Transferring Patients From Methadone to Buprenorphine: The Feasibility and Evaluation of Practice Guidelines

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Introduction and Aims: Transfer from methadone to buprenorphine is problematic for many opioid-dependent patients, with limited documented evidence or practical clinical guidance, particularly for the range of methadone doses routinely prescribed for most patients (>50 mg). This study aimed to implement and evaluate recent national Australian guidelines for transferring patients from methadone to buprenorphine.

Design and Methods: A multisite prospective cohort study. Participants were patients who transferred from methadone to buprenorphine-naloxone at 1 of 4 specialist addiction centers in Australia and New Zealand. Clinicians were trained in the guidelines, and medical records were reviewed to examine process (eg, transfer setting, doses, and guideline adherence) and safety (precipitated withdrawal) measures. Participants completed research interviews before and after transfer—assessing changes in substance use, health outcomes, and side effects.

Results: In all, 33 participants underwent transfer, 9 from low methadone doses (<30 mg), 9 from medium doses (30–50 mg), and 15 from high doses (>50 mg). The majority of high-dose transfers occurred in inpatient settings. There was reasonable guideline adherence, and no complications identified in the low and medium-dose transfers. Three high-dose transfers (20%) experienced precipitated withdrawal, and 7/33 participants (21%) returned to methadone within 1 week of attempted transfer.

Discussions and Conclusions: Transfer is feasible in outpatient settings for those transferring from methadone doses below 50 mg; however, inpatient settings and specialist supervision is recommended for higher-dose transfers. The Australian clinical guidelines appear safe and feasible, although further research is required to optimize high-dose transfer procedures.

Key Words: buprenorphine, guidelines, methadone, opioid dependence, transfer

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The most widely prescribed medicines in the treatment of opioid dependence are methadone and buprenorphine. Whereas both are safe and effective medicines for this indication, optimizing treatment outcomes for individual patients requires some patients to transition from one to the other. More common reasons for transitioning from methadone to buprenorphine are in response to side effects to methadone, dose not holding (eg, rapid metabolizers), or in attempts to withdraw off opioid agonist treatment (Winstock et al., 2009). However, transitioning from methadone to buprenorphine is complicated by the potential for precipitated withdrawal on commencing buprenorphine—thought to be due to buprenorphine's higher receptor affinity, but lower intrinsic activity (partial agonist) at μ-opioid receptors. Early clinical guidelines recommended patients reduce to a low methadone dose (eg, 30–40 mg or less) before transferring to buprenorphine or to discontinue methadone for several days before initiating buprenorphine dosing (Lintzeris et al., 2001; Center for Substance Abuse Treatment, 2005; Lintzeris et al., 2006). Yet, these approaches can be problematic as most methadone patients require much higher doses to achieve positive treatment outcomes (eg, 60–100 mg), and risk relapse to unsanctioned substance use, and/or deterioration in health or social status while attempting dose reductions.

There is limited documented evidence reflecting the experience of transferring patients from methadone to buprenorphine. A systematic review of such transfers (Mannelli et al., 2012) identified 16 studies reporting on 240 patient transfers—most were uncontrolled studies with few cases, and few studies reported on transfers from high doses (designated as ≥70 mg). The review identified that transfers from doses

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below 70 mg were feasible using abrupt cessation or taper on an outpatient basis, often with ancillary medications and a 24-hour interval between medications. In contrast, transfers from higher methadone doses usually required inpatient treatment and ancillary medications, and precipitated withdrawal was reported in a substantial minority of cases. The authors concluded that ''due to differences in design and individual variability, a single protocol cannot be formulated'' (p. 5).

Nevertheless, the need for clinical guidance is highlighted by the potential problems associated with attempted transfers that have served as transfer barriers. These include patients becoming ''unstable'' during methadone dose reductions or following transfer, with relapse to substance use or deterioration in mental health; precipitated withdrawal on initiating buprenorphine treatment; adverse events after transfer; and patients requesting transfer back to methadone.

The most recent Australian Medication Assisted Treatment of Opioid Dependence (MATOD) clinical guidelines (Gowing et al., 2014) make a series of evidence-informed recommendations regarding transfers, the key features of which are summarized in Table 1. The more comprehensive national MATOD guidelines are included in Appendix 1 (http://links.lww.com/JAM/A78). The Australian guidelines make broadly similar recommendations to even more recent American Society Addiction Medicine Guidance (ASAM; Kampman and Jarvis, 2015).

This project aimed to evaluate the feasibility of implementing MATOD guidance regarding methadone to buprenorphine transfer in a number of specialist addiction treatment settings, and to examine patient outcomes associated with transfer attempts. Specifically, the project examined how transfers were conducted, and whether clinicians were able to adhere to key aspects of the guidance (feasibility); and patient outcomes and experiences with the transfer—specifically, did adverse outcomes occur during the transfer period (eg, precipitated withdrawal, treatment dropout), and were there any significant changes for patients on buprenorphine after transferring from methadone, including side effects, substance use, health, and psychosocial outcomes.

METHODS

Design

This was a multisite prospective observational cohort study examining the feasibility, transfer practices, and patient outcomes associated with the implementation of clinical guidelines for transferring from methadone to buprenorphine-naloxone (BNX). Sites included specialist Drug and Alcohol (D&A) settings in Australia (South East Sydney Local Health District (SESLHD), Sydney; Hunter New England Local Health District (HNELHD), Newcastle; Drug and Alcohol Services South Australia (DASSA), Adelaide; and New Zealand Community Alcohol and Drug Services (CADS, Auckland). The project was approved by the SESLHD Human Research Ethics Committee (#12/285 and 15/241).

Participants

Participants were recruited from participating specialist opioid agonist treatment (OAT) services and inpatient hospital units involved in transferring patients from methadone to BNX. Participant selection criteria were broad: aged 18 and over, in methadone treatment at least 1 month; seeking to transfer from methadone to BNX at 1 of the participating sites; and able to give informed consent. Participants were asked to participate in additional research data collection regarding their experience of the transfer process, with research interviews before transfer and 1 to 3 months after transfer.

Research staff reviewed clinic records of all patients transferring from methadone to BNX at participating sites during the recruitment period (identified through notification by clinical staff and structured audit of clinical record data bases). Recruitment was ''open'' at the SESLHD clinical sites (approximately 350–400 methadone patients at any 1 time) over an 18-month period. Recruitment was restricted to approximately 6–9 months at each of the other sites, with each having approximately comparable numbers of methadone patients.

Clinical Interventions and Implementation

The study examined the feasibility and outcomes associated with the implementation of clinical guidelines for transferring from methadone to BNX in specialist D&A settings. Each site had a lead investigator/physician who acted as clinical lead for each team. Clinicians were disseminated clinical guidance based upon MATOD (Appendix 1, http://links.lww.com/JAM/A78), and trained during a series of forums at each site. Clinician autonomy in clinical practice (including which patients transferred and how transfers were conducted) was allowed, reflecting that the guidelines had the status of ''clinical guidance informing practice'' rather than

TABLE 1. Overview of Clinical Guidelines for Transferring From Methadone to Buprenorphine

Assessment, treatment planning, and patient education—examine patient expectancies, reasons for transfer, and discuss transfer procedures. Identify, and where possible stabilize, any risks for patient safety during the transfer, including unstable substance use, physical, mental health, or social conditions
Unless urgent transfer required (eg, severe side effects to methadone), gradually reduce methadone dose until patient starts to experience mild to moderate opioid withdrawal between doses
Consider treatment setting: inpatient settings recommended for patients transferring from high methadone doses or significant health comorbidities or unstable social conditions
Cease methadone and monitor the patient regularly (at least daily) for evidence of opioid withdrawal symptoms. Initiate buprenorphine treatment when patient experiencing moderate opioid withdrawal severity (Clinical Opioid Withdrawal Scale [COWS] >12), at least 24 h after last methadone dose
Initiate low-dose buprenorphine treatment (2 mg), and monitor hourly for evidence of precipitated withdrawal, preferably using a withdrawal scale (eg, COWS). Administer further 6 mg after 1 h. Further doses (4 or 8 mg at a time) are symptom-triggered, and continue regular monitoring and dosing until patient comfortable
On subsequent days, buprenorphine dose = previous days dose + additional dose based upon withdrawal severity (symptom triggered)

''procedures to be followed.'' The key features of the transfer guidance are highlighted in Table 1. As highlighted in the guidance, some ''high-risk'' transfers were conducted under inpatient hospital conditions, although most occurred in ambulatory settings. Where clinicians deviated markedly from the guidelines, they were requested to identify in the clinical notes reasons for their decision-making, and this was extracted by researchers at a later time.

Measures and Outcomes

Describing the Transfer Process and Related Outcomes

The following measures were used to describe how the transfers occurred, and outcomes associated with the transfer process, extracted from clinical records using structured data collection techniques by research staff.

1. Methadone doses and plasma levels in pretransfer period (specifically doses in the 7 days before cessation of methadone treatment). In addition, a subsample of self-selected participants consented to blood sampling (5 mL) immediately before the first BNX dose, and was assayed for methadone plasma levels. The samples were analyzed by the Discipline of Pharmacology, University of Adelaide. Plasma (R)- and (S)-methadone concentrations were quantified by high-performance liquid chromatography using previously described methods (Foster et al., 2000). Precision and inaccuracies were $<10\%$ for all quality control samples (high 300 ng/mL, medium 100 ng/mL, and low 30 ng/mL^{1}) for all analytes. The concentration range of the standard curve was 15 to 1000 ng/mL for each enantiomer.
2. Interval duration between last methadone and first BNX dose, operationalized as number of days between last methadone and first BNX dose.
3. Evidence of precipitated withdrawal on initiating BNX, operationalized as an increase in the Clinical Opiate Withdrawal Scale (COWS; Wesson and Ling, 2003) score of 6 or more points within 6 hours of the first BNX dose. Nursing staff assessed opioid withdrawal severity (COWS) at regular intervals as part of clinical care (eg, before and at hourly intervals after BNX doses on day of transfer, and before dosing on subsequent days)—see Appendix Clinical Guidance http://links.lww.com/JAM/A78) for details. Where there was ''missing'' COWS data, clinical notes were examined by the research team for mention of significant withdrawal discomfort consistent with a clinical presentation of precipitated withdrawal.
4. BNX doses used over the first 14 days, including evidence of symptom-triggered and split-dosing on day of transfers.
5. Whether the guidelines were adhered to. Although the clinical guidance described a number of clinical decision points, clinicians were adjudged to have adhered to the transfer guidance where 2 key aspects of the guidance occurred: where the first BNX dose was deferred until the patient was experiencing moderate withdrawal severity (COWS score >10), and when the doses on first day of BNX treatment were ''split'' doses with a small first dose (2 or 4 mg), with subsequent doses later in the first day of BNX dosing (as opposed to a higher [>4 mg] first dose, or given as a single day 1 dose).
6. Was the transfer ''successful''—operationalized as whether the patient was still in BNX treatment 7 days after transfer, and reasons for not remaining in BNX treatment. The 7-day window was considered adequate to examine success of the transfer process—longer-term outcomes (beyond the initial week) were considered subject to many factors (eg, other life events) beyond the ''success'' of the transfer itself.

Patient-reported Outcomes and Experiences Before and After Transfers

Participants were interviewed by a researcher before and again 1 o 3 months after the transfer attempt regarding the following:

(1) Reasons for seeking transfer from methadone to buprenorphine were ascertained in research interviews conducted before transfer using a structured questionnaire (Winstock et al., 2009).
(2) Changes in clinical outcomes, including substance use (% any use, and mean days used in those using), physical and mental health, and also overall quality of life (QoL) measures, collected using the Australian Treatment Outcome Profile (ATOP; Ryan et al., 2014). The ATOP is a brief patient reported outcome measure administered by clinician/researchers, and validated in Australian treatment populations. ''Days used in past 28'' is reported for each substance. Psychological, physical, and overall QoL is self-reported on a scale of 1 to 10, with higher scores indicating better self-rated health outcomes. The Short Form 36 (SF-36; Ware and Sherbourne, 1992) physical and mental health subscales, and the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005; where higher scores indicate better cognitive performance on the assessment) were employed before and after the transfer.
(3) Patient satisfaction with transfer process and OAT medication—participants were asked to rate their experience and the success of the transfer using visual analog scale (VAS) from 1 to 100 for the following questions: ''Please provide an overall rating of your current maintenance treatment''; and ''Overall, how happy are you with your transfer experience to buprenorphine?''. Participants were also asked to rate, using Likert scales, their preferred maintenance treatment (5-point scale, 1 = strongly prefer methadone to 5 = strongly prefer buprenorphine), a rating of current daily dose adequacy (1 = much too low to 5 = much too high), and whether their dose should change (3-point scale, 1 = go down, 2 = stay the same, 3 = go up).

Participants were reimbursed for participating in research interviews, but not for clinical procedures.

Data Management and Statistics

Deidentified data were extracted from clinical records and entered into an SPSS database. Cases were categorized into 3 groups according to the mean daily oral methadone

dose in the 5 days before cessation of methadone treatment: low-dose (LD) transfers (30 mg or less), medium-dose (MD) (31–50 mg), and high-dose (HD) transfers (>50 mg). The low-dose category (30 mg or less) reflected the recommendations in the current product registration for Suboxone in Australia (Australian Register of Therapeutic Goods, 2016). All data were analyzed using SPSS v23. Independent-samples *t* tests and analysis of variance (ANOVA) were used for continuous variables; chi-square or Fisher *z* tests were used for categorical measures.

RESULTS

Participant Recruitment, Characteristics, and Reasons for Transfer

Recruitment

Thirty-three participants underwent transfer from methadone to BNX as part of the study. The majority of participants were recruited from the SESLHD site (n = 23, 70%), reflecting a longer period of site activation and recruitment compared with the other sites. Recruitment was spread evenly across the other sites (n = 4 SA [12%], n = 3 HNELHD [9%], and n = 3 NZ [9%]). Twenty transfers occurred in inpatient hospital settings, and 13 in outpatient settings, with comparable proportions of inpatient transfers occurring at the SESLHD site (14/23, 61%) compared with other sites combined (6/10, 60%).

Demographics and Treatment Characteristics

The mean age ± SD at recruitment was 40 ± 10 years (range 20–61) and the majority were male (n = 21, 64%). Vocational status reported by participants were: any employment and/or study (24%); temporary benefits (eg, unemployed) 55%, permanent benefits (eg, disability) 15%, other (6%). Participants generally had long lifetime histories of opioid use (age first opioid use: 18.8 ± 6.2 years; age first regular opioid use: 21.8 ± 4.6 years).

Substance use details in the 28-day period before transfer was available for 22 participants. Alcohol use was reported by 7/22 participants (mean days used ± SD = 3.7 ± 2.9), cannabis was used by 11/22 (50%) (13.5 ± 10.1 days); methamphetamines 7/22 (%) (2.1 ± 1.1 days); benzodiazepines 6/22 (%) (15.2 ± 12.4 days); and heroin 3/22 (%) (3.3 ± 2.5 days).

Nine cases (27%) were LD transfer group, 9 (27%) were MD, and 15 (46%) were HD. Of the 15 HD transfers, 5 were on a methadone dose of ≥100 mg 1 week before transfer, 7 were between 70 and 95 mg, and 3 were 57.5 to 60 mg. Whereas there were no significant differences regarding sex between the groups, the HD group was significantly younger (34.8 ± 9.6 years) than the LD group (46.7 ± 10.5 years) ($F[2,30] = 4.514$, $P = 0.019$).

Reasons for Transfer

Patients reported their main reason for attempting transfer included: buprenorphine easier to come off than methadone (n = 8, 24%), side effects to methadone (n = 7, 21%), methadone dose not ''holding'' between doses (n = 4, 12%), wanting greater access to unsupervised doses with BNX (n = 4, 12%), better pain relief with BNX (1, 3%), methadone interaction with other medications (n = 1,3%), or other reasons (8, 24%). The most common reason in LD transfers was ''easier to come off'' (4/9, 44%), whereas ''side effects to methadone'' was the most common reason for moderate or HD transfers (7/24, 29%).

Describing the Transfer Process and Related Outcomes

Treatment processes are described in Table 2. Almost all of the HD transfers occurred in inpatient settings (93%) in contrast to the MD and LD transfers (combined 33%) ($z[1] = 3.5$, $P < 0.01$). Inpatient admissions were of short duration, with a mean inpatient stay of 2.2 days (range 1–3).

Pretransfer methadone doses and post-transfer BNX doses are shown in Fig. 1. The general trend was for patients to reduce their methadone dose in the days before transfer, and in general, higher BNX dose requirements increased with higher pretransfer methadone doses. Twenty-two patients' (67%) total BNX doses were >8 mg on day 1, with 14 patients (42%) using 16 mg or more (total) on day 1. Most patients had stabilized their daily BNX dose by the third day of BNX dosing, with the majority using doses ≥12 mg (24/29 on day 2, and 27/28 by day 3).

Plasma levels for R-methadone and withdrawal severity (COWS) immediately before the first dose of BNX are shown in Fig. 2. Two cases which have methadone plasma levels

TABLE 2. Summary Data Regarding Transfers by Dose Categories

	Low-dose Transfer (n = 9)	Medium-dose Transfer (n = 9)	High-dose Transfer (n = 15)	Significance
Setting for transfer				
Inpatient	2 (22%)	4 (44%)	14 (93%)	$P < 0.05$
Outpatient	7 (78%)	5 (56%)	1 (7%)	
Adherence to guidelines				
Yes	7 (78%)	6 (67%)	10 (67%)	
No	2 (22%)	3 (33%)	5 (33%)	NS
Did precipitated withdrawal occur?				
Yes	0	0	3 (20%)	
No	9 (100%)	9 (100%)	12 (80%)	NS
In BNX treatment 7 d after transfer				
Yes	8 (89%)	8 (89%)	10 (67%)	
No	1 (11%)	1 (11%)	5 (33%)	NS

BNX, buprenorphine-naloxone; NS, not significant.

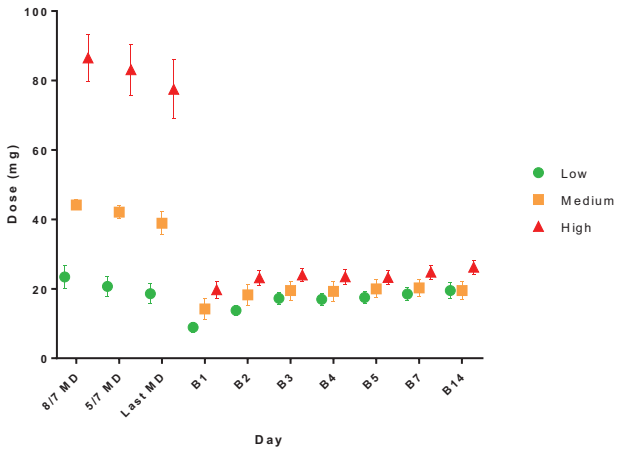

FIGURE 1. Methadone dose in 7 days preceding transfer, and buprenorphine doses dose in 14 days after transfer (mean, SE error bars). MD, methadone dose; B1, buprenorphine dose day 1, B2, buprenorphine dose day 2, etc).

available and experienced precipitated withdrawal are highlighted in the figure, indicating they were the cases with the highest and lowest plasma levels of the 16 cases.

Adherence to Guideline

Using the criteria established for guideline adherence (see ''Methods'' section), 70% (n = 23) of transfers occurred consistent with the guidance, with similar rates of adherence across the 3 transfer groups (Table 2). Nonadherence with the guidance due to initiation of BNX dosing before a COWS >10 occurred in 7 cases—6 of these occurred in an inpatient setting. In most cases this happened in the late afternoon or early evening, with staff reporting they did not want to initiate BNX dosing late at night when fewer staff were available to manage any complications. Nonadherence due to a first BNX dose >4 mg occurred on 6 occasions. Adherence to the guidelines occurred in 2/4 SA (50%), 3/3 HNELHD, 3/3 NZ, and 15/23 (65%) of SESLHD cases; and in similar proportions of inpatient (15/20, 75%) and outpatient transfers (9/13, 69%).

Precipitated withdrawal was adjudged to have occurred on 3 occasions—all occurred in the HD transfer group. In 1 case, a dosing error was made and the patient incorrectly received as initial dose of BNX of 8 mg instead of 2 mg; in another case, BNX dosing was commenced, despite the patient not being in moderate or severe opioid withdrawal (COWS = 5), and in the third case (inpatient setting) the clinical guidance was generally followed. In all 3 cases, the patients refused further BNX doses after the onset of precipitated withdrawal and requested resumption of methadone dosing. Three of the 5 cases who were on a methadone dose ≥100 mg 7 days before transfer and 6 of the 7 cases receiving doses between 70 and 90 mg did not experience precipitated withdrawal.

Data are available for the 3 cases of precipitated withdrawal and highlight the sequence of events, including COWS scores, BNX doses, and concomitant medications used. These are presented in Table 3.

Retention in BNX treatment at day 7 was used as a marker of overall success of the transfer. Overall, 26/33 participants (79%) were still in BNX treatment at day 7. Three participants resumed methadone soon after experiencing precipitated withdrawal, 3 resumed methadone within 2 days of attempted transfer due to side effects with BNX treatment (anxiety and poor sleep, but not precipitated withdrawal), 1 participant ''dropped out of treatment'' and used heroin for several days before returning to methadone treatment approximately 1 week later.

Prepost Transfer Changes in Substance Use, Health Outcomes, and Treatment Satisfaction

Only 15 participants (45%) had research interviews conducted before and after attempted transfers.

Satisfaction With Transfer and OAT Medication

After the transfer, 11 of the 15 (73%) participants post-transfer indicated that they either somewhat or strongly preferred BNX, 20% (n = 3) had no preference, and 7% (n = 1) indicated that they somewhat preferred methadone. Additionally, while 73% (n = 11) indicated their BNX dose was adequate, the remaining 27% (n = 4) indicated they thought their dose was either slightly or much too high. The majority of participants (67%) indicated they wanted their current BNX dose to stay the same, 27% wanted their dose to decrease (consistent with their intention of withdrawing off OAT), and 6% wanted a dose increase. The mean patient satisfaction with the transfer process (0–100) was 64 ± 36, with higher rating in the LD (61 ± 38, n = 5) and MD (78 ± 35, n = 7) than the HD group (43 ± 34, n = 4), although not statistically significant. Participants who successfully transferred to BNX had higher process satisfaction (n = 13, 72 ± 33) than unsuccessful transfer (n = 3, 31 ± 36) ($t[14] = 1.91$, $P = 0.077$).

Patient-reported Outcome Measures

Based on ATOP scores, there were no significant differences regarding substance use, physical or psychological

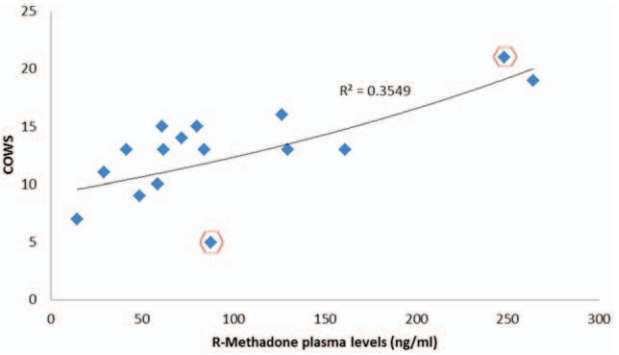

FIGURE 2. R-methadone plasma levels (ng/mL) and COWS scores immediately before first BNX dose in 16 participants. The 2 ⬡ represent cases in which precipitated withdrawal occurred. BNX, buprenorphine-naloxone; COWS, Clinical Opiate Withdrawal Scale.

TABLE 3. Sequence of Events in Cases of Precipitated Withdrawal, Including COWS, Buprenorphine, and Concomitant Medications

	Details of Transfer
Case 1: outpatient transfer	Last methadone dose 155 mg 24 h before first BNX dose. On day of transfer: 10.30 COWS score = 21, 8 mg BNX administered (note in error, instead of 2 mg initial dose). 11:30—COWS = 24 and 8 mg BNX administered. Concomitant medications paracetamol 1000 mg oral and metoclopramide 10 mg IM administered at 11.40 (considered to have little effect). 12:00—COWS = 27, and transfer abandoned on patient request. Methadone 40 mg dose administered at 13:00, with further dose 40 mg that evening. The next day, COWS = 4, methadone dose 170 mg administered (routine dose).
Case 2: inpatient transfer	Last methadone dose 75 mg 27 h before first BNX dose. On day of transfer: at 13:00—COWS = 5, 2 mg administered 13:50. At 14:50 h, COWS = 11, 6 mg BNX administered. At 16:20 COWS = 17, 8 mg BNX administered. At 17:20, COWS = 17, 8 mg BNX administered. At 19:00, COWS = 15, 8 mg BNX administered (total 32 mg day 1). At 22:00, temazepam 20 mg oral. The next day, at 08:00 COWS = 7 and 32 mg BNX administered. Patient resumed methadone (75 mg) later that day before discharge home, indicating uncomfortable on BNX.
Case 3: inpatient transfer	Last methadone dose 95 mg 28 h before first BNX dose. On day of transfer, at 20:00 h, COWS = 13, 2 mg BNX administered. At 21:00 h 6 mg administered. At 22:00 h, COWS = 20, 8 mg BNX administered. At 23:00 h, hyoscine butylromide 20 mg oral, 10 mg metoclopramide (IM), and temazepam 20 mg administered. At 24:00 h, COWS = 20, no BNX administered. At 02:00 h, COWS = 14, no BNX administered; At 06:00 h, COWS = 9. 07:00 h BNX 16 mg administered. At 08:00 h, COWS = 16. At 09:20 h, 16 mg BNX administered. At 10.30, COWS = 12 and at 14:00 h COWS = 8.

BNX, buprenorphine-naloxone; COWS, Clinical Opiate Withdrawal Scale.

health before and after transfer (all $P > 0.25$); however, ATOP QoL significantly improved after transfer (pre: 4.8 ± 2.2, post 6.8 ± 2.1, t[d.f.] = 15, $P = 0.004$). There were significant improvements in psychological health according to the SF-36 mental health subscale score (pre: 32.7 ± 12.5, post 45.4 ± 8.7, t[d.f.] = 14, $P = 0.002$). No significant changes from baseline to follow-up were observed for SF-36 physical health, or cognition scores (MoCA).

DISCUSSION

This is the first attempt to document the feasibility and outcomes of implementing the recent Australian guidance regarding transfers from methadone to buprenorphine in the treatment of opioid dependence. The Australian MATOD guidance is similar in principle to the recent ASAM guidance, both highlight the need to, where possible, reduce methadone doses to low doses, stop methadone dosing and defer initial buprenorphine doses until the patient is experiencing mild to moderate opioid withdrawal (eg, COWS >12). Initial sublingual buprenorphine doses should be low (eg, 2–4 mg), and rapidly titrated upwards with regular monitoring. The Australian guidance provides a symptom-triggered approach to buprenorphine dosing, and also describes circumstances where transfers may be considered ''higher risk,'' requiring specialist supervision and possibly inpatient admission for a safer transfer.

Our findings are consistent with the previous documented experience of transfers (Mannelli et al., 2012). Eighteen individuals underwent transfers from doses below 50 mg, with no cases of precipitated withdrawal, and the majority (89%) successfully transferring and remaining in buprenorphine treatment. In contrast, difficulties were experienced in a minority of HD transfers (>50 mg): 20% experienced precipitated withdrawal, and one-third returned to methadone treatment within 1 week of attempted transfer, including all cases who had experienced precipitated withdrawal. Nevertheless, the majority of patients, including 9 out of 12 patients who had been on methadone doses ≥70 mg 1 week before transfer (and as high as 125 mg) did not experience precipitated withdrawal. This suggests that while it is preferable to reduce methadone doses below 70 mg in the week before transfer, it may not be necessary for all patients, and under appropriate conditions (informed consent, inpatient setting with specialist supervision), transfers from higher doses may be attempted if patients cannot comfortably or safely reduce their methadone dose further.

Transfers from higher methadone dose also required higher buprenorphine doses. Of note, the majority of patients required buprenorphine ≥12 mg from day 1—much higher doses than had been recommended in earlier guidelines, and highlight the need for rapid upwards buprenorphine dose titration. Also of note, plasma methadone levels immediately before initiating buprenorphine do not appear to be useful clinically in directing treatment decisions, and indeed, in this group, there was little relationship between plasma methadone levels, COWS scores, and onset of precipitated withdrawal.

The clinical guidance for higher dose transfer assessed in this study appeared feasible to implement within the specialist treatment settings under which these transfers occurred. The greatest area of discrepancy with the guidance was in inpatient settings, where the first buprenorphine dose

was sometimes initiated prior to the patients experiencing moderate withdrawal (eg, COWS >8 and based upon patient and clinician preference) to minimize late night transfer activity. The large number of inpatient admissions highlights the need for specialist referral for HD transfers, albeit the length of inpatient stay was usually limited to 2 days. In our view, HD transfers should not generally be attempted in community settings overseen by primary healthcare providers. Day procedure centers may prove to be a useful alternative where inpatient admission may not be possible.

There are several study limitations. The restriction to specialist settings is a limitation of the study, and it remains uncertain as to the ability for nonspecialists to adhere to the guidelines in community settings. Furthermore, more widespread generalizability of the findings would be strengthened if a greater number of treatment sites had participated. The conclusions that can be made regarding patient-reported outcomes are limited, as this was an observational study of clinical practice, with small participant numbers and high rates of missing data in research follow-ups. Whereas the findings indicate many patients demonstrated improvements in mental health and QoL indicators, the low follow-up rates require caution, and further research with larger numbers is required. Nevertheless, the within-subject design is a useful approach when examining differences between methadone and buprenorphine, and provides an alternative approach to assessing the safety of these medications than observational cross-sectional studies. Our observational case series builds upon, but does not fundamentally shift, conclusions from the previous review of this subject.

Although demonstrating that these guidelines are feasible and enable safe transfer for patients from lower methadone doses and for most patients even at higher doses, it does not exclude that other transfer approaches may prove to be useful, particularly for HD transfers. In particular, the use of shorter-acting full opioid agonists (eg, morphine, oxycodone) as a transition between methadone and buprenorphine warrants further exploration.

CONCLUSIONS

This implementation study indicates that the Australian MATOD guidelines are feasible and effective for transferring patients from methadone doses below 50 mg, and indeed from higher doses for many patients, although a quarter of HD transfers experienced precipitated withdrawal, and 21% of all patients had returned to methadone treatment within 7 days of the attempted transfer. Further research is required to understand the predictors of which patients will experience complications in transfers, and to develop more reliable approaches to HD transfers.

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