

Successful Transition from High-Dose Methadone to Buprenorphine via Microdosing in the Outpatient Setting: A Case Report

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INTRODUCTION

Transitioning from full μ -receptor agonists, such as methadone, to buprenorphine can be challenging because of the potential for precipitated withdrawal.¹ Buprenorphine is a partial μ -receptor agonist and has lower intrinsic activity at μ receptors than methadone and other full μ -receptor agonists.² Because of its high affinity for μ receptors, buprenorphine replaces methadone and results in precipitated withdrawal.² Conventionally, to make the transition to buprenorphine, the methadone dose had to be gradually tapered, to 30 mg daily, and then stopped, followed by induction of buprenorphine 36 to 72 h later, once moderate opioid withdrawal symptoms were detected.³ Not only is this conventional technique time-consuming, but it also puts clients at risk of relapse and overdose due to the extended period of destabilization. Consequently, clinicians are searching for other novel approaches that decrease the extent of destabilization. One such method, known as the Bernese model, involves gradual upward titration of very small doses of buprenorphine while maintaining the same dose of methadone.¹ This method of titration results in a very gradual increase in the percentage of receptors occupied by buprenorphine while allowing the remaining μ receptors to interact with methadone.¹

One common reason for transitioning from methadone to buprenorphine is concern about prolongation of the QT interval. The methadone formulations available in Canada are racemic mixtures with propensity to increase corrected QT interval (QTc) in a dose-dependent fashion.⁴ It has been shown that the (S)-enantiomer of methadone (dextromethadone) is the cause of this dose-related adverse effect.⁵ Prolongation of the QTc interval is a marker of the impending possibility of torsade des pointes and sudden death. The risk of sudden cardiac death increases 4-fold when QTc is 500 ms or longer.⁶

Buprenorphine has been shown to be as effective as methadone in suppressing illicit opioid use, though perhaps

slightly less effective in terms of patients remaining in treatment.⁷ Furthermore, when taken as recommended, buprenorphine currently is not known to potentiate the risk of torsade des pointes,⁸ and it is considered first-line treatment for opioid use disorder because of its safety profile.⁹

There is no specific guideline for the interval of dosing or speed of titration to be used in buprenorphine microdosing, and the published evidence to date consists only of case series.^{1,10} To contribute to the available literature, we present a case of transition from methadone to buprenorphine by the Bernese method, in the outpatient setting, in a patient with acquired QTc prolongation. The sublingual formulation of buprenorphine used in this case was combined with an opioid antagonist, naloxone, which is not absorbed sublingually. This combination is designed to discourage abuse of buprenorphine, as naloxone can precipitate withdrawal symptoms in patients with opioid use disorder.³

CASE REPORT

A 29-year-old man with a long history of opioid use disorder, who had been receiving methadone for more than 5 years, was transferred to our outpatient clinic; the daily dose at the time of transfer was 160 mg orally.* His past medical history was significant for depression and anxiety; however, he was not receiving any other medications or supplements at the time of transfer. Secondary to continuous illicit opioid use, the methadone dose was gradually increased to 220 mg daily.

Upon the performance of electrocardiography (ECG), as part of regular annual care, it was noted that QTc was prolonged, at 502 ms; previous ECG 2 years earlier had shown QTc of 464 ms. The dose of methadone was reduced while Holter monitoring and echocardiography were performed, for which the results were normal. After we reviewed potential risks and benefits with the client, he informed us that his wish was to

*The client provided written informed consent for publication of this report.

use buprenorphine/naloxone instead of methadone. Different approaches to transitioning from methadone to buprenorphine/naloxone were described, and the client expressed interest in pursuing the microdosing (Bernese) method.

At the time of initiation of buprenorphine/naloxone, in November 2018, the client was receiving 200 mg of methadone daily. The combination product was initiated at 0.5 mg of buprenorphine and 0.125 mg of naloxone daily, and the client did not report any withdrawal symptoms. Buprenorphine/naloxone was increased to 1/0.25 mg daily after 5 days, and the dose was then increased by 1/0.25 mg weekly until the dose of 8/2 mg daily was reached. Concurrently, the methadone dose was decreased by 10 mg weekly. As such, after 8 weeks of therapy (in early 2019), the client was receiving 8 mg of buprenorphine, 2 mg of naloxone (in combination), and 110 mg of methadone daily.

At that time, the client moved to a recovery program, with care being managed by another provider. When he returned to our care, he was receiving 22 mg buprenorphine, 5.5 mg naloxone (in combination), and 90 mg methadone daily. From that point, we slowly increased the buprenorphine/naloxone dose (by 2/0.5 mg every few days) and very quickly decreased his methadone dose from 90 mg to zero (Figure 1). The optimal maintenance dose of buprenorphine/naloxone should be able to suppress physical withdrawal signs and symptoms. It also should enable the patient to cease illicit opioid use. Consequently, the buprenorphine/naloxone dose needed to achieve these goals will differ from one person to another.² In this case, titration up to 32/8 mg of buprenorphine/naloxone daily was elected, as per the client's preference. The client consistently reported fewer psychological cravings at higher doses.

Psychological and physical withdrawal symptoms were assessed during interactions at clinic visits and through client self-reporting. There were no documented physical withdrawal scales available for us to report. The client did not exhibit or report any physical withdrawal symptoms during the buprenorphine/naloxone initiation or methadone tapering. Furthermore, while under our care, the results of all urine drug screening during clinic visits were negative for illicit opioids. Follow-up ECG 2 weeks after discontinuation of methadone indicated QTc of 373 ms.

DISCUSSION

In this case report, we have described buprenorphine/naloxone microdosing for a client who was receiving 220 mg of methadone daily. The reason for switching from methadone to buprenorphine/naloxone was QTc prolongation. Considering the current lack of guidelines for switching from high-dose methadone to buprenorphine/naloxone, our experience supports the concept of using an appropriate microdosing schedule to safely switch motivated clients from high-dose methadone to buprenorphine/naloxone. Starting the buprenorphine/naloxone at 0.5/0.125 mg daily and increasing the dose slowly made it possible to accomplish induction successfully. Tapering of the methadone dose is not required before initiation of buprenorphine/naloxone microdosing¹⁰; however, to ensure that we had taken appropriate actions to prevent risks related to QTc prolongation, we started reducing the methadone dose even before starting buprenorphine/naloxone. This case is unique in that methadone and buprenorphine/naloxone were taken simultaneously for an extended period, partly because of an

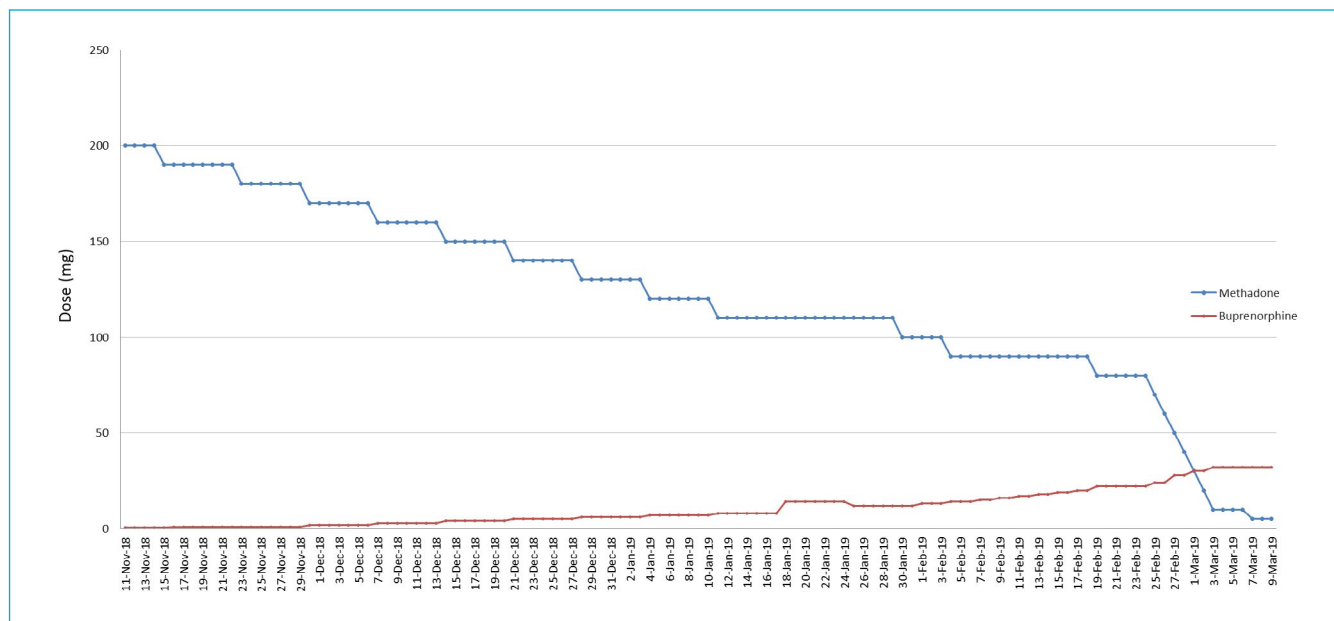


FIGURE 1. Time course of induction of buprenorphine/naloxone by microdosing (with data shown only for the buprenorphine component of the combination product) and tapering of methadone.

interruption in care and partly because of the client's anxiety about discontinuing methadone too quickly. However, no serious incident or adverse effects resulted from the simultaneous administration.

We recommend that any care plan should consider all potential changes to clients' living conditions, baseline functioning, and social stability. It must also be communicated to clients whose therapy is being transitioned to buprenorphine/naloxone that they will need regular, more frequent assessment. Such an approach provides an opportunity to promptly deal with adverse events and anxiety related to medication changes, which could improve adherence to the microdosing plan.

References

1. Hämmig R, Kemter A, Strasser J, von Bardeleben U, Gugger B, Walter M, et al. Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. *Subst Abuse Rehabil.* 2016;7:99-105.
2. Jones HE. Practical considerations for the clinical use of buprenorphine. *Sci Pract Perspect.* 2004;2(2):4-20.
3. *A guideline for the clinical management of opioid use disorder.* British Columbia Centre on Substance Use and BC Ministry of Health; 2017 Jun 5 [cited 2020 Nov 17]. Available from: www.bccsu.ca/care-guidance-publications/
4. Anchersen K, Clausen T, Gossop M, Hansteen V, Waal H. Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: a mortality assessment study. *Addiction.* 2009;104(6):993-9.
5. McCance-Katz EF. (R)-methadone versus racemic methadone: what is best for patient care? *Addiction.* 2011;106(4):687-8.

6. Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MCP. QTc interval screening in methadone treatment. *Ann Intern Med.* 2009;150(6):387-95.
7. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev.* 2014;2:CD002207.
8. Woosley RL, Heise CW, Gallo T, Tate J, Woosley D, Romero KA. *QTdrugs list* [searchable database online]. AZCERT, Inc; [cited 2019 Nov 15]. Available from: www.Crediblemeds.org
9. Bruneau J, Ahamad K, Goyer ME, Poulin G, Selby P, Fischer B, et al.; CIHR Canadian Research Initiative in Substance Misuse. Management of opioid use disorders: a national clinical practice guideline. *CMAJ.* 2018;190(9):E247-57.
10. Terasaki D, Smith C, Calcaterra SL. Transitioning hospitalized patients with opioid use disorder from methadone to buprenorphine without a period of opioid abstinence using a microdosing protocol. *Pharmacotherapy.* 2019;39(10):1023-9.

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