; starting and maintenance doses ranged from 0.03 to 1.0 mg, and 8 to 32 mg, respectively. We calculated rate of increase to 8 mg.

All patients achieved the desired maintenance dose. Among 54 patients in whom precipitated withdrawal was not reported, mean increases were 1.36 mg/day (SD 0.41). For three patients in whom precipitated withdrawal was specifically reported, mean increase was 1.17 mg/day (SD 0.11).

All studies were low quality.

Discussion: Described regimens are highly variable. Inconsistent reporting, selection bias, and poor quality evidence limit conclusions regarding optimal dosing, and patient characteristics and clinical settings in which micro-induction is likely beneficial.

Conclusions: This systematic review provides the most up-to-date synthesis on buprenorphine micro-induction regimens. Rigorous studies evaluating effectiveness and safety of micro-induction, and patient and clinical factors influencing its success, are needed.

1. Introduction

Buprenorphine, a first line opioid agonist therapy, has unique pharmacological properties: it is a partial agonist at mu opioid receptors and an antagonist at kappa opioid receptors, and also binds with higher affinity than most other opioids. These characteristics mean that buprenorphine may precipitate opioid withdrawal in an opioid-tolerant patient if they have ingested other lower affinity full agonist opioids (e.g. heroin, morphine) that buprenorphine displaces. To avoid precipitated withdrawal, providers must wait until a recommended amount of

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time since last opioid use, and the patient is in moderate opioid withdrawal before initiating buprenorphine at standard doses (Canadian Research Initiative in Substance Misuse, 2018). The requirement to be in withdrawal before initiating buprenorphine is a potential barrier for patients, and a possible correlation exists between withdrawal symptoms experienced by patients taking buprenorphine and higher dropout rates compared to methadone within two weeks of initiation (Teruya et al., 2014; Mattick et al., 2003).

Micro-induction, also known as the "Bernese method," is a novel approach to buprenorphine induction aiming to improve patient comfort, and thereby to eliminate deterrents to treatment initiation. This method initiates small doses that do not require patients to be in withdrawal before initiation, and that minimize risk of precipitated withdrawal. The seminal 'Bernese method' publications described initiating patients on buprenorphine doses of 0.2 mg[4] (whereas standard induction doses are generally 2 mg or greater), however no universally accepted dosing protocol exists. The authors hypothesized that small buprenorphine doses gradually accumulate and eventually replace full agonists at opioid receptors (Hämmig et al., 2016). This allows patients to continue and taper concurrent opioid use while slowly increasing buprenorphine doses. Given its theoretical basis, micro-induction can and has been applied with a range of overlapping opioid agonists (e.g. heroin, methadone, hydromorphone, fentanyl) (Hämmig et al., 2016; Klaire et al., 2019; Azar, Nikoo, & Miles, 2018). This method is increasingly being used in multiple clinical settings, despite a lack of robust evidence supporting its safety and effectiveness, and a lack of guidance regarding specific patient populations in which this methodology is indicated. There is an urgent need to summarize available data on effectiveness of buprenorphine micro-induction to ensure optimal and safe treatment of patients with opioid use disorder.

1.1. Objectives

The primary objective of this systematic review was to synthesize available evidence on effectiveness of micro-induction approaches to buprenorphine induction compared to standard dosing or other approaches, or evaluated without a comparator group.

Our second objective was to summarize micro-induction regimens (e.g. dose, route, schedule, duration) described in the available scientific and grey literature.

2. Methods

This systematic review was registered in PROSPERO and follows PRISMA guidelines (Moher et al., 2015). Full details are available in a published protocol (Moe et al., 2020).

2.1. Eligibility criteria

We included studies examining adults and adolescents with opioid use disorder for whom opioid agonist therapy was deemed clinically indicated by their healthcare providers, and included any micro-induction regimens defined by study authors. Our search captured interventional and observational studies and case reports/series.

2.2. Data sources and searches

Our search strategy combined concepts *buprenorphine* AND *micro-induction.* We searched for studies published from 2005 onwards. We examined abstracts in all languages but only included studies published in English, French or German for full text review. We searched MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), APA PsycInfo, and the Science Citation Index (Web of Science Core Collection [WOS]) from Clarivate Analytics. We conducted database searches between November 26, 2019 and January 9, 2020.

We performed an electronic grey literature search using the search engine Google, by examining websites of professional organizations, harm reduction initiatives, opioid use disorder treatment guidelines, conference proceedings, and table of contents of pertinent journals. We performed the grey literature search from December 3 to 13, 2019. We included recent studies identified by expert consultation up to October 24, 2020.

2.3. Study selection, extraction and quality assessment

Two reviewers assessed abstracts and full-text articles independently for eligibility. Independent reviewers then extracted data from eligible articles and assessed their quality. Reviewers completed all assessment and extraction in duplicate using pilot tested, standardized forms. We resolved disagreements through discussion or arbitration. We attempted to email authors twice for missing information.

The independent reviewers used an adapted Downs & Black tool to assess quality. This tool was developed for randomized and non-randomized studies including observational and case studies/series. It assesses reporting, external validity, bias, confounding, and power (Downs and Black, 1998).

3. Results

Our search strategy yielded 4,752 citations. We included 20 studies comprising 57 patients in our systematic review (Fig. 1; Supplementary Table 1) (Hämmig, 2010; Payler, 2016; Hämmig et al., 2016; Azar et al., 2018; Klaire et al., 2019; Terasaki, Smith, & Calcaterra, 2019; Vogel et al., 2019; Sandhu et al., 2019; Martin, Lennox, Regenstreif, & O'Shea, 2019; Jafari, 2019; Rozylo et al., 2020; Lee et al., 2020; American, 2019; Azar et al., 2020; De Aquino, Fairgrieve, Klaire, & Garcia-Vassallo, 2020; Malcho & Virtual, 2020; Hamata, Rezazadeh-Azar, Hann, & Griesdale, 2020; Brar, Fairbairn, Sutherland, & Nolan, 2020; Moe et al., 2020; Cortina, Mihic, Fennemore, & McLean, 2017; Centers for Disease Control and Prevention, xxxx; Reichle, Smith, Gravenstein, Macris, & Beecher, 1962). Inter-rater reliability for abstract and full text screening were high (Cohen's kappa = 0.59 [91% agreement] and 0.65 [97% agreement], respectively). Due to a lack of studies directly comparing micro-induction to standard dosing, we could not summarize comparative effectiveness or safety. Instead, we summarized data on micro-induction without a comparator group and separately analyzed patients reported to have experienced, and to not have experienced, precipitated withdrawal. Given poor quality and heterogeneity, we did not attempt meta-analysis and instead summarized studies narratively.

Sixteen included studies were from North America and four from Europe. Most (19/20) were case studies/series; one was a feasibility study. Fifteen (75%) were published in 2019–2020. Where reported, 57.3% (33/57) of included patients were male and their mean age was 38 years (SD 12.0). Studies differed in selection criteria for including patients into a micro-induction intervention (n = 7 unspecified; n = 4 patient concerns for withdrawal; n = 3 difficulty weaning from fentanyl; n = 2 failed standard induction; n = 2 patient choice; n = 1 provider deemed most indicated; n = 1 study allocation by convenience then randomization).

Included studies described 26 dosing regimens (Supplementary Table 1). Starting doses ranged from 0.03 to 1.0 mg (median 0.5 mg, [inter-quartile range {IQR}: 0.50–0.50]). Maintenance doses ranged from 8 to 32 mg (median 16 mg [IQR: 12–22]). Regimen durations varied widely, ranging from 3 to 112 days (median 6 days [IQR: 6–8]). Most inductions occurred in observed settings (17/57 [30%]). We summarized regimens with respect to daily rate of dose increase to reach 8 mg, consistent with evidence that 8 mg provides some protective opiate agonist effect, which would therefore replace patients' need to seek other opioids (Greenwald et al., 2014; Buprenorphine-naloxone, 2017) Studies differed in specified overlapping opioid agonists during the micro-induction: among 57 patients described, 26 had an

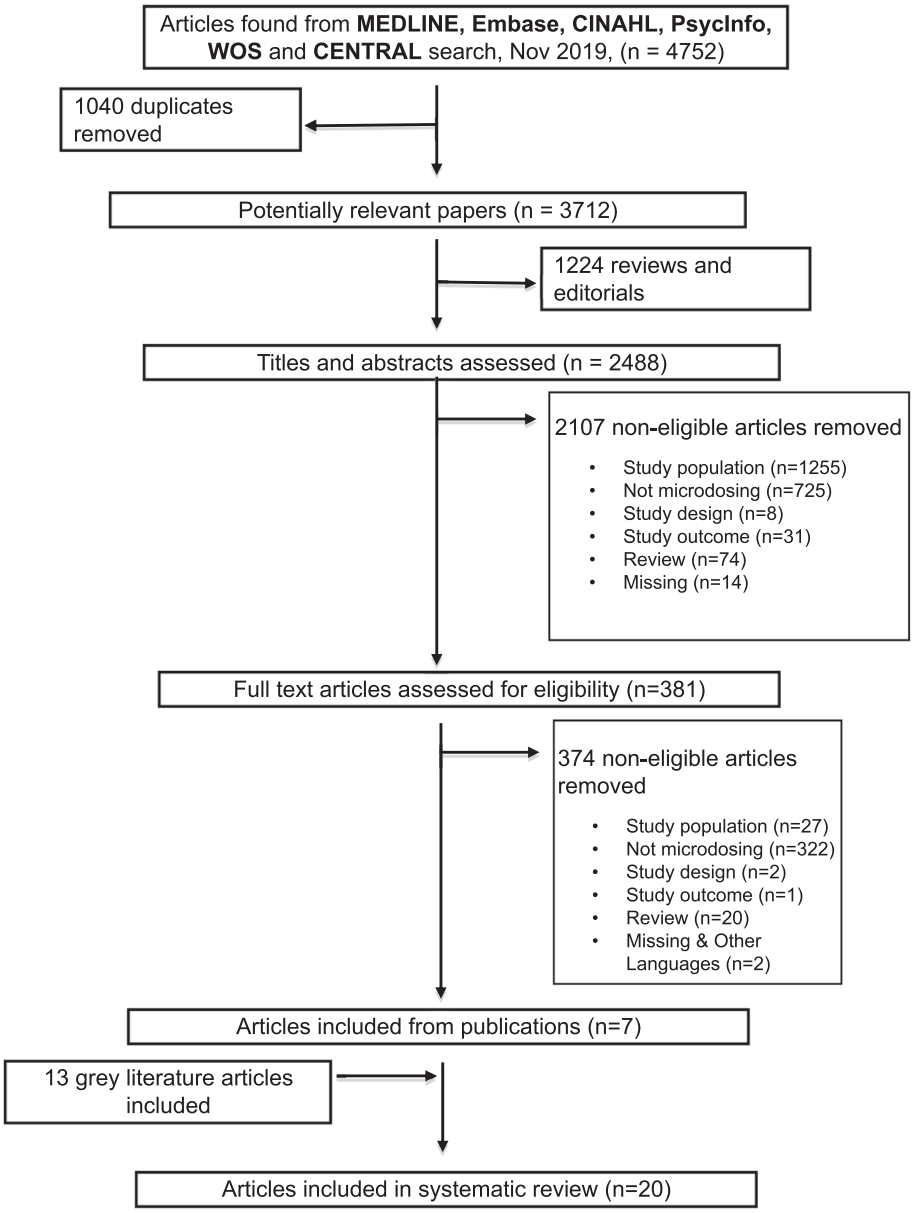

Fig. 1. Evidence Search and Selection.

overlapping agonist prescribed by a healthcare provider (n = 9 methadone; n = 5 fentanyl; n = 5 hydromorphone; n = 3 morphine; n = 4 multiple), and 31 were not prescribed a specific overlapping opioid and used illicit opioids during the induction period. We also summarized doses of overlapping opioid agonist therapy, and morphine milligram equivalents (MME) associated with the overlapping opioid reported.

Included studies described different patient outcomes. All were reported to have successfully achieved the maintenance dose, although some patients took multiple attempts and subsequent relapse was reported among 5/57 (8.8%) patients. Only two studies reported patient attainment of a maintenance dose as an *a priori* outcome of interest. All but one study described opioid withdrawal symptoms among included patients. Most studies (n = 14) did not specify how withdrawal was determined or indicated patient self-report; only six studies used standardized methods to ascertain withdrawal (n = 5 clinical opiate withdrawal scale; n = 1 short opiate withdrawal scale). Although difficult to disentangle withdrawal symptoms due to buprenorphine under-dosing from the occurrence of precipitated withdrawal, 19 studies (n = 54 patients) did not report precipitated withdrawal, and three studies (n = 3 patients) specifically reported that precipitated withdrawal occurred.

Among studies not reporting precipitated withdrawal, the median starting dose was 0.50 mg (IQR: 0.50–0.50), median duration 6 days (IQR: 6–8), median maintenance dose 16 mg (IQR: 12–21), and mean rate of dose change to 8 mg was 1.36 mg/day (SD: 0.41). Where microinduction regimens specified an overlapping opioid agonist, hydromorphone was used in five patients (21.7%), methadone in six (26.1%), morphine in three (13.0%), fentanyl in five (21.7%), and multiple opioids in four patients (17.4%). The median MME doses of overlapping opioid agonist therapy among patients not experiencing precipitated withdrawal were 300 mg on Day 1 (IQR: 106–1025), 280 mg on Day 2 (IQR: 96–900), and 320 mg on Day 3 (IQR: 144–1050).

All three studies reporting precipitated withdrawal described regimens overlapping with methadone. For these cases, the median buprenorphine starting dose was 0.40 mg (IQR: 0.21–0.50), median duration 6 days (IQR: 5.5–7.0), median maintenance dose 12 mg (IQR: 10–18), and mean rate of dose change to 8 mg was 1.17 mg/day (SD: 0.11). Median doses (and corresponding MME) of overlapping methadone among patients experiencing precipitated withdrawal were 20 mg (IQR:

20–45) on Day 1 (median MME 80 mg, IQR: 80–460), 30 mg (IQR: 25–35) on Day 2 (median MME 80 mg, IQR: 80–80), and 28 mg (IQR: 21–34) on Day 3 (median MME 70 mg, IQR: 65–75).

We examined a subgroup of eight studies (n = 11 patients) describing regimens overlapping with methadone. The median starting dose was 0.50 mg (IQR: 0.30–0.75), median duration 8 days (IQR: 6.5–11.5), median maintenance dose 16 mg (IQR: 12–24), and mean rate of dose increase to 8 mg was 1.04 mg/day (SD: 0.52). For eight patients who did not experience precipitated withdrawal, the median starting dose was 0.50 mg (IQR: 0.42–1), median duration 10 days (IQR 7.8–17.3), median maintenance dose 20 mg (IQR: 15–24), and mean rate of dose increase to 8 mg was 1.01 mg/day (SD: 0.59). Characteristics of regimens used in three patients in whom precipitated withdrawal was reported are described above.

Overall quality of included studies was poor (Supplementary Fig. 1).

4. Discussion

This systematic review provides the most up-to-date synthesis on reported buprenorphine micro-induction regimens in the scientific and grey literature.

Our primary objective, to summarize effectiveness of micro-induction, was impeded by a lack of standardized outcome measures among included studies (e.g., induction completion, treatment retention) and a lack of rigorous comparative effectiveness studies. We examined avoidance of precipitated withdrawal as an effectiveness outcome, as this is a major potential benefit of micro-induction vis-à-vis standard dosing approaches. We separately summarized characteristics of micro-induction regimens among patients in whom precipitated withdrawal either was not, or was, reported. However, our ability to draw conclusions is limited by the small number of patients (n = 3) in whom precipitated withdrawal was specifically reported. The small patient number likely reflects inconsistencies in adverse events reporting among included studies, in particular a lack of rigorous assessment of withdrawal and precipitated withdrawal. Furthermore, difficulty differentiating general opioid withdrawal symptoms from precipitated withdrawal, and a lack of *a priori* definitions, standardized data collection, and pre-specified methods for identifying and reporting precipitated withdrawal among included studies limit our ability to interpret these results.

Regarding our second objective, to summarize specific micro-induction regimens described in the scientific and grey literature, our review highlights a marked variability and lack of standardization in micro-induction approaches to-date. We report wide ranges of reported starting and maintenance doses, rate of dose increases, and regimen durations with no clearly accepted approach.

This systematic review addresses an important current need to methodically summarize existing evidence on buprenorphine micro-induction. Given its novel nature, we deliberately included non-traditional data sources from case reports/series, and the grey literature to maximize breadth and ensure that we captured the most up-to-date evidence. However, non-controlled studies are limited by selection and reporting bias, and an inability to control for confounders. Heterogeneity among included studies did not allow us to perform a meta-analysis.

5. Conclusions

In conclusion, our systematic review highlights a paucity of high-quality evidence on buprenorphine micro-induction, and a lack of understanding of the patient characteristics and clinical settings in which this method is likely to provide most benefit. Despite this knowledge gap, micro-induction is increasingly being used in both inpatient and outpatient settings. Wide application of this method without clear evidence-based guidance on optimization of dosing regimens, nor on characteristics of patients and settings in which micro-induction is likely beneficial, risks wide use of unstandardized, suboptimal regimens and "indication creep," both of which are potentially detrimental to patient outcomes. There is therefore a crucial need for rigorous studies to formally evaluate the comparative effectiveness and safety of micro-induction regimens using reproducible protocols in clearly defined populations. Only by generating high-quality evidence will we be able to implement low-barrier and effective approaches to buprenorphine initiation as a key component of the response to the ongoing opioid crisis.

CRediT authorship contribution statement

Jessica Moe: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Supervision, Project administration. **Fiona O'Sullivan:** Methodology, Formal analysis, Investigation, Writing - review & editing. **Corinne M. Hohl:** Conceptualization, Methodology, Investigation, Formal analysis, Writing - review & editing. **Mary M. Doyle-Waters:** Conceptualization, Methodology, Formal analysis, Writing - review & editing. **Claire Ronsley:** Formal analysis, Investigation, Writing - review & editing. **Raymond Cho:** Formal analysis, Investigation, Writing - review & editing. **Qixin Liu:** Formal analysis, Investigation, Writing - review & editing. **Pouya Azar:** Conceptualization, Methodology, Investigation, Formal analysis, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.addbeh.2020.106740.

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