OPEN

Clinical Case Conference: Strategies for Transferring From Methadone to Buprenorphine

Duncan Hill, BSc (Hons), Pharmacy, Victoria Hayes, MBBS, MPH, FAFPHM, FAChAM, Apo Demirkol, MD, MSc, MMed (Pain Mgt), PhD, FAFPHM, FAChAM, and Nicholas Lintzeris, BMedSci, MBBS, PhD, FAChAM

The mainstay of treatment for opioid use disorder are medications, methadone (a full opioid agonist), or buprenorphine (a partial opioid agonist), in conjunction with psychosocial interventions. Both treatments are effective but safety, efficacy, and patient preference can lead to a decision to change from one treatment to the other. Transfer from buprenorphine to methadone is not clinically challenging; however, changing from methadone to buprenorphine is more complex. Published reports describe varied approaches to manage this transfer to both minimize patient symptoms associated with withdrawal from methadone and reduce risk of precipitating withdrawal symptoms with introduction of the partial agonist buprenorphine [Lintzeris et al. *J Addict Med*. 2020; in press]. There is no single approach for methadone to buprenorphine that is superior to others and no approach that is suitable for all case presentations. This case conference describes three different approaches to achieve a successful methadone to buprenorphine transfer and provides commentary on how the case may be managed based on published transfer ''strategies.''

From the NHS Lanarkshire, Motherwell, UK (DH); The Langton Centre, South East Sydney Local Health District, NSW Health, Surry Hills, New South Wales, Australia (VH, AD, NL); School of Public Health and Community Medicine, University of New South Wales, Sydney, Australia (VH, AD); University Sydney, Division Addiction Medicine, Sydney, Australia (NL).

Received for publication November 11, 2020; accepted March 1, 2021.

Duncan Hill and Apo Demirkol have no conflicts of interest to disclose. Victoria Hayes has received money from Camurus and Viiv for providing education and training sessions. Nicholas Lintzeris has served on Advisory Boards for Mundipharma, Indivior, GW Pharmaceuticals and Camurus, and has received funding for conducting research from Camurus.

Send correspondence to Nicholas Lintzeris, BMedSci, MBBS, PhD, FAChAM, Drug and Alcohol Services, South East Sydney Local Health District, Specialty of Addiction Medicine, University of Sydney, NSW Drug and Alcohol Clinical Research and Improvement Network, NSW Health, c/o The Langton Centre, 591 South Dowling Street, Surry Hills, New South Wales 2010, Australia.
E-mail: Nicholas.lintzeris@health.nsw.gov.au.

ISSN: 1932-0620/21/1602-0152
DOI: 10.1097/ADM.0000000000000854

Key Words: buprenorphine, methadone, opioids, transfer

(*J Addict Med* 2022;16: 152–156)

The mainstay of treatment for opioid use disorder (OUD) are medications, methadone (a full opioid agonist) or buprenorphine (a partial opioid agonist), in conjunction with psychosocial interventions. Both treatments are effective but safety, efficacy, and patient preference can lead to a decision to change from one treatment to the other. Transfer from buprenorphine to methadone is not clinically challenging; however, changing from methadone to buprenorphine is more complex. Published reports describe varied approaches to manage this transfer to both minimize patient symptoms associated with withdrawal from methadone and reduce risk of precipitating withdrawal symptoms with introduction of the partial agonist buprenorphine.[1] There is no single approach for methadone to buprenorphine that is superior to others and no approach that is suitable for all case presentations. This case conference describes 3 different approaches to achieve a successful methadone to buprenorphine transfer and provides commentary on how the case may be managed based on published transfer ''strategies.''

CASE DESCRIPTION

Throughout the case, buprenorphine refers to buprenorphine monotherapy sublingual tablet and the combination tablet or film (buprenorphine with naloxone).

Presenting Complaint

A 38-year-old man currently in methadone treatment for opioid dependence seeks to transfer to sublingual buprenorphine and seeks your advice.

History of Presenting Complaint

The patient reports commencing heroin use at 21 while studying computer programming at university. Before commencing heroin use, he had a history of heavy alcohol and cannabis use but ceased these after commencing heroin use. The patient reports several brief OUD treatment episodes in his mid to late 20s including occasions of residential rehabilitation, buprenorphine and methadone treatment. Previous buprenorphine daily dose stabilised at 16 mg for 18 months, previous methadone treatment episodes daily dose 50 mg for

5 months, daily dose 120 mg for 16 months and 90 mg daily dose for 10 months.

Aged 29, the patient recommenced methadone treatment and was abstinent from nonprescribed opioids after 3 months of treatment with a prescribed methadone dose of 120 mg. During the following 12 months, the patient returned to work as a computer software programmer and did not use nonprescribed opioids. At this time, he requested to reduce his dose of methadone with a view to eventual cessation. His dose was reduced by 5 mg every 4 weeks initially; however, he found reducing the dose below 80 mg difficult to tolerate reporting that he experienced symptoms similar to normal withdrawal symptoms, including rhinorrhea, tearing, increased anxiety, sweating, increased agitation and restlessness, insomnia, diarrhea, and stomach cramps.

The patient continued methadone 80 mg for a further 2 years remaining abstinent from nonprescribed opioids during this time. The patient reports his 5-year-old son died in a motor vehicle accident at this time, which led to a period of grief and depression and triggered a relapse to heroin use. After several months of episodic heroin use, he increased his dose of methadone to 140 mg and was able to eventually cease his heroin use and resumed work.

In recent months, he has been gradually reducing his methadone dose at a rate of 5 mg every 4 weeks, and he is currently on 110 mg oral methadone. He reports no heroin or other opioid use for over 2 years (confirmed with opiate negative urine tests), and no use of alcohol, benzodiazepines, or stimulants in recent years.

Apart from a period of depression and grief after the death of his son, there seems to be no other mental health concerns, and he is not taking any medication. He is hepatitis C virus polymerase chain reaction positive, has normal liver function tests, and is considering antiviral treatment. He has a history of accidental overdose 5 years ago whilst using heroin.

He is separated from his wife and has no other children. He works as a computer software programmer for a small IT company, which he describes as enjoyable but at times stressful.

His main motivation to seek transfer to buprenorphine is that he is seeking to withdraw completely off opioid agonist treatment. He had previously found methadone withdrawal very difficult to cope with, especially at doses below 80 mg. In contrast, he describes coming off buprenorphine as somewhat easier, and would like to transfer to buprenorphine as soon as he can, with a view to coming off opioids altogether – ideally at some point in the next 6 months.

Preparing the Patient for the Transfer

The patients' motivation is key to the transition and the success of the change in treatment; reasons can vary but there is a need for a clear commitment and drive for the change from the patient. In this case, the patient is looking for abstinence from opioids eventually; he has struggled to achieve this with methadone treatment before and has found the process less challenging using buprenorphine treatment previously. The patient should be reminded of the potential differences in treatments and encouraged to relate his buprenorphine experiences back to you. In particular, the mental health issues after the patient's son's death might be worth checking as patients can report difficulty adjusting to perceived increased clarity of thinking after discontinuation of high doses of full opioid agonists.[2,3] The patient may need additional support and wraparound services in case he starts to struggle with persistent negative thoughts unclouded by partial opioid agonist effects.[2] Other factors to be discussed include the reason for the change to buprenorphine and assessing whether the patient is likely to do well on buprenorphine.

Key considerations when transferring individuals from higher doses of methadone to sublingual buprenorphine are the risk of precipitating withdrawal on initiation of buprenorphine and the risk of destabilizing the patient regarding their substance use, or medical, psychiatric, or social conditions. To minimize the risk of these occurring, it is important to complete a comprehensive assessment of the current physical and mental health and substance use history focusing on the most recent drug use, thereby ensuring that the transfer process is not complicated by other substance use including benzodiazepines, pharmaceutical opioids, or other sedating agents.

As with any of the transition between treatments discussed below, it is necessary to discuss the process and options clearly, explaining the advantages and disadvantages and confirming the patient's expectations from this and for treatment after the transfer. Even in this case, where the patient has had both treatment options previously, it is important to remind the patient of the different effects he may experience due to the different treatments. Once the patient has consented and is well prepared for the admission, if undergoing an inpatient transfer, and the regulatory processes are completed as appropriate, the procedure can be initiated.

Case Progression

Several approaches have been described for management of transfer from methadone to buprenorphine, which were discussed with the patient. The following sections provide alternative scenarios for progression of this case, based on these different treatment approaches. For 2 methods being discussed, tapering and higher dose transfers, there is a requirement for the patient to present in a state of withdrawal. As part of the pretransition discussions for these methods, the importance of presenting in moderate withdrawal is key to the successful transfer, as well as awareness of the possibility of slight worsening of withdrawal symptoms as the patient's buprenorphine is rapidly titrated.

Taper and Inpatient Transfer

This approach is in line with the NSW Clinical Guidelines for the Treatment of Opioid Dependence,[4] which have been drawn from the Australian National Guidelines for Medically Assisted Treatment of Opioid Dependence.[5] In Australia, the opioid agonist treatment for OUD is run through a permit system, which is regulated by the State Health Departments, and it is illegal to prescribe these medications in an outpatient setting without an authority.

Given the dose of methadone that this patient is prescribed, the most suitable setting in which to conduct the transfer would be an inpatient setting. As discussed,

preparation of the patient is key to a successful transference, especially with regard to the risk of precipitated withdrawal and the need for the patient to be in moderate withdrawal before commencing sublingual buprenorphine. Often, it is necessary for the patient to miss a dose of methadone before presenting for admission to allow enough time for the patient to develop sufficient withdrawal before buprenorphine is initiated. The patient must be cognizant of each step of the process including what happens after discharge.

The patient's methadone dose is withheld the day before and on the day of his admission. On admission day, it is important to reassess the patient's recent substance use, as this may affect your management. Once admitted, the patient's withdrawal severity is assessed regularly, every 4 hours, using a validated assessment instrument such as the Clinical Opiate Withdrawal Scale (COWS).[6] Once he is in moderate withdrawal, which correlates to a score of $\geq$13 on the COWS, and he is observed to have objective signs of withdrawal such as dilated pupils and tachycardia, a test dose of 2 mg of sublingual buprenorphine is given. The patient is observed for precipitated withdrawal and other adverse events and reassessed using the COWS after 1 hour. If there have been no adverse events, a further 6 mg of sublingual buprenorphine is given. Withdrawal severity assessment continues every 2 hours and supplemental doses of 2 to 8 mg are administered depending on the severity of the withdrawal until such a time as the majority of the opioid withdrawal symptoms have abated and the patient is not sedated. The maximum daily dose of sublingual buprenorphine in Australia is 32 mg.

The admission can be used opportunistically to address other health problems and complete investigations such as blood borne virus screening and organize referrals as appropriate.

The patient is discharged 24 hours after the first dose of buprenorphine to the care of their community prescriber and last dosing details are provided to ensure that the prescriber is able to write a prescription and that there is no disruption to treatment. It is best practice that the prescriber reviews the patient as soon as is practical after discharge, ideally within the first 4 days. The prescriber is then able to adjust the dose according to clinical need.

Taper and Outpatient Transfer (2 Options – Slow Taper and High-Dose Transfer)

NHS Lanarkshire, Scotland, provides 2 taper outpatient options, one of which is a slow taper at the rate of 5 to 10 mg per 4 weeks with the advantage of minimal withdrawal with transfer once 30 mg methadone dose is reached. However, this taper can take 1 to 2 years to achieve and may expose the patient to a longer period of suboptimal dosing for him, which is not considered as suitable given this patient's history.

Therefore, an alternative method of a high-dose transfer (HDT) would be preferred because of the minimal time for the patient being on a low dose of methadone, thus reducing potential for a relapse. Rapid transition from doses of over 30 mg methadone to buprenorphine have been successfully conducted for a number of years now on an outpatient basis.[7,8]

With HDT, the main presenting risk is precipitated withdrawal, which can occur if the methadone has not been eliminated before transfer. The introduction of buprenorphine too early may cause this set of symptoms; however, this can be reduced through the counselling and advice to the patient and assessment of withdrawal symptoms before commencing treatment.

The patient continues with their usual dose of methadone daily until 36 to 48 hours before their clinic appointment. The patient is advised to stop his dose, which can be facilitated by accurate prescribing, ensuring the final dose prescribed is 2 days before the transition appointment. They need to be advised that they may feel uncomfortable due to withdrawals in this time frame, but they should refrain from using any illicit substances. A further explanation is that the service needs to see them at the clinic before starting the transition as they are; they need to be seen in withdrawal before commencing the process, as such symptoms should not be masked, as this may prevent the start of the transition. The service encourages 100% honesty with this because if they have used any opioids (particularly methadone), the transition can become unpleasant. It is important that they are made aware that on some occasions patients may experience withdrawal symptoms that worsen during the transition, which may be due to the final opioids being displaced from receptor sites by buprenorphine; this is normally transient and diminishes with additional buprenorphine doses.

Patients are advised they will need to stay at the clinic for at least half a day (process takes several hours), whilst the buprenorphine dose is titrated quickly, but there is the need for observation between doses as well as evaluation of the patient and their symptoms. Doses are given every 45 to 60 minutes and increase to a maximum of 24 mg.[7] The dose regimen is 2 mg, 2 mg, 4 mg, 8 mg, and 8 mg. Some patients may wish to stop at 16 mg; however, we would encourage a dose of 24 mg, which produces a high degree of opioid receptor saturation. Patients may wish to leave the clinic for a break, drink (nonalcoholic) or to smoke tobacco and if well they may be allowed to do this, but they should only be away for a short period of time. Patients are assessed and opioid withdrawal scales are completed (and agreed with patient) before each dose is given. Throughout, communication about the process and the expectations between the prescriber (or worker) and the patients are essential for a good outcome.

Microdosing Transfer (Bernese Method)

A third option for the patient would be the use of microdosing. This is a relatively new development by NHS Lanarkshire and is based on experiences reported in the little published literature and anecdotal reports from other services with the UK.[9–12]

The principle underlying the process is to slowly but gradually introduce buprenorphine to the patients' opioid agonist treatment, whilst they are on a full opioid agonist, titrating the dose up to a therapeutic dose before discontinuing their full opiate agonist. The dose of buprenorphine gradually increases and gently displaces the full opioid agonist from the receptor sites replacing this with buprenorphine, a partial opioid agonist, but with greater receptor affinity. The buprenorphine dose increases should be small initially and gradually increased to ensure there is not a rapid replacement of the full opioid agonist by the partial agonist, which could

introduce withdrawal symptoms to the patient. The increases of buprenorphine should be made daily, with the methadone dose remaining the same as before the transfer started, until a therapeutic dose has been achieved of buprenorphine. At this stage, the methadone can be either reduced or stopped, whilst the final stages of the buprenorphine titration are completed. Once at a therapeutic dose of buprenorphine, ceasing the daily dose of methadone should cause no significant issues in relation to withdrawal symptoms due to the buprenorphine occupancy of opioid receptors.

The main advantage of the microdosing method is that the patient should only experience mild withdrawal symptoms at worst (if any) from any previous prescribed daily dose of methadone, although the negative is that the process takes a number of weeks to complete, but by the end, the patient should be on a stable daily dose of buprenorphine and no longer be on any methadone, providing a crossover in opioid agonist treatment.

The guidance developed locally for this method is to commence with sublingual 400 μg buprenorphine and gradually increase this dose every 24 hours initially by 400 μg, then as the dose has increased, increasing the dose increment at a greater rate (eg, 800 μg after dose reaches 3 mg, 1200 μg after dose reaches 8 mg, etc), whilst maintaining the methadone dose. Once the buprenorphine dose is over 12 mg, consideration to reducing the daily methadone dose can be made, up to 50%. Then as the buprenorphine increases further and the patient stabilizes on the dose, the methadone can be quickly reduced with few withdrawal symptoms expected, as the buprenorphine is occupying the majority of the receptor sites. The process can take 3 to 4 weeks to complete, but this is dependent on the individual patient and the rate of buprenorphine increase.

Once the process has started for the patient, it is necessary to work closely with them, with appointments more regularly than normal (a minimum of weekly appointments during the transition) to ensure the titration for buprenorphine is being tolerated and there are no signs of opioid toxicity. Appointments can be altered on an individual basis in response to the patient's progress or symptoms, thus altering the rate of increase of buprenorphine or reducing full opioid agonist doses as required.

For the patient in this scenario, this may be a good option as he has been treated with both methadone and buprenorphine previously but finds the reductions in methadone dose challenging and he struggles more with the withdrawal symptoms experienced. Additionally, looking beyond the transfer to buprenorphine, he reported that in the past he has found detoxing from buprenorphine is easier for him. The microdosing technique may provide a method of transitioning involving few if any withdrawal effects and, as such, appeal to the patient more than the other options of a slow and gradual reduction in methadone dose or the potential withdrawals (albeit for a brief period of time) experienced with the transition phase of an HDT. The process is then through the regular reviews tailored to his progress. However, one of the negatives for the process is the need for the regular contact and that the process can extend over a few weeks to complete.

DISCUSSION

The ability to transition from methadone to buprenorphine medication has long been a challenge given the pharmacology of the 2 opioids. In some countries (eg, USA), methadone and buprenorphine are delivered in different treatment sectors, such that relatively few patients seek to make the transition. Elsewhere (eg, UK, Australia, and Europe), methadone and buprenorphine are routinely provided by the same service providers, and there seems to be greater experience in attempting transfers. Additionally, the treatment process and available resources in each country or state may differ (eg, access to inpatient facilities) and will be dependent on practices, facilities and product availabilities, but the review[1] and this case study series are based on evidenced and peer reviewed articles and the clinical experience of the authors.

In 2020, 2 factors have highlighted the need for ''smoother'' transitions between the 2 medications. The introduction of depot buprenorphine medications[13–15] in many countries, with once-a-week or once-a-month dosing greatly increases treatment convenience and satisfaction and is likely to result in many patients seeking to transition from methadone to depot products. The second factor has been the emergence of COVID-19, and the need to minimize direct contact of patients attending and congregating at services. The greater safety profile of buprenorphine compared to methadone makes it a medication better suited to large numbers of unsupervised doses. Again, the depot formulations have also been encouraged in many services to reduce COVID-19 risks.[15,16]

Having a range of potential options for the transition between methadone and buprenorphine is essential, and it is important to discuss these with each patient in advance to identify which method may be preferable for them, discussing the pros and cons of each and addressing any fears or concerns that they may have in relation to the process. By involving the patient in the choice of transition method, they will have more involvement in the process. In respect to the recent review,[1] it can be seen that various options have been investigated, which all have advantages and disadvantages, therefore providing a number of possible options for patients dependent on their risks and preferences. Offering a range and getting the patient involved in these discussions may increase their engagement in the process and hopefully their success in transferring treatments. The review,[1] however, does point out that there is still a limited evidence base for the transfer processes and unfortunately there is no clear strategy that one is better than the others. It is therefore important to note that while the available research does not support routine application of a single transfer strategy, it does support the narrative of positive outcomes described in these case vignettes. The review[1] clearly indicates that most patients who initiate a transfer from methadone to buprenorphine do achieve a stable buprenorphine dose and successfully complete the transfer.

It is important to recognize that these results (based on the review[1] and the above cases) are achieved in settings where patients are managed by experienced clinicians. In the absence of clear evidence, clinical experience and expert opinion are necessary to guide treatment. Available international clinical guidelines are derived from published clinical

experience, therefore providing recommendations consistent with the available evidence. However, clinical guidelines should be seen as providing ''guidance'' rather than ''protocols'' for adherence. Although new approaches[8,10–12] seems promising, further evidence of the safety and effectiveness of such approaches are required before they can be considered ''routine'' practice or occur outside of specialist sector services. This emphasizes the importance of clinicians and patients preparing in advance for the transfer exercising their judgment, based on the available evidence, as to which procedure is best suited for their particular transfer.

Concluding Comment Regarding the Application of the Case Conference to Practice

As a final thought, through the process (irrespective of the transition method), it should be remembered that the patient is going to go through a challenging time as they transition from methadone to buprenorphine, which can allow other suppressed emotions to come to the surface and be a potential time for relapse, and as such the warning signs and dangers of using illicit substances should be clearly discussed and the provision of take home naloxone should be made to further encourage the patient's safety.

REFERENCES

1. Lintzeris N, Mankabady B, Rojas-Fernandez C, Amick H. Strategies for transfer from methadone to buprenorphine for treatment for opioid use disorders and associated outcomes: a systematic review. *J Addict Med*. 2022;16:143–151.
2. Bishop B, Gilmour J, Deering D. Readiness and recovery: transferring between methadone and buprenorphine/naloxone for the treatment of opioid use disorder. *Int J Ment Health Nurs*. 2019;28(1):226–236.
3. Hill D, Gardner D, Baldacchino A. Comparing cognitive function in patients receiving chronic methadone or buprenorphine for opioid dependence: a systematic review. *Heroin Addict Relat Clin Probl*. 2018;20(5):35–49.
4. New South Wales Clinical Guidelines: Treatment of Opioid Dependence – 2018. Available at: https://www.health.nsw.gov.au/aod/Publications/nsw-clinical-guidelines-opioid.pdf. Accessed August 6, 2020.
5. National Guidelines for Medically Assisted Treatment of Opioid Dependence 2014. Available at: https://www.health.gov.au/sites/default/files/national-guidelines-for-medication-assisted-treatment-of-opioid-dependence.pdf. Accessed August 6, 2020.
6. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*. 2003;35(2):253–259.
7. Hill D, Conroy S. Case note review – transfer of patient to buprenorphine from daily doses of methadone greater than 30 mg. *Heroin Addict Relat Clin Probl*. 2014;16(1):55–64.
8. Conroy S, Hill D. Transfer to buprenorphine from daily doses of methadone greater than 30 mg – initial review of transfers. *Heroin Addict Relat Clin Probl*. 2013;15(3):19–28.
9. Cassells N, Hill DR, Marr E. Stewart E. Microdosing case study series – transferring from methadone to oral buprenorphine. *Heroin Addict Relat Clin Probl*. 2020 Dec 4. [Epub ahead of print]. Available at: https://www.heroinaddictionrelatedclinicalproblems.org/harcp-archives-doi-articles.php.
10. De Aquino JP, Fairgrieve C, Klaire S, Garcia-Vassallo G. Rapid transition from methadone to buprenorphine utilizing a micro-dosing protocol in the outpatient veteran affairs setting. *J Addict Med*. 2020;14(5):e271–e273.
11. Haemmig R, Kemter A, Strasser J, et al. Use of micro-doses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. *Subst Abuse Rehabil*. 2016;7:99–105.
12. Terasaki D, Smith C, Calcaterra SL. Transitioning hospitalised patients with opioid use disorder from methadone to buprenorphine without a period of opioid abstinence using a micro-dosing protocol. *Pharmacotherapy*. 2019;39(10):1023–1029.
13. Ling W, Nadipelli VR, Solem CT, et al. Patient-centered outcomes in participants of a buprenorphine monthly depot (BUP-XR) double-blind, placebo-controlled, multicenter phase 3 study. *J Addict Med*. 2019;13:442–449.
14. Ling W, Nadipelli VR, Aldridge AP, et al. Recovery from opioid use disorder (OUD) after monthly long-acting buprenorphine treatment: 12-month longitudinal outcomes from RECOVER, an observational study. *J Addict Med*. 2020;14(5):e233–e240.
15. Frost M, Bailey GL, Lintzeris N, Strang J, et al. Long-term safety of a weekly and monthly subcutaneous buprenorphine depot (CAM 2038) in the treatment of adult out-patients with opioid use disorder. *Addiction*. 2019;114(8):1416–1426.
16. Lintzeris N, Hayes V, Arunogiri S. Interim guidance for the delivery of medication assisted treatment of opioid dependence in response to COVID-19: a national response. Available at: https://www.racp.edu.au/docs/default-source/news-and-events/covid-19/interim-guidance-delivery-of-medication-assisted-treatment-of-opiod-dependence-covid-19.pdf?sfvrsn=e36eeb1a_4. Accessed August 6, 2020.