

Observational Study

Marijuana Correlates with Use of Other Illicit Drugs in a Pain Patient Population

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Background: A significant number of chronic pain patients may use marijuana. Physicians treating those patients can benefit by knowing whether their patients using marijuana are at higher risk for using other illicit drugs such as cocaine and/or methamphetamine.

Objective: Our objective was to determine whether marijuana-using chronic pain patients have a higher incidence of cocaine and/or methamphetamine use.

Study Design: A retrospective study of the incidence of pain patients using marijuana and/or other illicit drugs such as methamphetamine and cocaine versus the incidence of pain patients not using marijuana but using methamphetamine and/or cocaine.

Methods: Urine specimens from chronic pain patients were analyzed by LC-MS/MS to determine the co-occurrence of these abused substances.

Results: In this study 21,746 urine specimens were obtained from chronic pain patients. We found a 13.0% incidence of patients positive for the acid form of Tetrahydrocannabinol (THCA). The percentage of those positive for cocaine was 4.6%, those positive for methamphetamine totaled 1.07%. Using both chi-square and a Logistic Regression analysis, we determined that there was a correlation between marijuana use and the use of other illicit drugs. The odds ratio was > 3.7 for other illicit drug use.

Limitations: The study is limited in that we obtained no data as to the causal relationships of this type of drug use.

Conclusions: Pain physicians should be aware that this relationship exists and marijuana-using patients are at greater risk for use of other illicit drugs although no causal relationship is implied. Increased monitoring of these patients may help minimize potential morbidity due to drug interactions as well as identify patients who may be diverting prescriptions in order to pay for illicit drugs.

Key words: Marijuana, Tetrahydrocannabinol (THCA), Cocaine, Methamphetamine, Pain patients, correlation study

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In randomized placebo clinical trials, synthetic cannabinoids have been shown to be effective in reducing pain, and patients perceive it improves their well being and helps with sleep (1-6). It is also associated with numerous deleterious effects, with

marijuana being described as a gateway for drug abuse (7-22). Up to 19% of the chronic pain patient population uses cannabinoids (7).

Manchikanti et al (7-14) have established that the use of marijuana and more powerful and dangerous

illicit drugs is common in this population. This has been verified by reports from independent laboratories serving this population (23-25). Cocaine has many deleterious effects on the heart (26-28). Chronic use of methamphetamine can result in powerful negative effects as well (29). These include extremely violent behavior, anxiety, confusion, and insomnia. Elements of psychosis including intense paranoia, visual and auditory hallucinations, mood disturbances, and delusions are common as well. Additionally, long-term use can affect the central and peripheral nervous systems, and can cause liver and brain damage, blood clots, heart failure, stroke, and other undesired complications (26-31).

Patients using illicit drugs in conjunction with prescribed opioids are at risk for reactions from the illicit drugs themselves as well as from drug-drug interactions. Doctors treating these patients are not only motivated to identify patients using illicit drugs because of potential health risks, they are required to monitor those patients to establish compliance and determine if those patients are at risk for diversion and use of illicit drugs (7-14,24,32,33). As the National Drug Intelligence Center (NDIC) states in its 2009 report on the drug threat assessment, "...abusers of Schedule II controlled prescription drugs usually acquire the drugs through traditional diversion methods such as prescription fraud and doctor-shopping" (32).

Having established the value and necessity in determining which pain patients are using illicit drugs, traditional Substance Abuse and Mental Health Services Administration (SAMHSA) cutoffs established in the 1980s for detection of illicit drug use in truck drivers and other Department of Transportation populations did not capture all of the drug users (23-25). Testing by Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) utilizes lower cutoffs than by traditional immunoassay methods, thereby providing a more vivid picture of the drug use of this population. These analyses can be used to test the hypothesis that there is a correlation between Tetrahydrocannabinol (THCA), cocaine, and methamphetamine use.

MATERIALS AND METHODS

This human research was approved by the Aspire IRB, 9320 Fuerte Dr. Suite 105, La Mesa, CA, 91941. All data was collected at the San Diego facility that houses Millennium Laboratories and Millennium Laboratories Research Institute. Physicians in their office practices initiated the test requests and collected the urine specimens for this study. Most physicians conducted initial

drug screens using point-of-care devices. These results were used to select the test menu for the additional screening and confirmation testing performed at Millennium Laboratories. As this study was retrospective in nature, treatment of patients was not affected. No outside funding was provided for this study.

The cohort was comprised of 21,746 patients treated with opioids for chronic pain. No exclusion criteria were used in the selection of these patients. The patients selected for testing were part of the usual practices of the treating physicians. It was not known whether patients were on long- or short-acting opioids. Nor was it known whether patients were taking methadone or buprenorphine for opioid dependence. The urine specimens from these pain patients were tested for the listed drugs and metabolites (Table 1) according to methods developed at Millennium Laboratories. Drugs were scored as present or absent using the Table 1-listed nominal cutoffs. These scores were generated in silico and there was no operator interpretation. This was a retrospective study, and the reference standard was the LC-MS/MS determination of the presence of the drug or its metabolite.

The LC-MS/MS procedures were performed on Agilent 6410 instruments (Agilent Corporation, 5301 Stevens Creek Blvd, Santa Clara CA 95051, USA). The method was that described by Moshin and Yang (34). The LC-MS/MS cutoffs are the lower limit of quantitation of the investigators' procedure and are listed in Table 1. The accuracy of the LC-MS/MS determinations is $\pm 20\%$ of the target value as determined by proficiency testing data. Data were retrieved from Millennium's LIMS system onto an Excel spreadsheet.

An Agilent 1200 series binary pump SL LC system, well plate sampler, thermostatted column compartment, paired with an Agilent 6410 QQQ mass spectrometer and Agilent Mass Hunter software was used for analysis of all drugs. The method used an acetonitrile-aqueous formic acid gradient running at 0.4 mL/min. A 2.1 x 50 mm, 1.8 mm Zorbax SB C 18 column was used for chromatography. The column temperature was 50°C. Mobile phase A = 0.1% formic acid in water, B = 0.1% formic acid in acetonitrile. The Agilent 6410 Triple Quadrupole mass spectrometer (QQQ) was used in the positive ESI mode. The nitrogen drying gas temperature was 350°C, and the flow was 12 L/min, nebulizer gas (nitrogen) 40 psi, and the capillary voltage was 3000V. Dwell times were 50 msec. High performance liquid chromatography (HPLC) water, acetonitrile, methanol, and formic acid HPLC grade were obtained from VWR Westchester, PA.

Calibrators 100mg/mL and deuterated internal standards 100mg/mL in methanol were obtained from Cerrilant Corp (Round Rock, Texas). The deuterated internal standards were diluted to 1000 ng/mL by adding them to synthetic urine (Microgenics Corp Fremont CA).

Samples were prepared for injection by incubating with 25 µL of urine with 50 units of b-Glucuronidase Type L-II from *Patella vulgata* (keyhole limpet) Sigma Product number G 8132 (Sigma-Aldrich Corp 3050 Spruce Street, St. Louis, MO 63103) in 50µL 0.4M pH 4.5 acetate buffer for 3 hours at 45°C. Five microliters of sample were injected.

Statistical analysis was conducted using a chi-square test for a 2 X 2 contingency table. Where a patient's result was negative for amphetamine or cocaine, that patient entry was deleted in the analysis. This accounts for the discrepancy between the total number of positives and the pairs in the chi-square and regression analyses. The software used for the analyses was SAS Version 9.1, SAS Institute Inc., Cary, NC.

RESULTS

Table 1 describes the analytical cutoffs and the number of positive results for the 3 analytes, benzoylecgonine, methamphetamine, and THCA. The null hypothesis is that the 2 variables, testing positive or negative for THCA and testing positive or negative for the other

drugs, are independent. This hypothesis was rejected; thus, the 2 variables are related/dependent.

The values for the chi-square analysis are presented in Table 2.

Pos THCA is defined as positive for THCA at values > 20 ng/mL. Pos for illicit is defined as positive for any one of the 2 illicit drugs (Cocaine, Methamphetamine). Patients may be positive for more than one illicit drug.

The chi-square analysis (*P* value <.0001) shows there is a relationship between positive THCA and other illicit drug use. Of the 1,007 patients positive for illicit, 30% were also taking marijuana. Of all the people taking marijuana (32,34), 86% were not taking cocaine or methamphetamines. However, by our calculation 4.6% of the cohort in this study were using one or both of those drugs.

Of the people using marijuana, 13.7% were taking cocaine or methamphetamine, whereas only 4.6% of the population as a whole were taking those illicit drugs. Another statistical analysis was performed using Logistic Regression (Response = Positive for Other Drug [Cocaine or Methamphetamine]).

The Odds Ratio (OR) Point Estimate is 4.261 with a confidence limit of 3.696 to 4.913. The *P* Value for this calculation was <.0001. Thus, we are 97.5% confident that the OR for using other drugs is > 3.7 for those individuals positive for THCA versus those negative for THCA.

Table 1. Analytical cutoffs used to establish positive testing for illicit drugs

| Cutoff (ng/mL) | Drug | Number of Positives | Percent Positive of Total Specimens |
|----------------|--|---------------------|-------------------------------------|
| 50 | Cocaine (Benzoylecgonine) | 1011 | 4.6 |
| 100 | Methamphetamine | 234 | 1.07 |
| 20 | THCA (Δ-9-tetrahydrocannabinolic acid) | 2834 | 13.0 |

Table 2. Values for Chi-Square Analysis

| | | |
|--------------------------------|-----------------------------------|-----------------|
| Pos THCA and Pos Illicit = 305 | Pos THCA and Neg Illicit = 1919 | Total 2224 |
| Neg THCA and Pos Illicit = 702 | Neg THCA and Neg Illicit = 18,820 | Total 19,522 |
| Total = 1007 | Total = 20739 | Total 21,746 |

Pos THCA is defined as positive for THCA at values > 20 ng/mL. Pos for illicit is defined as positive for any one of the 2 illicit drugs (Cocaine, Methamphetamine). Patients may be positive for more than one illicit drug.

DISCUSSION

Many chronic pain patients seek relief from their symptoms by going to pain physicians. However, studies show that this group also seeks other ways to alleviate their symptoms. This is manifested by their use of illicit drugs including marijuana, which, as cited above, has some effect on relieving pain.

Marijuana use is common in this population. While recognizing that marijuana does have certain pain relief benefits, other motives for using it should not be ignored. The confounding issue is that use of other illicit drugs also occurs in this population, and pain physicians should have clear concern about potential morbidity and mortality resulting from concomitant use of those illicit drugs and prescribed opioids.

The suggested practice guidelines indicate that drug testing is an essential component of the care of chronic pain patient opioid therapy (15,18). Treating physicians often rely on patient self-reports and it has been shown that a significant proportion of pain patients regularly obfuscate the truth in their self-reports which can confound physicians who have to make important treatment decisions. Earlier reports indicate that marijuana use often precedes the use of other illegal drugs (33,35) That having been said, although it is understandable in today's more relaxed climate regarding the use of marijuana (punishment for which can be a simple ticket) that patients would be more likely to report to their physician that they are taking that drug than cocaine or methamphetamine, reporting marijuana use would likely result in their being denied health insurance (36). This means that patients are unlikely to

report use of this drug, and physicians are unlikely to test for this drug.

However, since this study shows that there is roughly a 4-fold incidence of the use of cocaine and methamphetamine among marijuana users in this population, and these drugs can have grave health consequences when used in combination with prescribed opioids, physicians prescribing opioids should strongly consider testing patients for marijuana and other illicit. On a side note, it is reasonable to assume that at least some of the prescribed opioid medications may be diverted in order to pay for these illicit drugs. This is further reason for monitoring these patients.

CONCLUSIONS

Based on the large cohort used in this study, it can be extrapolated that a significant number of pain patients take marijuana (13%). Using a logistic regression analysis, the odds ratio is 4-fold greater for patients using marijuana to also use methamphetamine or cocaine. It is important to note that the present authors do not purport that there is a causal relationship between the use of marijuana and the use of other illicit drugs, only that a significant co-morbidity exists.

Physicians treating patients for chronic pain may be well advised to screen for marijuana or follow more closely those patients they know are using marijuana.

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