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REDUCED CANNABIS USE FOLLOWING LOW DOSE NALTREXONE ADDITION TO OPIOID DETOXIFICATION

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To the Editors

Although the influence of cannabis use on the abuse of other drugs or their treatment may vary, [1,2] the increasing severity of cannabis use and its resistance to treatment warrant looking for more effective intervention strategies.[3] Multiple interactions exist between opioid and cannabinoid systems; opioid antagonist medications such as naltrexone at low doses have been proposed to reduce cannabis reinforcement and consumption.[4] In a randomized, double-blind, placebo-controlled clinical trial, we found that daily addition to methadone taper of very low dose naltrexone (VLNTX, 0.125 mg/day, 0.250 mg/day) was associated with attenuated opioid withdrawal during inpatient detoxification and with reduced use of opioids and cannabis, measured by urine drug testing and self-report the day following discharge (D1) and 1 week later (D7).[5] The study was carried out in accordance with the Declaration of Helsinki and was approved by the institutional review boards of Duke University, Durham NC; and Thomas Jefferson University, Philadelphia PA.

We examined follow up data to explore factors associated with cannabis use following detoxification, in addition to VLNTX treatment, and determine whether such use affected short-term outcomes after discharge.

It is difficult to identify new cannabis use with urine testing at weekly intervals, due to the long excretion half-life in urine of cannabinoid metabolites.[6] As self-reported use of other drugs was reliably associate with urine test results in this sample (Fisher's exact test, opioids

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Conflict of Interest
No author has declared potential conflict of interest with the present work.

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p = 0.01 and cocaine p = 0.001), self-reports were utilized as the primary data source for cannabis use at follow-up. Of 120 subjects completing detoxification, 96 were evaluated on D1, 48 of whom were using cannabis at study entry. Among the 61 evaluated on D7, 27 were positive for cannabis at admission. There was no significant difference in proportion of cannabis users randomized to VLNTX or placebo treatment groups (NTX0.125mg= 26.9%, NTX0.25mg= 35.9%, placebo= 37.2%). There were no significant differences in demographic or clinical characteristics between subjects lost to follow up and those who participated in the evaluation (data not shown). There were no significant differences at admission between cannabis users receiving different treatments and between users and non users who participated in follow-up evaluations in terms of demographic, other drug use and clinical characteristics, or proportion of subjects lost to follow up (data not shown), except that cannabis users reported less frequent alcohol use (χ^2=7.0 (2); p=0.03).

Cannabis use was detected in 22.9% of all patients on D1 and 34.5% on D7. Cannabis use on D1 was significantly associated with cannabis use at admission (Fisher's exact test, p = 0.03), with use by D7 (Fisher's exact test, p = 0.001) and with opioid use on D1 (Fisher's exact test, p = 0.001) and D7 (Fisher's exact test, p = 0.001). Cannabis use was not significantly associated with alcohol or any other drug use (data not shown). Cannabis use on D1 was also significantly associated with opioid withdrawal and craving intensity, measured by the Subjective and Objective Opioid Withdrawal Scales,[7] after adjusting for admission ratings by analysis of covariance: subjective, F= 20.4 (1, 94); p = 0.001; objective, F = 16.4 (1, 93); p = 0.001; craving, F = 9.9 (1, 89); p = 0.002.

VLNTX addition to detoxification was associated with significantly less cannabis use, both on D1 (χ^2= 42.3 (2); p=0.001) and D7 (χ^2= 28.4 (2); p = 0.001). Fifty-one percent of subjects receiving placebo used cannabis within 24 hours after treatment completion, vs. 12% of the VLNTX-treated patients. At D7, 41% of subjects (25/61) were attending drug-free structured outpatient programs. Fifty-six percent of subjects in treatment (14/25) were using drugs; no poly-substance use was detected. Cannabis use was significantly less among patients in post-detoxification treatment (12%) than among those who were not in treatment (50%) (Fisher's exact test, p = 0.002). Patients in post-detoxification treatment also had less opioid use (12% vs 41.7%, Fisher's exact test, p = 0.02), but not less cocaine or alcohol use.

The influence of variables on cannabis use at follow-up was analyzed using binary forward stepwise logistic regression. Only cannabis use at admission and VLNTX use during methadone detoxification added significance to the model (Table 1). In particular, patients who used cannabis and received NTX daily during methadone taper were 25 and 7 times less likely to use cannabis respectively at Day 1 and 7, compared to those who received methadone alone (Wald χ^2). VLNTX treatment was a stronger predictor of non-use of cannabis than was non-using cannabis at admission (Table 1).

Discussion

The proportion of patients who smoked cannabis following detoxification was significantly lower among those receiving VLNTX in addition to methadone taper. Cannabis use after discharge from inpatient detoxification was clinically significant in this sample because it was associated with increased opioid use and reduced engagement in outpatient treatment. These associations were not influenced by differences in socio-demographic and drug use characteristics.

Several factors may explain the effects of VLNTX treatment on cannabis use. Increased cannabis use was associated with more severe opioid withdrawal and craving at discharge. Cannabinoids attenuate the sympathetic hyperactivity associated with opioid withdrawal,[8]

and opioid addicts may have attempted to mitigate withdrawal by using cannabis.[2,9] Activation of the cannabinoid CB1 receptor facilitates the reinforcing effects of opioids.[10] Thus, reduced cannabis use could promote abstinence from opioids. Conversely, opioid receptor activity may influence reduced cannabis use. It has been suggested that agonist action at the μ-opioid receptor increases cannabis reward and seeking behavior.[11] NTX reduces the reinforcing effects of cannabis in non-human experiments[12] However, 50 mg NTX enhances subjective and reinforcing effects of cannabis in chronic users.[13], although a lower dose of naltrexone (12 mg) blunts these effects.[4] Thus, addition of VLNTX during detoxification may indirectly reduce cannabis use by reducing μ-opioid receptor activity, thereby reducing cannabis reward. There are indications that VLNTX may also act directly at the cannabinoid receptor. In preclinical studies, VLNTX increases analgesic and anticonvulsant effects of cannabis by acting at the CB1 receptor,[14,15] similar to effects observed with the CB1 receptor antagonist rimonabant.[16]

This study has several limitations. Cannabis use was not taken into account in the prospective randomization of subjects. It is possible that the association between VLNTX administration and reduced use of cannabis is accounted for by unmeasured confounds, although this likelihood is reduced by the randomized assignment to treatment groups. Confounding by socio-demographic, drug use, or treatment variables is unlikely because cannabis users and non-users did not significantly differ in such characteristics. Another potential confounder is the high attrition rate observed during the study, which could have led to selection bias. Such bias is unlikely because the patients lost to follow-up did not differ significantly in socio-demographic characteristics or drug use history from those who participated in this follow-up study. We also limited the sensitivity of our analyses by dichotomizing cannabis use as present or absent. However, this approach does not detract from the validity of the results.

In spite of these limitations, this study supports the validity of our earlier findings, the first to show that opioid manipulation significantly reduced cannabis use in a clinical setting. Further investigations are needed to confirm the efficacy of VLNTX in reducing secondary cannabis use, improving the outcome of outpatient treatment, and as possible treatment for primary cannabis abuse and dependence.

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Table 1

Binary forward stepwise logistic regression model of variables predicting no

VARIABLE	W (df)	O.R.	95% C.I.	LR (df)	P
Day 1 follow-up (N=96)					
Negative urine for cannabis at admission	4.7 (1)	4.4	4–14.5	10.6 (1)	0.03
VLNTX addition to detoxification	25.6 (1)	20.4	12.8–28.1	34.8 (2)	0.001
Day 7 follow-up (N=61)					
Negative urine for cannabis at admission	4.3 (1)	4.7	1.1–11.7	12.2 (1)	0.02
NTX 0.250 mg addition to detoxification	7.6 (1)	9.8	4.1–12.3	19.2 (1)	0.001

cannabis use after discharge from inpatient opioid detoxification

W = Wald χ^2, df = degrees of freedom, O.R. = odds ratio, C.I. = confidence interval, LR = likelihood ratio of significance of the model, VLNTX = very low dose naltrexone