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Original Article

Methadone Dose and Timing of Administration as Predictors of Sleep Apnea Syndrome During Methadone Maintenance Treatment: A Retrospective Cross-sectional Study

Clément Guillet[1,2], Francky Teddy Endomba[3,4*], David Aravantinos[1,5], Aymard Hussami[1], Florence Beye[6], Jean Claude Girod[1], Ludwig Serge Aho Glélé[7]

[1]Sleep Exploration Centre, La Chartreuse Psychiatric Hospital, 21000 Dijon, France
[2]Depression Unit, La Chartreuse Psychiatric Hospital, 21000 Dijon, France
[3]Medical Mind Association, Yaoundé, Cameroon
[4]Sleep Specialized Transversal Training, Psychiatry Internship Program, University of Burgundy, 21000 Dijon, France
[5]Addictology Unit, La Chartreuse Psychiatric Hospital, 21000 Dijon, France
[6]Pharmacy Unit, La Chartreuse Psychiatric Hospital, 21000 Dijon, France
[7]Service D'épidémiologie Et D'hygiène Hospitalière, CHU Hôpital D'enfants, 14 Rue Paul 10 Gaffarel, 21079, Dijon, France

Abstract

Background: This study aimed to assess the association of sleep apnea syndrome (SAS) with methadone dose and timing of administration in patients receiving methadone maintenance treatment (MMT) for opioid use disorder (OUD).

Methods: This retrospective cross-sectional study was conducted on adult patients receiving MMT who had a nocturnal respiratory polygraphy between November 2015 and December 2021. Data on methadone treatment and polygraph recording, including the apnea-hypopnea index (AHI) were collected.

Findings: A total of 40 patients, mostly male (72.5%), with a mean age of 35 ± 6.7 years and a mean body mass index (BMI) of 25.1 ± 4.5 kg/m² were included. The daily dose of methadone was significantly associated with an AHI ≥ 15 events/h as well as an AHI ≥ 30 events/h, even after adjustment for age, gender, BMI, and benzodiazepine use. However, these associations were not preserved when the time of administration (day vs evening) was considered, while the evening administration was significantly associated with an AHI ≥ 15 events/h. The best sensitivity and specificity for the prediction of AHI ≥ 15 events/h and AHI ≥ 30 events/h were obtained with daily methadone doses of ≥ 72.5 mg and 77.5 mg, respectively.

Conclusion: In this sample of MMT patients, methadone doses of 72.5 mg and 77.5 mg were the best cut-off values for predicting AHI ≥ 15 and ≥ 30 events/h, respectively, especially when taken in the evening. These results should draw clinicians' attention to the importance of SAS screening, and further studies are needed, notably comparisons with buprenorphine.

Keywords: Opioid-related disorders, Methadone, Sleep apnea syndrome

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Introduction

Opioid or opiate substitution treatments (OSTs), including methadone maintenance treatment (MMT), are one of the main components of care for opioid use disorders (OUDs).[1,2] These disorders include the use of heroin, morphine, and synthetic opioids the morbidity and mortality of which has increased in the last few decades, more precisely during the last two years with the COVID-19 pandemic.[1,3,4] However, the therapeutic interest of OSTs is counterbalanced by various somatic consequences, including qualitative and quantitative sleep disturbances.[5,6] For instance, 75% to 84% of patients receiving MMT have been found to have poor sleep quality, defined in previous studies by a Pittsburgh Sleep Quality Index (PSQI) score of more than five.[7,8] As a consequence, OSTs have been associated with a greater probability of sleep-related breathing disorders (SRBDs), also called sleep-disordered breathing.[6,9] Likewise, this is of interest considering the higher cardiovascular risk reported in MMT patients.[10,11]

Numerous published studies have shown an association between methadone and SRBD, especially sleep apnea syndrome (SAS), either obstructive (OSAS) or central (CSAS).[6,9] A review study in 2016 found that the frequency of SRBD varied between 42.3% and 70% among MMT patients, with 0% to 60% for CSAS and 10%

*Corresponding Author: Francky Teddy Endomba, Email: franckyteddyea@gmail.com

to 35.2% for OSAS.[6] Among the determining factors of the OST– SAS association, the most frequent are BMI, weight gain, OST treatment duration, comorbid psychiatric conditions such as anxiety and depression, disorders with chronic pain, and benzodiazepine use.[6,12,13] Nevertheless, findings pertaining to the role of methadone dose in SAS occurrence are discrepant, with some studies finding no associations,[12,14] and others reporting the opposite.[9,13]

To our knowledge, there are no published reports suggesting a dose threshold for methadone that can potentially predict SAS risk. Moreover, the literature lacks data on the association between the timing of methadone administration and SAS risk. Accordingly, this study was conducted to assess the associations of SAS with methadone dose and timing of administration in patients receiving MMT.

Methods

Study and participant characteristics

This cross-sectional study was conducted using data from the Sleep Centre of La Chartreuse Psychiatric Hospital in Dijon, France. The exhaustive data were retrospectively collected from the medical files of adult patients prescribed MMT who had an overnight respiratory polygraphy between November 2015 and December 2021. The overnight polygraphy was done while patients were hospitalized for psychoactive substance cessation, especially alcohol. More specifically, patients taking OSTs for at least three months, with no alcohol consumption for at least 3 weeks were enrolled in the study. The patients with known SAS before home testing, or those treated with another morphine derivative were excluded.

Polygraphy studies

For overnight polygraph recording, the same equipment, specifically the Nox-T3® standard home respiratory monitoring system, was used for all patients.[15] In our Sleep Centre, explanations and instructions regarding the monitoring system's connections were provided by a trained sleep technologist the afternoon before the overnight recording. At the end of the session, patients were required to try to apply the sensors, with guidance from the technologist if needed. After verification of appropriate installation, patients were asked to wear the equipment to bed and to remove it when they got up the next day. Nasal pressure, movements of the rib cage and the abdomen, body position, heart rate, and oxygen saturation were recorded. Data from the overnight cardiorespiratory monitoring were extracted from the device and events were manually identified on the basis of the recommendations established by the American Academy of Sleep Medicine (AASM) for adults.[16] Considering these recommendations, for each overnight respiratory polygraphy, apnea was scored when there was a decrease in the peak signal excursion by at least 90% of pre-event baseline for 10 seconds or more. Hypopnea was scored when the peak signal excursions dropped by at least 30% from pre-event levels for 10 seconds or more, in association with either arterial oxygen desaturation of at least 3% or arousal.

Data collection

The following data were collected from patient medical files: age (at the moment of recording), sex, weight, height, body mass index (BMI), galenic form, dose (total, in mg/kg, in mg/BMI) and timing of administration of methadone (in the morning or in the evening), and the prescription of benzodiazepine drugs. From the polygraph recording, the apnea-hypopnea index (AHI) was extracted with characterization as central or obstructive. SAS was classified as mild, moderate, or severe for respective AHI thresholds of 5, 15, and 30 respiratory events (apnea or hypopnea) per recording hour.[17]

Ethical considerations

This study was conducted in line with ethical standards for medical research involving humans, as defined in the Declaration of Helsinki. Data were collected from previously mentioned sources, and anonymized while entered in appropriate software for analysis, to ensure patient confidentiality. This study was approved by a regional (Bourgogne – Franche-Comté, France) ethics committee for the protection of persons participating in biomedical research programs.

Statistical analyses

Data were analyzed using the SPSS software package, version 21.0. The categorical data (such as sex, evening methadone administration, concomitant benzodiazepine treatment, SAS diagnosis) were expressed as absolute and relative frequencies (percentages). For numerical variables, mean values ± standard deviation or median values with interquartile range (if indicated by the results of the Kolmogorov-Smirnov test) were utilized. To assess the association between methadone dose and SAS, Pearson or Spearman correlation test was performed between apnea hypopnea index (count of respiratory events/h) and total dose (in mg/d). The mean or median values of methadone dose were compared between patients with and without SAS while considering AHI 15 and 30 as thresholds, respectively. Through regression analysis, the association between SAS and methadone daily dose was assessed with adjustments for sex, BMI, age, use of benzodiazepines, and the timing of administration. In case of normal distribution, the means of AHI were compared using the student's t-test in groups defined by the timing of methadone administration. The comparisons of AHI distribution (Mann-Whitney U test) and medians were utilized if AHI did not follow the assumption of normality. The Chi-square test was

performed to assess the association between an AHI ≥ 15 events/h (same for AHI ≥ 30 events/h) and timing of administration. A receiver operating characteristic (ROC) analysis was performed to estimate the sensitivity, specificity, and likelihood ratios (positive and negative) of several daily doses of methadone in identifying SAS, considering a cut-off of 15 or 30 for the AHI. Through an appraisal based on the Index of Union method, the daily cut-off points were later determined for methadone dose with the best sensitivity and specificity. This approach outlines the optimal cut-off as the value whose sensitivity and specificity are the nearest to the value of the area under the ROC curve, and for which the absolute value of the difference between sensitivity and specificity is the smallest[18]. Results were considered significant for a *P* value of 0.05 or less.

Results

General characteristics

Overall, 40 patients, including 29 (72.5%) males participated in the study. The mean age was 35 ± 6.7 years (minimum and maximum values of 20 and 56 years). The mean daily dose of methadone was 74.6 ± 42.6 mg. The dose was significantly higher when methadone was prescribed for administration in the evening compared to the daytime (98.6 ± 41.1 mg/d vs 65.5 ± 40.1 mg/d). The overall characteristics of the participants are presented in Table 1.

Main results

The analysis of data showed the AHI was not normally distributed in the sample (*P* value of 0.02 with the Kolmogorov-Smirnov test). The median value of AHI was 11.9 events/h [4.35–29.02]. However, the mean value was 18.9 ± 18.9 events/h. An AHI above 5 events/h was observed in 29 patients, which represents a SAS frequency of 72.5% (95% CI, 57.5% to 87.5%). In addition, 37.5% (95% CI, 22.5% to 54.9%) of patients had moderate (five cases) to severe (10 cases) SAS according to the AHI.

Table 1. General characteristics of participants

Variables	Patients on methadone treatment (N = 40)
Quantitative variables, mean ± SD	
Age (y)	35 ± 6.7
Body mass index (in kg/m²)	25.1 ± 4.5
Methadone daily dose in mg	74.6 ± 42.6
Methadone daily dose in mg/kg	1.01 ± 0.6
Methadone daily dose in mg/BMI	3.03 ± 1.8
Qualitative variables, No. (%)	
Males	29 (72.5%)
Benzodiazepine use	36 (90.0%)
Evening administration of methadone	11 (27.5%)

BMI, body mass index; SD, standard deviation.

While assessing the relationship between daily methadone dose (in mg) and AHI, there was found a significant and positive correlation with a Spearman's rho = 0.348 (95% CI, 0.014 to 0.627; *P* = 0.028). Considering the dose in mg/kg, there was found a Spearman's rho = 0.329 (95% CI, -0.023 to 0.626; *P* = 0.038).

The daily methadone dose was significantly higher in patients with an AHI ≥ 15 events/h versus AHI < 15 events/h, and an AHI ≥ 30 events/h versus AHI < 30 events/h (Table 2). Among individuals classified as moderate to severe SAS, the proportion of central events (percentage of central sleep apneas among all respiratory events) varied from 1.6% to 86.2%, and the daily dose of methadone (in mg/d) was significantly correlated with the proportion of central events (Pearson's correlation coefficient = 0.577, *P* value = 0.024).

Given a cut-off of 15 respiratory events/h, the results of regression analysis revealed a significant association between SAS and methadone dose, and this association was maintained with the addition of sex, age, and BMI to the model. This was also the case when benzodiazepine prescription was added to the model. However, the statistical association was not maintained following adjustment on administration time (day versus evening), as shown in Table 3. Considering AHI ≥ 30 instead of 15 events/h, a similar pattern of results was found, notably for the role of administration time on the association between methadone daily dose and an AHI ≥ 30 events/h.

For the prediction of an AHI ≥ 15 events/h, the best methadone cut-off dose was 72.5 mg/d (sensitivity = 80.0%, specificity = 64.0%, positive LR = 2.22, and negative LR = 0.31). The area under the curve (ROC analysis) was 0.761 (Figure 1).

For the prediction of an AHI ≥ 30 events/h, the best methadone cut-off dose was 77.5 mg/d (sensitivity = 80.0%, specificity = 63.3%, positive LR = 2.18, and negative LR = 0.31). The area under the curve (ROC analysis) was 0.747 (Figure 2).

Significantly higher levels of AHI were found in patients who took methadone in the evening versus the daytime (median values of 31.6 events/h [interquartile range = 35.7] versus 10 events/h [interquartile range = 10.4], *P* = 0.002). The multivariable binary logistic regression showed the evening prescription was

Table 2. Methadone daily dose in groups defined by AIH cut-offs

		Mean ± SD of methadone dose (mg/d)	*P* value
AHI ≥ 5 events/h	Yes (n = 29)	78.9 ± 43.3	0.302
	No (n = 11)	63.1 ± 40.5	
AHI ≥ 15 events/h	Yes (n = 15)	98.6 ± 45.6	0.004
	No (n = 25)	60.2 ± 34.0	
AHI ≥ 30 events/h	Yes (n = 10)	105.5 ± 52.1	0.006
	No (n = 30)	64.3 ± 34.0	

AHI, apnea-hypopnea index; SD, standard deviation.

Table 3. Multivariable binary logistic regression between moderate to severe sleep apnea and total daily dose of methadone

Blocks of variables	AHI ≥ 15		Odds ratios (95% CI)	*P* value	Pseudo R^2 Nagelkerke coefficient
	Yes	No			
Unadjusted model (Total methadone daily dose)	25 (62.5%)	15 (37.5%)	1.027 (1.005, 1.049)	0.014	0.261
1st block of adjustment (Unadjusted model, sex, age, BMI)	25 (62.5%)	15 (37.5%)	1.028 (1.006, 1.051)	0.014	0.329
2nd block of adjustment (First block, benzodiazepine treatment)	25 (62.5%)	15 (37.5%)	1.029 (1.005, 1.053)	0.016	0.337
3rd block of adjustment (Second block, methadone in the evening)	25 (62.5%)	15 (37.5%)	1.022 (0.995, 1.049)	0.11	0.521

BMI, body mass index; AHI, apnea-hypopnea index.

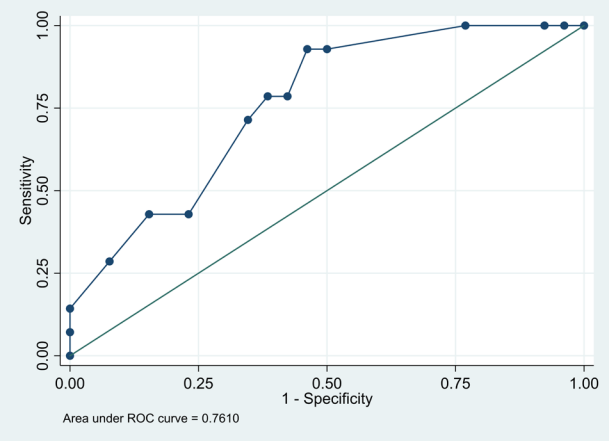

Figure 1. ROC analysis curve linking an AIH ≥ 15 and methadone daily dose

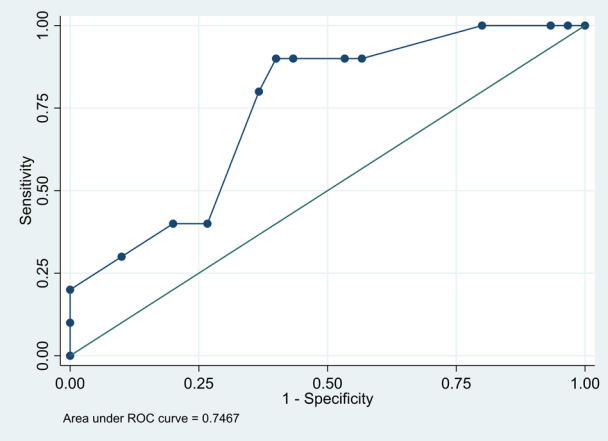

Figure 2. ROC analysis curve linking an AIH ≥ 30 and methadone daily dose

significantly associated with moderate to severe SAS, even after adjustment for age, sex, BMI, methadone daily dose, and benzodiazepine prescription (Table 4). However, the same results were not observed for the association between evening prescription and AHI ≥ 30 events/h after adjustments for the previously cited variables ($P = 0.056$).

Discussion

Summary of results

The results of this study suggest that there is an association between the daily dose of methadone and the AHI. Besides, the methadone dose was significantly associated with both an AHI ≥ 15 events/h and an AHI ≥ 30 events/h. The statistical relationship was maintained after the adjustment for age, sex, BMI, and benzodiazepine use. However, the association was not preserved when the time of administration was considered. A significant correlation was also observed between the proportion of central events and the daily dose of methadone. The best sensitivity and specificity for the prediction of an AHI ≥ 15 events/h and an AHI ≥ 30 events/h were obtained with methadone dose thresholds of 72.5 mg/d and 77.5 mg/d, respectively. The evening administration of methadone was significantly associated with the AHI and an AHI ≥ 15 events/h. This was not the case when an AHI ≥ 30 events/h was considered.

General interpretation of results

The dose-response relationship that was observed between methadone and sleep apnea-hypopnea corroborates the conclusions from previous studies reporting an association between opioid treatments and SAS.[6,9,13,19] It is worth noting that we found no study specifically addressing a daily threshold in patients under MMT that could be predictive of OSAS or CSAS. Webster et al, in a study evaluating the relationship between chronic pain medications and sleep apnea, found a significant and direct association between the daily methadone dose and the AHI as well as the central apnea index.[13] While looking at the role of chronic opioid use in the development of central sleep apnea and ataxic breathing by comparing 60 chronic opioid users and 60 controls, Walker et al noticed a dose-response association between morphine equivalent daily dose (MEDD) and apnea-hypopnea.[19] They also showed that ataxic or irregular breathing was more common at a morphine dose of ≥ 200 mg, and that every 100 mg increase in the MEDD augmented the rate of apneas by 14.4% and of central apneas by 29.2%.[19] Through a review study focusing on chronic opioid use and central sleep apnea, including eight studies involving 560 patients, Correa et al. found that the MEDD was potently related to the severity of the SRBD, predominantly CSAS, with a MEDD of > 200 mg being a threshold of specific interest.[9] As a reminder, a MEDD of 200 mg corresponds to a daily methadone dose varying from 20 to 40 mg according to available dosing ratios, notably the ones defined by Ripamonti et al (6:1),[20] Ayonrinde et al (5:1),[21] Mercadante et al (8:1),[22] and the

Table 4. Multivariable binary logistic regression between moderate to severe sleep apnea and the timing of methadone administration

Blocks of variables	AHI ≥ 15		Odds ratios (95% CI)	*P* value	Pseudo R^2 Nagelkerke coefficient
	Yes	No			
Unadjusted model (Total methadone in the evening)	25 (62.5%)	15 (37.5%)	8.381 (1.733, 40.53)	0.008	0.246
1st block of adjustment (Unadjusted model, sex, age, BMI)	25 (62.5%)	15 (37.5%)	23.215 (2.738, 196.799)	0.004	0.416
2nd block of adjustment (First block, benzodiazepine treatment)	25 (62.5%)	15 (37.5%)	33.496 (3.317, 338.219)	0.003	0.456
3rd block of adjustment (Second block, methadone daily dose)	25 (62.5%)	15 (37.5%)	18.917 (1.782, 200.841)	0.015	0.521

AHI, apnea-hypopnea index; SD, standard deviation.

information leaflet provided with methadone products (10–20% of daily morphine dose).[23] The greater threshold obtained (approximately twofold higher than the one derived from MEDD) might support some specificities pertaining to methadone. Contrasting with the previously mentioned dose-response relationship linking opioids to sleep hypopnea and apnea, some studies reported no significant relationship between opioid dose and AHI or SAS.[12,24,25] Hassamal et al, while reviewing the influence of opioids on SRBDs in chronic pain patients (16 studies) and patients treated with methadone (six studies), found that higher opioid doses predicted more obstructive and central apneas in chronic pain patients but not in MMT patients.[6] They also reported that the prevalence of SRBD in MMT patients ranged from 42.3% to 70%,[6] which is close to the frequency of AHI ≥ 5 events/h observed in the present study (72.5%). However, as indicated in the meta-analysis conducted in 2021 by Ahmad et al, most studies reported no association between opioid treatment (especially methadone) and obstructive sleep apnea.[12,24] The present study, however, found a significant association between methadone dose and the proportion of central apnea.

The mechanisms potentially connecting methadone and SAS could be divided into central and peripheral mechanisms, respectively predictive of CSAS and OSAS. Regarding the central aspect, the pathophysiology of opioid-induced CSAS is recognized to be based on the dysregulation of the respiratory center located in the brainstem, as well as the dysfunction of the ventilatory chemoreflexes.[26-28] Opioid treatments alter the ability of these centers to detect decreasing partial pressure of oxygen or increasing partial pressure of carbon dioxide.[26-28] This results in an irregular respiratory rhythm, with a mix between episodes of (hypercapnic) central sleep apneas and episodes of ataxic breathing (Biot's respiration).[27,28] Concerning the peripheral component, despite the discrepancies in the literature, it appears that methadone and other opioid therapies can potentially decrease upper airway tone and increase collapsibility.[27-29] Notably, the presence of obstructive sleep apnea increases the risk of opioid-induced respiratory depression, and hence the risk of central sleep apnea.[29,30] Some other factors could explain the occurrence of SAS, specifically in MMT patients. Indeed, past history of cerebrovascular events could participate in the impairment of ventilation and thereby increase the risk of CSAS.[6,31] Moreover, methadone specifically influences the development of morphine tolerance through its N-methyl-D-aspartate (NMDA) receptor antagonist activity, with delayed tolerance to the respiratory depression pertaining to methadone.[32,33] This can potentially contribute to both obstructive and central SAS. The concomitant use of benzodiazepine could be another explanation of SAS development in MMT patients.[13,14]

To our knowledge, there are no published studies addressing the timing of methadone administration in the occurrence of SAS. In the present study, methadone administration time (day/evening) was a cofounding factor regarding the association between the daily dose of methadone and moderate to severe SAS. This could be related to the fact that methadone taken orally reaches peak plasma concentrations at 2.5-4 hours.[34–36] The evening prescription of methadone is usually preferred in patients with severe and/or nocturnal cravings, and these patients tend to have higher daily dose, as indicated by the results of this study.

Limitations

Despite being one of the first studies to address both the methadone dose threshold and the role of timing of methadone administration in the occurrence of SAS, some concerns need to be mentioned. First is the retrospective nature of the study, making it impossible to adjust the results on factors such as the diagnosis of comorbid mental health conditions reported to be associated with higher frequencies of SAS (depressive disorders, psychotic disorders, tobacco addiction) as well as comorbid cardiometabolic disturbances. Furthermore, as a result of collecting data retrospectively, neither the sleep habits and complaints that could contribute to the establishment of SAS phenotypes nor the impact of methadone dose according to these phenotypes could be specifically and extensively assessed. In addition, there was no access to the information on methadone concentrations, and by extension the ability to distinguish slow metabolizers from rapid ones, which could influence the association between timing of methadone administration and SAS. The relatively small sample size and the lack of a control group, for example patients treated for OUD with another

OST such as buprenorphine, are additional limitations. Another point to highlight is that the tool used to objectify overnight respiratory events was nocturnal respiratory polygraphy. It is a more accessible sleep exploration tool, but it is less accurate than polysomnography.

Implications of the results

The results of the present study draw the attention of clinicians managing patients with OUD by using methadone, especially when the daily dose is greater than 75 to 80 mg and/or the treatment is administered in the evening. Indeed, the findings suggest that there is a need to take into account performing SAS screening in these cases. This is all the more important considering that these patients might have a misperception of their somatic health, including sleep; in case of sleep complaints, the potentially sedative effect of methadone obscures the possibility of sleep apnea. This study also suggests that there is a need for further studies with larger sample sizes and prospective designs, the investigation of sleep habits and complaints, the assessment of psychiatric and somatic comorbidities, and the comparison with buprenorphine (alone or with naloxone). On this last point, two case reports described an improvement in SAS (AHI decrease with or without clinical improvement) by switching from methadone to buprenorphine with or without naloxone.[37,38]

Conclusion

The present study suggests that daily methadone dose and administration time in the evening, are associated with sleep hypopnea-apnea among people treated with methadone for OUD. More precisely, it was found that 72.5 mg and 77.5 mg were the best thresholds for the prediction of AHI ≥ 15 events/h and ≥ 30 events/h, respectively, implying that patients taking more than 75 or 80 mg/d require particular attention in clinical practice. Further research is warranted on SAS in people treated by OST for OUD, especially comparing methadone with buprenorphine.

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Authors' Contribution

Conceptualization: Clément Guillet, Jean Claude Girod, Ludwig Serge Aho Glélé.
Data curation: Clément Guillet, Francky Teddy Endomba, David Aravantinos, Jean Claude Girod
Formal analysis: Francky Teddy Endomba,
Investigation: Clément Guillet, Francky Teddy Endomba, David Aravantinos, Aymard Hussami, Florence Beye, Jean Claude Girod
Methodology: Clément Guillet, Francky Teddy Endomba, David Aravantinos, Aymard Hussami, Florence Beye, Jean Claude Girod, Ludwig Serge Aho Glélé.
Project administration: Ludwig Serge Aho Glélé.
Resources: Ludwig Serge Aho Glélé.
Software: Francky Teddy Endomba, Ludwig Serge Aho Glélé.
Supervision: Clément Guillet, Francky Teddy Endomba, Ludwig Serge Aho Glélé.
Validation: Clément Guillet, Francky Teddy Endomba, Ludwig Serge Aho Glélé.
Visualization: Francky Teddy Endomba, Ludwig Serge Aho Glélé.
Writing–original draft: Clément Guillet, Francky Teddy Endomba
Writing–review & editing: Clément Guillet, Francky Teddy Endomba, David Aravantinos, Aymard Hussami, Florence Beye, Jean Claude Girod, Ludwig Serge Aho Glélé.

Competing Interests

The authors declare no competing interest.

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