

IN CONVERSATION

An Interview with Manuel Guzman

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Dr. Guzman, PhD, is professor of biochemistry and molecular biology at Complutense University in Madrid, Spain. He was profiled in National Geographic in June 2015 in an article titled "Science Seeks to Unlock Marijuana's Secrets." He was interviewed via Skype on October 10, 2015.

Please describe how you got into this line of work and what exactly your research entails.

I started to work in cannabinoids 20 years ago. I did my PhD and post-doctorate on lipid metabolism, specifically on how the liver metabolizes fat to obtain energy. When I came back to Madrid after my post-doc and I got my position here at the university, I started to do a little bit of study on metabolism in brain cells. This was the period when cannabinoids started to explode because cannabinoid receptors were discovered, and then endocannabinoids were discovered as well. So because endocannabinoids are fatty acid derivatives, and I was working with fatty acids, I said, "Well I have the technology and the knowledge to work with lipids, so why not start to see how these compounds are produced and metabolized in the brain?" So that was how I started—just for fun—and then here I am after 20 years. Our whole group is devoted to cannabinoid research. We are about 25 people, and we have different lines of research, but all of us work on the cannabinoid system and receptors and how they signal in the brain and other tissues. The lab is split into three major lines of research: cancer, neuroprotection, and neurogenesis.

Where are cannabinoid receptors found in the body?

There are two types of cannabinoid receptors: CB1 receptor and CB2 receptor. They are very similar one to each other. They have the same amino acids and the same structure, and they bind essentially the same lipids and same cannabinoids. CB1 receptor, which was originally called the central cannabinoid receptor, should be called the "ubiquitous" cannabinoid receptor because it's ba-

sically everywhere in the body. I don't know of any tissue that doesn't have at least a small amount of CB1. Of course, there are very large amounts of CB1 in precise parts of the brain, in the cortex, in the hippocampus, in the basal ganglia, in the cerebellum. And there is very little CB1, for instance, in blood cells, or in lung cells, or in kidney cells. I would say that all the cells in the body express at least a little bit of CB1 receptors, whereas CB2 receptors were originally called peripheral cannabinoid receptors because they're mostly located in circulating blood cells. They should be called "restricted" receptors because they're present in very few cellular populations in the body, mostly in the immune system.

In the United States, we use the term "medical marijuana." How do you refer to it in your work?

Medical marijuana is a very vague term, but we use it because it makes it easy to know what we're referring to. But in fact marijuana has more than 100 different types of cannabinoids and more than 400 known compounds that are noncannabinoids. In most marijuana preparations the major ingredient is THC and usually the second ingredient is CBD. We can talk about high THC to CBD ratio marijuana, we can talk about balanced or one-to-one THC to CBD ratio marijuana, and we can talk about high CBD/low TCH marijuana. I would divide the medicinal cannabis preparations into those three major types of preparations.

So what are the medicinal uses of marijuana, and what can be the major responsible ingredients? Overall, THC is the most active compound, for the good and the bad. THC has a psychoactive compound that people take for recreational purposes, but many

patients that are taking marijuana especially for very long periods of time want to get rid of that property. CBD is a way of buffering the high that his produced by THC. For instance, the discoordination and convulsions that can be produced by high amounts of THC are usually decreased by CBD. In other words, one can tolerate higher amounts of THC if that THC is accompanied by CBD rather than being alone. The second property of CBD is that it may have some medicinal applications by itself. For instance, CBD is antioxidant, anti-inflammatory, and anticonvulsant; it is being used in pediatric epilepsy. So altogether I believe that it is usually good to combine THC with CBD in medicinal marijuana.

To me, the most reported and the most established properties of medicinal marijuana, which are mostly due to THC, are first, chronic pain. Most of the patients in the world use cannabinoids for attenuating, palliating, and managing chronic pain. For many different types of chronic pain, arthritic pain, migraines, fibromyalgia, post-herpetic pain, cancer-related pain, and neuropathic pain in multiple sclerosis, cannabinoids can be effective. The second indication is spasticity and other motor problems in neurodegenerative diseases, especially in multiple sclerosis. I would say those two have the strongest clinical evidence.

Still, cannabis is not a miracle. It is true that it can be a medicine—or I would say cannabinoids are drugs that can be useful for therapy—and in the end for any medicine it is clear that it is the therapeutic balance that counts. It's the clinical efficacy that is balanced by the secondary effects, the non-desired effects.

Those are the two major applications, to me, of marijuana: chronic pain
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and motor disorders, specifically in MS. Second, there are other applications that are well known, but to me they are not so widely used—maybe because cannabinoids are not so effective and/or there are other medicines that can replace cannabinoids. One is the treatment of vomiting and nausea in chemotherapy, and the second is cachexia and weight loss in all sorts of diseases like cancer and AIDS. It is true that cannabinoids are used for that, but in general patients do not use them so much for those services. The third group involves newer applications, and there I would highlight the antiepilepsy profile of CBD, especially for pediatric epilepsy.

Are there any major side effects you've seen so far in your animal models that that concern you?

Cannabis has one advantage, and it's that it's not toxic—no one dies because of cannabis. So that is one great step forward. If someone has a strong heart problem and they take very high doses of THC or if someone takes a designer drug that is contaminated with a synthetic cannabis, it can induce problems. Of course we have undesired psychoactive actions; some people cope with them very well, but there's a small portion of patients who suffer from bad trips—and no one likes to have a bad trip. You can also have convulsions, phobias, and psychosis, so that is something to be aware of. Some people are more susceptible to these side effects, as with any medicines. What we have to do first is educate and also try to provide the patient with dosing regimes that are rational, that are escalating, and that are very closely monitored so that one can go step-by-step from low doses. That way people can develop tolerance to the bad actions of cannabinoids. We

can also use wash-out periods. For example, for three weeks one can use marijuana and then have one week of washout because, as you know, cannabinol is very lipophilic, and it stays in the body for days—not just hours. So I recommend wash out periods from time to time.

Who prescribes medical marijuana in Spain?

There is no official prescribing here. No physician can prescribe marijuana; however, they can prescribe Sativex. Sativex is a medicinal marijuana preparation that is legal and is produced by GW Pharma in UK. The company intends to introduce it in the United States with the name Nabiximols. Nabiximols is a marijuana extract with a one-to-one ratio of THC and CBD, and it's allowed in most if not all countries in Europe for the treatment of spasticity due to MS. I'm sure that in the next few months or years it will also be prescribed for other purposes, such as chronic pain. Here in Spain, doctors officially can only prescribe Sativex for spasticity due to MS or for compassionate use for other purposes. A new development is the formation of clubs or associations of patients that [because they are private and located in private venues] can use marijuana legally. So patients can go [to the club], they can take marijuana there, and they can obtain their marijuana there as long as they prove that it is for individual use. Some primary [care] doctors collaborate with those associations and provide counseling to the patients.

But they don't have to get permission from a doctor to obtain the marijuana?

No. Ideally it would be nice if they did; it would be great, for example, if

an oncologist treated someone with cancer pain or a neurologist knew that his/her patient was taking marijuana. Ideally it should be much more open, and everyone should have the confidence to tell his/her doctors what they are taking. But the reality is that only a small fraction of patients tell their physicians that they are taking marijuana. They usually go to the clubs, and they obtain their marijuana under the supervision of a primary [care] doctor, which is nice because at least there is someone who is usually familiar with the medicinal uses of marijuana.

How should we, as a internal medicine physicians, participate in the development of medical marijuana?

Primary [care] doctors are absolutely key in the development of medical marijuana. As I told you, most of the patients rely much more on the primary [care] doctor than on their specialist. So here, those primary [care] doctors are taking care of the administration of medical marijuana as a complementary therapy to the conventional therapies. They are playing a key role.

Why do you think it has fallen to the primary [care] doctors to do this monitoring of medical marijuana?

Maybe because the care that is given by primary [care] doctors is usually more integrative. I think whenever people are closer to the patient and they see what the real needs of the patient are in the broad meaning of the word—the holistic meaning of the word—I think they are more prone to look for shortcuts or complements to conventional approaches. That's my belief, and that's what I see here in Spain. *SGIM*