Smoking Cannabis Does Not Cause Cancer Of Lung or Upper Airways, Tashkin Finds; Data Suggest Possible Protective Effect

By Fred Gardner

Marijuana smoking — “even heavy longterm use” — does not cause cancer of the lung, upper airways, or esophagus, Donald Tashkin, MD, reported at this year’s meeting of the International Cannabis Research Society. Coming from Tashkin, this conclusion had extra significance for the assembled drug company and university-based scientists (most of whom get funding from the U.S. National Institute on Drug Abuse). Over the years, Tashkin’s lab at UCLA has produced irrefutable evidence of the damage that marijuana smoke wreaks on bronchial tissue.

With NIDA’s support, Tashkin and colleagues have identified the potent carcinogens in marijuana smoke, biopsied and made photomicrographs of pre-malignant lesions in human lung tissue, and identified the cellular changes occurring within them.

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It is Tashkin’s research that the Drug Czar’s office cites in ads linking marijuana to lung cancer. Tashkin himself has long believed in a causal relationship, despite a study in which Stephen Sidney, MD, examined the files of some 64,000 Kaiser patients and found that marijuana users did not develop lung cancer at a higher rate or die earlier than non-users.

Of five smaller studies on the question, only two — involving a total of about 300 patients — concluded that marijuana smoking causes lung cancer.

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Tashkin decided to settle the question by conducting a large, population-based, case-controlled study. “Our major hypothesis,” he told the ICRS, “was that heavy, longterm use of marijuana will increase the risk of lung and upper-airways cancers.”

The Los Angeles County Cancer Surveillance program provided Tashkin’s team with the names of 1,209 L.A. residents aged 59 or younger with cancer (611 lung, 403 oral/pharyngeal, 90 laryngeal, 108 esophageal).

Interviewers collected extensive lifetime histories of marijuana, tobacco, alcohol and other drug use, and data on diet, occupational exposures, family history of cancer, and various “socio-demographic factors.”

Exposure to marijuana was measured in “joint years” — average number of joints per day x years that number smoked. Thus if a person had smoked two joints a day for 15 years they’d have consumed 30 j-yrs.

Controls were found based on age, gender and neighborhood. Among them, 46% had never used marijuana, 31% had used for less than one joint year, 12% had used for 1-10 j-yrs, 5% had used 10-30 j-yrs, 2% had used for 30-60 j-yrs, and 3% had used for more than 60 j-yrs.

Tashkin controlled for tobacco use and calculated the relative risk of marijuana use resulting in lung and upper airways cancers. A relative risk of .72 means that for every 100 non-users who get lung cancer, only 72 people who smoke marijuana get lung cancer. All the odds ratios in Tashkin’s study turned out to be less than one.

Compared with subjects who had used less than one joint year, the estimated odds ratios for lung cancer were .78 for 1-10 j-yrs (.ac- cording to the abstract book and .74 according to notes from the talk); .74 for 10-30 j-yrs; .85 for 30-60 j-yrs; and 0.81 for more than 60 j-yrs.

The estimated odds ratios for oral/ pharyngeal cancers were 0.92 for 1-10 j-yrs; 0.89 for 10-30 j-yrs; 0.81 for 30- 60 j-yrs; and 1.0 for more than 60 j-yrs.

“Similar, though less precise results were obtained for the other cancer sites,” Tashkin reported. “We found absolutely no suggestion of a dose response.”

The data on tobacco use, as expected, revealed “a very potent effect and a clear dose-response relationship — a 21-fold greater risk of developing lung cancer if you smoke more than two packs a day.” Similarly high odds obtained for oral/pharyngeal cancer, laryngeal cancer and esophageal cancer. “So, in summary,” Tashkin concluded, “we failed to observe a positive association of marijuana use and other potential confounders.”

There was time for only one question, said the moderator, and San Francisco oncologist Donald Abrams, M.D., was already at the microphone: “You don’t see any positive correlation, but in at least one category, it almost looked like there was a negative correlation, i.e., a protective effect. Could you comment on that?” (Abrams was referring to Tashkin’s lung-cancer data for marijuana-only smokers, 1-10 j-yrs.) “Yes,” said Tashkin. “The odds ratios are less than one almost consistently, and in one category that relationship was significant, but I think that it would be difficult to extract from these data the conclusion that marijuana is protective against lung cancer. But that is not an unreasonable hypothesis.”

Abrams’s Favorable Results

Abrams had results of his own to report at the ICRS meeting. He and his colleagues at San Francisco General Hospital had conducted a randomized, placebo-controlled study involving 50 patients with HIV-related peripheral neuropathy. Over the course of five days, patients recorded their pain levels in a diary after smoking either NIDA-supplied marijuana cigarettes or cigarettes from which the THC had been extracted. About 25% didn’t know or guessed wrong as to whether they were smoking the placebo, which suggests that the blinding worked.

Abrams’s results show marijuana providing pain relief comparable to Gabapentin, the most widely used treatment for a condition that afflicts some 30% of patients with HIV.

After Abrams’s presentation, a questioner bemoaned the difficulty of “separating the high from the clinical benefits.” Abrams responded: “I’m an oncologist as well as an AIDS doctor and I don’t think that a drug that creates euphoria in patients with terminal diseases is having an adverse effect.”

—Donald Abrams, MD

Francisco, was the sole clinician from California. Medical student Sunil Aggarwal, Farmacy manager Mike Ommaha and therapist/cultivator Pat Humphrey audited the proceedings.

Some of the younger European scientists expressed consternation over the recent U.S. Supreme Court ruling and the vote in Congress re-enforcing the cannabis prohibition. “How can they dispute that it has medical effect?” an investigator working in Germany asked us earnestly. She had come to give a talk on “the role of different neuronal populations in the pharmacological actions of delta-9 THC.”

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For most ICRS members, the holy grail is a legal synthetic drug that exerts the medicinal effects of the prohibited herb. To this end they study the mechanism of action by which the body’s own cannabinoids are assembled, function, and get broken down. A drug that encourages production or delays dissolution, they figure, might achieve the desired effect without being subject to “abuse.”

News on the scientific front included the likely identification of a third cannabinoid receptor expressed in tissues...
of the lung, brain, kidney, spleen and smaller branches of the mesenteric artery. This work stems from Toshio Kline and AstraZeneca both reported finding the new receptor but had different versions of its pharmacology. It may have a role in addiction, obesity and cancer. Several talks and posters described the safety and efficacy of Sativex, G.W. Pharmaceuticals’s (CMG) product containing high levels of THC and cannabidiol (CBD) formulated to spray in the mouth. See “Dr. X’s Top Talks,” on page 11. G.W. director Geoffrey Guy seemed upbeat despite the slide his company’s stock took this spring when UK regulators withheld permission to market Sativex for the treatment of MS in Canada. Currently granted approval for doctors to prescribe Sativex, and five sales reps from Bayer (to whom G.W. sold Canadian marketing rights) are promoting it to neurologists. Sativex was approved for treatment of neuropathic pain in 2011 and can be prescribed for other purposes as doctors see fit.

Most of the work being done with CBD and CBN is done with materials provided by GW, and some two dozen papers and posters gave them acknowledgment. But last there is a research alternative to NIDA for the young researchers to look to for support (and plant cannabinoinds to study). GW has contributed to significant shift in attitudes.

On numerous occasions during the meeting a NIDA-funded researcher would describe the negative effects of THC and immediately a scientist with a British accent would be at the mike pointing out that such a high dose injected into the stomach of a rat had nothing to do with the human experience with cannabis. It has must happened five or six times. The Brits were always very diplomatic, but they functioned like a truth squad.

Roger Pertwee of the University of Aberdeen reported intriguing results from experiments using a cannabis strain bred by GW to be high in THCV (tetrahydrocannabivarin).

What they did was that THCV strongly antagonizes anandamide while hardly antagonizing THC! ThCV strongly antagonizes anandamide while hardly antagonizing THC!

The existence of cannabinoinds receptors in the brain — proteins on the outside of certain cells to which cannabinoinds bind, triggering a cascade of molecular events with in the cells — was established in 1988 by Alynn Howlett and Brian Kozlowski and is very, very important. It’s been long known that people have to have a truth squad.

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You explained “It’s as if the plant contains a first-aid kit giving the body everything it needs to get better, and the body uses which components to employ... The endocannabinoid system begins to kick in in abnormality, in pathology. Perhaps it kicks in whether the pathology is increase in something or a decrease in something. Whatever it’s trying to do is get whatever that abnormality is back to homeostasis.

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We’re on plateau one or two and the answer is on plateau 12. So we could spend the next 30 years on receptors and still not fully understand them. — Geoffrey Guy
Osteopathic Manipulation Boosts Endocannabinoid System

John McPartland of GW Pharmaceuticals reported that osteopathic manipulative treatment (OMT) was able to increase the endocannabinoid system. McPartland and co-workers conducted a randomized, placebo-controlled study involving 31 patients in New Zealand. A self-assessment questionnaire was used to measure anxiety, depression, and pain levels. The sham practitioners sabotaged their own massage and mental healing by silently reciting “backwards serial seven”, while the applied manual contact to the patient’s head.

Subjects receiving OMT indeed reported feeling cannabis-mimetic effects (more creativity, less coherence, for example) and their serum anandamide levels increased 168% over pre-treatment levels. Subjects receiving sham manipulation reported no changes in the questionnaire and there was no change in their serum anandamide levels.

McPartland et al. noted that patients receiving OMT often experienced an improved sense of well-being, sedation and euphoria—similar to those brought on by cannabis consumption. Previous studies indicated these psychotropic effects are not elicited by endocannabinoids (as once had been hypothesized). A recent study by Andrea Giaufreda, who contributed to the OMT study, showed that “runner’s high” correlated with elevated anandamide and not endorphins. Patients receiving chiropractic, massage, acupuncture, and energy healing also experience parallel psychotropic effects. The authors speculated that the endocannabinoid system may be mediating a widespread but heretofore unrecognized therapeutic phenomenon.

Goldberg’s Monkeys Bat Last

Steven Goldberg (right) in conversation with John McPartland, maintains a colony of monkeys in Balti-more, Maryland that have been trained to self-administer THC (by injection). Goldberg and Zuzana Justinova presented a poster on "The Abuse Potential of the Endocannabinoid Transport Inhibitor AM404: Self-Administration by Squirrel Monkeys." AM404 is one of the many compounds that corporate- and government-funded scientists have developed in hopes of achieving higher cannabinoid levels by means of an herbal herb. Goldberg’s monkeys liked AM404 enough to self-administer it, which means, in NIDA’s terms, that AM404 is a drug with potential for abuse. After all their effort to create an alternative to medical marijuana, the drug companies will have to run their products by Goldberg’s monkeys!

The Goldberg-Justinova poster concluded “AM404 functioned as an effective reinforcer (comparable to THC), anandamide and cocaine under identical conditions, and achieved a fixed-ratio schedule of drug injection. Our findings suggest that medications which promote the actions of endocannabinoids throughout the brain by inhibiting their membrane transport have a potential for abuse. It remains to be seen whether medications such as FAAH inhibitors, which augments CB1 signaling on certain regions of the nervous system, would be self-administered in a similar manner.”

Your correspondent had always heard that monkeys couldn’t be trained to self-administer THC. Why did they self-administer it? The research team used “Old World monkeys,” whereas he used squirrel monkeys from South America. But the real key to his success, he added, was the very low doses with which he rewarded the monkeys. This made sense — most of the primates I know prefer a slight amount of mood to getting knocked-out-loaded. It also resonated with an ICSR talk on neurotransper内衣on by Italian investigators who found that a synthetic can-nabinoid was beneficial only at the lowest concentrations tested, and detrimental at high concentrations. When the name of the game is cannabinoids, less can be more.

A team at Glaxosmithkline went “ligand fishing” and discovered that GPR55 has affinity for anandamide, CPS5,940, and SR141716A. Simulta-neously, a team at AstanzaZeneca reported GPR55 is a G13-coupled receptor that activates the intracellular signaling mediat-er RhoA. GPR55 is expressed in the brain as well as mesenteric arteries, and regulates blood pressure.

The efficacy of THC at CB1 is regulated by other cannabinoids. Chris Breivogel gave an update on beta- arrestine 2 (BAPZ), a protein implicated in desensitization and other G-protein-coupled receptors. Experiments with mice suggested that BAPZ shuts down CB1 signaling by THC, yet does not affect other cannabinoid ligands. Whether BAPZ shuts down THC in humans remains to be seen; the B2 gene is actively evolving, its sequence is different in humans, and its gene is un-dergoing positive selection.

Deborah Lewis presented research on CRIP (cannabinoid receptor interacting protein 1 and 2). CRIP1 may regu-late the membrane localization of CB1. Intriguingly, CRIP 1b has only been identified in human postmortem brain binding sites for WIN55 and other cannabinoid ligands. In fact, the binding site for THC may be a “side door,” a part of the receptor that faces the lipid bilayer, rather than the extracellular portion of the receptor. Reggio identified two beta-branching amino acid residues on the receptor that specifically interact with THC (which she wonderfully called “groove residues,” because of their chemical structure).

Many scientists have suspected the presence of a third cannabinoid receptor. Two research groups converged upon a molecular entity called “GPR55” as the long-sought “CB3” receptor. GPR55 was identified six years ago, but was labeled an “orphan receptor” because its endogenous ligand was unknown.

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In a similar “synergy” theme, Roger Breivogel and his team found that a unique characteristic of tetrahydrocanabinol (THCV), a minor variant of THC (THC and 50% CBD) for over one year experi-enced minor and transient disturbances of sleep and appetite when withdrawn from drugs. The most important finding was that cannabis is more than simply THC. It represents a new mechanism of action that is different from classical cannabinoid receptors. The authors suggest that THC may alter the effects of other cannabinoids and other ligands that bind to CB1 receptors. They propose that THC competes with endocannabinoids for binding to CB1 receptors and that THC has a lower affinity for CB1 receptors than other cannabinoids.

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