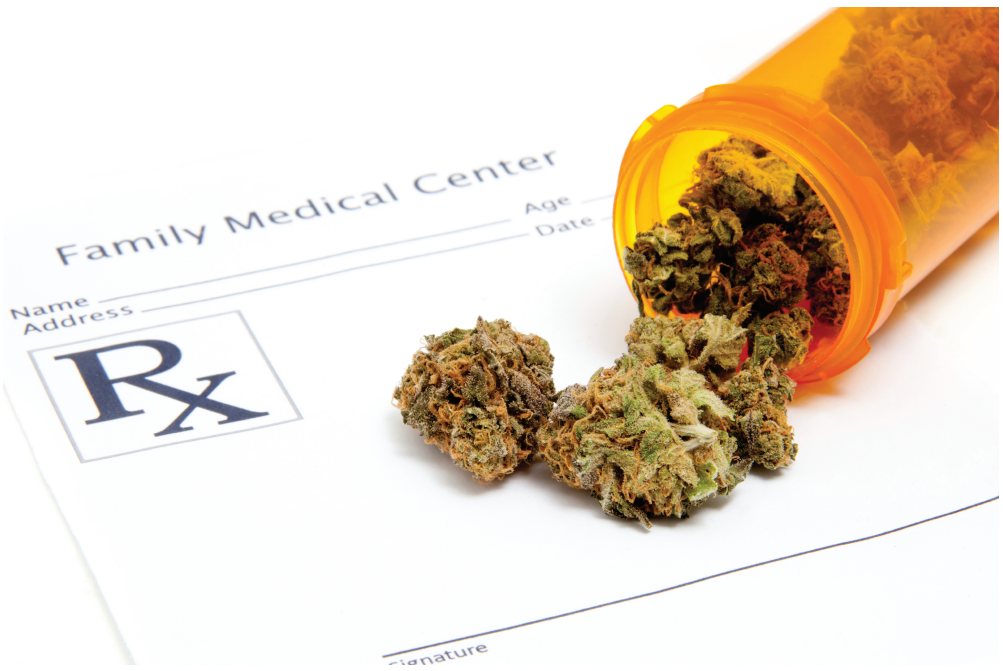
The Interface



Marijuana and Body Weight

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This ongoing column is dedicated to the challenging clinical interface between psychiatry and primary care—two fields that are inexorably linked.

ABSTRACT

Acute marijuana use is classically associated with snacking behavior (colloquially referred to as "the munchies"). In support of these acute appetite-enhancing effects, several authorities report that marijuana may increase body mass index in patients suffering from human immunodeficiency virus and cancer. However, for these medical conditions, while appetite may be stimulated, some studies indicate that weight gain is not always clinically meaningful. In addition, in a study of cancer patients in which weight gain did occur, it was less than the comparator drug (megestrol). However, data generally suggest that acute marijuana use stimulates appetite, and that marijuana use may stimulate appetite in low-weight individuals. As for large epidemiological studies in the general population, findings consistently indicate that users of marijuana tend to have lower body mass indices than nonusers. While paradoxical and somewhat perplexing, these findings may be explained by various study confounds, such as potential differences between acute versus chronic marijuana use; the tendency for marijuana use to be associated with other types of drug use; and/or the possible competition between food and drugs for the same reward sites in the brain. Likewise, perhaps the effects of marijuana are a function of initial weight status—i.e., maybe marijuana is a metabolic regulatory substance that increases body weight in low-weight individuals but not in normal-weight or overweight individuals. Only further research will clarify the complex relationships between marijuana and body weight.

KEY WORDS

Body weight, cancer, cannabis, human immunodeficiency virus, marijuana, tetrahydrocannabinol, weight, weight effects

INTRODUCTION

The transitory effects of acute marijuana use on appetite and snacking behavior are well-known and colloquially described as, "the munchies." A humorous cinematic example of this phenomenon is displayed in the 2005 film, "Gettin' Da Munchies." In this film, the protagonist decides to have several friends over for a video-game tournament. However, his plans go awry and, through frustration, he winds up smoking marijuana for the first time, which results in the proverbial munchies. Throughout the remainder of the film, the protagonist is on an eternal and ravenous search for food. But beyond these acute effects on appetite, are there more sustained relationships between the use of marijuana and body weight? In this edition of The Interface, we examine these possible relationships through a review of the literature.

We begin by reviewing the known physiological effects of marijuana on the regulation of appetite and body weight, and then proceed to review the few available empirical studies on this relationship.

THE PHYSIOLOGICAL EFFECTS OF CANNABINOIDS ON APPETITE/ WEIGHT REGULATION

Marijuana and its multiple chemical components (i.e., cannabinoids) as well as substances produced within the body that activate cannabinoid receptors (i.e., endocannabinoids) appear to exert specific influences on the regulation of feeding behavior. In empirical support of this conclusion, Vemuri et al[1] state that the endocannabinoids are important biomediators and metabolic regulators in mammalian physiology, with diverse and ubiquitous modulating actions, including the regulation of body weight. In mammalian organisms, the two most relevant receptors in the endogenous cannabinoid system are the CB_1 and CB_2 receptors, which are located predominantly in the brain and the immune system, respectively.[2] In addition to their foremost locations in the brain (e.g., hypothalamus, limbic forebrain), some CB_1 receptors are located in other areas of the body, including the stomach and intestinal tissue.[3] Agonism of CB_1 receptors is known to stimulate feeding behavior.[3] According to Kirkham,[4] stimulation of the CB_1 receptors in the mammalian cannabinoid system specifically increases food craving and enjoyment, and promotes the deposition of energy as fat into adipose tissues.

In keeping with this paradigm, in recent years, researchers have been examining the effects of antagonizing CB_1 receptors in an effort to *reduce* feeding behavior. Theoretically, the antagonism of this cannabinoid receptor site should result in reduced caloric intake and subsequent weight loss. As anticipated, empirical studies in rats and mice indicate that pharmacological blockade of the CB_1 receptor does indeed result in the inhibition of normal weight gain,[5] reduced feeding behavior,[6] and suppression of food intake and impaired weight gain in both fasted and non-fasted animals.[7]

Because of the observed clinical effects of CB_1 antagonism in animal studies, investigators have been exploring the possible use of CB_1 receptor antagonists for the treatment of weight disorders such as obesity.[8] Unexpectedly, in examining two different CB_1 receptor antagonists, rimonabant in post-marketing trials and taranabant in Phase-III trials, empirical findings among obese European study participants were somewhat clinically disappointing.[2] While participants on these pharmacological treatments did lose weight, they did not experience weight loss beyond that achieved with currently approved anti-obesity medications. In addition, researchers found that the clinical use of rimonabant and taranabant could precipitate adverse and severe psychiatric symptoms, including suicidal ideation.[9,10] However, these two CB_1 antagonists fulfilled the scientific vision that they could cause a reduction in body weight.

Given this preamble, the relationship between marijuana and body weight appears relatively simplistic: stimulation of CB_1 receptors causes weight gain, whereas antagonism of CB_1 receptors causes weight loss. However, some of the findings in studies on marijuana use and body weight are surprising.

ACUTE MARIJUANA USE AND CALORIE INTAKE IN NORMAL INDIVIDUALS

According to a study in normal volunteers, low doses of marijuana (e.g., a single cigarette) have no effect on food intake.[11] However, higher doses of marijuana (e.g., two or three cigarettes) increase daily calorie intake, which is primarily due to increased food intake between meals rather than an increase in meal size.[11] This finding sets the stage for the various studies in patients with human-immunodeficiency virus (HIV) and cancer, which constitute a large percentage of the research in this area. In both clinical venues, marijuana has been purported to stimulate appetite.[12]

MARIJUANA AND BODY WEIGHT IN PATIENTS WITH HIV/AIDS

As for the effects of marijuana among patients with HIV, Haney[13] found in an empirical study that oral and smoked cannabinoids were both effective in increasing food intake. In a study comparing smoked marijuana, dronabinol (an oral medication approved by the United States Food and Drug Administration [FDA] that contains the same active ingredients as marijuana), and placebo, researchers at the University of California found that the two active treatments resulted in more weight gain than placebo in patients with either HIV or acquired immunodeficiency syndrome (AIDS).[14] Specifically, during the study period, participants in the marijuana, dronabinol, and placebo groups gained 3.51kg, 3.18kg, and 1.3kg, respectively. In a study among HIV-positive marijuana smokers, Haney et al[15] reported that both marijuana and dronabinol produced substantial and comparable increases in food intake among participants. Finally, Bedi et al[16] examined HIV-

positive marijuana smokers and found that high-dose dronabinol effectively increased calorie intake, but repeated dosing appeared to result in a tolerance to these effects. Importantly, the sample sizes in most of these studies were small.

MARIJUANA AND BODY WEIGHT IN PATIENTS WITH CANCER

As for cancer patients, in a review of the literature examining studies published between 1975 and 1996, Voth and Schwartz[17] reported that marijuana was promising as a means of treating nausea as well as stimulating appetite. More recent studies, however, indicate modest outcomes. For example, in a six-week study of 243 Swiss patients with cancer-related cachexia, researchers compared the weight-inducing effects of cannabis extract to placebo.[18] An independent review board for this study recommended that the trial be discontinued prematurely after analyzing the results of 156 initial patients, because there were no statistically significant differences between active drug and placebo.

Jatoi et al[19] examined 469 patients with advanced cancer who were randomized to oral megestrol, oral dronabinol, or both agents. Participants taking megestrol gained more weight than participants on dronabinol (11% vs. 3% of baseline weight). In addition, combination treatment offered no further benefit than megestrol, alone.

To put these findings into a risk/benefit perspective, according to Yeh et al,[20] potential clinical challenges with the use of marijuana include euphoria, somnolence, sedation, fatigue, and hallucinations—risks that are particularly problematic for unsteady or confused elderly patients as well as debilitated patients. This, of course, does not address the additional clinical concern regarding the risk of drug diversion with marijuana.

MARIJUANA AND WEIGHT STUDIES IN COMMUNITY SAMPLES

In addition to studies examining the weight effects of marijuana in patients with HIV/AIDS and cancer, there are several large epidemiological studies that have explored relationships between marijuana use and body weight. For example, using data from a 15-year longitudinal study, the Coronary Artery Risk Development in Young Adults (CARDIA) study, researchers examined 3,617 participants, ages 18 to 30 years, who were representative of the underlying populations of black and white individuals living in selected community sites.[21] The researchers compared participants with no prior use of marijuana (2,252; 62%) to those with prior histories of use (1,365; 38%). More extensive use of marijuana was associated with higher daily caloric intake (e.g., 3,365 kcal/day in participants who used marijuana for 1,800 or more days during the 15-year period versus 2,746 kcal/day in non-users), but not with an increase in body mass index.[21]

Le Strat and Le Foll[22] examined data from two large epidemiological studies, the National Epidemiologic Survey on Alcohol and Related Conditions[23] (NESARC; N=41,633) and the National Comorbidity Survey Replication study[24] (NCS-R; N=9,103). The adjusted prevalence rates of obesity in the NESARC and NCS-R among participants reporting no marijuana use were 22.0 percent and 25.3 percent, respectively, whereas the adjusted prevalence rates of obesity among participants using marijuana in the preceding 12 months (at least 3 times per week) was 14.3 percent and 17.2 percent, respectively. The authors concluded that the prevalence of obesity is actually lower in those who use marijuana compared to nonusers.

Smit and Crespo[25] examined data on adults from the Third National Health and Nutrition Examination Survey (Hanes III; N = 10,623), and compared current marijuana users with non-current users. While current marijuana users reported higher calorie intakes than non-current users, body mass index was again lower in current users. Incidentally, among current users, researchers also found higher rates of tobacco use.

Finally, in an 21-year longitudinal follow-up study from Australia, Hayatbakhsh et al[26] studied the relationship between marijuana use and body weight in 2,566 young adults. Like previous investigators, they found a lower prevalence of overweight and obesity among the cohort who used marijuana.

While the preceding findings in large epidemiological studies appear paradoxical (i.e., that marijuana use is associated with a lower rather than a higher body mass index), they seem to be supported by a study of obese rats.[27] In this study, obese and normal-weight rats were injected with cannabis extract over a 28-day period. At the end of the study, the weight increase in the obese group occurred at a slower rate than in the normal-weight group. In other words, the obese rats gained weight more sluggishly.

These community studies clearly challenge the traditional notion that marijuana causes weight gain. What might explain these epidemiological findings beyond potential confounds (e.g., varying dose, frequency, and/or components of marijuana; various exercise levels; co-prescribed

medications; psychiatric comorbidity) and possible nuances in methodologies? First, there could be differences between short-term and chronic marijuana use, with the former resulting in weight gain and the latter not. Second, in individuals who use marijuana, there appear to be higher rates of other substance usage, which may secondarily account for weight findings. For example, Degenhardt et al[28] found that users of marijuana were nearly five times more likely to abuse or be dependent on alcohol and six times more likely to abuse sedatives, stimulants, or opiates. In addition, according to data from the National Comorbidity Survey, 90 percent of participants with cannabis dependence had a lifetime mental disorder, commonly alcohol dependence.[29] In other words, perhaps the use of adjunctive drugs (e.g., stimulants, narcotics) results in depressed appetite and/or weight loss. As a third possibility, Warren et al[30] found a negative relationship between marijuana use and body mass index among women referred for weight management. They concluded that both food and drugs compete for the same reward sites in the brain, thus explaining why drug use is inversely related to body mass index.

MARIJUANA: A REGULATORY EFFECT?

Current data indicate that while low-weight individuals are likely to gain weight with acute marijuana use, individuals in community samples display an inverse relationship between marijuana use and body mass index. While purely speculative, perhaps marijuana truly has a broad-spectrum regulatory effect with regard to body weight—increasing weight in those who are underweight, but not in those who are normal or overweight. Only further studies will tease out this intriguing possibility.

CONCLUSION

Marijuana is a clinically controversial substance, but one potential medical benefit may be weight gain. According to available studies, appetite stimulation as well as weight gain may occur in patients with physical debilitation due to HIV/AIDS and/or cancer. However, while weight gain may occur, it is not greater than currently available agents for inducing weight gain (e.g. megestrol). As for the effects of marijuana on body weight in the general population, use appears to be associated with a lower body mass index. This observation may be partially explained by differences in short-term versus long-term use, comorbid polydrug use, and/or the intriguing theory that food and drugs may compete for the same reward sites in the brain. Alternatively, marijuana may genuinely be a regulatory compound, increasing weight in those with low weight, but not in those who are normal or overweight. Only additional research will unravel the answer to the seemingly multi-faceted weight effects of marijuana.

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