



Clinical pain research

Opioid tapering in patients with prescription opioid use disorder: A retrospective study



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HIGHLIGHTS

- Opioids were successfully tapered off in 27.9% of patients with prescription opioid use disorder.
- These patients maintained opioid abstinence over 14.3 ± 13.0 months.
- The use of mirtazepine, topiramate, and likely bupropion were associated with successful opioid tapering.
- Opioid tapering may be a practical option for managing prescription opioid use disorder.

ARTICLE INFO

Article history:

Received 4 September 2017

Received in revised form 6 September 2017

Accepted 9 September 2017

Available online 5 October 2017

Keywords:

Opioid use disorder

Chronic non-cancer pain

Medication assisted treatment

Methadone

ABSTRACT

Background and aims: Opioid use disorder (OUD) refers to a maladaptive pattern of opioid use leading to clinically significant impairment or distress. OUD causes, and vice versa, misuses and abuse of opioid medications. Clinicians face daily challenges to treat patients with prescription opioid use disorder. An evidence-based management for people who are already addicted to opioids has been identified as the national priority in the US; however, options are limited in clinical practices. In this study, we aimed to explore the success rate and important adjuvant medications in the medication assisted treatment with temporary use of methadone for opioid discontinuation in patients with prescription OUD.

Methods: This is a retrospective chart review performed at a private physician office for physical medicine and rehabilitation. We reviewed all medical records dated between December 1st, 2011 and August 30th, 2016. The initial evaluation of the included patients ($N=140$) was completed between December 1st, 2011 and December 31st, 2014. They all have concomitant prescription OUD and chronic non-cancer pain. The patients (87 female and 53 male) were 46.7 ± 12.7 years old, and had a history of opioid use of 7.7 ± 6.1 years. All patients received the comprehensive opioid taper treatments (including interventional pain management techniques, psychotherapy, acupuncture, physical modalities and exercises, and adjuvant medications) on top of the medication assisted treatment using methadone (transient use). Opioid tapering was considered successful when no opioid medication was used in the last patient visit.

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Results: The 140 patients had pain of 9.6 ± 8.4 years with 8/10 intensity before treatment which decreased after treatment in all comparisons ($p < 0.001$ for all). Opioids were successfully tapered off in 39 (27.9%) patients after 6.6 ± 6.7 visits over 8.8 ± 7.2 months; these patients maintained opioid abstinence over 14.3 ± 13.0 months with regular office visits. Among the 101 patients with unsuccessful opioid tapering, 13 patients only visited the outpatient clinic once. Significant differences were found between patients with and without successful opioid tapering in treatment duration, number of clinic visits, the use of mirtazepine, bupropion, topiramate, and trigger point injections with the univariate analyses. The use of mirtazepine (OR, 3.75; 95% CI, 1.48–9.49), topiramate (OR, 5.61; 95% CI, 1.91–16.48), or bupropion (OR, 2.5; 95% CI, 1.08–5.81) was significantly associated with successful opioid tapering. The associations remain significant for mirtazepine and topiramate (not bupropion) in different adjusted models.

Conclusions: With comprehensive treatments, 27.9% of patients had successful opioid tapering with opioid abstinence for over a year. The use of mirtazepine, topiramate, or likely bupropion was associated with successful opioid tapering in the medication assisted treatment with temporary use of methadone. Opioid tapering may be a practical option and should be considered for managing prescription OUD.

Implications: For patients with OUD, indefinite opioid maintenance treatment may not be necessary. Considering the ethical values of autonomy, nonmaleficence, and beneficence, clinicians should provide patients with OUD the option of opioid tapering.

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1. Introduction

Opioid use disorder (OUD) refers to a maladaptive pattern of opioid use leading to clinically significant impairment or distress [1]. The maladaptive pattern of prescription opioid use causes (and vice versa) misuse and abuse of opioid medications which are four times more prevalent than heroin use disorders [2]. Common OUD symptoms include a strong desire to use opioids, increased amounts of or longer-than-needed opioid use, giving up important life events due to opioid use, need for increased opioid doses, excessive time spent related to opioid use, persistent wish or unsuccessful effort to control opioid use, social impairment in fulfilling major role obligations, opioid tolerance and withdrawal, and continued opioid use despite of all these issues. [1] For the diagnosis of OUD, patients have to have at least two of the aforementioned symptoms within a 12-month period [1].

In 2012, an estimated 2.1 million people were affected by prescription opioid use worldwide [3]. In the US, prescription opioids had been linked with more than 0.18 million deaths during 1999–2015 [4]. The economic burden of prescription opioid use was estimated at \$78.5 billion for the American society in 2013 [5]. Prescription OUD affects 21.5% patients with chronic opioid therapy from intervention clinics that had implemented opioid dose and risk reduction initiatives for more than 4 years and 23.9% from clinics that had not [6]. Side effects of prescription opioids and social problems related to opioids have also drawn significant social attention in recent years. The U.S. Surgeon General at the time wrote letters to health professionals in the US, calling for actions to end the opioid epidemic [7]. And recently, President Trump declared the opioid crisis a national emergency.

The potential solutions to the America's escalating opioid epidemic may include better pain management to prevent prescription OUD [8], and an evidence-based management for people who are already addicted to opioids. The latter has been identified as a national priority in the US [7]. Currently, the US Food and Drug Administration has approved three major types of medications for the pharmacotherapy of OUD, including a full opioid agonist (methadone), partial opioid agonists (buprenorphine, buprenorphine–naloxone, and implantable buprenorphine), and opioid antagonists (oral and extended-release naltrexone) [2,9–12]. Among them, the medication-assisted treatment using methadone maintenance or buprenorphine maintenance has been widely recognized as a standard treatment, as it efficiently increases patient retention and improves opioid-abstinence outcomes, while decreasing drug use, infectious disease transmission, and criminal activities [2,10,11].

However, methadone and buprenorphine may carry similar or even additional side effects when compared with other opioid medications [13]. For example, the use of methadone requires screening and continuous monitoring of electrocardiogram, as it prolongs QTc interval and has been linked to a similar or higher risk of non-fatal or fatal overdose [14,15]. The use of buprenorphine among patients on sedatives or hypnotics (especially diazepam) may pose an increased risk of sedation and respiratory compromise [11]. In addition, the use of methadone or buprenorphine maintenance treatment for OUD is also limited by the possibility of long-standing opioid resistance (especially among patients with high doses of medication and long-term treatments), and lack of evidence on risk factors and mitigation strategies for methadone-overdose deaths [16]. On the other hand, only fewer than half of all patients with OUD have actual access to methadone or buprenorphine maintenance treatment, with lack of medical prescribers of these medications for over half of the US counties [17]. Therefore, many clinicians face the daily challenge to treat patients with OUD who experience intolerable side effects from opioids, or those who simply want to stop opioid treatment for personal or professional reasons [9–12].

Under such circumstances, medication assisted treatment using methadone or buprenorphine (transient use) for successful opioid tapering and discontinuation are increasingly appealing [9–12,17,18]. Nevertheless, relevant literature is sparse, and the results of the limited studies exploring the effectiveness of potential adjuvant treatments remain inconclusive, especially among patients with their initial opioid use for mitigating chronic pain conditions [2,19]. In this retrospective study, we aimed to explore the success rate and important adjuvant medications in the medication assisted treatment with temporary use of methadone for opioid discontinuation in patients with prescription OUD.

2. Methods

2.1. Study background and design

A retrospective chart review was performed at the Academic Buffalonnias in Physical Medicine and Rehabilitation, a private physician office specializing in outpatient rehabilitation and pain management. The Institutional Review Board at the University of Buffalo, State University of New York, approved the study protocol.

With clinical expertise and experiences, the practicing physician of the clinic has been helping tapering opioid medications among OUD patients, by using medication assisted treatment with

temporary use of methadone since 2011. The comprehensive opioid tapering protocol mainly consists of medication assisted treatment with temporary use of methadone, psychotherapy, exercises, and adjuvant medications. More specifically, methadone, clonidine, antidepressants, lamotrigine, trigger point and epidural injections, non-steroidal anti-inflammatory drugs, anticonvulsants, occasional manual therapy, physical exercises, and psychological counselling were used in all patients when appropriate. The selection of specific adjuvant medications or assistive therapies was individualized based on its appropriateness in specific patients.

Patients were initially prescribed with 2.5 mg or 5 mg per day for one week tolerance (allergy) test without change in other opioid medications. Then, all patients were stabilized by receiving a dose of methadone to mitigate withdrawal symptoms [2,9–12,19] while decreasing the use of other opioids by 10–20% every one to two weeks. The dose of methadone to mitigate withdrawal symptoms was usually 2.5–5 mg (in certain patients, it could be as high as 10 mg) given three to five times a day depending on patient's response and patient's original opioid medication dosing. The daily methadone dose was then decreased by 2.5 mg (or higher for patients on higher dosing patients) every one to two weeks after the discontinuation of other opioid medications. The last 2.5 mg or 5 mg daily dose of methadone was usually difficult to taper, and the comprehensive taper protocol was especially important during this phase for successful opioid discontinuation. Opioid tapering was considered successful only if in a patient's chart, there was a clear documentation of no opioid use, by both a subjective statement and a negative urine toxicology test, and no opioid medication was used in visits thereafter.

2.2. Study sample and selection

Using the term “methadone”, we searched the electronic medical records dated between December 1st, 2011 (around the inception of the clinic) and August 30th, 2016 in the Medication Report (prescribed medications) and also hard copy medical records manually, to identify all patients with methadone use history. Further inclusion criteria included: 1) age ≥ 18 years at first clinic visit; 2) diagnosis of chronic non-cancer pain (CNC), defined as pain duration longer than 3 months, excluding cancer pain or pain at the end of life; 3) prescription opioid use longer than one year; 4) satisfaction of at least two criteria for the diagnosis of OUD [1]; 5) administration of medication assisted treatment with temporary use of methadone at the clinic; and 6) initial evaluation completed between December 1st, 2011 and December 31st, 2014.

A total of 181 medical records were identified, and 41 were excluded from the final study sample: 10 were excluded due to lack of documented opioid use at initial evaluation; 15 were excluded due to lack of documentation in the duration of opioid use; 3 were excluded with unknown pain intensity at first visit; 13 were excluded with duration of opioid use less than 12 months at first visit. As a result, 140 (87 female and 53 male) patients were included in final analyses, noting that 11 (2 were tapered off) of them were on methadone maintenance treatment seeking help due to severe side effects and none was taking buprenorphine.

Patients' socio-demographic characteristics included patients' age at first clinic visit, gender, marriage status, living status, employment status, and body mass index. Information of medical history such as history of prescription opioid and illegal opioid use, pain history, and clinical diagnosis of anxiety or depression, visits and treatment duration were also retrieved. Among them, treatment duration was calculated as the date of the last clinic visit for prescribing opioid medications minus the date of the first clinic visit for unsuccessful patients, and as the date of the first clinic visit for reporting successful opioid tapering minus the date of the first

clinic visit for successful patients. Because tapering medications were usually prescribed for half month upon each visit, a value of 0.5 month was added for treatment duration of all patients. The length for opioid abstinence, defined as the follow-up duration after successful opioid tapering (only for successful patients), was calculated as the date of the last documented clinic visit minus the last date of self-reported opioid use. The morphine equivalent dose for each patient at the first clinic visit was also calculated.[20]

2.3. Adjuvant treatment

Besides patient and family education, treatments at the clinic for these patients included the following (from high to low in frequency of being used): selective serotonin reuptake inhibitors, clonidine, injection therapy (as a whole), bupropion, manual therapy, trigger point injections, mirtazepine, sacroiliac joint injections, topiramate, acupuncture, and epidural injections (Table 1). Additional treatments like the use of lamotrigine were also used in some patients, but, relevant data were not extracted for this study. Oral medications were routinely used during and after successful opioid tapering; whereas procedural interventions (i.e., trigger point and epidural injections) were occasionally used prior to successful opioid tapering. Patients usually visited the clinic once a week initially for half to one month and then once a month.

Table 1

Socio-demographic information, medical history, and received treatment of all patients included in the study ($n = 140$).

Characteristics	Mean $\pm$ SD or %
Socio-demographic information	
Age at first visit (unit: years)	46.7 $\pm$ 12.7
Gender (female/male)	62.1/37.9
Marriage status	
Single	49.5
Married	27.8
Other	22.7
Living status (alone/with other)	33.0/67.0
Employment status (yes/no)	16.5/83.5
Body mass index (unit: kg/m ²)	30.9 $\pm$ 7.9
Medical history	
Drug use	
Previous street drug use (yes/no)	34.3/65.7
Street drug use during treatment (yes/no)	16.4/83.6
Opioid use duration (unit: years)	7.7 $\pm$ 6.1
Morphine equivalent dose (unit: mg)	83.5 $\pm$ 123.4
Pain history	
Pain duration (unit: years)	9.6 $\pm$ 8.4
Pain intensity at first visit (scale: 0–10) [*]	8.0 $\pm$ 1.2
Pain intensity at last visit (scale: 0–10) [*]	5.9 $\pm$ 2.3
Previous surgery for pain (yes/no)	41.4/58.6
Clinic visits/diagnosis	
Number of clinic visits	11.5 $\pm$ 12.2
Treatment duration (unit: years)	0.8 $\pm$ 1.1
Anxiety, depression, or both (yes/no)	90.0/10.0
Successful opioid discontinuation (yes/no)	27.9/72.1
Treatment (yes/no)	
Acupuncture	9.3/90.7
Bupropion	42.1/57.9
Clonidine	77.9/22.1
Epidural injection	7.9/92.1
Manipulation	40.0/60.0
Mirtazepine	23.6/76.4
Sacroiliac joint injections	16.4/83.6
Selective serotonin receptor inhibitors	85.7/14.3
Topiramate	15.7/84.3
Trigger point injections	26.4/73.6

^{*} Pain intensity was measured via a visual analogue scale on a scale of 0–10 (0 = no pain, 10 = most severe).

2.4. Statistical analyses

Patients' socio-demographic characteristics, and information of medical history and adjuvant treatments received at the clinic were summarized. Chi-squared tests (for categorical variables) and *t*-tests (for continuous variables) were conducted to identify significant disparities in those characteristics between patients with successful and unsuccessful opioid tapering. Wilcoxon signed-rank test was used to compare pain intensity before and after treatments. Backwards elimination (Wald) logistic regression models were used to examine the associations of adjuvant treatments with successful opioid tapering, after controlling for patients' gender, age at first clinic visit, employment status, and treatment duration. Odds ratios (OR) and 95% confident intervals (CI) were presented. All analyses were conducted in SPSS 17.0 software for Windows (SPSS Inc, Chicago, IL, USA).

3. Results

As shown in Table 1, the included patients were 46.7 ± 12.7 years old, had a history of opioid use of 7.7 ± 6.1 years with a daily morphine equivalent dose of 83.5 ± 123.4 mg. The majority of the patients were not working (83.5%), had either anxiety, depression, or both (88.7%). The included patients had pain of 9.6 ± 8.4 years and of 8.0 ± 1.2 intensity which decreased after treatment as a

whole ($p < 0.001$). The number of patients using street drugs was 48 before treatment at the clinic and patients all agreed to stop street drug use as per opioid treatment contract signed prior to treatment. Nonetheless, 23 patients were found to have used street drug during treatments.

Among these patients, opioids were successfully tapered off in 39 (27.9%) patients after 11.9 ± 7.9 visits over 0.7 ± 0.6 years (8.8 ± 7.2 months); these patients maintained opioid abstinence over a period of 1.2 ± 1.1 years (14.3 ± 13.0 months) with regular office visits (12.1 ± 10.5 visits). Among the 101 patients with unsuccessful opioid tapering, 13 patients only visited the outpatient clinic once. Pain in both groups of patients decreased significantly after treatment ($p < 0.001$ for both). Significant differences were found between the two groups in treatment duration, number of clinic visits, the use of mirtazepine, bupropion, topiramate, and trigger point injections with the univariate analyses. No between-group differences were found in other variables (Table 2).

Table 3 depicted the results of logistic regression models. In the unadjusted model, the use of bupropion (OR, 2.5; 95% CI, 1.08–5.81), mirtazepine (OR, 3.75; 95% CI, 1.48–9.49), or topiramate (OR, 5.61; 95% CI, 1.91–16.48) was strongly associated with successful opioid tapering. Mirtazepine and topiramate remained as two significant factors associated with successful opioid tapering when the model was controlled for patients' gender, age at first clinic visit, employment status, and treatment duration [OR = 3.70 for mirtazepine

Table 2
Comparisons between patients with successful ($n = 39$) and unsuccessful opioid discontinuation ($n = 101$).

Characteristics	Mean $\pm$ SD or %		<i>p</i> -value ⁱ
	Successful (<i>n</i> = 39)	Unsuccessful (<i>n</i> = 101)	
Socio-demographic information			
Age at first visit (unit: years)	47.8 $\pm$ 13.8	46.2 $\pm$ 12.4	0.509
Gender (female/male)	66.7/33.3	60.4/39.6	0.493
Marriage status			0.281
Single	37.9	54.4	
Married	31.0	26.5	
Other	31.0	19.1	
Living status (alone/with other)	36.4/63.6	31.5/68.5	0.622
Employment status (yes/no)	10.3/89.7	19.0/81.0	0.213
Body mass index (unit: kg/m ²)	30.0 $\pm$ 6.4	31.3 $\pm$ 8.4	0.402
Medical history			
Drug use			
Previous street drug use (yes/no)	10.3/89.7	18.8/81.2	0.221
Street drug use during treatment (yes/no)	23.1/76.9	38.6/61.4	0.083
Opioid use duration (unit: years)	6.9 $\pm$ 5.9	8.0 $\pm$ 6.2	0.318
Morphine equivalent dose (unit: mg)	89.8 $\pm$ 174.6	81.1 $\pm$ 97.9	0.770
Pain history			
Pain duration (unit: years)	8.7 $\pm$ 8.3	9.9 $\pm$ 8.5	0.452
Pain intensity at first visit (scale: 0–10) [*]	8.0 $\pm$ 1.2	8.0 $\pm$ 1.2	0.949
Pain intensity at last visit (scale: 0–10) [*]	5.4 $\pm$ 2.6	6.0 $\pm$ 2.1	0.152
Previous surgery for pain (yes/no)	43.6/56.4	40.6/59.4	0.747
Clinic visits/diagnosis			
Number of clinic visits	11.9 $\pm$ 7.9	6.7 $\pm$ 7.0	<0.001
Treatment duration (unit: years)	0.7 $\pm$ 0.6	0.4 $\pm$ 0.5	<0.001
Number of clinic visits after success	12.1 $\pm$ 10.5	—	—
Treatment duration after success (unit: years)	1.2 $\pm$ 1.1	—	—
Anxiety, depression, or both (yes/no)	92.3/7.7	89.1/10.9	0.572
Treatment (yes/no)			
Acupuncture	12.8/87.2	7.9/92.1	0.371
Bupropion	64.1/35.9	33.7/66.3	0.001
Clonidine	71.8/28.2	80.2/19.8	0.283
Epidural injection	2.6/97.4	9.9/90.1	0.148
Manipulation	38.5/61.5	40.6/59.4	0.817
Mirtazapine	35.9/64.1	18.8/81.2	0.033
Sacroiliac joint injections	23.1/76.9	13.9/86.1	0.187
Selective serotonin receptor inhibitors	92.3/7.7	83.2/16.8	0.166
Topiramate	33.3/66.7	8.9/91.1	<0.001
Trigger point injections	41.0/59.0	20.8/79.2	0.015

[†] *p*-values were based on chi-squared tests for categorical variables or *t*-tests for continuous variables between successful and unsuccessful patients.

^{*} Pain intensity was measured via a visual analogue scale on a scale of 0–10 (0 = no pain, 10 = most severe). Boldfaced numbers indicate statistical significance.

Table 3
Associations between patient characteristics and successful opioid tapering.

Treatment	Odds ratio [95% confidential interval]					
	Model 1		Model 2		Model 3	
Bupropion	2.50	[1.08, 5.81]*	2.33	[0.98, 5.56]	2.20	[0.91, 5.30]
Mirtazapine	3.75	[1.48, 9.49]**	3.70	[1.45, 9.47]**	3.17	[1.19, 8.40]*
Topiramate	5.61	[1.91, 16.48]**	6.31	[2.02, 19.72]**	5.09	[1.54, 16.76]**

Model 1 – unadjusted model resulted from backwards elimination (Wald) logistic regression.

Model 2 – Model 1 with gender, age at first visit, and employment status controlled.

Model 3 – Model 2 with treatment duration (unit: years) controlled.

Boldfaced numbers indicate statistical significance (* $p < 0.05$, ** $p < 0.01$).

and 6.31 for topiramate] or was controlled for treatment duration [OR = 3.17 for mirtazapine and 5.09 for topiramate].

4. Discussion

In the present study, 27.9% of patients with prescription OUD had successful opioid tapering with an opioid abstinence period of 14.3 ± 13.0 months and decreased pain. Currently, OUD is generally considered as a chronic disease with no cure. Rather than a “stepped care” approach, the use of methadone or buprenorphine maintenance treatment is often indiscriminately considered as the “first line treatment” for OUD [9–12]. Besides the benefits, reasons for this indiscriminate approach may include the high success rate in patients’ adherence and a relatively simple treatment approach as compared to opioid tapering [9–12]. The encouraging success taper rate of 27.9% in our study is similar to the opioid abstinence rate (31.7%) at Month 42 in a buprenorphine–naloxone taper protocol [21]. Our study adds further evidence that opioid tapering may be a practical option for the treatment of OUD related to chronic prescription opioid use.

Interestingly, rather than non-modifiable demographic factors, for example, age and gender, the univariate analyses only identified that treatment visits, duration, and ancillary treatments were different between groups with and without successful opioid tapering. With appropriate treatments, patients with prescription OUD can be tapered off opioids. This is rather striking as it is completely against the widely accepted idea that patients with OUD should universally be treated with indefinite opioid maintenance treatment [22]. Opioid tapering may thus be a potential solution to the current prescription opioid epidemic. Besides expansions in access to methadone or buprenorphine maintenance treatment, we may also need to establish large pain management centres providing a comprehensive and stepped approach including opioid tapering for the management of patients with OUD.

Opioid tapering is an arduous journey for both clinicians and patients [19]. Patients with successful opioid tapering were treated 11.9 times over 8.8 months in the present study. Appropriate adjuvant treatments, like mirtazapine, topiramate, trigger point injection, and bupropion likely facilitate opioid tapering in these patients. Mirtazapine increases the release of norepinephrine and serotonin in the nervous system; it calms cravings and reduce drug-seeking behaviours [23]. Bupropion, a dopamine agonist, improves motivation and is effective for smoking cessation and increasing the proportion of patients achieving sustained cocaine and heroin abstinence [14]. Topiramate is an anticonvulsant medication; it blocks sodium channels, facilitates gamma-aminobutyric acid (GABA) transmission and inhibits glutamatergic transmission. Topiramate causes sedation and mental dulling and has been reported as a well tolerated and efficacious medication for opioid detoxification and withdrawal [23]. Additionally, mirtazapine, bupropion, and topiramate have all been found effective for the management of CNCP in some studies [24]. Additionally, mirtazapine, bupropion, topiramate may also enhance patients’

adherence to treatments via the incentive of weight optimization. Mirtazapine improves appetite and induces weight gain; whereas bupropion and topiramate cause weight loss [14,23]. Our findings add evidence to the use of these three adjuvant medications for opioid tapering in prescription OUD [14,23,25].

To maximize success in opioid tapering, clinicians have to have thorough considerations in the timing, speed, dropouts, and methods of opioid tapering. Evidence suggests chronic opioid use may lead to clinically significant impairment or distress, and no evidence supports the use of long-term opioids in patients with CNCP [5,19]. In the present study, opioid were tapered off when patients experienced unbearable side effects and/or uncontrolled pain while on long-term heavy dose opioids. This timing of opioid tapering is consistent with the generally accepted consensus that opioids should be tapered off when harm exceeds benefit [8,19].

In certain conditions, such as life threatening overdose, a more rapid (for example, one or two weeks) detoxification protocol may be warranted [19]. Nevertheless, experts believe that a more gradual taper of four or more weeks as well as the addition of psychotherapeutic or pharmacologic treatments may lead to better patient outcomes, such as less and milder withdrawal symptoms, fewer relapses, and better quality of life [19]. Although quality of life measure was not available in the present study, patients undergoing the slow tapering protocol in our study demonstrated less pain as a whole and in separate groups. Slow tapering seems a logical and practical method for opioid tapering.

Dropouts pose a significant threat to the success of opioid tapering [14,19]. In our study, 13 patients without success only visited the clinic once; whereas patients with successful opioid tapering were treated for 12.0 (versus 6.7) visits over 8.8 (versus 4.8) months, much more visits and longer treatment duration than patients without success. The high dropouts in clinical practice may be related to the current social problem of patients’ doctor shopping which not only decreases the likelihood of successful treatment but also increases the likelihood of opioid side effects including death [26]. The potential solutions for decreasing dropouts may thus include educating our pain management clinicians in the local community regarding the importance and the arduous journey of opioid tapering and the negative impacts from the bottleneck factor of doctor shopping which hinders opioid tapering and management of OUD [26].

An additional cause of dropouts may include withdrawal syndrome which is characterized by anxiety, hypertension, tachycardia, restless, mydriasis, tremor, piloerection, diaphoresis and others [19]. These symptoms peak at 48 to 72 h and resolve within 7–14 days [19]. Other reasons may include secondary abstinence syndrome which include general malaise, fatigue, poor tolerance to stress and decreased well-being [19]. Secondary abstinence syndrome may last up to 6 months. Management of these symptoms is essential for decreasing dropouts and encouraging patients’ adherence.

In the present study, withdrawal symptoms were common in the patients as per their medical records in the study; 90%

of patients has anxiety, depression, or both. Because of withdrawal symptoms, psychiatric co-morbidities [19], and CNCP are all involved in the complex interaction between biopsychosocial factors and the nervous system [27], comprehensive managements are essential during opioid tapering. Clonidine was effective for controlling withdrawal symptoms by some research evidence [19] and the use of selective serotonin reuptake inhibitors (SSRIs) produced better outcomes in detoxification [19]. In the present study, clonidine was used in 77.9% of patients and SSRIs were used in 85.7% of patients. Even though we did not capture specific data, the use of psychotherapy and physical exercises was common in the included patients.

The medication assisted treatment with temporary use of methadone serves as the key component of the comprehensive managements for the successful opioid taper with long periods of opioid abstinence in these patients. In the present study, methadone was used three or four times a day with gradual tapering. Onset of methadone analgesia occurs 30–60 min after oral administration and usually last 6–8 h at the beginning, increasing to 22–48 h after chronic administration [28]. This medication assisted treatment with temporary use of methadone, in combination with the aforementioned adjuvant treatments, thus would minimize side effects, maximize pain relief benefits, decrease drug seeking behaviours, and increase patient compliance.

5. Ethical issues

With regards to the possible side effect of developing OUD, the use of opioid medication in chronic pain management has long been debating. Undoubtedly, physicians' job is to relieve pain and suffering, but we should also make sure we do no harm. The tapering of opioids in OUD faces a similar ethical dilemma. The arduous tapering journey is likely uncomfortable because of opioid withdrawal. However, patients with OUD have the autonomy to request opioid tapering and as a physician, we need to provide patients the options including opioid tapering, balance benefits versus harms and provide necessary help. Opioid (methadone or buprenorphine) maintenance treatment is certainly one solution for OUD; opioid tapering may offer a viable alternative.

6. Limitations

This study was a retrospective study conducted at a single outpatient physician office; symptoms, diagnoses, interventions were captured through medical notes. This comprehensive opioid tapering protocol utilized multiple adjuvant medications which raises concerns for polypharmacy. Due to the small sample size, the logistic regression models may create biased odds ratios. Future prospective trials are warranted to validate findings in the present study and compare effectiveness and socioeconomic costs of opioid tapering with medication assisted treatment with temporary use of methadone in comparison with opioid maintenance treatment.

7. Conclusion

Opioid tapering was successful in 27.9% patients with an opioid abstinence period of over one year. The use of mirtazepine, topiramate, and likely bupropion are significantly associated with successful opioid tapering using medication assisted treatment with temporary use of methadone. Opioid tapering with a comprehensive protocol may be a practical option and should be considered for the treatment of OUD. For patients with OUD, indefinite opioid maintenance treatment may not be necessary. Considering the ethical values of autonomy, nonmaleficence, and

beneficence, clinicians should provide patients with OUD the option of opioid tapering.

Conflicts of interest

The authors report no conflicts of interest.

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