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PHARMACOKINETICS AND DISPOSITION

Cannabis and benzodiazepines as determinants of methadone trough plasma concentration variability in maintenance treatment: a transnational study

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Abstract
Purpose To assess tobacco, alcohol, cannabis and benzodiazepine use in methadone maintenance treatment (MMT) as potential sources of variability in methadone pharmacokinetics.
Methods Trough plasma (*R*)- and (*S*)-methadone concentrations were measured on 77 Australian and 74 Swiss MMT patients with no additional medications other than benzodiazepines. Simple and multiple regression analyses were performed for the primary metric, plasma methadone concentration/dose.
Results Cannabis and methadone dose were significantly associated with lower 24-h plasma (*R*)- and (*S*)-methadone concentrations/dose. The models containing these variables explained 14–16% and 17–25% of the variation in (*R*)- and (*S*)-methadone concentration/dose, respectively. Analysis of 61 patients using only CYP3A4 metabolised benzodiazepines showed this class to be associated with higher (R)-concentration/dose, which is consistent with a potential competitive inhibition of CYP3A4.

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Conclusion Cannabis use and higher methadone doses in MMT could in part be a response to—or a cause of—more rapid methadone clearance. The effects of cannabis and benzodiazepines should be controlled for in future studies on methadone pharmacokinetics in MMT.

Keywords Benzodiazepine · Cannabis · Drug interaction · Enantiomer · Methadone · MMT · Pharmacokinetics

Introduction

Methadone is the most widely used opioid replacement treatment for opiate dependency. It is usually given as a racemic mixture of (*R*)- and (*S*)-methadone, with (*R*)-methadone accounting for most of the opioid effects.

Wide interindividual variability has been shown in the clinical pharmacokinetics of methadone [1]. A 17-fold variation was reported in plasma (*R*)-methadone concentration-to-dose ratios in patients taking no other medications, with a 41-fold variation among those taking other medications [2]. Interindividual variability in the function of cytochrome P450 (CYP) enzymes CYP2B6 and CYP3A4 may account for much of this variation and may be due to genetic polymorphisms and environmental factors, including the use of medications and non-prescribed substances [1, 3]. *ABCB1* genetic polymorphisms, which encode for the permeability efflux transporter P-glycoprotein (P-gp), may also contribute to the interindindividual variability of methadone plasma and central nervous system pharmacokinetics [3, 4].

Methadone also displays large interindividual pharmacodynamic variability [1], with polymorphisms in the mu and delta opioid receptors and dopamine D2 receptors as possible candidates for this variability [5, 6].

While numerous studies have found high levels of alcohol, benzodiazepine, tobacco and cannabis use in subjects receiving methadone maintenance treatment (MMT) [7–16], there have been very few studies of pharmacokinetic interactions of these substances with methadone. Based on a study of MMT patients, Hallinan et al. [17] reported that benzodiazepine (mostly diazepam), but not alcohol, use was associated with lower plasma (*R*)-methadone concentration adjusted for dose and body weight ($p=0.001$) in patients taking no other known medications. This result suggests that the use of some benzodiazepines may increase the clearance of methadone or be a response to increased inherent methadone clearance [17]. However this study did not examine cannabis or tobacco use. Other studies have found no acute effects of diazepam on methadone pharmacokinetics [18, 19], although diazepam has significant acute pharmacodynamic effects in methadone maintained patients [20, 21]. Diazepam could theoretically decrease the clearance of methadone by inhibiting CYP3A4 [22].

We have used an epidemiological approach to examine the hypothesis that tobacco, alcohol, cannabis and benzodiazepine use in MMT may be sources of methadone pharmacokinetic variability. The aim of our study was to assess the effect of concurrent use of tobacco, alcohol, cannabis and benzodiazepines on the 24-h trough plasma concentrations of methadone.

Materials and methods

The data used in this study was collected independently from MMT centers in Australia and Switzerland.

Australian study group

Data from the Australian study group have been previously reported elsewhere [23] and include MMT patients who had 24-h trough methadone concentration testing (their previous methadone dose supervised, a blood sample collected just before the next dose, with no dose change in the preceding 2 weeks) at the time of routine blood tests, which are done twice yearly. The study results reported here are derived from a subset of this group—those patients who were not taking any known medications other than methadone and benzodiazepines.

Current prescribed medications and substance use data were recorded at the time of pre-test or post-test counseling. Substance use data were recorded by the physician (RH) as the Occasions of Drug Use Index (ODUI) [24] for the previous month, based on patient self-report with supportive evidence derived from the clinic protocol of regular medical consultations and urine toxicology. These occur generally every 1 to 4 weeks, depending on progress in treatment according to clinical indicators, including previous urine toxicology results. A physician is available to see patients whenever the clinic is open, such as when drug or alcohol use affects a patient's presentation. Positive urine tests do not lead to punitive actions, but they are indicators for more intensive engagement including more frequent urine tests.

Initial toxicology screening is carried out with an enzyme immunoassay (Microgenics CEDIA, Fremont, CA) for opiates, benzodiazepines and metabolites, cannabinoids, sympathomimetic amines, cocaine metabolites, barbiturates, with follow-up thin layer chromatography testing (Toxilab; Ansys Technologies, Lake Forest, CA) as required, including that for codeine, morphine/monoacetylmorphine, amphetamine/methamphetamine and pseudoephedrine.

Collection of these data and their group-wise analysis for purposes of clinical audit and potential publication

was reviewed by the Ethics Committee at Central Sydney Area Health Service (CSAHS Protocol Nr X04-0030 "Audit Activities at the Byrne Surgery"). All patients gave informed consent to urine and blood testing.

Swiss study group

Data from the Swiss study group have been previously reported elsewhere [3] and includes 276 patients in MMT at five methadone-dispensing centers in Geneva, Lausanne, Bern and Montreux (Switzerland). For the study reported here, patients who were not taking any known medications other than benzodiazepines were selected from among those who were receiving once daily methadone dosing and who also had a measured trough methadone concentration. Classification of current substance use status was by subject self-report of the frequency of use during the previous 3-month period (never; up to 2×/week; 3×/week or more) in a confidential questionnaire. The only exception to this was the test for heroin and cocaine use, where classification was confirmed by the presence or absence of positive urines for opiates or cocaine metabolites over a period of 3 months prior to inclusion, with urine tests randomly performed at least once a week (this reflects the protocols of the original studies). Subjects were assured that no negative consequences would result from self report. Information on prescribed medications was available from the medical files of the patients. The study was approved by the local ethics committees of the participating centers, and written informed consent was obtained from all patients.

Data

Main outcome measures were trough plasma (*R*)- and (*S*)-methadone concentration adjusted for methadone dose by dividing the plasma (*R*)- and (*S*)-methadone concentration for each subject by their daily dose. This composite measure is widely used [1, 2] and has the benefit of being a better reflection of the bioavailability and clearance of methadone than unadjusted methadone concentrations, whereas adjustment for body weight is now accepted to be inappropriate [23, 25].

Other clinical data collected were: age, gender, body weight, body mass index (BMI), duration of current methadone treatment episode. Substance use data were treated as categorical variables, as follows:

- alcohol intake—exceeding or not exceeding low-risk drinking limits, i.e. 40 g/day or 280 g/week for men and 20 g/day or 140 g/week for women [26];
- smoking—current smokers and non-smokers of tobacco;
- cannabis use—current users and non-users (any use at all in reference period);
- heroin use—current users and non-users (any use at all in reference period);
- benzodiazepine use—those currently using benzodiazepines, whether prescribed or non-prescribed (any use at all in reference period; note patients taking zolpidem and zopiclone were excluded).

The periods of reference for alcohol, cannabis, heroin and benzodiazepine use were "last 30 days" for the Australian groups and "last 3 months" for the Swiss groups. The above limits for alcohol use were chosen as a convenient measure for dichotomizing alcohol consumption and have no particular significance for methadone metabolism or efficacy in MMT.

Analysis of (*R*)-methadone and (*S*)-methadone by high-performance liquid chromatography

For the Australian Study Group, plasma was separated from the blood samples within 4 h, and the specimens were transported to the laboratory where they were frozen and stored at −20°C until testing. Analysis of (*R*)-methadone and (*S*)-methadone was performed by high-performance liquid chromatography (HPLC) adapted from [28]. Calibration curves for (*R*) and (*S*)-methadone were linear over the concentration range 20–1000 ng/mL with a coefficient of variance (CV) ≤6.3%. The limit of quantitation was 20 ng/mL with a CV > 10.3% and deviation from the nominal value of less than 2.5%.

For the Swiss study group, plasma was separated from the ethylenediaminetetraacetic acid-treated blood samples and the specimens stored at −20°C until testing. Analysis of (*R*)-methadone and (*S*)-methadone was performed by liquid chromatography coupled with mass spectroscopy as previously described [27, 29, 30]. The method was fully validated over a concentration range of 5–800 ng/mL for each methadone enantiomer with satisfactory relative bias (−1.0 to 1.0%), repeatability (0.9–4.9%) and intermediate precision (1.4–12.0%).

Data analysis

Simple and multiple regression analyses, including backward stepwise regression, were performed on both data sets separately for the effects of gender, age, months of treatment, daily methadone dose and use versus non-use of tobacco, alcohol, heroin, cannabis and benzodiazepines on outcome measures. Duration of treatment and daily dose were included as variables, owing to reports that methadone might induce its own metabolism at the beginning of treatment [25, 31, 32]. Multiple linear regression models

were evaluated for normality of residuals and homogeneity of variance. Statistical analyses were undertaken with the statistical package STATA, ver. 8.2 and 9.2 (2004; Stata Corporation, College Station, TX). Statistical significance was taken as $P \leq 0.05$. Summary measures are presented as the mean ± standard deviation (SD) for normally distributed data, and as the median with 25th and 75th percentiles for non-normally distributed data.

Results

Among the Australian study group, 77 of 158 patients receiving MMT between June and December 2003 met the inclusion criteria and were using no medications other than benzodiazepines and methadone, with blood samples taken at a mean 24.3 h (SD 1.2 h) after a witnessed dose. From the Swiss Study group, results were available for a total of 74 patients who were using no medications other than benzodiazepines and methadone: for all but eight of these patients there was no dose change in the 2 weeks preceding blood testing, and the minimum duration since the last dose change for these eight patients was 4 days. Blood samples were taken at a mean 23.3 h (SD 3.6 h) after a witnessed dose.

Table 1 shows summary statistics for the two study groups. Recent cannabis, benzodiazepine and tobacco use were common in both study groups (for Australian and Swiss groups, respectively: 46 vs. 57%; 36 vs. 46%; 83 vs. 96%), while alcohol use exceeding low-risk limits was more common in the Swiss group (38 vs. 16%) and recent heroin was use less common (15 vs. 48%). Prescribed diazepam was the benzodiazepine primarily reported by 14 of 28 benzodiazepine users in the Australian study group, with smaller numbers reporting use of prescribed alprazolam (one patient), oxazepam (two) and 11 patients reporting the use of whichever benzodiazepine was opportunistically available. This was most commonly diazepam, according to general patient report and the doctors' knowledge of benzodiazepine availability in the area, and less commonly oxazepam, alprazolam or clonazepam. A greater range of benzodiazepines used was reported from the Swiss study groups: oxazepam (11 patients), clonazepam (six), clorazepam (four), lorazepam (four), bromazepam (five), alprazolam (three), midazolam (four), diazepam (two), flurazepam (two), flunitrazepam (one) and triazolam (one).

Table 1 Demographic and plasma methadone concentrations summary statistics—dependent and independent variables for the Australian and Swiss study groups

Variable	Australian Study Group (n=77)	Swiss Study Group (n=74)
Duration of MMT, months[a]	31 (11–102)	45 (15–89)
Age, years[b]	36.6 (7.6)	36.8 (8.2)
Weight, kg[b]	72.9 (14.5)	75.2 (15.7)
Body mass index, kg/m^2[b]	24.3 (4.2)	24.2 (4.9)
Methadone dose, mg/day[a]	95 (50–140)	82.5 (45, 150)
Time since previous supervised dose, h[b]	24.3 (1.2)	23.3 (3.6)
Plasma (*R*)-methadone concentration, ng/mL[a]	160 (85–229)	166 (91–281)
Plasma (*R*)-methadone/dose, ng × day/mL × mg[c]	1.8 (0.7; 0.65–3.81)	2.2 (1.7; 0.6–12.8)
Plasma (*S*)-methadone concentration, ng/mL[a]	138 (80–190)	157 (89–254)
Plasma (*S*)-methadone/dose (ng × day/mL × mg[c]	1.7 (0.8; 0.4–4.1)	2.1 (2.0; 0.2–15.0)
Plasma (*R*,*S*)-methadone concentration, ng/mL[a]	304 (150–435)	336 (177–546)
Plasma (*R*,*S*)-methadone/dose, ng x day/mL × mg[c]	3.4 (1.4; 1.1–7.9)	4.3 (3.7; 1.0–27.7)
Plasma (*R*)/(*S*)-methadone ratio[c]	1.1 (0.3; 0.6–2.0)	1.2 (0.4; 0.7–3.4)
Gender male (%)	60/77 (77.9%)	59/74 (79.7%)
Current cannabis use (%)	35/77 (45.5%)	42/74 (56.8%)
Current benzodiazepine use (%)	28/77 (36.4%)	34/74 (46.0%)
Exceeding low risk alcohol limits (%)	12/77 (15.6%)	28/74 (37.8%)
Tobacco smokers (%)	64/77 (83.1%)	71/74 (96.0%)
Current heroin use (%)	37/77 (48%)	11/74 (14.9%)

MMT, Methadone maintenance treatment; SD, standard deviation;

[a] Values are given as the median with 25th and 75th percentiles

[b] Values are given as the means ± SD

[c] Values are given as the mean with the SD and range given in parenthesis

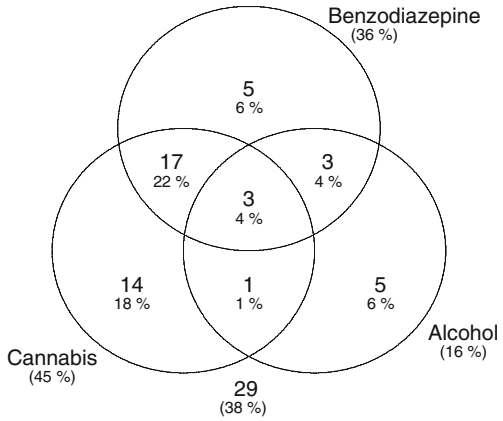

Fig. 1 Number and percentage of patients with benzodiazepine, cannabis and/or alcohol consumption in the Australian study group (29 patients did not use these substances)

As shown in Figs. 1 and 2, there was substantial overlap between benzodiazepine and cannabis use in the Australian group, and among benzodiazepine, alcohol and cannabis use in the Swiss group.

Lower 24-h trough plasma (*R*)-methadone concentration/dose ratios were significantly associated with the following variables (Supplementary table): higher methadone dose (Australian group $R^2 = 0.072$, $P = 0.019$; Swiss group $R^2 = 0.072$, $P = 0.021$); cannabis use (Australian group $R^2 = 0.088$, $P = 0.009$; Swiss group $R^2 = 0.087$, $P = 0.011$); benzodiazepine use (Australian group only $R^2 = 0.060$, $P = 0.032$); alcohol use (Swiss group only $R^2 = 0.059$, $P = 0.037$); heroin use (Swiss group only $R^2 = 0.069$, $P = 0.024$).

Lower 24-h trough plasma (*S*)-methadone concentration/dose ratios were significantly associated with the following (Supplementary table): higher methadone dose (Australian group $R^2 = 0.176$, $P < 0.001$; Swiss group $R^2 = 0.103$, $P = 0.005$); cannabis use (Australian group $R^2 = 0.076$, $P = 0.015$; Swiss group $R^2 = 0.083$, $P = 0.013$; heroin use (Australian group $R^2 = 0.0381$, $P = 0.049$; Swiss group $R^2 = 0.063$, $P = 0.032$); benzodiazepine use (Australian group only $R^2 = 0.099$, $P = 0.005$); alcohol use (Swiss group only $R^2 = 0.055$, $P = 0.044$). No significant associations were found between (*R*)- or (*S*)-methadone concentration/dose ratios and duration of MMT, age, weight, BMI, gender or tobacco smoking in both groups (data not shown).

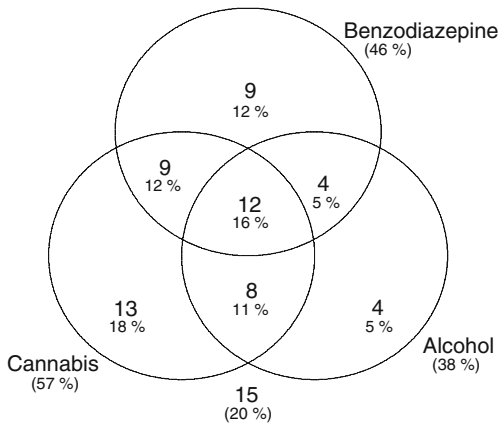

Fig. 2 Number and percentage of patients with benzodiazepine, cannabis and/or alcohol consumption in the Swiss study group (15 patients did not use these substances)

After backward stepwise regression (Table 2), cannabis and methadone dose remained significantly associated with lower 24-hour trough plasma (*R*)-methadone/dose and (*S*)-methadone/dose for both study groups. The models containing these variables explained 16 and 25% of the variation in plasma (*R*)- and (*S*)-methadone/dose ratios, respectively, for the Australian study group and 14% and 17% for the Swiss study group.

An additional analysis was performed for the Swiss group after excluding those receiving oxazepam and lorazepam, which are mainly glucuronidated with no significant contribution of CYP3A4 in their metabolism. As shown in Table 2, cytochrome P450 metabolized benzodiazepines remained in the multivariate model for this group (n=61), associated with higher trough plasma (*R*)-methadone/dose.

Discussion

After stepwise regression, cannabis use and higher daily methadone dose were found in both study groups to be significantly and negatively associated with 24-h trough (*R*)-methadone/dose and (*S*)- methadone/dose; the latter were not associated with gender, alcohol, tobacco smoking or duration of MMT treatment. Multiple regression also revealed that body weight and BMI were unrelated to 24-h methadone concentration/dose, which is consistent with a previous report that methadone clearance is unrelated to body weight [25].

An association of higher methadone dose with lower methadone plasma concentration/dose ratio has been previously reported [2, 25] and may be explained by the induction of drug metabolism at higher methadone doses and/or saturation of plasma binding, which would lower the total plasma concentration/dose ratio without affecting unbound concentrations.

An association of cannabis use with lower plasma (*R*)-methadone/dose and (*S*)-methadone/dose has not been previously reported. One possible pharmacokinetic explanation could be induction of the isoenzyme CYP1A2 by smoke, leading to the increased metabolism of methadone; however, no association of tobacco smoking with trough methadone concentrations was found in our study nor in

Table 2 Stepwise regression for (*R*)-methadone/dose and (*S*)-methadone/dose

Variable	(*R*)-Methadone/dose (ng day/mL mg)			(*S*)-Methadone/dose (ng day/mL mg)		
	Coefficient (SE)	*P* value	95% CI	Coefficient (SE)	*P* value	95% CI
Australian Study Group (n=77)						
Methadone dose (mg/day)	−0.003 (0.001)	0.015	−0.005 to −0.001	−0.005 (0.001)	<0.001	−0.008 to −0.003
Cannabis (current users vs. non-users)	−0.393 (0.142)	0.007	-0.678 to −0.109	−0.431 (0.160)	0.009	−0.750 to −0.112
Constant	2.239 (0.149)	0.000	1.942–2.536	2.411 (0.167)	0.000	2.077– 2.744
	(R^2=0.1582; P=0.002)			(R^2=0.2496; P<0.0001)		
Swiss Study Group (n=74)						
Methadone dose (mg/day)	−0.005 (0.002)	0.034	−0.009 to −0.0004	−0.007 (0.003)	0.009	−0.012 to −0.002
Cannabis (current users vs non-users)	−0.931 (0.382)	0.017	−1.693 to −0.169	−1.052 (0.447)	0.021	−1.942 to−0.162
Constant	3.259 (0.367)	0.000	2.527– 3.992	3.505 (0.429)	0.000	2.649–4.360
	(R^2=0.1433; P=0.004)			(R^2=0.1680; P=0.002)		
Swiss Study Group (n=61)[a]						
Methadone dose (mg/day)	−0.007 (0.003)	0.012	−0.013 to −0.002	−0.008 (0.003)	0.013	−0.014 to −0.002
Cannabis (current users vs. non-users)	−1.146 (0.437)	0.011	−2.020 to −0.271	−1.213 (0.524)	0.024	−2.263 to −0.164
Benzodiazepine (1)	0.995 (0.484)	0.045	0.025–1.964	Not applicable[b]		
Constant	3.352 (0.428)	0.000	2.495–4.209	3.750 (0513)	0.000	2.723–4.776
	(R^2=0.2070; P = 0.004)			(R^2=0.1771; P=0.004)		

CI, Confidence interval; SE, standard error

[a] Excluding users of oxazepam and lorazepam

[b] Not significant in the multivariate analysis and therefore not included in the model

previous ones [3]. As the *ABCB1 3435TT* genotype is associated with lower P-gp activity as well as slightly lower trough (*R*,*S*)-methadone plasma concentrations [3], another possible explanation involves P-gp inhibition by cannabinoids [33].

Alternatively, as the plasma methadone concentration–response relationship for withdrawal and mood symptoms is very steep [34, 35], cannabis use may be a compensatory response to opioid withdrawal symptoms in some individuals who have more rapid methadone clearance.

Contrary to data reported earlier by the Australian Study Group [17], subsequent multivariate analysis revealed no evidence of a relationship between benzodiazepine use and lower 24-h trough plasma methadone/dose. Although the Australian Study Group found that the most common benzodiazepine used was diazepam (according to patient report), patients can obtain benzodiazepines by visiting multiple doctors; in addition, benzodiazepines are readily available on the black market. Consequently, patients may use a range of benzodiazepines, depending on what is available. By contrast, the Swiss group generally used benzodiazepines prescribed by their methadone prescribing doctor, and analysis of the subgroup using CYP3A4 metabolized benzodiazepines showed this class to be associated with higher trough plasma (*R*)-methadone/dose, which is consistent with a potential competitive inhibition of CYP3A4.

The results for (*S*)-methadone/dose generally paralleled those for (*R*)-methadone/dose; however, the association of higher methadone dose with lower trough methadone concentration/dose was substantially stronger for (*S*)--methadone. Differences in the clearance of (*R*)- and (*S*)-methadone may be of clinical importance as (*S*)-methadone has been incriminated in dysphoric effects at higher methadone doses [36] and shown to be a more potent hERG current inhibitor than (*R*)-methadone, with a higher risk for methadone-induced QT interval prolongation [37].

The limitations of this study should be mentioned. The validity of self-report measures of substance use may be questioned, with the potential systematic bias that MMT subjects may under-report their use of other substances. However, self-report of substances using populations has a high validity [38, 39], especially where honest self-reporting is encouraged without being linked to negative consequences [40, 41], as was true for both study groups described here. Self-report can reveal substance use not detected by urine analysis, which only detects recent use [39, 42, 43]. In a clinical setting, optimum results may be achieved by combining urine tests and self-reported drug use [44, 45], as occurs at the Australian Study Center and also partially at the Swiss Study Center.

The categorization of subjects as current users and non-users of substances is rudimentary as it gives no indication of the amount or frequency of use. Cannabis use in

particular is difficult to quantify, owing to the variety of methods of smoking and of the different potencies of the cannabis smoked. Allowing that MMT subjects may under-report their use of other substances and that information is lost in categorical classification, these factors would bias results towards the null, implying the significant associations of cannabis use identified in this study may be stronger in reality.

An inherent limitation of the epidemiological methodology of our study is that it is not capable of determining the causal direction of the associations found. It should also be noted that neither study group was selected to be representative of their respective MMT populations; differences in the univariate analyses for these groups may reflect different rates of alcohol and heroin use, or the differing methods and periods (1 vs. 3 months) of substance use assessment. However it is likely that, for most MMT patients, the use of benzodiazepines, cannabis and tobacco is relatively constant over such time frames.

The major strength of the study lies in its replication of findings in two independent and transnational study populations. These findings are all the more robust given the differences in the methods used by the Australian and Swiss groups to derive substance use data.

If the lower trough methadone concentrations/dose reported in this study actually do reflect methadone clearance, cannabis use and higher methadone doses in MMT may be either a response to—or cause of—more rapid methadone clearance. If the former, one would expect benzodiazepines, depending on their availability, to be used by patients in a similar way. However, we found no indication of this in our study. If the latter, the coefficients of variation (R^2) on univariate analysis suggest that cannabis use may explain about 9% and methadone dose about 7% of the interindividual variation of the plasma (*R*)-methadone/dose ratio. Although in the cross-sectional analysis the scale of these associations is modest compared to the overall interindividual variation, their effects may be more substantial within individuals.

Conclusion

Cannabis use is common in MMT and may be considered by clinicians to be of minor importance. This study suggests the need for further experimental and clinical studies of the effects of cannabis on methadone pharmacokinetics. Future clinical studies of possible effects of benzodiazepines on methadone metabolism will require control for the effects of other substances, especially cannabis, and of the type of benzodiazepine used.

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Conflicts of interest None

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