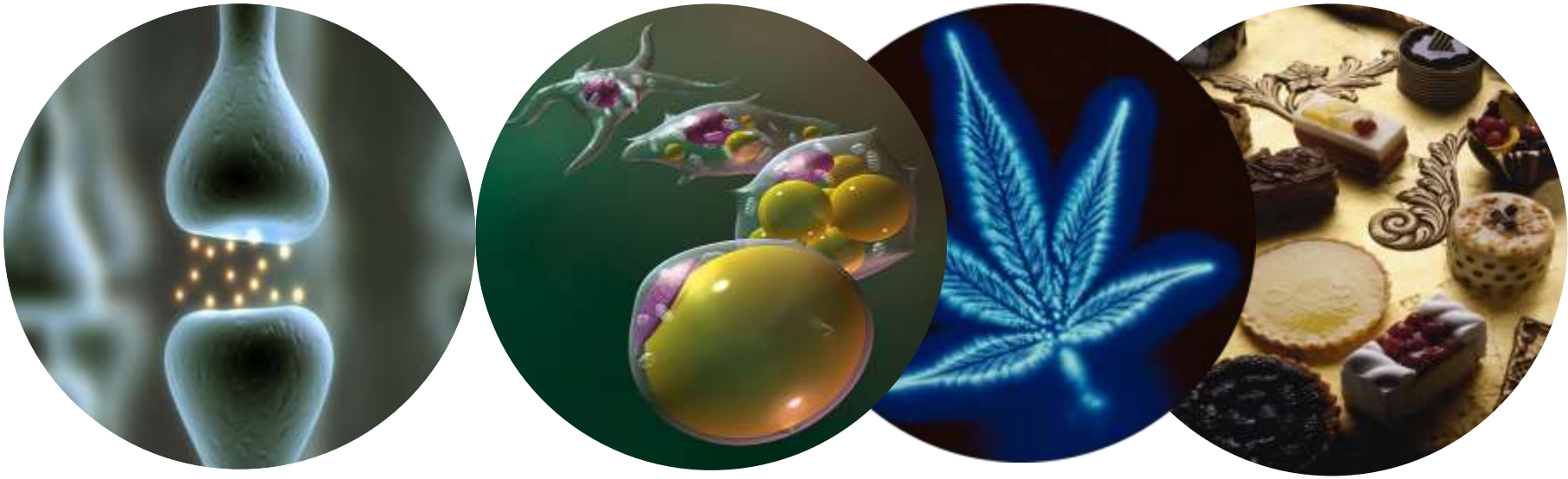
# Lessons learned from CB1 blockers: did we try to crack a nut with a sledgehammer ?



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Prof. Renger F. Witkamp
Nutrition and Pharmacology

# Sanofi-aventis to Discontinue all Clinical Trials with rimonabant

first MERCK

ODUCTS | NEWSROOM | INVESTOR RELATIONS | CAREER

Research & Development News

**Paris, November 5, 2008 -** Sanofi-aventis announced today that it has decided to discontinue the ongoing rimonabant clinical development program in all indications.

Today's company decision has been taken in light of recent demands by certain national health authorities. As a result the feasibility of the global clinical development program has been compromised.

Sanofi-aventis will inform Health Care Professionals as of today. Persons currently enrolled in these clinical trials should consult their clinical investigator to discuss their treatment.

**Merck Discontinues Development of Investigational Medicine Taranabant for Obesity**

WHITEHOUSE STATION, N.J., Oct. 2, 2008 - Merck & Co., Inc. will not see regulatory approval for taranabant, an investigational medicine, to treat ob and is discontinuing its Phase III clinical development program for tarana for obesity.

"Available Phase III data showed that both efficacy and adverse events we dose related, with greater efficacy and more adverse events in the higher doses. Therefore, after careful consideration, we determined that the ove profile of taranabant does not support further development for obesity," sa John Amatruda, M.D., senior vice president and research head, diabetes obesity, Merck Research Laboratories. "We thank the patients and investigators around the world who collaborated with us on the research program for taranabant and look forward to developing new medicines fo obesity to address the significant medical need posed by this disease."

# Pfizer Discontinues Development Program for Its Phase 3 Obesity Compound (CP-945,598)

NEW YORK--(BUSINESS WIRE)--Pfizer, Inc announced today that it is terminating the phase 3 development program for its investigational compound (CP-945,598) for weight management. CP-945,598 is a selective antagonist of the cannabinoid type 1 (CB1) receptor. Based on all currently available information and an ongoing review of the phase 3 program by an independent Data Monitoring Committee, Pfizer believes that the CP-945,598 compound has the potential to be a safe and effective treatment for weight management. However, the Company has decided to discontinue the development program based on changing regulatory perspectives on the risk/benefit profile of the CB1 class and likely new regulatory requirements for approval.

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sanofi aventis

Because health matters

press release

**ACOMPLIA® (RIMONABANT) RECEIVES MARKETING AUTHORISATION IN THE EUROPEAN UNION**

***First-in-class $CB_1$ blocker approved for the treatment of obese patients, or overweight patients with associated risk factors, such as type 2 diabetes or dyslipidaemia***

**Paris, France – June 21, 2006** – Sanofi-aventis announced today that the European Commission has granted marketing authorisation for ACOMPLIA® (rimonabant 20 mg/day) in all 25 European member states. ACOMPLIA®, discovered and developed by sanofi-aventis, is the first in a new class of drugs called $CB_1$ blockers. ACOMPLIA® is indicated as an adjunct to diet and exercise for the treatment of obese patients (BMI $\geq$ 30kg/m$^2$), or overweight patients (BMI >27kg/m$^2$) with associated risk factors, such as type 2 diabetes or dyslipidaemia.

The marketing authorisati
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# Depression and anxiety with rimonabant

The first endogenous cannabinoid was isolated in the early 1990s, followed soon after by identification of the endocannabinoid receptors $CB_1$ and $CB_2$. Clinical observations that cannabis stimulates appetite (the "munchies") suggested that the endocannabinoid system is involved in the control of energy balance.[1] Rimonabant, the first of the $CB_1$-receptor antagonists to be marketed, was developed as an anti-obesity agent on the premise that blocking central cannabinoid activity might reduce food intake.[2] Its efficacy for weight

showed that these adverse events developed early in treatment. Moreover, in a broader suite of rimonabant studies, the FDA identified substantial evidence for an increased risk of suicide attempts or suicidal ideation in participants who took rimonabant 20 mg compared with placebo (odds ratio 1·9, 95% CI 1·1–3·1).

These clinical findings coincide with reports of animal studies that implicate the $CB_1$ receptor in mediation of antidepressant-like or anxiolytic-like effects of the endocannabinoid system. Inhibition of the breakdown of

Lancet, 2007

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# Clearly, these side-effects were not expected, but....

- Where did it go wrong (if at all) ?
- Could (should) we have foreseen this ?
- What can we learn from it ?

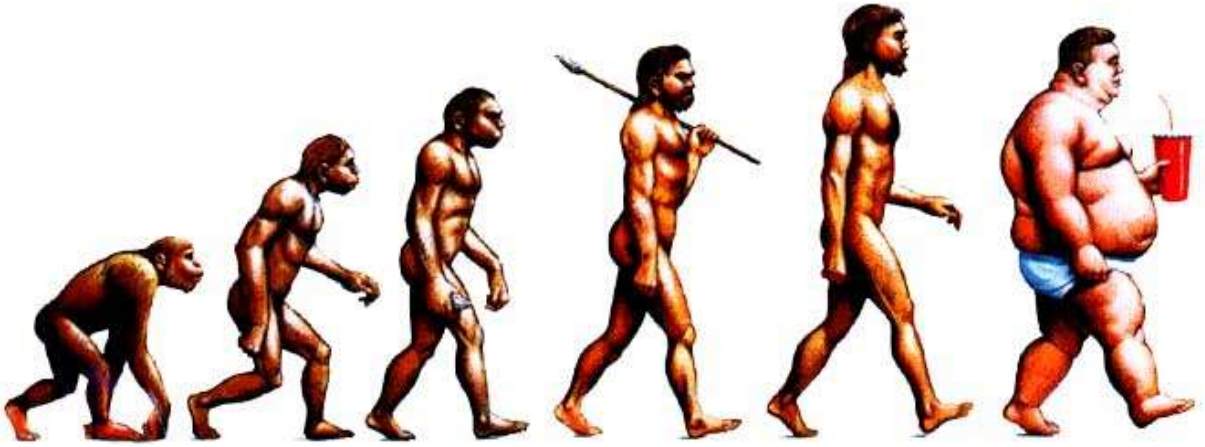
# Analysis: elements and drivers

- The obesity and metabolic syndrome market
- A pharmacological battle difficult to win
- A pleiotropic system as target
- First in class & relatively new target
- Risk-benefit balance : not too much credit

# Weight management market

- Problem with high prevalence
- Clear unmet medical and social need
- Not much competition so far
- Succesful drug will become blockbuster

# Pharmacological management of body weight: a battle against the most powerfull instincts



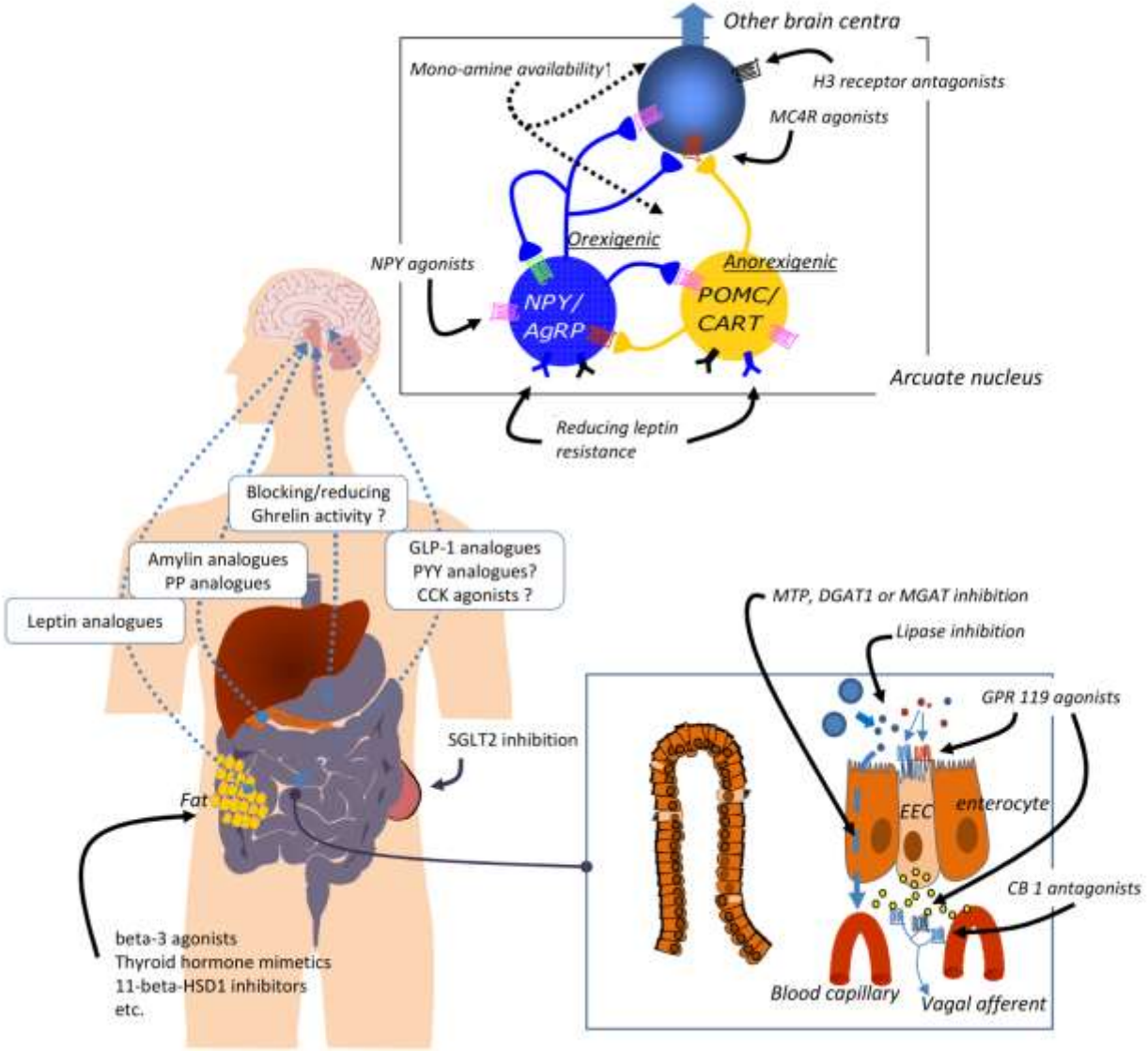
# Story of weight loss drugs is cumbersome and full of serendipity

*Unintended consequences of some treatments for obesity*

| Year | Drug | Consequence |
|---|---|---|
| 1893 | Thyroid | Hyperthyroidism |
| 1932 | Dinitrophenol | Cataracts/neuropathy |
| 1937 | Amphetamine | Addiction |
| 1968 | Rainbow pills | Deaths: arrhythmias |
| 1985 | Gelatin diets | Cardiac deaths |
| 1997 | Phentermine/fenfluramine | Valvulopathy |
| 1998 | Phenylpropanolamine | Strokes |
| 2003 | Ma huang | Heart attacks/strokes |

Bray GA & Greenway FL (2007) Pharmacological Reviews 59(2): 151-184.

# Some pharmacological targets under development




Witkamp, Pharm Res (2011) 28:1792–1818

# Development pipeline (mid 2012)

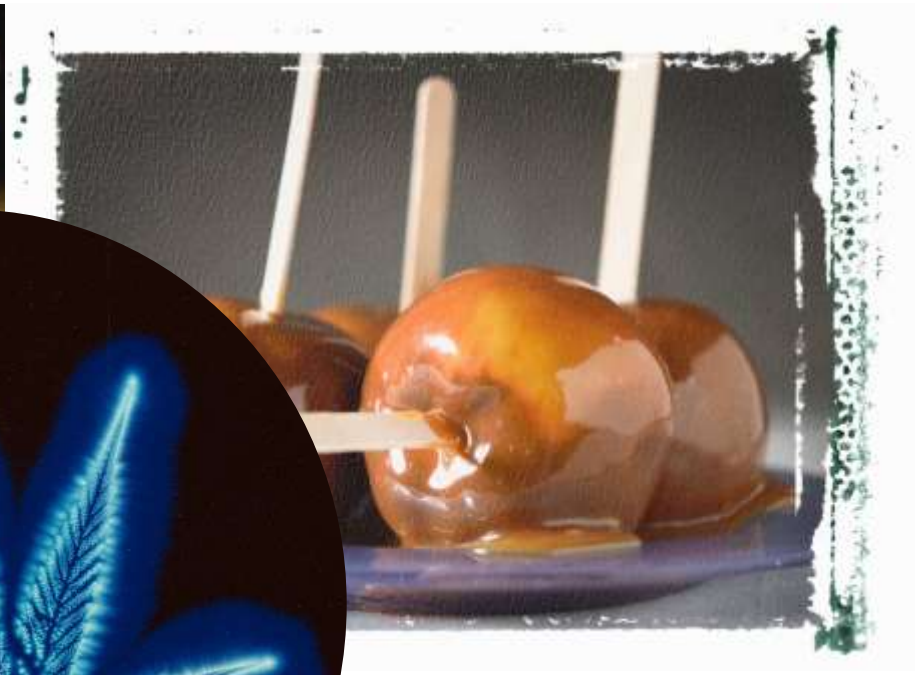
| Drug | Brand name (developer) | Stage of development | Frequency and route of administration | Mechanism of action | Efficacy* | Safety and tolerability concerns | Notes |
|---|---|---|---|---|---|---|---|
| Phentermine + topiramate FDC | Qsymia (Vivus) | Approved July 2012 | Once-daily oral | Noradrenergic agent, antiepileptic drug | 9–10% | Birth defect risk, minor elevation in heart rate | FDA has requested ten post-marketing studies and a CVOT |
| Lorcaserin | Belviq (Arena and Eisai) | Approved June 2012 | Twice-daily oral | Selective serotonin receptor agonist | 3–4% | Possible risk of valvulopathy in obese type 2 diabetics | FDA has requested six post-marketing studies and a CVOT |
| Bupropion + naltrexone FDC | Contrave (Orexigen and Takeda) | Pre-registered | Twice-daily oral | Dopamine and norepinephrine reuptake inhibitor, opioid receptor antagonist | 4–5% | Minor increase in heart rate and blood pressure | Undergoing 10,000 patient FDA-mandated pre-marketing CVOT |
| Liraglutide | Victoza‡ (Novo Nordisk) | Phase III¶ | Once-daily injectable | Glucagon-like peptide 1 analogue | 5–6% | Nausea, hypoglycaemia, risk for pancreatitis | A lower dose formulation is on the market for type 2 diabetes |
| Cetilistat | Cametor (Norgine and Takeda) | Phase III | Three times daily oral | Lipase inhibitor | <5% | Gastrointestinal side effects | No data reported since 2010 |
| Bupropion + zonisamide FDC | Empatic (Orexigen) | Phase II | Twice-daily oral | Dopamine and norepinephrine reuptake inhibitor, antiepileptic drug | 8–10% | Somnolence, dizziness, confusion, nausea | Development on hold |
| Tesofensine | (Neurosearch) | Phase II | Once-daily oral | Dopamine, norepinephrine and serotonin reuptake inhibitor | 9–11% | Increase in heart rate and blood pressure, mood alteration | Previously in development for Parkinson's and Alzheimer's disease |
| Velneperit | (Shionogi) | Phase II | Once-daily oral | Neuropeptide Y5 receptor antagonist | <5% | Potential liver signal | Follow-on compound in development |

CVOT, cardiovascular outcomes trial; FDC, fixed-dose combination. *Mean placebo-adjusted weight loss demonstrated in clinical studies. ‡Liraglutide is marketed as Victoza for type 2 diabetes. ¶Liraglutide was approved in Europe and in the United States in 2009 and 2010, respectively, as a treatment for type 2 diabetes.



Nature Reviews Drug Discovery sept 2012





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cannabinoids

endo-cannabinoids

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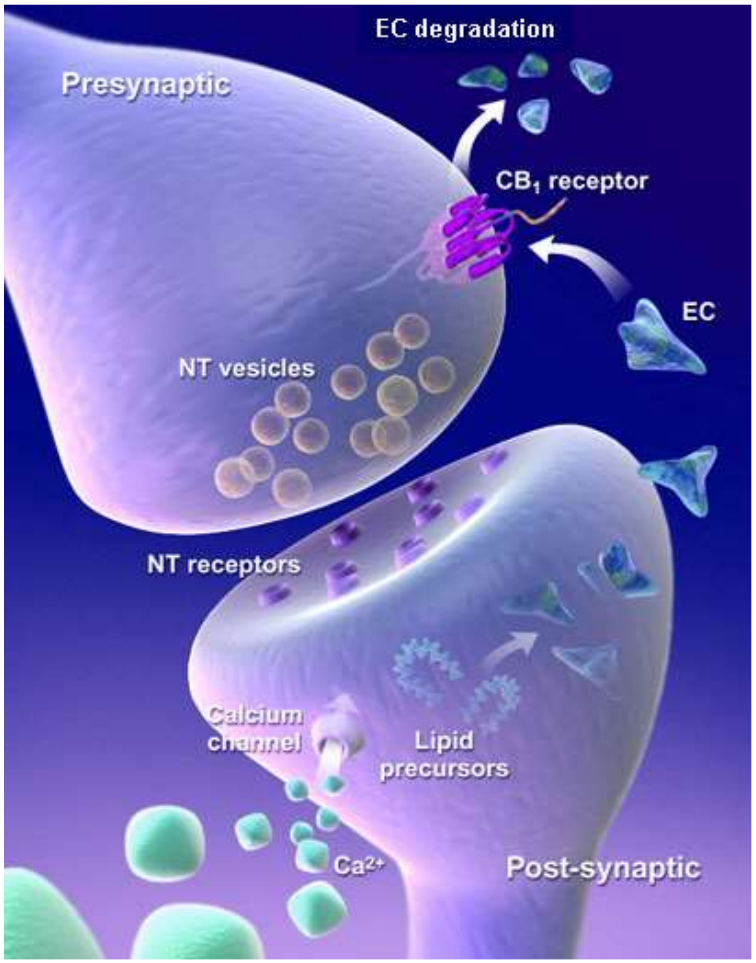
# The endo-cannabinoid system (ECS):

- Endocannabinoids:
  - Formed “on demand” from lipid precursors in postsynaptic cells
  - Many ligands, partly non-specific and overlapping with TRPV1, PPARα etc
  - Retrograde messengers, but also other routes
- Receptors: CB1,CB2….
  - Essential role in energy metabolism, satiation, rewarding, craving, inflammation etc
  - CB1 : central but also peripheral
  - CB2 : mainly peripheral



# Effects of CB1 stimulation: *non homeostatic* overconsumption and fat storage

***Hypothalamus*: hunger**
***N. Accumbens*: motivation to eat**

**Entero endocrine regulation: continue eating**

**Liver and adipose tissue: lipogenesis en lipid storage**

- ↑ Insuline resistance
- ↓ HDL-cholesterol
- ↑ Triglycerides
- ↓ Glucose uptake
- ↓ Adiponectine

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# In the brain: ECS stimulates *Hedonic Hunger*

Consumption of food just for pleasure and not to maintain energy homeostasis.

Food is consumed uniquely because of its gustatory rewarding properties.


FOOD SCIENCE

# Potato chips — the other natural way to get stoned

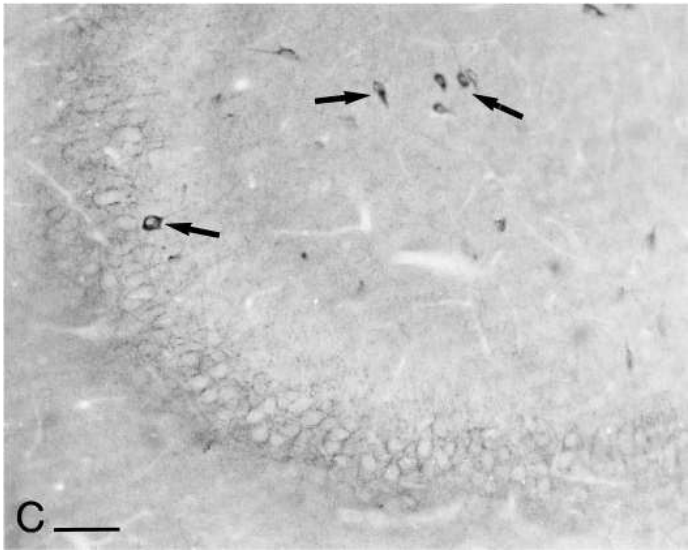
BY ESTHER INGLIS-ARKELL JUL 5, 2011 7:00 AM



Scientists have found out why people can put the brakes on eating sugar, but will go through an entire bag of potato chips, followed by a plate of fries. It turns out that fats get us stoned.

As much as extra desserts are blamed for the national waistline, it seems that most weight is gained not because of sweets, but because of fatty foods. Potato chips and french fries lead the way in American expansion, and it seems there's a reason for that. They make us feel good not just because of personal taste, but because of physical processes that start the moment they hit the tongue.

# CB1 receptor is highly abundant in brain



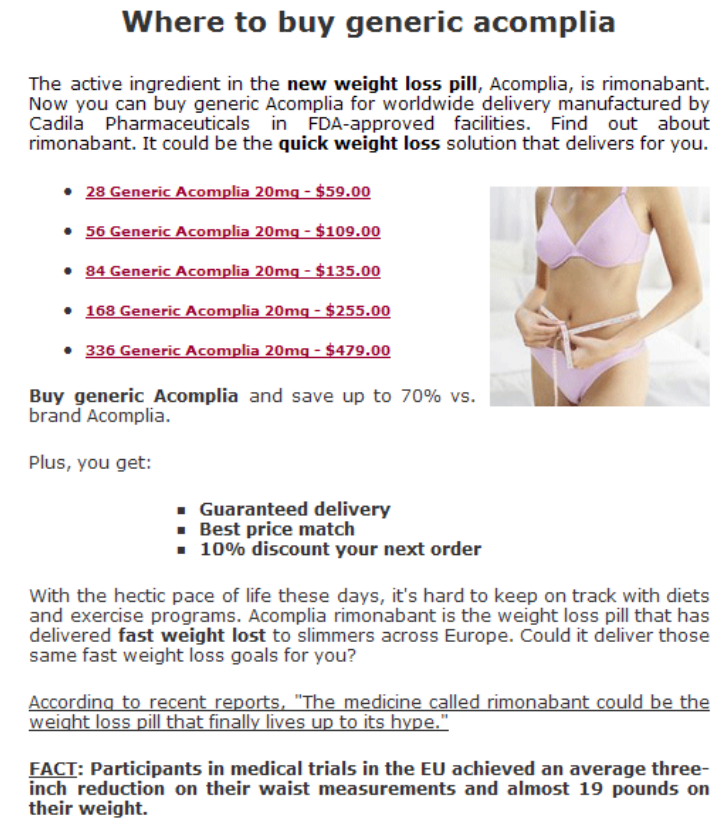

….. and linked to “hedonic hotspots”

# Rimonabant was an effective and promising drug

- Produced consistent weight loss.
- Caused also direct metabolic effects of peripheral $CB_1$ blockade (next to weight-dependent cardiometabolic effects)
- Approximately half of the overall effect of rimonabant was due to direct action on peripheral tissues for HDL-cholesterol, triglycerides, $HbA_{1c}$, insulin and adiponectin

# But what were the problems?

- CB1 = Pleiotropic target; ligands determine selectivity.
- Inverse agonists may not be good idea here
- Difficult kinetics, linked to side-
- Difficult endpoint: Rewarding/He
- Side-effects less well accepted i
- CNS side-effects difficult to mea



**Where to buy generic acomplia**

The active ingredient in the **new weight loss pill**, Acomplia, is rimonabant. Now you can buy generic Acomplia for worldwide delivery manufactured by Cadila Pharmaceuticals in FDA-approved facilities. Find out about rimonabant. It could be the **quick weight loss** solution that delivers for you.

- 28 Generic Acomplia 20mg - $59.00
- 56 Generic Acomplia 20mg - $109.00
- 84 Generic Acomplia 20mg - $135.00
- 168 Generic Acomplia 20mg - $255.00
- 336 Generic Acomplia 20mg - $479.00

**Buy generic Acomplia** and save up to 70% vs. brand Acomplia.

Plus, you get:

- **Guaranteed delivery**
- **Best price match**
- **10% discount your next order**

With the hectic pace of life these days, it's hard to keep on track with diets and exercise programs. Acomplia rimonabant is the weight loss pill that has delivered **fast weight lost** to slimmers across Europe. Could it deliver those same fast weight loss goals for you?

According to recent reports, "The medicine called rimonabant could be the weight loss pill that finally lives up to its hype."

**FACT: Participants in medical trials in the EU achieved an average three-inch reduction on their waist measurements and almost 19 pounds on their weight.**

# Possible rescue of the target: Second generation CB1 blockers

- Different kinetics : relatively lower brain concentrations and more peripheral action

- Different dynamics : no inverse agonists like rimonabant, but neutral antagonists or partial agonists

# Conclusions

- Weight loss is a difficult indication
  - Linked to well-being; hedonics
  - Multi-factorial, so are complications like MetSyndrome
- Did it go too fast ?
  - Still relatively new and complex target
  - Pharmacology not optimal
- Risk-benefit balance of class = challenging

# Lessons for the future ?

- Improvements of clinical trial design taking into account mechanism of action.
- Improve technical attrition (translational target to medicine)
- Develop/Hire experienced drug hunters (who don't just kill but ask the right questions)

# Lessons for the future (2) ?

- Human patient data and identification of best indication in early clinical development
- Tailoring for specific patient (sub)populations (pathology, genotype, etc.)
- Introduce creativity in translational and clinical research