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Israel's First Successful Low Dose Initiations of Buprenorphine for Fentanyl, Oxycodone and Tramadol Use Disorders in an Outpatient Public Medication Assisted Treatment Center: A Case Series

Stacy Shoshan*

Clalit Health Services, Eilat Region, Israel

***Corresponding author**: Stacy Shoshan. Clalit Health Services, Eilat Region, Israel

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Abstract

Background: Opioid use disorder to prescription medications is an increasing problem worldwide, including in Israel. Medication assisted treatment options for opioid use disorder include buprenorphine, but traditional initiation methods are challenging both for clinicians and patients. To overcome the roadblocks that prevent initiation, low dose buprenorphine induction protocols are being developed. Only a few countries in the world have published reports of low dose buprenorphine initiations, however none in Israel.

Case presentations: Four patients who suffered from addiction to oxycodone, oxycodone/paracetamol, fentanyl and tramadol, presented for medication-assisted treatment and requested buprenorphine. These four patients were offered low dose buprenorphine inductions because they were not able to stop their opioid medication before starting treatment, which is necessary to initiate a traditional buprenorphine protocol.

Results: Using low dose initiation protocols, all four patients were successfully stabilized on a therapeutic dose of buprenorphine in parallel to being completely tapered off the prescription medication to which they were addicted.

Discussion: This four case series is the first of its kind done in Israel and successfully shows that low dose buprenorphine inductions can be carried out in an outpatient public medication assisted treatment center in this country. Furthermore, this is the first published case of a person suffering from tramadol use disorder to undergo low dose buprenorphine induction.

Keywords: Low Dose Initiation; Buprenorphine; Fentanyl; Oxycodone; Tramadol; Opioid Use Disorder.

Abbreviations: am morning; bid: twice a day; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; h/o: history of; MAT: medication assisted treatment; MEDD: morphine equivalent daily dose; n/a: not applicable; OTC: over the counter; pm: evening; qd: once a day in the morning; s/p: status post; tid: three times a day.

Introduction

In 2020, Israel was ranked number one in the world in opioid consumption per capita as measured by morphine equivalents [1]. Chronic opioid use is associated with numerous serious risks including misuse, addiction and overdose [2]. Furthermore, it was shown that Israel is just like other countries in that increased opioid use is associated with increased all-cause mortality among non-oncological patients [3]. Beginning with the publication of the seminal paper on methadone as treatment for heroin addiction in 1965 [4], there has been more than 50 years of data showing that the best way to alter the course of the fatal disease of opioid addiction is medication treatment with either methadone, buprenorphine or naltrexone, along with biopsychosocial support [5].

Buprenorphine's potential utility for the management of addiction, the most severe form of opioid use disorder, has been discussed in the literature since the 1970s [6]. Buprenorphine offers several advantages as a treatment medication, which include its high binding affinity to the mu opioid receptor and slow dissociation kinetics. Due to its high affinity, buprenorphine will displace other opioids such as fentanyl, oxycodone, morphine and methadone, and bind to the receptors in their place. In addition, the slow dissociation or disengagement from the receptors contributes to its long duration of action and blocks other opioids from binding [7].

Buprenorphine is a partial mu receptor agonist, which means that its maximal effect is less than that of the aforementioned full agonists and at a certain dose, it reaches a ceiling. This ceiling makes it much safer than full opioid agonists because respiratory depression, which can be the cause of overdose death, is limited. However, unlike full agonists where an increase in dose equates to a stronger effect, once buprenorphine reaches its ceiling, higher doses do not increase the effectiveness of the medication [7,8].

Buprenorphine as part of medication assisted treatment (MAT) for opioid use disorder has the ability to both relieve and induce opioid withdrawals depending upon when it is ingested. When a patient has stopped using opioids and is in withdrawals, buprenorphine will bring relief through its partial agonist effect. However, because of buprenorphine's high affinity and only partial agonism, if it is consumed while other high efficacy full agonist opioids are occupying the mu receptors, it will displace them and precipitate severe withdrawals. Therefore, patients regularly using opioids must completely stop taking them before beginning treatment using traditional buprenorphine protocols, which many individuals are unable to do because of their addiction. Furthermore, despite these precautions, the induction of buprenorphine can precipitate severe opioid withdrawals resulting in physical and psychological agony, dropping out of treatment, resistance to reengaging in treatment, and relapse with the risk of overdose and death [9]. For all of these reasons, traditional buprenorphine initiation methods remain challenging both for clinicians and patients.

To overcome the roadblocks that prevent buprenorphine initiation, a breakthrough low dose buprenorphine induction protocol was developed in Switzerland, originally called the Bernese method. It was published in German in 2010 [10] and then in English in 2016 [9]. Low dose initiation protocols are based upon induction of buprenorphine treatment with overlapping full opioid agonist use. They work by repetitive administration of very small buprenorphine doses, previously called microdoses, with sufficient dosing intervals, such as every 12 hours, to allow for the buprenorphine to gradually accumulate at the mu opioid receptors. Over time, an increasing amount of buprenorphine will slowly displace and replace the full mu agonist, thereby avoiding precipitated withdrawals. Because of the high affinity and long receptor binding time, buprenorphine will preferentially accumulate at the mu receptors until it is the only bound opioid. Therefore, using a low dose protocol, overlapping induction of buprenorphine with ongoing use of opioids, whether prescribed or illicit, is possible without precipitating severe opioid withdrawals [11].

Whereas buprenorphine is available for treatment of opioid use disorder in many countries, only a few have published reports of low dose buprenorphine initiations [12], none of which were from Israel. Since 2002, buprenorphine as part of MAT has been prescribed in Israel by doctors who have undergone a two day specialized training course and work in either public MAT centers or are private providers [13]. Since then, the only protocols used in Israel to date are the traditional ones. This four case series is the first of its kind done in Israel using low dose buprenorphine initiations to treat patients who suffer from opioid addiction. Furthermore, this is the first case in the literature of a person suffering from tramadol use disorder to undergo low dose buprenorphine induction. Four individuals presented to an outpatient public MAT and requested treatment with buprenorphine (as opposed to methadone), but could not stop their opioid medication before starting treatment. They were offered to be the first individuals in the country to undergo low dose buprenorphine initiations.

Case Presentations

Between May – October 2022, four patients who met DSM-5 criteria for severe opioid use disorder due to prescription medications presented to an outpatient public MAT center in Israel.

Each patient insisted on treatment with buprenorphine, they were not willing to take methadone. These four patients were offered an overlapping low dose buprenorphine initiation because they were unable to stop their opioid use for a sufficient amount of time to begin buprenorphine without being at high risk of precipitated withdrawals.

The four patients were all males, two Israeli Arab individuals and two Israeli Jewish individuals. None suffered from the daily pain issues which had initially led to their being prescribed opioids. One patient had occasional neck and back pain, which had been the original reason he was prescribed opioids, and managed his pain using over the counter (OTC) medications as the prescribed opioid he was still taking and had become addicted to (fentanyl patch), was no longer effective. At presentation to the MAT Center, the four patients were taking the following opioids daily: 60 tablets of oxycodone 20mg, 75mcg fentanyl patch every 3 days, 12 tablets of tramadol 100mg (down from 50 tablets of oxycodone 20mg), and 5 tablets of oxycodone/paracetamol 10mg. Table 1 summarizes the demographics, medical history and morphine equivalent daily dose (MEDD) at buprenorphine initiation. All buprenorphine medication was in the form of buprenorphine/naloxone film, either 2mg/0.5mg film that was used whole, or cut as needed in quarters (0.5mg) or halves (1mg), or 8mg/2mg film.

Results

Using low dose buprenorphine initiation protocols, all four patients were successfully stabilized on a therapeutic dose of buprenorphine in parallel to being completely tapered off the opioid medication to which they were addicted as shown in Tables 2-5. All four patients tolerated low dose buprenorphine initiation without precipitated withdrawal. All of the patients were offered supportive medications in case they experienced withdrawals symptoms: clonidine for anxiety/restlessness/diaphoresis, olanzapine for agitation, loperamide for diarrhea, ondansetron for nausea/vomiting, paracetamol or ibuprofen for pain, and trazodone for insomnia [14,15,16]. Only one patient used olanzapine, otherwise, none of the patients required any supportive medications while transitioning onto buprenorphine. The treatment day at which stabilization occurred involved full induction on a therapeutic dose of buprenorphine (at least 8mg) and was the time point at which the prescribed opioid medication to which they were addicted was stopped.

Of note, Patient 1 overcame many challenges before stabilizing in treatment. Besides opioid addiction, he also suffered from addiction to stimulants and benzodiazepines. The low dose protocol had to be modified from its original schedule, and he did not always follow the agreed upon schedule, as noted in Table 2. Nonetheless, by Day 9, he had completely stopped using oxycodone as he both stated and was evidenced by his ongoing urine drug screens in which he consistently tested negative for oxycodone. On Day 15 of buprenorphine, the patient did not show up for treatment but instead took 14mg buprenorphine and an unknown amount of benzodiazepines until he lost consciousness. Nonetheless, despite overdosing on benzodiazepines, he restabilized on buprenorphine. Ultimately, he did not feel that buprenorphine 24mg daily adequately managed his cravings, and on Day 30 he switched to methadone.

Patient	Age (years)	Full agonist opioid at time of buprenorphine initiation	MEDD (mg)	Active comorbidities	Past comorbidities
1	30	60 tablets of oxycodone 20mg	2400	Stimulant use disorder, Benzodiazepine use disorder	n/a
2	22	75mcg fentanyl patch every 3 days	225	h/o neck and back injury with occasional pain flares managed with OTC medications	h/o cannabis use disorder – in remission
3	29	12 tablets of tramadol 100mg (down from 50 tablets of oxycodone 20mg)	180 (was 2000)	n/a	h/o gastroesophageal junction cancer, s/p surgery and chemotherapy – in remission
4	73	5 tablets of oxycodone/ paracetamol 10mg	100	Benzodiazepine use disorder	h/o Non-Hodgkin's lymphoma, s/p chemotherapy and bone marrow transplant – in remission

MEDD – morphine equivalent daily dose; OTC – over the counter; MAT – medication assisted treatment; s/p – status post; h/o – history of; n/a – not applicable.

Table 1: Demographics and Clinical Features of Patients.

Treatment Day	Day of the Week	Oxycodone (# of pills)	Original Buprenorphine Plan	Modified Buprenorphine Plan	What the Patient Actually Did
1	Monday	60	0.5mg qd	0.5mg qd	0.5mg qd
2	Tuesday	60	0.5mg bid	0.5mg bid	0.5mg bid
3	Wednesday	60	1mg bid	3mg qd	3mg qd
4	Thursday	60	1mg bid	1mg bid	1mg bid
5	Friday	60	2 mg bid	1mg bid	1mg qd
6	Saturday	60	3mg bid	1mg bid	1mg qd
7	Sunday	30	4mg bid	1mg bid	1mg bid
8	Monday	30	5mg bid	1mg bid	1mg bid
9	Tuesday	Stop	12mg + stabilization	1mg bid	1mg am, 2mg pm
10	Wednesday	----	----	2mg am, 1mg pm	2mg am 1mg pm
11	Thursday	----	----	2mg am, 1mg pm	2mg am
12	Friday	----	----	2mg am, 1mg pm	----
13	Saturday	----	----	2mg bid	----
14	Sunday	----	----	2mg bid	----
15	Monday	----	----	8mg + stabilization	14mg + overdose on benzodiazepines
16	Tuesday	----	----	----	----
17	Wednesday	----	----	8mg tid	8mg tid

18	Thursday	----	----	8mg tid	8mg tid
19	Friday	----	----	8mg tid	8mg tid
20	Saturday	----	----	8mg tid	8mg tid
21	Sunday	----	----	8mg tid	8mg tid
22	Monday	----	----	8mg tid	8mg tid
23	Tuesday	----	----	8mg tid	8mg tid
24	Wednesday	----	----	16mg bid	16mg bid
25	Thursday	----	----	24mg qam	24mg qam
26	Friday	----	----	24mg qam	24mg qam
27	Saturday	----	----	24mg qam	24mg qam
28	Sunday	----	----	24mg qam	24mg qam
29	Monday	----	----	24mg qam	24mg qam
30	Tuesday	----	----	Methadone 40mg	Methadone 40mg
qd-once a day in the morning; bid- twice a day, tid-three times a day; am-morning; pm -evening					

Table 2: Patient 1 Low Dose Buprenorphine Initiation Protocol.

Treatment Day	Day of the Week	Fentanyl patch (mcg)	Buprenorphine Morning Dose (mg)	Buprenorphine Evening Dose (mg)
1	Monday	25	0.5	----
2	Tuesday	25	0.5	0.5
3	Wednesday	25	1	1
4	Thursday	25	2	2
5	Friday	25	2	2
6	Saturday	25	2	2
7	Sunday	25	3	3
8	Monday	25	4	4
9	Tuesday	Stop	8 + stabilization = 8	----

Table 3: Patient 2 Low Dose Buprenorphine Initiation Protocol.

Treatment Day	Day of the Week	Tramadol (# of pills)	Buprenorphine Morning Dose (mg)	Buprenorphine Afternoon Dose (mg)	Buprenorphine Evening Dose (mg)
1	Wednesday	12	0.5	----	0.5
2	Thursday	12	1	----	1
3	Friday	6	2	----	2
4	Saturday	3	2	2	2
5	Sunday	Stop	8 + stabilization = 12	----	----

Table 4: Patient 3 Low Dose Buprenorphine Initiation Protocol.

Treatment Day	Day of the Week	Percocet (# of pills)	Buprenorphine Morning Dose (mg)	Buprenorphine Evening Dose (mg)
1	Tuesday	5	0.5	----
2	Wednesday	5	1	1
3	Thursday	2	2	2
4	Friday	2	2	2
5	Saturday	1	2	2
6	Sunday	Stop	4 + stabilization = 12	----

Table 5: Patient 4 Low Dose Buprenorphine Initiation Protocol.

1. Before starting the low dose buprenorphine initiation protocol, the doctor met with the patient and made a printout for the patient of the planned schedule which included day in treatment, day of the week, opioid prescription (either number of pills or patch), and low dose buprenorphine dosing schedule, as shown in Tables 2-5. 2. All of the patients were offered supportive medications in case they experienced withdrawal symptoms. 3. The patient stayed on their baseline dose of prescribed opioid medication to which they were addicted at buprenorphine initiation, after which it was slowly tapered off. 4. On Day 1 of treatment, after seeing the doctor, the patient began the low dose buprenorphine initiation with 0.5mg sublingual buprenorphine once a day in the clinic under the doctor's supervision. 5. After Day 1, the frequency of taking buprenorphine was increased to twice a day 12 hours apart, once a day in the morning in the clinic under supervision and once a day in the evening at home.	6. After Day 1, the buprenorphine dose was increased daily until full induction on a therapeutic dose at which point the prescribed opioid medication to which they were addicted was stopped. 7. All of the patients saw a doctor and/or nurse five days per week for at least one week while transitioning onto buprenorphine and then the frequency of clinic visits was progressively decreased. (MAT treatment centers in Israel are closed two days per week, usually Fridays and Saturdays.) 8. Since MAT treatment centers in Israel are not open on Fridays and Saturdays, the dose that the patient would take on Thursday would stay the same on Friday and Saturday so as not to cause any distress to the patient over dose changes that could potentially cause withdrawal symptoms on days when the MAT center is closed. 9. All of the patients had support from at least one family member who was aware that they were engaging in MAT. 10. All of the patients began weekly therapy sessions with a clinical social worker to address their biopsychosocial needs and plan for recovery.

Table 6: 10 Factors that led to successful low dose buprenorphine initiations.

Discussion

This four case series is the first of its kind done in Israel and successfully shows that low dose buprenorphine initiations can be carried out in an outpatient public MAT center in this country. Furthermore, this is the first published case of a person suffering from tramadol use disorder to undergo low dose buprenorphine initiation. The protocols were reviewed in order to identify which features led to the success of the low dose buprenorphine initiations so that they could be applied to more patients, as listed in Table 6. These factors were consistently true for most of the patients, but not necessarily for all of them. Each protocol was fundamentally based upon discussions accompanying a partnership and therapeutic relationship between the doctor and patient, as should be the case with every patient.

These protocols serve as general guidelines for the low dose buprenorphine initiation process that can be applied to a wide range of patients who suffer from opioid use disorder. They can be modified as needed with variations in dosing and speed of full agonist taper depending upon patient preferences and clinical circumstances. Low dose buprenorphine initiations can improve care of patients with opioid use disorder by avoiding opioid withdrawal symptoms and reducing the dropout rate from treatment due to fear of or suffering from withdrawals.

Similar to methadone, buprenorphine has been proven to be life-saving medication [17,18]. The role of buprenorphine in the treatment of opioid addiction is not simply replacement of an illicitly used opioid for a medically supervised one, but rather as a medication that corrects many of the neurobiological processes

contributing to impaired function, relapse and overdose deaths [5]. Using low dose buprenorphine initiation protocols will allow more patients to successfully engage in MAT, which ultimately improves the quality of their lives, their families and their communities.

Conclusion

Regrettably, stigma and treatment barriers prevent most Israelis who suffer from opioid use disorder from having access to MAT, the most effective treatment for helping them live in recovery [19]. By showing that low dose buprenorphine initiations can be successfully carried out in Israel, this publication will advance the knowledge of Israeli physicians and help them learn how to initiate low dose buprenorphine, which will allow more individuals to engage in life-saving treatment. Low dose buprenorphine initiation protocols were developed in Europe more than 10 years ago and since then have been incorporated into guidelines in countries around the world including the Best Practices of the American Society of Addiction Medicine [20] and The College of Physicians and Surgeons of Manitoba, Canada [21]. I hope they will now be added to the Israeli opioid addiction treatment guidelines as well.

Conflict of interest: None.

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