JOBNAME: joa 38#1 2005 PAGE: 1 OUTPUT: Thu December 2 15:41:42 2004
lww/joa/91064/V8672R1

Marijuana Use and Its Association With Adherence to Antiretroviral Therapy Among HIV-Infected Persons With Moderate to Severe Nausea

Bouke C. de Jong, MD, Diane Prentiss, MA, MPH,† Willi McFarland, MD, PhD,‡ Rhoderick Machekano, MPH,† and Dennis M. Israelski, MD*†*

Background: Adherence to antiretroviral therapy (ART) is essential to successful treatment of HIV infection. Two recent studies reported a negative correlation between marijuana use and adherence to ART. Some patients, however, report that smoking marijuana improves adherence to ART. This study therefore sought to identify which subgroups of patients may have differential adherence to ART in association with recent marijuana use.

Methods: Cross-sectional survey design within a public health care system for HIV/AIDS.

Results: With a 5% refusal rate, 252 patients completed the interview, 175 (69%) were on ART, and 168 (67%) provided ART adherence data. Forty-one subjects (24%), predominantly whites, used marijuana. In bivariate analysis, no association between ART adherence and marijuana use was found (odds ratio [OR] = 0.92, 95% CI = 0.4–1.9). Adherence was positively associated with undetectable plasma virus and negatively associated with alcohol and other illicit drug use. Examining subgroups of patients, among those with nausea, marijuana users were more likely to show an association with adherence than nonusers (OR = 3.3), while among those without nausea, marijuana use was lower associated with adherence (OR = 0.52, *P* for homogeneity 0.02). This relationship was confirmed in multivariate analyses controlling for the interactions between nausea and marijuana use, in which other illicit drug use remained a factor related to nonadherence.

Discussion: These data suggest that medicinal use of marijuana may facilitate, rather than impede, ART adherence for patients with nausea, in contrast to the use of other illicit substances, which were associated with lower rates of ART adherence. To demonstrate any causal relationship between marijuana and adherence would require a longitudinal or controlled study.

Received for publication February 20, 2004; accepted August 10, 2004.
Supported by grant #TW 06083-01 from the National Institutes of Health (NIH) (BdJ), a research grant from the San Mateo County Board of Supervisors, and additional support from the AIDS Research fund of the San Mateo Medical Center Foundation.
From the *Division of Infectious Diseases, Stanford University School of Medicine, Stanford, CA; †Clinical Trials and Research, San Mateo Medical Center, San Mateo, CA; and ‡San Francisco Department of Public Health, San Francisco, CA.
Reprints: Diane Prentiss, Research and Trials Unit, San Mateo Medical Center, 222 W. 39th Ave., San Mateo, CA 94403 (e-mail: dprentiss@co.sanmateo.ca.us).

Key Words: marijuana, cannabis, adherence, antiretroviral therapy, highly active antiretroviral therapy, nausea, appetite

(*J Acquir Immune Defic Syndr* 2005;38:43–46)

Marijuana has been smoked for its medicinal properties for centuries. The main active component, tetrahydrocannabinol (THC), in the form of dronabinol, is approved for treating chemotherapy-associated nausea and emesis as well as AIDS wasting.[1] In addition to use for appetite stimulation, HIV-infected patients use marijuana to counter antiretroviral (ART)-related nausea. Despite the efficacy of THC in relieving symptoms,[2] several reservations about the use of marijuana remain.

Concern that treatment with cannabinoids could negatively affect HIV suppression through immune modulation or interactions with protease inhibitors was addressed in a recent study. Patients on ART were randomly assigned to smoke marijuana or ingest dronabinol or placebo pills 3 times daily in a directly observed environment of an inpatient research center.[3] In this setting both smoked marijuana and dronabinol were demonstrated to be safe and, more specifically, were not associated with increased numbers of copies of HIV in plasma or decreased CD4 counts over a 21-day period.

Another concern is the potential for decreased adherence to ART medications due to the psychoactive effects of marijuana. Adherence to medications is a challenge to any chronically ill patient and is critically important to HIV-infected individuals, as sustained high levels of adherence are required for long-term viral suppression.[4,5] Excellent adherence to ART medication (often defined as >95% of medication taken) is related to having a suppressed viral load, increased CD4 response, slower disease progression, lower rates of hospital admission, and prolonged survival.[6,7] Concerted efforts have identified several barriers to adherence. Depression, severity of side effects, and levels of social support,[8] as well as knowledge levels about regimen dosing,[9] distinguish patients with good and poor adherence. In addition, substance abuse can lower adherence, and several studies have demonstrated adverse effects of active injection drug use, including heroin, cocaine and speed, on adherence to ART.[10,11] In contrast to active injection drug users, former substance abusers appear to have rates of adherence to ART similar to patients with no history of substance abuse.[11] Less is

JOBNAME: joa 38#1 2005 PAGE: 2 OUTPUT: Thu December 2 15:41:43 2004
lww/joa/91064/V8672R1

known about the effects of marijuana on adherence, although 2 recent studies found similar negative association between marijuana use and adherence to ART.[12,13]

In contrast, observations from previous work in this population suggest that patients who use marijuana do so for several different reasons, including relief from symptoms of nausea associated with ART.[14] Since the reason for marijuana use may influence its effect on adherence, we examined the relationship between marijuana and adherence to ART in subgroups of patients with nausea and other clinical characteristics.

METHODS

Study personnel recruited eligible subjects through consecutive sampling procedures at 3 public health clinics and a satellite office of the San Mateo County AIDS Program in Northern California, during a 6-month period in 2001, as reported elsewhere.[14]

Assessments of adherence to ART have varied widely in the scientific literature. Self-report measures recall time frames as brief as 24 hours and as long as 30 days.[11,13,15–18] No consensus existed during the design phase of this study regarding best definitions of adherence. The questionnaires used here included ART regimen data and self-report of adherence in the 4 weeks preceding the interview, asked as both the number of the last 28 days on which all medications were taken, and duration since the last missed dose. These measures were highly correlated. Since patient recall beyond 1 week could be problematic for some patients, the 7-day time frame was deemed appropriate, available, and showed precedent in the literature.[13,16,17,19] Those who reported $\geq$1 missed doses in the previous 7 days were classified as "nonadherent," and those who missed no doses in the previous week were labeled "adherent" to ART.

To assess symptoms of nausea, participants were directed to rate severity for the previous 4 weeks. Any patient whose history included a mental health diagnosis or prescribed psychiatric medications, as extracted from the medical record, was classified for the purpose of this analysis as having a history of mental distress. The Descriptor Differential Scale was adapted for self-assessment of participants' physical pain.[20]

The questionnaire assessed use of marijuana in the participant's lifetime and in the 4 weeks preceding the interview. Marijuana use in the last 4 weeks was further evaluated for frequency, reasons for use, and perceived benefit. Other illicit drug use in the past month was determined by specifically asking about cocaine, heroin, amphetamines, hallucinogens, and club drugs and reasons for their use. For the purpose of this analysis, we combined heroin, cocaine, and amphetamine use as "other illicit drugs."

Bivariate analyses on adherence included estimates of prevalence, odds ratios (ORs), and 95% CIs. We then performed stratified analyses of the relationship between adherence and marijuana use using the Mantel-Haenszel equation. Stratified analyses specifically examined the association of marijuana use with ART adherence among subjects who reported nausea and among subjects who did not report nausea. The interaction terms found in the latter analysis were included with other independent variables in a multivariate logistic regression model. Subjects with missing data on adherence were excluded from the analysis. The independent variables associated with adherence at $P < 0.20$ were tested in the multivariate model. Models were evaluated using a backward stepwise regression strategy. Variables were eliminated from the model if they did not achieve a significance level <0.05. Interaction terms between all clinical variables and marijuana were tested for significance and retained in the model if $P < 0.05$. Independent variables with $P > 0.20$ on bivariate analysis were later added to the final model and tested for significance ($P < 0.05$). We used Stata version 8 for all analyses. P values were 2-tailed.

RESULTS

With a 5% refusal rate, 252 patients completed the interview, 175 (69%) were on ART for at least 2 months, and 168 (67%) provided ART adherence data. Forty-one subjects (24%), predominantly whites, used marijuana (Table 1) in the previous month.

Nonadherent participants (n = 55) represented one-third of the sample. In bivariate analysis, no overall positive or negative association between ART adherence and marijuana use was found (OR = 0.92, 95% CI = 0.4–1.9) (Table 2). In addition, no dose-response relationship was evident when marijuana use was analyzed by frequency of use. Adherence was positively associated with undetectable plasma virus and

TABLE 1. Patient Demographics, Rates of Drug Use, and Treatment Characteristics

	n (%) (n = 168)
Age (median)	43
Gender (% male)	128 (76)
Ethnicity	
African American	50 (30)
Hispanic	48 (29)
White	58 (35)
Other	12 (7.1)
Marijuana use ever	134 (80)
Marijuana use in last month	41 (24)
Once or twice/month	12 (29)
A few times/month	9 (22)
A few times/week	4 (9.8)
Almost every day	6 (15)
Every day	10 (24)
Other illicit drug use, in last month	15 (8.9)
Alcohol use, in last month	79 (47)
Heavy use	11 (14)
AIDS (any of last 3 CD4 <200)	48 (29)
VL ND (last VL ≤50)	79 (47)
On PI	93 (55)
On NNRTI	118 (70)

ND, nondetectable; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; VL, viral load.

TABLE 2. Variables Associated With Highly Active Antiretroviral Adherence From Fitting a Bivariate and Multivariable Logistic Regression Model

Variable	Adherent n (%) n = 113	Nonadherent n (%) n = 55	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Age >44 y	43 (38)	27 (49)	0.64 (0.33–1.3)	0.17	—	—
Ethnicity						
White	42 (40)	16 (32)	1		—	—
African-American	31 (29)	19 (38)	0.62 (0.28–1.4)	0.25	—	—
Hispanic	33 (31)	15 (30)	0.84 (0.36–1.9)	0.68	—	—
Substance use, in last month						
Marijuana in last month	27 (24)	14 (25)	0.92 (0.44–1.9)	0.83	0.59 (0.22–1.6)	0.30
Frequency of use						
None			1		—	—
1–2× month	8 (7)	4 (7)	0.95 (0.27–3.3)	0.94	—	—
A few times/month	4 (4)	5 (9)	0.38 (0.097–1.5)	0.17	—	—
A few times/week	3 (3)	1 (2)	1.4 (0.14–14)	0.76	—	—
Almost every day	3 (3)	3 (5)	0.48 (0.092–2.5)	0.38	—	—
Every day	9 (8)	1 (2)	4.3 (0.53–35)	0.17	—	—
Other illicit drugs	6 (5)	9 (16)	0.29 (0.10–0.85)	0.025	0.27 (0.089–0.83)	0.022
Alcohol	47 (42)	32 (58)	0.51 (0.27–0.98)	0.045	—	—
Symptoms						
Nausea	26 (23)	17 (31)	0.67 (0.33–1.4)	0.27	0.33 (0.13–0.84)	0.020
Pain	35 (31)	15 (27)	1.2 (0.59–2.4)	0.62	—	—
HIV-related						
AIDS	35/99 (35)	13/51 (25)	1.6 (0.75–3.4)	0.22	—	—
VL < 50	58/98 (59)	21/50 (42)	2.0 (1.0–4.0)	0.049	—	—
Other						
Mental distress	66 (58)	23 (42)	1.95 (1.0–2.8)	0.045	—	—
Low QOL	44/109 (40)	24/53 (45)	0.82 (0.42–1.6)	0.55	—	—
Interaction term marijuana-nausea					6.2 (1.2–33)	0.030

QOL, quality of life; VL, viral load.

having had mental distress about one's health and negatively associated with recent use of other illicit drugs and with alcohol. In bivariate analysis there was no association between adherence and gender, age, ethnicity, low quality of life, pain, or use of protease inhibitors or nonnucleoside reverse transcriptase inhibitors.

Analysis of subgroups of patients by symptoms revealed that among those with moderate to severe nausea (n = 43), marijuana users were more likely to be adherent (n = 20, 75% adherent) (OR = 3.3, $P = 0.07$), compared with those who did not smoke marijuana (n = 23, 48% adherent). In contrast, among those with mild or no nausea at all (n = 125), marijuana users (n = 21, 57% adherent) were less likely to be adherent than nonusers (n = 104, 72% adherent) without nausea (OR = 0.52, 95% CI = 0.19–1.36, P for homogeneity 0.02).

The relationship between marijuana use and adherence, stratified by nausea, was confirmed in multivariate analysis that controlled for the interaction between nausea and marijuana use (Table 2). Other illicit drug use remained a predictor of nonadherence in this analysis.

DISCUSSION

No crude association was found between marijuana use and adherence, and no dose-response relationship was evident when marijuana use was analyzed in terms of frequency of use. Our data do suggest that use of smoked marijuana specifically for amelioration of nausea may be associated with adherence to ART among patients with HIV/AIDS. In addition, our data confirm previously reported findings that use of other illicit drugs is associated with lower rates of adherence to ART among patients with HIV/AIDS.

The cross-sectional nature of this study precludes assumptions of causality. The selection of patients from waiting rooms might have introduced selection bias, as patients who are nonadherent with their physician visits, and patients seen infrequently because of their excellent response to therapy, were potentially undersampled, although the high rate of respondents and the 6-month interval of study would minimize this likelihood. We used self-reported data on adherence, which is known to overestimate true adherence due to patient bias.[21] However, self-reported adherence in the past few days to 1 week is a commonly used measure,[22,23] and no gold standard for measuring adherence was available at the outset of this study.[11,15,16] The fact that we found a relationship between adherence and having an undetectable viral load on bivariate analysis validates to some degree our measurement of adherence. Our racially balanced patient sample might enhance the generalizability of our findings to other populations, although use of marijuana was very low among Hispanics.

Use of marijuana for medicinal purposes remains controversial, and we do not here advocate its widespread use. Our observations do suggest, however, that in certain circumstances, specifically when patients are using marijuana to relieve nausea, marijuana is not associated with lower rates of adherence.

More conclusive assessments of the salutary effect of combustible and noncombustible cannabinoids on adherence await controlled longitudinal studies and randomized clinical trials.

ACKNOWLEDGMENTS

The authors thank the Board of Supervisors and people of San Mateo County, CA. The authors also thank Ms. G. Tsuang and Dr. S. Morrow for their input on study design and K. Peterson, MD, for expert review of the manuscript. Special thanks are extended to M. Nevin and J. Maltbie from San Mateo County Government for their championship of these studies.

REFERENCES

1. Robson P. Therapeutic aspects of cannabis and cannabinoids. *Br J Psychiatry*. 2001;178:107–115.
2. Beal JE, Olson R, Lefkowitz L, et al. Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. *J Pain Symptom Manage*. 1997;14:7–14.
3. Abrams DI, Hilton JF, Leiser RJ, et al. Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial. *Ann Intern Med*. 2003;139:258–266.
4. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med*. 2000;133:21–30.
5. Sethi AK, Celentano DD, Gange SJ, et al. Association between adherence to antiretroviral therapy and human immunodeficiency virus drug resistance. *Clin Infect Dis*. 2003;37:1112–1118.
6. Bangsberg DR, Hecht FM, Charlebois ED, et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *AIDS*. 2000;14:357–366.
7. Chesney M. Adherence to HAART regimens. *AIDS Patient Care STDS*. 2003;17:169–177.
8. Catz SL, Kelly JA, Bogart LM, et al. Patterns, correlates, and barriers to medication adherence among persons prescribed new treatments for HIV disease. *Health Psychol*. 2000;19:124–133.
9. Miller LG, Liu H, Hays RD, et al. Knowledge of antiretroviral regimen dosing and adherence: a longitudinal study. *Clin Infect Dis*. 2003;36:514–518.
10. Gebo KA, Keruly J, Moore RD. Association of social stress, illicit drug use, and health beliefs with nonadherence to antiretroviral therapy. *J Gen Intern Med*. 2003;18:104–111.
11. Stone VE. Strategies for optimizing adherence to highly active antiretroviral therapy: lessons from research and clinical practice. *Clin Infect Dis*. 2001;33:865–872.
12. Tucker JS, Burnam MA, Sherbourne CD, et al. Substance use and mental health correlates of nonadherence to antiretroviral medications in a sample of patients with human immunodeficiency virus infection. *Am J Med*. 2003;114:573–580.
13. Kalichman SC, Rompa D. HIV treatment adherence and unprotected sex practices in people receiving antiretroviral therapy. *Sex Transm Infect*. 2003;79:59–61.
14. Prentiss D, Power R, Balmas G, et al. Patterns of marijuana use among patients with HIV/AIDS followed in a public health care setting. *J Acquir Immune Defic Syndr*. 2004;35:38–45.
15. Turner BJ. Adherence to antiretroviral therapy by human immunodeficiency virus-infected patients. *J Infect Dis*. 2002;185(Suppl 2):S143–S151.
16. Liu H, Golin CE, Miller LG, et al. A comparison study of multiple measures of adherence to HIV protease inhibitors. *Ann Intern Med*. 2001; 134:968–977.
17. Cook RL, Sereika SM, Hunt SC, et al. Problem drinking and medication adherence among persons with HIV infection. *J Gen Intern Med*. 2001; 16:83–88.
18. Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). *AIDS Care*. 2000;12:255–266.
19. Gifford AL, Bormann JE, Shively MJ, et al. Predictors of self-reported adherence and plasma HIV concentrations in patients on multidrug antiretroviral regimens. *J Acquir Immune Defic Syndr*. 2000;23:386–395.
20. Gracely RH, Kwilosz DM. The Descriptor Differential Scale: applying psychophysical principles to clinical pain assessment. *Pain*. 1988;35:279–288.
21. Wagner GJ, Rabkin JG. Measuring medication adherence: are missed doses reported more accurately then perfect adherence? *AIDS Care*. 2000;12:405–408.
22. Kleeberger CA, Buechner J, Palella F, et al. Changes in adherence to highly active antiretroviral therapy medications in the Multicenter AIDS Cohort Study. *AIDS*. 2004;18:683–688.
23. Johnson MO, Catz SL, Remien RH, et al. Theory-guided, empirically supported avenues for intervention on HIV medication nonadherence: findings from the Healthy Living Project. *AIDS Patient Care STDS*. 2003;17:645–656.

