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Drugs
AlterNet / *By Steven Wishnia*

Is Big Pharma Trying to Take All the Fun out of Pot?

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Drug researchers are trying to replicate marijuana's therapeutic effects, but without the "side effect" of getting people high.

Pricey pharmaceutical-marketing newsletters have touted cannabis-derived drugs as the next blockbuster for the industry, but the biggest companies are primarily researching drugs whose effect is the opposite of the cannabis herb.

Numerous drug researchers are trying to develop medications that replicate the herb's therapeutic effects without the harm of inhaling smoke and the side effect of getting people high.

Others are looking into cannabinoid agonists, drugs that enhance the body's natural cannabinoid system -- or cannabinoid antagonists, which disrupt it, and have been the pharmaceutical industry's main focus. Despite the millions of medical-marijuana users, both U.S. government restrictions and drug companies' need for exclusive ownership have limited research into herbal cannabis.

In any case, it will likely be a while before many cannabis-derived drugs arrive in your local pharmacy.

"There's a lot of interest out there, but there's nothing that's going to be released in the next week," said a longtime medical-cannabis researcher who asked to remain anonymous.

So far, only three such drugs are on the market.

- Cesamet (Valeant Pharmaceuticals), used for chemotherapy-nausea treatment, went on sale in the United States in 2006. It contains nabilone, a synthetic analog of THC, the primary psychoactive ingredient in cannabis.
- Marinol, synthetic THC in capsules, has been on the market since 1986. It is now manufactured by the Belgian firm Solvay Pharmaceuticals, and generic versions are beginning to come out.
- Sativex, a whole-cannabis-extract spray produced by the British firm GW Pharmaceuticals, is available in Canada. It is oromucosal, meaning it is absorbed by the mucous membranes under the tongue and on the inside of the cheeks, and it contains approximately equal proportions of THC and cannabidiol (CBD). CBD is a cannabinoid

thought to reduce both pain and the more nerve-jangling aspects of the marijuana high. The spray is undergoing Phase III trials -- large-scale human studies of its efficacy -- for multiple sclerosis in Europe and cancer pain in the U.S.

At least five of the world's top 10 pharmaceutical companies have looked into the field. In 2006, there were about 18 cannabinoid-related compounds under active pharmaceutical development, says Dr. George Kunos, scientific director of the National Institute on Alcohol Abuse and Alcoholism at the National Institutes of Health. They were primarily cannabinoid antagonists.

Many of those, however, may never make it to market. New drugs need to be proven safe and effective, drug companies want them to be profitable, and the approval process can take as long as 10 years.

In January, Novartis announced that it had completed Phase I tests of a cannabinoid agonist called CRA13, which might be used to treat chronic pain. Phase I tests are a small-scale study of the drug's safety, how well human subjects tolerate it, and its "pharmacokinetics" -- how quickly it gets into the body, where it goes and how long it stays.

Big Pharma's first move into cannabinoid drugs, however, ended in failure. In 2006, the French company Sanofi-Aventis began selling in Europe rimonabant, a cannabinoid antagonist, as an appetite suppressant under the brand name Acomplia.

By blocking the action of natural cannabinoids at "CB1 receptor" sites in the brain, Acomplia created the opposite of the "munchies." (As one drug company put it, activation of CB1 receptors "appears to provoke food intake even in the setting of satiety.") The drug also showed promise for diabetes, says Kunos, because it increased the body's sensitivity to insulin. A British pharmaceutical-business newsletter predicted that Acomplia would be "the first of the cannabinoid blockbusters."

The U.S. Food and Drug Administration, however, rejected Acomplia in 2007, because its side effects included suicidal thoughts. Last fall, the European Medical Agency recommended taking the drug off the market because it increased the risk of depression. In November, Sanofi-Aventis announced it was stopping all research on it.

Pfizer and Merck Sharp & Dohme, which had similar drugs in Phase III trials, suspended their development as well. Solvay, which had had a marketing deal with Bristol-Myers Squibb for a cannabis antagonist it called SLV319, also canceled its research. Phase II studies had found SLV319 an effective anti-obesity drug, but the company's head of research cited "high regulatory hurdles."

The risks might have been foreseen. Because the endocannabinoid system was not discovered until the early '90s, its role in regulating emotions and the effects of disrupting it are far from understood.

In 2003, neurochemist Dale Deutsch, former head of the International Cannabinoid Research Society, predicted that cannabinoid antagonists would be effective appetite suppressants, but that people taking them "might be really irritable."

Drug researchers are now trying to find a cannabinoid antagonist without the psychiatric side effects. Meanwhile, "online pharmacies" still advertise rimonabant with "discreet packaging" and "anonymous delivery."

Johnson & Johnson says it is not researching cannabinoid drugs, and a company spokesperson said it was "not aware of any" other companies doing so. On the other hand, drug companies are not likely to tell competitors about the research they're doing.

"This is all proprietary information," notes Paul Armentano of the National Organization for the Reform of Marijuana Laws. "I have reason to believe there has been an explosion in cannabinoid-based drug research, but we in the general public are not going to be made aware of it until these drugs are close to market."

5 Types of Pot Drugs

Researchers are looking into five main areas for cannabinoid drugs. The first two comprise plant extracts and purified forms of THC. The other three involve drugs that affect the endocannabinoid system.

GW Pharmaceuticals' Sativex is the whole-plant extract closest to U.S. availability. It has been in development for several years. It was designed as a spray so it would get into the body and act almost as quickly as smoked cannabis does. This would avoid the main complaints patients have about orally administered THC: that it can take an hour or more to take effect, that it is difficult to calculate whether a dose will be ineffective or overwhelming, and that oral medications are useless if you're too nauseous to keep them down.

GW has also just begun research on whether CBD combined with another cannabinoid, THCV, might help treat Type 2 diabetes.
Longtime medical-marijuana advocates Dr. Robert Melamede, a biologist at the University of Colorado at Colorado Springs, and California activist Steve Kubby co-founded Cannabis Science, Inc. The company says it plans to develop plant-based drugs and proprietary delivery systems for them, introducing them in the Canadian market first. It also offered "420 Commemorative Certificates" to anyone who bought stock before April 20. In early July, however, the company fired Kubby amid mutual accusations of financial malfeasance.

One major obstacle for U.S. researchers trying to develop plant-based cannabis drugs is the federal restrictions on the supply of the plant. The only legal source is the lab of Dr. Mahmoud ElSohly at the University of Mississippi. He has had an exclusive contract with the National Institute on Drug Abuse, which must approve researchers' requests to obtain cannabis, for almost 40 years.

NIDA has had a strong prejudice in favor of studies aimed at evaluating marijuana's abuse potential. It has denied a supply to several well-known researchers planning studies on medical cannabis.

The Drug Enforcement Administration has refused to grant anyone else a license to grow cannabis for research. In January, it denied one to Lyle Craker, a professor at the University of Massachusetts at Amherst, who had applied in 2001 and wound up suing to get the agency to act on his request. The DEA overruled its own administrative judge, who in 2007 had urged ending the federal monopoly. The judge summarized the testimony of one medical witness for the DEA as "he considers medical marijuana an excuse for legalization."

"You can't get permission to even touch the marijuana," says Armentano.

Fewer obstacles exist in Europe. But when Weleda AG, a German herbal-medicine and cosmetics company, funded a British study of THC-CBD extract for multiple-sclerosis spasticity, it was terminated for lack of volunteers.

Generic forms of Marinol, THC under the name "dronabinol," are beginning to reach the U.S. market. Two leading generic-drug manufacturers, Par Pharmaceutical and Watson Pharmaceuticals, began selling it last year, with Watson the authorized licensee of Solvay.

Bionorica AG, a veteran German herbal-medicine company, is seeking FDA approval for a version of dronabinol containing THC extracted from plants. The company has been selling it in pharmacies in Germany and Austria for the past 10 or 12 years, says Gary Klein, its U.S. representative. It's also looking at developing THC in droplets that would be absorbed on the underside of the tongue.

ElSohly, who has the U.S. government monopoly on research cannabis, is working with Mallinckrodt to develop a plant-extract form of Marinol. Medical-cannabis advocates sharply criticize him for that. Americans for Safe Access charges that he "benefits from such a monopoly by financially profiting from the research and sale of cannabis-based pharmaceuticals."

ElSohly has also patented a suppository containing THC hemisuccinate, which breaks down into THC once it is absorbed by the body. That is "not a popular form of drug delivery," observes the anonymous medical-marijuana researcher. (The 1960s comedian Lenny Bruce would disagree; he enjoyed morphine suppositories.)

Cannasat Therapeutics, a Canadian company, is applying to patent a THC pill called Relivar for neuropathic pain. Like some triptan migraine-abortive drugs, the pill would melt in the mouth instead of having to be digested. The company claims that this will make the drug act faster, get a higher proportion of it into the blood, and make it less intoxicating than oral THC pills. Cannasat is also working on a CBD-based treatment for schizophrenia.

Research into the cannabinoid agonists-drugs, which enhance cannabinoids binding to receptors in the brain and body, has mainly been "preclinical," with tests on animals instead of humans,

according to Kunos. Drug companies, he adds, have strong objections to them because they would be psychoactive, essentially mimicking the action of marijuana in the brain.

Pharmos, an Israeli company, had high hopes for a nonpsychoactive synthetic cannabinoid called HU-211. Preliminary studies indicated that it could protect the brain from the cascading neurochemical inferno set off by a stroke or traumatic injury, but Phase III studies in 2004 found it not significantly more effective than a placebo.

A fourth area is drugs that inhibit FAAH, the enzyme in the brain that breaks down the endocannabinoids anandamide and 2AG. These would work in a manner roughly analogous to antidepressants like Prozac, which inhibit the reuptake of serotonin. Danielle Piomelli of the University of California at Irvine has patented several possible FAAH-inhibiting medications, including an anxiety reducer, a cough suppressor and a pain reliever.

Finally, research into cannabinoid antagonists continues. Kunos says the goal now is to find one that's "non-brain-penetrant," a drug that would affect only cannabinoid receptors outside the brain, and therefore wouldn't have the psychiatric side effects that derailed rimonabant. He says the animal models are promising.

7TM Pharma, a Danish company that specializes in drugs for metabolic disorders, plans to start trials of a cannabinoid antagonist this year in the treatment of obesity and Type 2 diabetes. It says the drug "has been designed to exclusively exert its therapeutic effect through CB1 receptors located in the peripheral tissue" instead of those in the brain.

The Medical Possibilities of Cannabis

Meanwhile, numerous academic researchers are uncovering myriad medical possibilities for cannabis and the cannabinoids. In one study released in the last year, researchers at Complutense University in Madrid found that THC caused brain-cancer cells to destroy themselves.

At the University of Erlangen in Germany, a CB2-receptor agonist reduced the dermal thickening and fibrosis found in the early stages of multiple sclerosis, and it also diminished the damage done by lowered blood supply to the brain in an animal model of stroke.

A Canadian military psychiatrist said that nabilone reduced or eliminated nightmares in 34 of the 47 post-traumatic stress syndrome patients he studied.

The University of California at San Diego is currently investigating whether vaporized cannabis can help relieve diabetic neuropathic pain.

Medical-marijuana advocates maintain that whole-plant drugs will be the most effective. Research has shown that the synergy of multiple cannabinoids works better than any single molecule in the plant, argues Caren Woodson of Americans for Safe Access.

"The strongest drug isn't necessarily the best," adds the anonymous researcher. The body's systems are subtle and need "a gentle nudge, not a big shove," he argues, and potent synthetic molecules are more likely to be toxic than substances people have used for thousands of years. The liver, he says, will have a hard time processing "a hairy molecule with lots of fluorine and side chains."

The profit system puts the pure cannabis herb at a disadvantage. Drug companies are not going to put time and money into a substance they can't patent, notes Woodson. On the other hand, they can patent tinctures, methods of extraction, and vaporizers -- which boil the THC into an inhalable steam instead of burning the herb into a toxic smoke.

Those means of drug administration are also more likely to satisfy the medical community's anathema to smoking and its desire for precise, standardized doses.

Woodson suspects that the focus on synthetic cannabinoids may be a "backdoor way" to deny approval of medical marijuana. On the other hand, she notes, the FDA has approved four Phase I studies of smoked marijuana for pain relief in HIV-AIDS patients, and the state of California is funding them. At this point, she says, "anything that gets the FDA one step closer to approving cannabis" is a good thing.

"We could be looking at the aspirin of the 21st century," she says, but it's not going to happen until "pharmaceutical companies can investigate it in the same way that they investigate any other drug."