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) revoked 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 all clinical trials of a similar cannabinoid-blocker called Taranabant. The pattern of adverse psychiatric effects had become too obvious to conceal from Europe and European regulators.

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Regulators were concerned about Rimonabant use leading to an uptick in other cases that the cannabis 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 members 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 interferring 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 Mikos and others 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.)

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In collaboration with Philip McGuire’s lab in London, Crippa’s team employed functional magnetic resonance imaging (fMRI) and “observed that CBD affected activation in brain regions associated with affective and anxiety experiences. 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 anxigenic 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.”

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 the board. Dr. Denney anticipated sputtered out quickly.

The gusher of enlightenment that followed the rise and fall of Rimonabant, reporters and popularizers of 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 marijuana drug is made from cannabis. But thank you for the points you made. Best regards, Jeanne Whalen.”

This woman covers the pharmaceutical industry for the Wall St. Journal.

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, orthopedists, acupuncturists, osteopaths, and physical therapists, and prescribed Vioxx, 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 could, given his warning about Rimonabant in the summer of 2004.

Papers to be presented at the 2009 ICRS Meeting in Pescara, Italy, July 8-11, included:


• Cannabidiol May Act as a 5-HT1A Auto-Receptor Agonist to Reduce Pain: An Animal and Vomiting by Rock et al.

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

• Characterization of the Neuroprotective Effect of Cannabidiol After Oxygen and Glucose Deprivation of Newborn Mice Forebrain Slices by Romero et al.

• 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 Duh et al.

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

• Cannabidiol Reduces Lipopolysaccharide-Induced Vascular Dysfunction in the Mouse Brain: An Intravital Microscopy Study by Duh et al.

• CBD RESEARCHERS José Alexandre S. Crippa (standing, left), Antonio Waldo Zuardi (seated) and Jaime F. C. Hufak, Department of Neurosciences and Research, Division of Psychiatry, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto-SP, Brazil and INCIT-Translational Medicine, Brazil.