

Methadone for the treatment of Prescription Opioids Dependence. A retrospective chart review

Metadona para el tratamiento de la dependencia de opioides de prescripción médica.

Una revisión retrospectiva de historias clínicas

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Abstract

Prescription opioids (PO) addiction is increasing to an epidemic level. Few studies exist regarding its treatment. Although buprenorphine has been the mainstay so far, other treatment options might be considered, such as methadone. We conducted a retrospective assessment of all patients admitted to a psychiatry ward for PO detoxification using methadone between 2010 and 2013. The assessment and description was carried out during a 3-month follow-up period after their discharge. Although this is a retrospective chart review, our exploration included sociodemographic and treatment variables in addition to the abstinence rates for the whole sample. Eleven patients were included, mostly women (81.8%), with a median age of 50 years. The median duration of dependence was 8 years. Dependence on other substances and psychiatric comorbidities were high. Eight patients were monitored during three months. Of these, 7 (87.5%) were abstinent after that period. The results suggest that methadone deserves further exploration as a potentially efficacious treatment option for PO dependence.

Keywords: Prescription opioids; Methadone; Detoxification; Day Hospital.

Resumen

La adicción a opioides de prescripción médica (OPM) está incrementado a niveles epidémicos. Los pocos estudios que existen hasta la fecha sobre su tratamiento se basan principalmente en el uso de buprenorfina. Sin embargo, la metadona puede considerarse como otra opción. El objetivo de nuestro estudio fue revisar las historias clínicas de todos los pacientes ingresados en una unidad de psiquiatría para la desintoxicación de OPM usando metadona entre el 2010 y el 2013. El periodo de evaluación finaliza a los 3 meses desde el alta médico. Pese a ser una revisión de historia clínicas, se evaluaron las características sociodemográficas de la muestra, así como las variables relacionadas con el tratamiento y la tasa de abstinencia durante el estudio. Se incluyeron 11 pacientes, mayoritariamente mujeres (81,8%), con una mediana de edad de 50 años. La mediana de duración de la dependencia fue de 8 años. Hubo una alta prevalencia de adicción a otras sustancias así como de comorbilidades psiquiátricas. Ocho pacientes fueron seguidos durante al menos 3 meses. De estos, 7 (87,5%) estuvieron abstinentes hasta el final del periodo evaluado por el estudio. Los resultados sugieren la necesidad de estudios de mayor rigor metodológico para la correcta evaluación de la metadona como un tratamiento potencialmente eficaz para la dependencia de los OPM.

Palabras clave: Opioides de Prescripción Médica (OPM); Metadona, Desintoxicación; Hospital de día.

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Opioids, used medically for pain relief, have analgesic and central nervous system depressant effects as well as the potential to cause euphoria. Activation of endogenous mu opioid receptors results in the prototypic opioid effects of reward, withdrawal, and analgesia (Camí & Farré, 2003).

Despite not being a recent phenomenon (Tennant & Rawson, 1982), in recent years, there has been a dramatic increase in the prescription and abuse rates of prescription opioids (PO). In the US, the number of adults abusing prescription opioids increased from 4.9 million in 1992 to almost 12.5 million in 2012 and the rate of treatment receipt for prescription opioid use disorders is now second only to alcohol (Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, 2013). In Europe, emerging abuse of prescription opioids is of concern in Western and Central Europe, with treatment demand for abuse of opioids other than heroin increasing. Opioid-related deaths have decreased overall in Western and Central Europe, but the proportion of deaths attributable to fentanyl and methadone has increased (International Narcotics Control Board, 2014). Moreover, healthcare costs associated with opioid dependence have been found to exceed one billion dollars in the United States annually (National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction, 1998).

Given its recent epidemic level, little research exists regarding its treatment. To date, there exists only a large randomized controlled trial (Potter et al., 2015), which followed PO dependent patients for 40 months, using a buprenorphine-naloxone strategy. While results for the 18 month follow-up were promising, recently available data for the 40 month follow up (Weiss et al., 2015) suggest that, despite a clear overall improvement from baseline, there remains a large subset of patients with a worsening course, who initiate heroine use or opioid injection. All this has urged affected countries to set up educational and prevention policies, with moderate success, therefore arguing that the development of specific treatments for PO dependence is critically needed (Brady, McCauley & Back, 2015).

Given all that, other treatment strategies should be considered for prescription opioids addiction. Such is the case of methadone, a well-established substitutive therapy for opioids use disorders. A previous comparative study between buprenorphine and methadone found similar outcomes in both groups, with methadone being better at preventing relapse (Neumann et al., 2013). Other retrospective studies, not specifically focused on PO dependent patients, have also suggested methadone might be an appropriate treatment strategy (Brands, Blake, Sproule, Gourlay & Busto, 2004; Sander & Hays, 2005). Actually, in spite of its greater toxicity when compared to buprenorphine or its more frequent and costly interactions (Roncero et al., 2015), methadone has consistently shown better outcomes in opioid dependent pa-

tients (Mattick, Breen, Kimber & Davoli, 2014; Barnett, Rodgers & Bloch, 2001). Here, we report the results of a small retrospective chart review of prescription opioids dependent patients receiving substitutive treatment with methadone. Some illustrating cases will be described, and also, an exploratory description of the whole sample will be conducted.

Method

Patients and setting

We conducted a retrospective assessment and description of all patients admitted between 2010 and 2013 to the Acute Psychiatric Ward of a tertiary hospital for prescription opioids detoxification. Patients were eligible if they met criteria for prescription opioids dependence according to DSM-IV (American Psychiatric Association, 2000), were at least 18 years old, had a stable residence, had no severe or disabling physical or psychiatric conditions and were detoxified using methadone. The study was approved by the corresponding ethics committee.

Measures

An exploration of descriptive statistics for the whole sample was conducted. At baseline, sociodemographic variables and psychiatric comorbidities were collected from patients' medical chart. A follow-up period of 3 months was established. Variables regarding prescription opioids dependence and methadone treatment were also collected. A special focus was placed on abstinence during the study period, defined as having taken no other opioids besides the prescribed methadone. Urine toxscreen and patient self-reports were used to verify this information.

Study procedures

All patients underwent the same procedures. Upon admission, they underwent a blood analysis, an ECG, a urine toxscreen and an initial psychiatric evaluation. Once assessed, according to patients' self-reports on their prescription opioids dose, the daily morphine equivalent dose was calculated. Then, a methadone conversion ratio, seen in table 1 (Ripamonti et al., 1998), was used to establish the adequate dose of methadone. However, it is well known that due to its long half-life (up to 7 days) and wide inter-individual pharmacodynamics (Ferrari, Coccia, Bertolini & Sternieri, 2004), methadone has a high risk among opioids of overdose and accumulation during initial titration to effect (as steady state levels are approached). Therefore, it is recommended that once the conversion to methadone has been established, the initial dose be reduced to a half and then dosed one third every 8 hours, and never exceed 30 mg the first day (Mancini, Lossignol & Body, 2000). However, it is the prescriber decision and personal experience that ultimately guide and prevail in choosing the initial dose of methadone.

Table 1. *Methadone conversion rates according to morphine doses.*

Oral MEDD (mg/day)	Methadone Dose Conversion Ratio
0 to 99	4:1
100 to 299	8:1
300 to 499	12:1
500 to 999	16:1
>1000	20:1

Note. MEDD: Morphine equivalent daily dose

A stop start approach was used (Mercadante et al., 2001; Mercadante, Ferrera, Villari & Casuccio, 2005), where prescription opioids were suppressed on the first day of admission, and methadone was started according to the rule explained before. After a few weeks of inpatient detox, the process continued in our psychiatric day hospital, which mainly focuses on the aftercare of addictions, where patients were followed for the rest of their treatment.

Both in the inpatient and day hospital settings, patients received daily individual therapy as well as twice a week non-directive group therapy. Once in the day hospital, patients received methadone in a daily, single morning dose. Urine toxscreens were conducted on a random basis to verify patient self-reports.

Statistical analysis

For continuous variables, given the small sample size, robust measures were selected. Therefore we used the median and the interquartile range to describe them. Dichotomous variables are presented with their respective percentages. As this is small sample size, mainly descriptive study, no adjusted analyses were conducted.

Results

First, summary statistics regarding all cases are presented. Next, a description of the most representative cases is outlined.

Summary statistics

Table 2 shows sociodemographic and treatment variables for the whole sample.

Eleven patients were identified, meeting the inclusion criteria. Eight of them could be followed for at least 3 months in the day hospital. All of them took prescription opioids for pain related diagnoses, except for one patient, who started taking codeine because of cough. The sample was composed mainly of women with a median age of 50 years. The duration of dependence was relatively long, with a median of 8 years. Of all the patients completing the study period,

Table 2. *Sociodemographic and treatment variables.*

Sample characteristics	
Sex: females n (%)	9 (81.8%)
Age: median (IQR)	50 (18)
Duration of hospital stay in days: median (IQR)	16 (6)
Duration of prescription opioids dependence in years: median (IQR)	8.3 (10.9)
Duration of follow up in days: median (IQR)	258 (446)
Expected methadone dose in mg: median	30
Maximum methadone dose in mg: median (IQR)	22.5 (15)
Methadone dose at discharge in mg: median (IQR)	10 (15)
Duration of methadone treatment in days: median (IQR)	77 (68.5)
Patients taking other psychotropic drugs at intake: n (%)	8 (73%)
Patients taking no prescription opioids previously: n (%)	1 (9%)
Patients with dependence to other substances: n (%)	6 (54.5%)
Benzodiazepines	3 (27.3%)
Alcohol and benzodiazepines	2 (18.2%)
Alcohol, benzodiazepines and heroine	1 (9.1%)
Lost to follow up: n (%)	2 (18.2%)
Patients relapsing during detoxification: n (%)	1 (9.1%)
Prescription opioid: n (%)	
codeine	3 (27.3%)
fentanyl	6 (54.5%)
oxycodone	1 (9.1%)
meperidine	1 (9.1%)
Psychiatric comorbidity: n (%)	5 (35.5%)
Affective disorder	4 (36.4%)
Anxiety disorder	1 (9.1%)

Note. IQR: interquartile range

only one relapsed. The two patients lost to follow-up were abstinent in the last assessment conducted. Of note, more than half of the patients were on psychotropic medication upon admission, more than half had dependence to other substances, and nearly half of them had psychiatric comorbidities diagnosed at the time of the study.

Methadone doses were relatively low, even lower than expected. Again, it highlights the necessity of a slow and careful titration when using methadone, and although indicative algorithms might be consulted, it is ultimately the clinician experience the one determining the appropriate dose. Regarding severe adverse events related to methadone treatment, none was observed during the time covered by the study.

Case 1

A 55 year-old woman was admitted to the psychiatry ward due PO addiction. The patient had a history of fibromyalgia and cervical disc herniation for which she had received analgesic treatment with oral oxycodone for 14 years. During this time, the patient developed dependence, with in-

creasing doses until a daily dose of 60 mg. Methadone was initially started up to 20 mg per day, then gradually reduced during her hospitalization, reaching 9 mg per day when discharged. He was also started on paracetamol and amitriptyline. During 10 weeks in the day hospital, a gradual reduction of dose was carried out. Finally, the patient was out of methadone, having shown no signs of withdrawal.

Case 2

A 52 year-old woman was admitted to the psychiatry ward due to PO addiction. The patient had a history of fibromyalgia for which she had received analgesic treatment with tramadol and fentanyl for 3 years. During this time, increasing doses were given, up to the habitual dose of tramadol 300 mg daily and fentanyl 25 µg daily. The patient suffered also from benzodiazepine dependence of about 15 years duration and a depressive syndrome. Methadone was started up to 20 mg daily then gradually reduced during the hospital stay, reaching 5 mg daily at hospital discharge. The outpatient control was conducted during 8 weeks in the day hospital, where methadone was finally suppressed, with no withdrawal signs or adverse effects observed.

Case 3

A 45 year-old man was admitted to the psychiatry ward due to transmucosal fentanyl dependence. The patient had a past history of chronic rectal pain due to radiotherapy of 3 years duration, the same time he had been receiving fentanyl for pain control. The habitual dose of transmucosal fentanyl was about 600 µg per day. Upon admission, methadone up to 90 mg per day was started. The patient did not present withdrawal signs or adverse effects. He also received duloxetine, pregabalin and carbamazepine as part of his routine pharmacological schedule. During 2 weeks, methadone was tapered to 70mg daily. He was then discharged to the day hospital, where during 12 weeks methadone was further tapered until total suppression. No withdrawal symptoms were observed.

Case 4

A 61 year-old woman was admitted to the psychiatry ward due to codeine addiction. The patient had a history of chronic arthropathy for which he had been receiving analgesic treatment with oral codeine for 16 years. Increasing doses had been given, until the present use of codeine at about 900 mg per day. The patient suffered also from benzodiazepine and alcohol addiction of long duration. Methadone was initially started up to 25 mg per day, and then gradually reduced during her two-week admission, reaching 15 mg per day at hospital discharge. The following 4 weeks she was in the day hospital, where a progressive reduction in methadone was carried out. The patient, however, moved to another city before a total suppression of methadone could be carried out.

Discussion

Overall, and despite being a small retrospective chart review, with a short follow-up period, the results obtained in this study are encouraging. Patient retention during methadone treatment was relatively high, a fact that has been observed for PO dependent patients in previous studies (Banta-Green, Maynard, Koepsell, Wells & Donovan, 2009). Of those being assessed for at least 3 months, only one patient relapsed. It should be taken into account that it was a patient with a previous history of heroin dependence, which has been shown to be associated with poorer outcomes (Potter et al., 2015).

Interestingly, psychiatric comorbidities as well as previous addictions were common in our sample. This fact, and given the increasing rate of prescription opioids addiction, implies that it is of vital importance to conduct an appropriate assessment before prescription opioids are initiated, and it calls for a close monitoring and supervision during treatment.

Although it is not possible to extract firm conclusions given the methodological shortcomings of this study, two elements should be mentioned. First, methadone as the medication used in the detoxification process. An extensive literature exists supporting its use for illicit opioids dependence (Marsch, 1998; Joseph, Stancliff & Langrod, 2000) which justifies and warrants research for its application in the field of prescription opioids. In our study, methadone doses were relatively low, no related severe adverse events were observed, and abstinence rates were high. Second, both inpatient and day hospital settings were the main sites of treatment, which allow for a close and daily monitoring of patients and its process of detoxification and dishabituation. This fact might have facilitated the good results of the study in interaction with methadone.

Being an inpatient sample which was subsequently transferred to a day hospital might mean it was a relatively selected group between the whole group of prescription opioids addicted patients: the most severely dependent. Whether buprenorphine might have been equally effective in a sample like this one remains to be determined.

Our approach with these patients was that of medically supervised withdrawal. It means methadone doses were slowly reduced until total suppression. The complementary approach would have been a maintenance paradigm. Heroin related literature suggests that a maintenance approach might be better suited for those patients. However, as previous studies suggest, one could consider whether PO dependent persons may differ from prior cohorts of heroin dependent patients and might be better candidates for medically supervised withdrawal to abstinence. Our data could suggest that supervised withdrawal is indeed a feasible approach with PO addicted patients.

Finally, it should be noted the relatively long duration of the dependence our patients had. It is the nature of addic-

tion itself that imposes a long time on patients before action towards change is taken, but it should also warn physicians prescribing opioids to try to detect early signs of a developing dependence and thus take the necessary steps to address it.

Limitations

Several limitations should be taken into account when interpreting the findings of this study. First, retrospective chart reviews offer evidence of poor quality, with no control group, small sample sizes and no analytic analysis. Also, we covered a short follow-up period. The descriptive and retrospective nature of the study remains also a relevant limitation. Therefore, no firm conclusions can be drawn from this study.

Conclusions

In conclusion, although methadone has some complexities regarding its prescription, which might limit its usefulness (Merrill et al., 2005), and despite the relevant methodological limitations of the present work, we believe methadone should remain an option when considering treatment for prescription opioids dependent patients. Further larger, randomized, comparative trials are warranted.

Declaration of interest

Pablo Barrio has received honoraria from Lundbeck S.A.. The rest of authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper. No financial issues to disclose for any of the authors.

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