Marijuana's Synthetic Cousin

Nabilone, a structural analog of THC may become the drug of choice to treat problems that can be treated with marijuana

BY RACHEL WEISMAN AND JULES ASHER

Marijuana as medicine has been in the news of late — as a promising treatment for glaucoma and for the nausea and vomiting side effects of cancer chemotherapy. And four states — Louisiana, Florida, New Mexico and Illinois — have recently legalized limited use of the drug for the experimental treatment of such conditions.

One might think that doctors will soon be writing prescriptions for THC. But a large pharmaceutical house has other plans. Eli Lilly and Co. has developed a synthetic structural analog of THC, called Nabilone, that appears to possess all of its chemical cousin's desirable therapeutic potential minus pot's notorious euphoria and other pharmacological properties — not to mention its stigma.

The odds are that Nabilone, not pot, will be the prescription drug of choice. Lilly's Robert Schulman says his firm plans to file for Food and Drug Administration approval sometime early next year, following completion of a final round of double-blind studies.

Lilly's drug could hit the market within two years, according to Edward Tocus, chief of the FDA's drug abuse staff. Commercial backing has kept clinical research with the synthetic moving and Lilly has been quietly racking up the scientific evidence of safety and efficacy needed for FDA approval. By contrast, THC's research portfolio remains in relative disarray, Tocus says.

Despite all the publicity about therapeutic marijuana, the drug industry has shunned THC for a number of reasons. A major deterrent is the sheer morass of red tape involved in conducting research with Schedule I drugs — those classified as having high abuse potential and no redeeming medical value. In addition, security requirements are stringent. Another problem: Encapsulating the resinous, sticky THC is a messy job. And then, oral THC is unevenly absorbed by the body. The alternative — smoking marijuana — is hardly a palatable method of administering medication in the eyes of the medical profession. The clincher, of course, is THC's medically undesirable side effect, its "high."

Crystalline, water soluble Nabilone escapes these regulatory, pharmaceutical, and social snags, although Lilly's Schulman admits that the drug produces a modicum of euphoria and hypotension in some subjects.

The advent of the medicinal marijuana analog was no accident. Lilly began work a decade ago to develop a THC-like drug free of pot's best-known traits. It first synthesized Nabilone in 1972, after experimenting with hundreds of newly synthesized substances. "By the time Nabilone had been run through about ten animal tests, we knew it had the best profile for clinical application we'd seen," recalled Robert Archer, the Lilly scientist responsible for the project.

Only Lilly currently has an FDA license to perform human studies with Nabilone, but independent researchers have obtained permission to conduct clinical studies under the firm's "umbrella."

At a May National Cancer Institute state-of-the-art conference on THC and Nabilone research, Lawrence Einhorn of Indiana University reported his study's findings with Lilly-supplied Nabilone: "When we compared Nabilone as an agent for reducing nausea and vomiting (emesis) in cancer chemotherapy patients with Compazine, a widely used antiemetic, we found Nabilone to be significantly better on the last four days of the five-day treatment course." On the first day, neither drug was very effective. But in subsequent trials when patients were medicated *before* chemotherapy, Einhorn said, they reported significant emesis relief with Nabilone, even on day one.

Terence Herman of the University of Arizona reported to the conference that doubling the usual Nabilone dose produced "significantly increased emesis protection" for patients who had become unresponsive to standard treatments. In another study, Herman said, patients with a history of exceptionally severe emesis fared "significantly better" with Nabilone than with Compazine. He noted, however, that more Nabilone than Compazine patients reported loss of coordination, dry mouth, somnolence and dizziness.

Reports of inadequacy plague the commercially available drugs for emesis, helping spur medical interest in both Nabilone and THC. Brian Lewis of the NCI's Division of Cancer Treatment, the conference sponsor, says he blames the aversiveness of severe nausea and vomiting for some cancer patients dropping out of chemotherapy. But researchers at the NCI conference agreed that the number and kind of studies presented did not warrant conclusions about the efficacy of either drug. Lewis is quick to underscore that point: "We simply don't have enough data. More research is needed before we can be certain."

Although Lilly reportedly has no plans for emesis-control studies comparing Nabilone with THC, Lewis says his division might conduct such a study on an in-house basis. NCI will not become a sponsor for extramural clinical studies, he says, because any additional research would require FDA evaluation and would hold up approval of Nabilone. Lewis says he thinks Nabilone looks good, and he would like to see it on the market as soon as possible.

Just as marijuana's THC has shown promise as an agent to reduce the intraocular pressure of glaucoma, so, according to research reports, has Nabilone. Paul Stark of Lilly reports a preliminary study under University of Chicago ophthalmology head Frank Newell that found a single oral dose of Nabilone lowered the intraocular pressure in glaucoma patients by an average of 34 percent. "These patients had all been resistant to conventional treatments," Stark comments. Corroborative studies with rabbits using eyedrops and intravenous injections as Nabilone vehicles were also done, Stark says, with comparable results. "We're planning studies which will compare Nabilone with THC," he adds.

In another Lilly-sanctioned experiment, Louis Fabre of Houston gave Nabilone to twenty anxious patients and found that their anxiety levels dropped dramatically within the first three days, according to Stark. He cautions that he wants to avoid "premature encouragement" to Nabilone's eye pressure reduction and anxiety reactions. "Results are preliminary only," Stark says.

Meanwhile, an FDA advisory group is recommending that THC be reclassified under Schedule II, which would acknowledge its therapeutic utility. And Lewis of NCI says his division will ask for FDA permission to conduct extramural emesis-control research with THC.

Marijuana's advocate, the National Organization for the Reform of Marijuana Laws, argues that it will take years before synthetics are perfected and that, in the meantime, many patients could benefit from the "natural form" of THC. "The people I deal with don't have five or ten years to wait," remarks Alice O'Leary, who heads NORML's Medical Reclassification Project.

If Nabilone's projected timetable is realistic, however, they may not have to wait quite that long. □

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