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A Case Series of Spouses Undergoing Rapid Micro-Induction Technique of Buprenorphine Initiation from Methadone

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INTRODUCTION

The impact of opioid use disorder (OUD) and opioid fatal overdoses continues to be a substantial source of lost economic value in the United States.[1] In 2017, the overall economic burden attributed to OUD and fatal overdoses totaled approximately $1.02 trillion, with $35 billion attributed to healthcare costs and $3.5 billion to OUD treatment. Medications used to treat individuals with OUD have demonstrated a reduction in the prevalence of opioid misuse, as well as the number of opioid overdose fatalities.[2,3] Historically, the population requiring treatment has outnumbered the capacity of available treatment.[4] The situation necessitates the implementation of safe and efficient treatment strategies for patients, while seeking cost-conscious solutions to address the rising economic burden on the healthcare system. Presently, individuals undergoing daily methadone treatment can anticipate an average annual cost of $6,552. Those who undergo buprenorphine treatment twice weekly may expect $5,980 annually, highlighting a savings of over $500 comparatively.[5]

There are three medications approved by U.S. Food and Drug Administration for Medications for Opioid Use Disorder (MOUD) treatment that target the opioid receptors: methadone, buprenorphine, and naltrexone.[6] Methadone is a full opioid agonist at the opioid receptor and is by far the oldest, evidence-based effective treatment for OUD. However, methadone has some limitations as it cannot be prescribed and is dispensed only by Opioid Treatment Programs, which are regulated federally and by the State. During the course of methadone treatment, patients face various constraints including daily clinic visits, the requirement to drink the formulation in the presence of staff, and participation in mandated counseling. Patients are allowed to take home the medication only after being enrolled in the program for a while, which may cause conflicts with their personal schedules.

Buprenorphine is used for the maintenance treatment of OUD.[6] Buprenorphine has potential advantages over methadone, including a lower overdose risk, a "ceiling effect" for respiratory depression, fewer pharmaceutical interactions, and the absence of risks of QTc-prolongation. It also can be prescribed for the employed and childbearing age groups.

Buprenorphine has a partial intrinsic activity but has a high affinity at the mu-opioid receptors.[6,7] Hence, if administered concomitantly with a full agonist, it potentially can displace the full agonist and cause a sudden, precipitated withdrawal. Traditional buprenorphine induction protocol requires full abstinence from opioid agonists for a period of 24 to 72 hours before initiation.[6,8-10] This can be challenging for patients who are taking methadone and trying to taper the dose, due to the need to stop or switch therapies. This can predispose them to withdrawal symptoms and cravings, threatening potential relapse.[6,11]

Micro-dosing or micro-induction is the practice of administering small escalating doses of buprenorphine to obtain benefit from its action with minimal side effects. This technique implies a slow build-up of buprenorphine at the opioid receptors with repeated small doses bypassing the precipitated withdrawal.[8,12-14] The literature review on micro-dosing techniques showed that most of them primarily have been performed in an inpatient setting.[15-18] Only a few transitions were performed in an outpatient setting.[19] Our case series was innovative as a successful transition from methadone to buprenorphine was described in two patients, using the micro-dosing technique in an outpatient setting.

CASE REPORT

A married couple, a 44-year-old male and a 43-year-old female, were evaluated at our facility for OUD. They were previously on methadone for the treatment of OUD and were transitioned successfully to buprenorphine via rapid micro-induction. The rapid micro-induction procedure was performed in an outpatient setting with ancillary medications administered for withdrawal symptom relief. Both patients were assessed and followed on-site by a team composed of an addiction psychiatrist, nursing staff, and an addiction fellow.

Patient A was a 44-year-old male patient with a past psychiatric history (PPH) of OUD and attention-deficit/hyperactivity disorder (ADHD) on treatment with methadone 50 milligrams (mg) for the past nine years. He had been stable on that regiment without any complications, but sought a change in treatment due to transportation difficulties and the driving distance to the clinic. Additional past medical history included melanoma and renal cell carcinoma status post left nephrectomy. He was started on hydromorphone and various prescription opioids following his left nephrectomy. The patient had chronic bilateral knee pain in addition to his post-surgical pain which was managed with opioid therapy. He then developed tolerance to the opioids, started to increase the dosage and frequency of opiates, and obtained them illicitly from the streets. He was diagnosed with OUD, started on methadone, and nine years later he decided to switch therapies.

Patient B was a 43-year-old female patient with a past medical history of hypothyroidism, PPH of OUD, and ADHD and was on treatment with methadone 67 mg. There were no reported issues or side effects with methadone, but she wanted to make the change to buprenorphine for reasons similar to her husband, including her job, transportation, and children at home.

Rapid micro-dosing of buprenorphine technique was explained to the patients, and they expressed interest in this method. For patient A, the micro-induction procedure began with a 2 mg sublingual film of buprenorphine. The film was divided into four parts of 0.5 mg buprenorphine that was administered in intervals of one-half to one

hour under direct supervision in the clinic. Following complete dosing, 50 mg of methadone was administered.

The Clinical Opiate Withdrawal Score (COWS) scale was used to quantify the severity of opiate withdrawal.[19] The COWS scale establishes severity ranges based on patients' signs or symptoms in the following manner: Scores 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal.[20] COWS was obtained at the start of micro-dosing and thirty minutes after completion (Table 1). Mild withdrawal symptoms of sweating, chills, fatigue, and nausea were observed on the first day with a COWS score of 9.

The dose of buprenorphine was increased to 3 mg on day two, followed by the administration of 50 mg of methadone. On day three, patient A was scheduled to take 6 mg of buprenorphine, but decided to take 4 mg to align his treatment course with his wife. On this day, he reported feeling anxious and had a COWS of 0. On day 4, he was administered 8 mg buprenorphine with methadone dosing. On day 5, he started on 12 mg of buprenorphine at home and discontinued methadone. He returned to the clinic the following week dosed at 16 mg buprenorphine, but reported cravings and mild withdrawal symptoms. He expressed interest in increasing the dosage greater than 16 mg. At that time, he was switched to 20 mg daily and entered the stabilization phase of buprenorphine treatment.

Patient B followed a similar treatment course, but needed an additional day of micro-induction to achieve the complete transition from methadone to buprenorphine. Micro-dosing of buprenorphine was followed by administration of 67 mg of methadone. She stopped her levothyroxine for hypothyroidism several days prior to starting micro-induction due to concern about medication interaction. On day one, she was started on 1 mg buprenorphine, but began to display withdrawal symptoms (chills, fatigue, nausea, myalgias, and anxiety) and had a COWS of 12. At that point, micro-induction was stopped, and methadone was dosed at 67 mg. The patient was administered hydroxyzine 25 mg and clonidine on day one and continued to receive them on days two and three (Table 2).

On day two, she was administered 2 mg buprenorphine and had a COWS of 8, reporting chills, fatigue, abdominal pain, diarrhea, nausea, itching, tremors, and headaches. On the third and fourth days, the patient was dosed with 4 mg and 8 mg of buprenorphine, respectively. On both days, the patient denied having withdrawal symptoms. The following days occurred over the weekend and her dose was increased to 16 mg. She reported having headaches, low energy, and insomnia over both days. She stated that she felt more comfortable at 12 mg and did not want to increase the dose.

Both the patients transitioned successfully to buprenorphine. Four days were required for patient A and five days for patient B to complete the transition, including a day for initial assessment and half days dedicated to clinical care. On follow-up in four weeks, both the patients were stable on buprenorphine and did not report relapse.

DISCUSSION

Two patients were transitioned from agonist therapy of methadone to sublingual buprenorphine in an outpatient setting in a short period of four to five days. The patients reached a therapeutic dose of buprenorphine while taking 50 mg (patient A) and 67 mg (patient B) daily without requiring a period of opioid withdrawal prior to initiation and tapering the daily dose of methadone. Supportive medications, such as hydroxyzine and clonidine, were used effectively as needed to counter any withdrawal symptoms. Following micro-induction for patient B, she was maintained on buprenorphine and did not experience withdrawal symptoms or cravings for illicit opioids. Patient A reported some withdrawal symptoms after completing micro-induction, which was addressed by increasing his dosage of buprenorphine slightly.

These cases illustrated that barriers to buprenorphine treatment can be overcome by unique techniques like above.[9] Utilization of rapid micro-induction confers many benefits for both patients and physicians by reducing the amount of time patients need to visit the clinic, removing the need to be in withdrawal prior to induction, and having added flexibility of dosing. The cases demonstrated that modifications to micro-doses transitioning from a full agonist to a partial agonist can be tailored to assist patients on an individual basis. Personalized transition creates a better experience for patients by reducing the overall burden of withdrawal and further compliance with MOUD.[9]

Table 1. Detailed information for Patient A.

			Dose 1	Dose 2	Dose 3	Dose 4	Total
Day 1	BPN (mg)		0.5	0.5	0.5	0.5[1]	2.0
	COWS	Before	9	9	7	7	
		After	9	8	7		
	Vitals		HR 87 RR 18 BP 133/79 SpO2 99% Temp 97.8	HR 77 RR 17 BP 135/76 SpO2 98%	HR 77 RR 16 BP 118/79 SpO2 97%	HR 79 RR 17 BP 143/85 98% SpO2	
	Withdrawal Symptoms		Pulse Chills Restlessness Mild diffuse discomfort Tearing eyes Nausea Anxiety Irritability	Chills Restlessness Mild diffuse discomfort Moist eyes Nausea Yawning Anxiety	Sweating/ chills Inability to sit still Moist eyes Diffuse discomfort Irritability/ anxiousness	Sweating Inability to sit still Diffuse discomfort Nausea Anxiety/ irritability	

			Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Total
Day 2	BPN (mg)		0.5	0.5	0.5	0.5	0.5	0.5[1]	3.0
	COWS	Before	4	4	7	0	1	6	
		After	4	7	0	1	6	16	
	Vitals		HR 84 RR 18 BP 135/78 SpO2 99% Temp 98.4	HR 84 RR 17 BP 127/81 SpO2 99%	HR 80 RR 17 BP 126/69 SpO2 98%	HR 78 RR 17 BP 133/83 SpO2 99%	HR 75 RR 17 BP 123/75 SpO2 100%	HR 74 RR 16 BP 131/82 SpO2 99%	
	Withdrawal symptoms		Pulse Sweating/ chills Stomach cramps Irritability/ anxiousness	Pulse Sweating/ chills Stomach cramps Irritability/ anxiousness	Beads of sweat on face Nausea Slight tremor observable	None	Yawning	Sweating Frequent shifting Nose running Stomach Cramps Slight tremor Irritable/ anxious Piloerection	

			Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8	Total
Day 3	BPN (mg)		0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5[1]	4.0
	COWS	Before	5	4	1	0	0	0	0	0	
		After	-	4	-	0	0	0	0	0	
	Vitals		HR 88 RR 17 BP 126/82 SpO2 99% Temp 97.8	HR 82 RR 16 BP 138/78 SpO2 97%	HR 81 RR 17 BP 132/75 SpO2 97%	HR 79 RR 16 BP 130/76 SpO2 100%	HR 73 RR 18 BP 144/81 SpO2 99%	HR 74 RR 17 BP 132/71 SpO2 97%	HR 76 RR 18 BP 130/76 SpO2 96%	HR 75 RR 19 BP 143/88 SpO2 98%	
	Withdrawal symptoms		Pulse Chills Nausea	Pulse Chills Nausea	Pulse	None	None	None	None	None	

[1]Upon completion of last BPN dose, 50 mg of methadone was administered daily.

Table 2. Detailed information for Patient B.

			Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8	Total
Day 1	BPN (mg)		0.5	0.5[1]							1.0
	COWS	Before	0	-							
		After	-	12							
	Vitals		-	-							
	Withdrawal symptoms		Chills Fatigue Nausea Myalgias Irritability/ anxiousness	Chills Fatigue Nausea Myalgias Irritability/ anxiousness							
Day 2	BPN (mg)		0.5	0.5	0.5	0.5[1]					2.0
	COWS	Before	8	4	2	1					
		After	4	2	1	1					
	Vitals		HR 104 RR 18 BP 133/82 SpO2 92% Temp 97.8	HR 94 RR 17 BP 130/84 SpO2 100%	HR 86 RR 16 BP 125/85 SpO2 100%	HR 87 RR 17 BP 116/75 SpO2 100%					
	Withdrawal symptoms		Pulse Loose Stools Flushing/ sweating Difficulty sitting still	Pulse Loose stools Irritability/ anxious	Pulse Chills/ flushing	Pulse					
Day 3	BPN (mg)		0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5[2]	4.0
	COWS	Before	3	1	2	0	1	0	0	1	
		After	1	2	0	1	0	0	1	1	
	Vitals		HR 95 RR 17 BP 135/83 SpO2 100 % Temp 97.8	HR 88 RR 16 BP 116/81 SpO2 100%	HR 103 RR 17 BP 130/76 SpO2 100%	HR 78 RR 16 BP 108/65 SpO2 97%	HR 89 RR 17 BP 121/81 SpO2 98%	HR 75 RR 16 BP 119/74 SpO2 99%	HR 72 RR 16 BP 116/74 SpO2 99%	HR 98 RR 16 BP 126/93 SpO2 100%	
	Withdrawal symptoms		Pulse Nausea Loose stool	Pulse	Pulse	None	Pulse	None	None	Pulse	

[1]Addition of clonidine and hydroxyzine 25 mg given after second dose due to withdrawal symptoms on Day 1 and then prior to first dose for Day 2 and Day 3.
[2]Upon completion of last BPN dose, 67 mg of methadone was administered daily.

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