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) has ordered Sanofi-Aventis to stop selling Rimonabant, a drug that reduces appetite by blocking cannabinoid receptors in the brain. Some 700,000 people have 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. On Oct. 23 the EMEA said "Enough" in 12 languages.

The pattern of adverse psychiatric effects became too obvious to conceal from U.S. and European regulators.

Earlier in October Merck had abruptly canceled five clinical trials of a cannabinoid-blocker called Taranabant. The pattern of adverse psychiatric effects had become too obvious to conceal from U.S. and European regulators.

Unpublicized to date are adverse effects involving cancer, seizures, and other illnesses that the cannabinoid system plays a role in suppressing. (In August researchers at the MD Anderson Cancer Center reported that mice on rimonabant develop potentially cancerous polyps at a higher rate than controls.)

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 Sanofiscientists reported that Rimonabant had proven safe and effective inclinical trials involving 13,000 patients. That year the ICRS's achievementaward went to three Sanofi researchers and was presented by Raphael Mechoulam, the grand old man of the field. Many ICRSers got grants from Sanofi and/or the National Institute on Drug Abuse to study the potential of Rimonabant and other cannabinoid-antagonist drugs. Only a few expressedmisgivings –off the record— about the basic approach.

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

The article with Hergenrather's warning first appeared in CounterPunch July 24, 2004 —http://www.counterpunch.org/gardner07242004.html— and in O'S Autumn 2004 issue.

Tod Mikuriya, MD, wrote a letter to the U.S. Food and Drug Administration advising against approval.

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, and the late Tod Mikuriya, MD, wrote a letter 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 newfound caution undoubtedly stemmed from the thousands of deaths attributed to Vioxx.)

Why did they think it would work?

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.

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 curriculum at most medical schools. 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 ad said that the ECS could be targeted by drugs to combat "Metabolic Syndrome," a cluster of risk factors for diabetes defined by Sanofi marketers as a disease unto itself.


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NHS approval for drug banned in US

SUICIDE FEAR 'FAT PILL' GETS GO AHEAD

A WEIGHT-LOSS drug banned in the U.S. over fears it can heighten the risk of suicide has been given the go-ahead in Britain.

By Daniel Martin
Political Reporter

Acomplia will be available to overweight or obese patients who cannot take, or who have had no success with, the two other weight-loss drugs available on the Health Service.

But a series of scientific studies have raised concerns that it can induce suicidal thoughts in those already suffering from depression.

The drug, taken orally as a pill once a day, has not been authorised in the U.S. because of safety fears, although it is available in France and Germany.

Acomplia, also known as rimonabant, went on sale in Britain in June 2006 but approval from the National Institute for Health and Clinical Excellence, or NICE, for use on the NHS was issued only yesterday.

Trials have shown that it could help two out of five patients lose 10 per cent of their weight.

In July last year, the European Medicines Agency warned that rimonabant may be unsafe for patients suffering major depression or who were taking anti-depressants.

Evidence suggested one in ten of those taking the drug may develop mental side-effects

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Victory cry: Surpr

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Acomplia's Las 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 from the European market for safety reasons.

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 outquickly. 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."

To those who suspect a conscious decision by Prohibitionist publishers to prevent the public from learning about the cannabinoid receptor system, we say: never underestimate the role of bone-ignorant journalists.

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 are "potdocs." Hergenrather spent part of this past weekend drafting a letter to a Butte County judge who won't allow a patient of his to medicate with cannabis while on probation unless the patient gets a second approval from an orthopedist.

The patient is a middle-aged construction worker with a well-documented history of back pain for which he has 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 is the judge playing doctor, she doesn'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 to the distinguished pharmacologists in the summer of 2004.