MARIJUANA USE AND THE RISK OF NEW ONSET SEIZURES*

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INTRODUCTION

Marijuana is the most widely used illicit drug in the United States (1). Animal and human studies of its effects on seizures have been conflicting (2, 3). To determine if marijuana is a risk factor for new onset seizures, we conducted a case control study at Harlem Hospital Center in New York City.

METHODS

Cases consisted of 308 patients over 15 years of age admitted with new onset seizures between December 1981 and February 1984. Childhood febrile seizures were not counted as previous seizures, and we included as new onset seizures those occurring within the previous 12 months but never evaluated medically. Seizures were classified as generalized (n = 193), partial (n = 89), or unclassified (n = 26) and by antecedents as either provoked (n = 81) or unprovoked (n = 227). Provoked seizures were those associated with acute metabolic derangements, stroke within 7 days of seizure onset, CNS infection, brain tumor, intravenous administration of epileptogenic drugs within an hour of the seizure, severe head trauma within 7 days of seizure onset, and body temperature exceeding 40.5 C (Table 1).

Controls were 294 patients admitted for the first time with an acute surgical condition (Table 2). Patients and controls were interviewed using a questionnaire that covered medical and medication history as well as use of alcohol, tobacco, and illicit drugs. Missing data for any variable occurred in less than 4 percent of subjects. For categorical exposure variables a missing entry was classified as unexposed. Statistical analysis included multiple logistic regression to adjust for potential confounders such as age, sex, head trauma, stroke, alcohol, and polydrug abuse.

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TABLE 1
Seizure Type Among Cases (n-308)

Unprovoked	227	
Provoked	81	
Metabolic		17
Acute stroke		29
CNS infection		9
Brain tumor		14
Epileptogenic drugs		5
Acute head trauma		5
Hyperthermia		2

TABLE 2
Admission Diagnoses Among Controls (n = 294)

Acute appendicitis	71
Acute cholecystitis	40
Intestinal obstruction	33
Perianal abscess	29
Hematuria	21
Rectal bleeding	14
Abdominal pain	13
Tonsillitis	10
Epididymitis or testicular torsion	8
Pneumothorax	7
Diverticulitis	5
Miscellaneous	43

RESULTS

Marijuana was the illicit drug most often reported by cases and controls, and among men its use was significantly less for cases than controls (28.9 percent vs. 40.6 percent, $p < 0.05$) (Table 3). Among women a smaller nonsignificant difference existed in the same direction (11.7 percent vs 15.2 percent). Use of other illicit drugs and alcohol was frequent among marijuana users. Frequency and duration of marijuana use was similar among cases and controls: about a third were daily users and two thirds were weekly users; 70 percent had used marijuana for at least 2 years and 50 percent for at least 5 years.

Reported use of marijuana at any time was less among all seizure patients than controls, but the adjusted odds ratio (OR) of 0.66 (95 percent confidence interval (CI) 0.39–1.12) was not statistically significant. Among men with unprovoked seizures, however, marijuana use was significantly less frequent (adjusted OR = 0.42, 95 percent CI 0.22–0.82)—ie marijuana use was protective. This effect was limited to those who had never used heroin. Marijuana use within 90 days of hospitali-

TABLE 3
Percent Illicit Drug Users for Each Sex in Cases and Controls

	Men		Women	
	Cases (n = 197)	Controls (n = 143)	Cases (n = 111)	Controls (n = 151)
Heroin	25.9	16.1	10.8	0.7
Methadone	14.2	11.9	10.8	0.7
Marijuana	28.9	40.6	11.7	15.2
Cocaine	21.3	23.8	12.6	6.6
Phencyclidine	3.6	4.2	0.9	2.0
LSD	1.5	3.5	0.9	0.7
Methaqualone	1.0	2.1	0.9	0
Amphetamine	4.6	6.3	2.7	0

TABLE 4
Adjusted Odds Ratio of Marijuana Use and New Onset Seizures

	Men	Women
	Odds ratio (95% confidence interval)	Odds ratio (95% confidence interval)
Unprovoked seizures		
Marijuana use ever	0.42 (0.22–0.82)	1.09 (0.35–3.40)
Marijuana use within 3 months of admission	0.36 (0.18–0.74)	1.87 (0.56–6.20)
Provoked seizures		
Marijuana use ever	1.03 (0.36–2.89)	0.79 (0.14–4.37)
Marijuana use within 3 months of admission	0.18 (0.04–0.84)	1.08 (0.12–9.79)

zation carried an even lower odds ratio and in non-heroin-using men was protective for both unprovoked and provoked seizures. Among women marijuana use was much less prevalent than among men, and although use was greater among controls than cases, there was no statistically significant protective effect for either use at any time or use within 30 days.

DISCUSSION

The protective effect of marijuana against new onset seizures is particularly striking in that marijuana use was positively correlated with other risk factors such as alcohol and heroin, which would tend to bias toward finding marijuana use a risk factor. Use within 30 days was protective in men for both unprovoked and provoked seizures. The lack of demonstrable protection in women might be attributable to the smaller number of users.

Marijuana contains numerous cannabinoid compounds, and animal studies have demonstrated their different pro- and anticonvulsant properties. In animal studies delta-9-tetrahydrocannabinol (THC), the major psychoactive compound in marijuana, has been either epileptogenic (4–8) or anticonvulsant (9–16) or had no effect on seizures, (13, 14, 17) depending on the species and experimental design. A strain of New Zealand rabbits is uniquely susceptible to seizures induced by THC and other similarly psychoactive cannabinoids (4, 8, 18, 19). THC protected chickens from photic-induced but not pentylenetetrazol (PTZ)-induced seizures (13). In mice THC was anticonvulsant for maximal electroshock seizures but proconvulsant for PTZ- and strychnine-induced seizures (20). In cats THC prevented kindled amygdaloid seizures if given early but not if given after seizures were partially or fully developed (15). In baboons THC blocked established kindled amygdaloid seizures but not photic-induced seizures (15). In genetically seizure-prone gerbils THC was anticonvulsant, but tolerance developed to this effect (16).

Cannabidiol (CBD), a non-psychoactive cannabinoid, has been more consistently anticonvulsant in a variety of experimental settings, (6–9, 21–23) as have some other non-psychoactive cannabinoids (3, 22, 24–26). In studies of transcallosal cortical evoked response in rats and spinal monosynaptic reflexes in cats, low doses of THC enhanced synaptic transmission, whereas higher doses of THC and all doses of CBD caused only depression (7). In rats CBD was anticonvulsant for both maximal electroshock and audiogenic seizures and enhanced the anticonvulsant potency of phenytoin while antagonizing that of ethosuximide, clonazepam, and trimethadione (27). Although CBD and phenytoin are effective against similar types of seizures, electrophysiologic studies suggest they have different mechanisms of action (3). The anticonvulsant effectiveness of *Cannabis indica* resin against maximal electroshock seizures in rats was inhibited by reserpine, and this inhibition was reversed by the serotonin precursor 5-hydroxytryptophan (28).

Marijuana's anticonvulsant properties were noted in the fifteenth century (29), yet few studies have been conducted in humans (2, 30–37). In a single case report marijuana smoking was reported to be necessary for seizure control (2). A New Mexico survey of 42 epileptics under age 30 found that 29% used marijuana; one subject reported that marijuana decreased seizures and another that it "caused" them (35). In another case report intravenous CBD did not alter (and maybe even increased) the electroencephalographic spike and wave abnormalities of a young man with well-controlled "tonic clonic seizures" (36). There has been only one prospectively designed treatment study, a double-blind placebo-controlled trial of patients refractory to other drugs. CBD, given to 8 of the 16 patients, acutely exacerbated electroencephalographic but not

behavioral seizures. After 4 to 5 months, however, 7 of 8 patients receiving CBD were electroencephalographically and behaviorally seizure-free compared to 1 of 8 controls. The only sign of toxicity was somnolence (37).

In conclusion, marijuana is protective against new onset seizures, and this effect is consistent with previous studies in animals and humans. Whatever the mechanisms, these findings imply that among marijuana's cannabinoid compounds are potentially useful anticonvulsant drugs.

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