At least for the time being

Adieu, Rimonabant

Failure of weight-loss drug was foreseen by pro-cannabis MDs

In November 2008 the European Medicines Agency (EMEA) ordered Sanofi-Aventis to stop selling Rimonabant, a drug that reduces appetite by blocking cannabinoid receptors in the brain. Some 700,000 people had taken Rimonabant, which was marketed in the UK and elsewhere as Acomplia.

Data from ongoing clinical trials showed that Rimonabant users suffer depression, anxiety, insomnia and aggressive impulses at twice the rate of subjects given placebo. In one study there were five suicides among Rimonabant users compared to only one among subjects on placebo. Finally the EMEA said "Enough" in a dozen languages.

A month earlier, Merck had abruptly canceled five clinical trials of a similar cannabinoid-blocker called Taranabant. The pattern of adverse psychiatric effects had become too obvious to conceal from U.S. and European regulators.

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Regulators were concerned about Rimonabant use leading to an uptick in other illnesses that the cannabinoid system helps to suppress. In August researchers at the MD Anderson Cancer Center reported that mice on Rimonabant develop potentially cancerous polyps at a higher rate than controls.

Dangers Were Foreseen

The dangers of drugs that block cannabinoid receptors were foreseen by California doctors who monitor cannabis use by large numbers of patients.

Jeffrey Hergenrather, MD, of Sebastopol, California, was first to go public with his misgivings. Hergenrather had attended the 2004 meeting of the International Cannabinoid Research Society meeting at which Sanofi scientists reported that Rimonabant had proven safe and effective in clinical trials involving 13,000 patients. That year the ICRS's achievement award went to three Sanofi researchers. Only a few ICRS membrers expressed misgivings –off the record, please– about the basic approach.

Hergenrather and Dr. John McPartland were lonely voices questioning the propriety of Sanofi's march to the market. "The consequences of interfering with the cannabinoid receptor system have not been evaluated in normal human physiology," Hergenrather stated in *O'Shaughnessy's* (Fall 2004).

Hergenrather suggested that before Sanofi marketed Rimonabant, "It would be ethical to design longitudinal studies to assess the consequences of interfering with the cannabinoid system."

It makes sense that doctors treating patients who augment their cannabinoid levels (by smoking or otherwise ingesting cannabis) would be sensitive to the effects of blocking the receptors they activate.

Hergenrather's pro-cannabis colleagues shared his misgivings about Rimonabant. He and the late Tod Mikuriya, MD, both wrote letters to the U.S. Food and Drug Administration advising against approval. To FDA's credit, a panel of physicians would unanimously turn down Sanofi's application in 2007. (Their decision was influenced by the belatedly revealed dangers of Vioxx.)

ACOMPLIA'S LAST ACCOMPLISHMENT, getting approved as a drug for which the UK National Health Service would reimburse, was announced in a Daily Mail headline on the day the 2008 ICRS meeting began in late June. Five months later the weight-loss drug would be pulled off the European market for safety reasons.

The receptors blocked by Rimonabant are prevalent in areas of the brain responsible for emotional control. Why did Sanofi and the scientists who jumped on the Rimonabandwagon think they could depress cannabinoid activity in the limbic system without depressing mood? How did they rationalize their hope that a cannabinoid-antagonist drug would not reverse the beneficial effects of natural cannabinoids?

Some hypothesized that when the CB1 receptor is blocked, the endocannabinoids are redirected to other targets. They spoke hopefully of "compensatory mechanisms" that would kick in.

A positive side effect?

Phil Denney, MD, saw a silver lining in the Rimonabant marketing drive. He figured it would serve to educate U.S. doctors about the cannabinoid receptor system, which was discovered in the late 1990s, and has not made it into the medical school curriculum.

Denney called his SCC colleagues' attention to a two-page Sanofi ad in the *Journal of the American Medical Assocation,* touting "A newly discovered physiological system... The Endocannabinoid System (ECS)."

The *JAMA* ad was one of about a dozen that Sanofi ran in medical journals to explain Rimonabant's mechanism of action. It said that the endocannabinoid system "consists of signaling molecules and their receptors, including the cannabinoid receptors (CB1 and CB2)." The CB1 receptors are "located centrally in the brain and peripherally in liver, muscle and adipose tissue" and "may assist in regulating physiologic processes, e.g., lipid and glucose metabolism."

But the gusher of enlightenment that Denney anticipated sputtered out quickly. Sanofi did not succeed in defining "Metabolic Disorder" as a real disease the way Eli Lilly had with "Clinical Depression." A nation that had been educated about the serotonin reuptake process did not get equivalent instruction about the cannabinoid receptor system. The information contained in a few medical-journal ads never crossed over into the mass media.

In most of the stories dealing with the rise and fall of Rimonabant, reporters avoided the term "cannabinoid receptor system" entirely. For example, in Jeanne Whalen's Oct. 24 *Wall St. Journal* piece about the EMEA withdrawing approval, she described Rimonabant as "a new kind of drug that blocks receptors in the brain that help control food intake."

In March 2007, when the FDA was evaluating Rimonabant, Whalen wrote a front-page piece with this doubly inaccurate phrase: "Cannabis, the active ingredient in marijuana, acts on the same receptors..."

I wrote a polite note to the editor explaining that "cannabis" and "marijuana" are synonyms, and that the plant contains more than one active ingredient. Ms. Whalen emailed back: "Thanks for writing — always good to hear from readers. I actually didn't mean to get that technical in my phrasing — I was really just saying that the drug marijuana is made from cannabis. But thank you for the points you made. Best regards, Jeanne Whalen."

This woman covers the European pharmaceutical industry for the *Wall St. Journal!*

Has any honor accrued to Hergenrather and the SCC doctors who joined in warning that Rimonabant would induce serious adverse side-effects? Of course not, they can be marginalized as "potdocs."

Soon after Rimonabant was taken off the market in Europe, Hergenrather had to write a letter to a Butte County judge who would not allow a patient of his to medicate with cannabis while on probation unless the patient got a second approval from an orthopedist.

The patient was a middle-aged construction worker with a well-documented history of back pain for which he had been hospitalized, treated by chiropractors, acupuncturists, osteopaths, and physical therapists, and prescribed Celebrex, Flexeril, Soma, Valium, Vicodin, Percodan, Percocet, Darvocet, Ultram, ibuprofen, naproxen, etc.

Not only was the judge playing doctor, she didn't understand that orthopedists have no expertise treating pain. Dr. Hergenrather put this much more diplomatically in his letter to her –as diplomatically as he put his warning about Rimonabant in the summer of 2004.

ICRS 2009: Examining More Facets of CBD

Papers to be presented at the 2009 ICRS Meeting in Pheasant Grove, Illinois, July 8-11, included:

• Cannabidiol as a Novel Inhibitor of ID-1 Gene Expression in Aggressive Breast Cancer Cells by McAllister et al.

• Anticonvulsant Effects of Cannabidiol Upon Spontaneous Epileptiform Activity in Acute Hippocampal Brain Slices by Jones *et al*.

• Cannabidiol as a Novel Anti-Acne Agent? Cannabidiol Inhibits Lipid Synthesis and Induces Cell Death in Human Sebaceous Gland-Derived Sebocytes by Biro *et al*.

• Cannabidiol May Act as a 5-HT1A Auto-Receptor Agonist to Reduce Toxin-Induced Nausea and Vomiting by Rock *et al*.

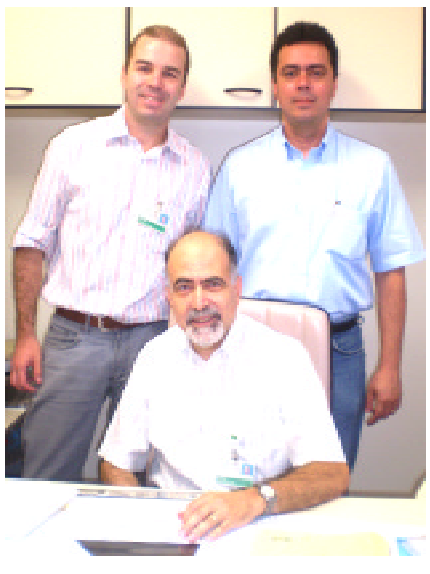
• Cannabidiol Controls Intestinal Inflammation Through the Modulation of Enteric Glial Cells by DeFilippis *et al*.

• Characterization of the Neuroprotective Effect of Cannabidiol After Oxygen and Glucose Deprivation of Newborn Mice Foregrain Slices -Romero et al

• The Effect of Cannabidiol and delta-9 THC On Social Interaction of Rats by Malone *et al*.

• Cannabidiol Reduces Lipopolysaccharide-induced Vascular Dysfunction in the Mouse Brain: An Intravital Microscopy Study by Ruiz-Valdepenas *et al*.

• Neural Basis of Anxiolytic Effects of Cannabidiol (CBD) in Generalized Social Anxiety Disorder by Crippa *et al*.



CBD RESEARCHERS José Alexandre S. Crippa (standing, left), Antonio Waldo Zuardi (seated) and Jaime E. C. Hallak, Department of Neurosciences and Behavior; Division of Psychiatry, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto SP, Brazil and INCT-Tranlational Medicine, Brazil

Dr. Crippa and colleagues have used single-photon emission computed tomography (SPECT) to study what happens in the brain when a subject experiences anxiety. He reports, "The anxiolytic-like effect of CBD in healthy volunteers was observed in a recent double-blind study that investigated its effects on regional cerebral blood flow... Because the procedure itself can be interpreted as an anxiogenic situation, it allows the evaluation of anxiolytic drug action. CBD induced a clear anxiolytic effect and a pattern of cerebral activity compatible with an anxiolytic activity."

In collaboration with Philip McGuire's lab in London, Crippa's team employed functional magnetic resonance imaging (fMRI) and "observed that CBD affected activation when subjects were processing intensely fearful stimuli, attenuating responses in the amygdala and cingulate cortex. The suppression of the amygdalar response was correlated to the drug effect of reducing fluctuations of skin conductance. Therefore, similar to the data obtained in animal models and results from studies in healthy volunteers, these results strongly suggest an anxiolytic action of CBD."