Published in final edited form as:
Psychopharmacology (Berl). 2009 July ; 205(1): 171–174. doi:10.1007/s00213-009-1506-7.

The future of endocannabinoid-oriented clinical research after CB_1 antagonists

Bernard Le Foll, MD, PhD[1], **David A. Gorelick, MD, PhD**[2], and **Steven R. Goldberg, PhD**[3]

[1] Translational Addiction Research Laboratory, Centre for Addiction and Mental Health, University of Toronto. 33 Russell Street, Toronto, Canada

[2] Office of the Scientific Director, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Department of Health and Human Services, Baltimore, Maryland, USA

[3] Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Department of Health and Human Services, Baltimore, Maryland, USA

Abstract

Great interest has been shown by the medical community and the public in the cannabinoid CB_1 receptor antagonists, such as rimonabant, for treatment of obesity, metabolic syndrome, and possibly drug addiction. This novel class of drug has therapeutic potential for other disorders, as the endocannabinoid system is involved in various health conditions. However, rimonabant, the first clinically available member of this class of drugs, has been linked to increased risk of anxiety, depression, and suicidality. Due to those risks, the European Medicines Agency (EMEA) called for its withdrawal from the market in October, 2008. Shortly after this decision, several pharmaceutical companies (Sanofi-aventis, Merck, Pfizer, Solvay) announced they would stop further clinical research on this class of drug. Here, we provide an overview of those events and make several suggestions for continuing such clinical research, while safeguarding the safety of patients and clinical trial subjects.

Keywords

Rimonabant; CB1 receptor antagonist; pharmacotherapy; safety; drug dependence; addiction; obesity

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Obesity and tobacco use are the two highest preventable causes of morbidity and mortality in the developed world (Flegal et al. 2005; Hossain et al. 2007; Ogden et al. 2006; U.S. Department of Health and Human Services 2004). Since blocking the cannabinoid CB_1 receptor was shown to decrease eating and nicotine self-administration in animals (Le Foll et al. 2008; Pacher et al. 2006), there has been a great deal of interest in this novel class of drug. More broadly, the endogenous cannabinoid system is implicated in a substantial number of severe and frequent clinical disorders (Table 1) (Pacher et al. 2006). Therefore, it is possible that blocking endocannabinoid transmission could have benefits in various fields of medicine.

Corresponding author: Bernard Le Foll, MD, PhD, CCFP; Head, Translational Addiction Research Laboratory, CAMH; Associate Professor, University of Toronto. Centre for Addiction and Mental Health, 33 Russell Street, Toronto, Canada M5S 2S1. Tel: 416.535.8501, ext. 4772; Fax: 416.595.6922; Email: bernard_lefoll@camh.net.

As one example, CB_1 receptor antagonists show promise in treating drug addiction (De Vries and Schoffelmeer 2005; Le Foll et al. 2008; Le Foll and Goldberg 2005; Wiskerke et al. 2008), for which there is a need for more effective treatments (Le Foll and George 2007; Reuter and Pollack 2006). Blocking CB_1 receptors reduces motivation for Δ^9-tetrahydrocannabinol, the active ingredient of cannabis, in a non-human primate model (Justinova et al. 2008; Tanda et al. 2000) and partially blocks the psychological and cardiovascular effects of smoking a cannabis cigarette in humans (Huestis et al. 2007). Clinically validating these promises would be of value to the field of drug addiction.

Rimonabant (Acomplia,® Sanofi-aventis) was the first selective CB_1 ligand introduced into clinical practice. This CB_1 receptor antagonist (with inverse agonist action) has been shown efficacious as a treatment for obesity (Despres et al. 2008; Hampp et al. 2008) and for improving dyslipidemias, diabetes, and metabolic syndrome (Despres et al. 2005; Scheen 2008; Van Gaal et al. 2005). It had been approved as an obesity treatment in more than 50 countries worldwide, including the European Union (EU). Rimonabant was also being developed for smoking cessation, with statistically significant, albeit modest, evidence for efficacy (Cahill and Ussher 2007; Le Foll et al. 2008; Rigotti et al. 2009), especially in minimizing weight gain often associated with smoking cessation.

Tempering this promise has been a growing concern about the psychiatric safety of CB_1 receptor antagonists (Christensen et al. 2007; Food and Drug Administration Endocrinologic and Metabolic Advisory June 13, 2007; Rucker et al. 2007), notably increased rates of depression, anxiety and suicidality related to drug use. These psychiatric concerns led to the October, 2008 decision by the European Medicines Agency (EMEA) to suspend marketing of rimonabant in the EU. Following this decision, the drug-maker Sanofi-aventis announced on November 5th 2008 its decision to withdraw rimonabant from the market worldwide and to discontinue its ongoing rimonabant clinical development program for all indications (Sanofi Aventis 2008). Around the same time, several other CB_1 receptor antagonists/ inverse agonists not yet approved for marketing were withdrawn from clinical development by their developers, including taranabant (Merck) and otenabant (Pfizer), both in phase 3, and ibipinabant (Solvay/Bristol-Myers Squibb) and surinabant (Sanofi-aventis) in phase 2 (Jones 2008; Merck 2008)

It should be noted that rimonabant was eventually withdrawn from marketing in the EU because its clinical use was not following the criteria established to maximize its benefit/risk ratio, i.e., community clinicians were prescribing it to patients at high risk for depression and suicidality and many patients were not taking it long enough to achieve the potential benefits. We agree that the public should be protected from medications with unfavorable risk-benefit ratios. However, the unfavorable conditions that existed with rimonabant prescriptions in the community do not exist in the clinical research environment, where subjects are rigorously screened for eligibility and drug administration must adhere to the protocol schedule. We consider it premature to stop further clinical research on cannabinoid antagonists in important human diseases as a result of the termination of clinical development of currently available CB_1 receptor antagonists/inverse agonists. It is possible that several conditions which currently have no treatment may benefit from the use of such a class of drugs (Table 1). Cannabinoid CB_1 receptor antagonists/inverse agonists and other ligands modulating endocannabinoid transmission may have a very positive benefit-risk ratio for other indications. We therefore make several suggestions for continuing such important clinical research, while safeguarding the safety of patients and clinical trial subjects.

First, we suggest that rimonabant and similar compounds remain available for clinical research under strictly controlled circumstances that maximize safety, such as single-dose

studies, inpatient studies, or short-term outpatient studies with rigorously screened subjects under close monitoring. This would allow researchers to perform 'proof of principle' or 'proof of concept' clinical trials. In this regard, full and transparent disclosure of all safety data from clinical trials would advance our understanding of the risks associated with this class of compounds and hopefully improve the design of future clinical trials.

Second, we suggest continued development of more selective CB_1 receptor ligands. It is possible that the observed psychiatric adverse events were due, at least in part, either to inverse agonism properties or to excessive blockade of CB_1 receptors. Both rimonabant and taranabant showed evidence of inverse agonist activity in preclinical studies. It is possible that "cleaner" compounds that are neutral (so-called "pure") CB_1 antagonists or inverse agonists with little antagonism may have a more favorable pharmacological profile. For example, in animal studies, both CB_1 receptor neutral antagonists and inverse agonist/antagonists reduce food intake and food-reinforced behavior, while only the former cause nausea and vomiting (Salamone et al. 2007). Whether this dissociation between desired effects and side-effects holds for human psychiatric indications remains to be evaluated.

Another approach is development of CB_1 receptor antagonists/inverse agonists that do not act in the central nervous system, and so presumably would be devoid of psychiatric side-effects. Although such novel ligands might be ineffective for CNS-mediated disorders such as drug addiction, there is evidence that a peripheral antagonist can reduce feeding and weight gain in animals (Pavon et al. 2008). Other indications, such as coronary artery disease (Nissen et al. 2008; Sugamura et al. 2009), liver and pancreatic disease (Izzo and Camilleri 2008), inflammatory bowel disorders (Izzo and Camilleri 2008), and arthritis (Richardson et al. 2008) may also benefit from peripheral CB_1 antagonism.

Third, we suggest continued research on pharmacological approaches that bypass the CB_1 receptor and modulate the endocannabinoid system by different means. Targeting the enzyme fatty acid amide hydrolase (FAAH) (Gobbi et al. 2005; Kathuria et al. 2003; Scherma et al. 2008a), which breaks down endocannabinoids, or the endocannabinoid membrane transporter system (Beltramo et al. 1997), may have therapeutic utility, notably for nicotine addiction (Scherma et al. 2008b), while avoiding psychiatric side-effects

In conclusion, there is increasing evidence that the endocannabinoid system plays a significant role in various human illnesses. It is important to continue clinical research in this area and to evaluate promising preclinical findings. The recent termination of clinical development of one class of compounds should not deter continued work in this field, which holds the promise for meaningful clinical benefits.

Acknowledgments

Drs. Gorelick and Goldberg are supported by the Intramural Research Program, NIH, National Institute on Drug Abuse. Dr. Gorelick was an investigator in clinical trials of rimonabant at NIDA sponsored by Sanofi. He did not personally receive any funding from Sanofi. Drs. Le Foll and Goldberg report no competing interests.

References

Batkai S, Pacher P, Jarai Z, Wagner JA, Kunos G. Cannabinoid antagonist SR-141716 inhibits endotoxic hypotension by a cardiac mechanism not involving CB1 or CB2 receptors. Am J Physiol Heart Circ Physiol. 2004; 287:H595–600. [PubMed: 15059774]

Beltramo M, Stella N, Calignano A, Lin SY, Makriyannis A, Piomelli D. Functional role of high-affinity anandamide transport, as revealed by selective inhibition. Science. 1997; 277:1094–7. [PubMed: 9262477]

Cahill K, Ussher M. Cannabinoid type 1 receptor antagonists (rimonabant) for smoking cessation. Cochrane Database Syst Rev. 2007:CD005353.

Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. Lancet. 2007; 370:1706–13. [PubMed: 18022033]

De Vries TJ, Schoffelmeer AN. Cannabinoid CB1 receptors control conditioned drug seeking. Trends Pharmacol Sci. 2005; 26:420–6. [PubMed: 15992935]

Despres JP, Golay A, Sjostrom L. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. N Engl J Med. 2005; 353:2121–34. [PubMed: 16291982]

Despres JP, Ross R, Boka G, Almeras N, Lemieux I. Effect of Rimonabant on the High-Triglyceride/Low-HDL-Cholesterol Dyslipidemia, Intraabdominal Adiposity, and Liver Fat. The ADAGIO-Lipids Trial. Arterioscler Thromb Vasc Biol. 2008

Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. JAMA. 2005; 293:1861–7. [PubMed: 15840860]

Food and Drug Administration Endocrinologic and Metabolic Advisory. Briefing information, NDA 21-888 ZIMULTI (rimonabant)-Sanofi Aventis. June 132007 [(accessed March 13, 2008)]. http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4306b1-fda-backgrounder.pdf

Gobbi G, Bambico FR, Mangieri R, Bortolato M, Campolongo P, Solinas M, Cassano T, Morgese MG, Debonnel G, Duranti A, Tontini A, Tarzia G, Mor M, Trezza V, Goldberg SR, Cuomo V, Piomelli D. Antidepressant-like activity and modulation of brain monoaminergic transmission by blockade of anandamide hydrolysis. Proc Natl Acad Sci U S A. 2005; 102:18620–5. [PubMed: 16352709]

Habayeb OM, Taylor AH, Finney M, Evans MD, Konje JC. Plasma anandamide concentration and pregnancy outcome in women with threatened miscarriage. JAMA. 2008; 299:1135–6. [PubMed: 18334688]

Hampp C, Hartzema AG, Kauf TL. Cost-utility analysis of rimonabant in the treatment of obesity. Value Health. 2008; 11:389–99. [PubMed: 18179661]

Hossain P, Kawar B, El Nahas M. Obesity and diabetes in the developing world--a growing challenge. N Engl J Med. 2007; 356:213–5. [PubMed: 17229948]

Huestis MA, Boyd SJ, Heishman SJ, Preston KL, Bonnet D, Le Fur G, Gorelick DA. Single and multiple doses of rimonabant antagonize acute effects of smoked cannabis in male cannabis users. Psychopharmacology (Berl). 2007; 194:505–15. [PubMed: 17619859]

Izzo AA, Camilleri M. Emerging role of cannabinoids in gastrointestinal and liver diseases: basic and clinical aspects. Gut. 2008; 57:1140–55. [PubMed: 18397936]

Jones D. End of the line for cannabinoid receptor 1 as an anti-obesity target? Nat Rev Drug Discov. 2008; 7:961–2. [PubMed: 19043439]

Justinova Z, Munzar P, Panlilio LV, Yasar S, Redhi GH, Tanda G, Goldberg SR. Blockade of THC-Seeking Behavior and Relapse in Monkeys by the Cannabinoid CB(1)-Receptor Antagonist Rimonabant. Neuropsychopharmacology. 2008

Kathuria S, Gaetani S, Fegley D, Valino F, Duranti A, Tontini A, Mor M, Tarzia G, La Rana G, Calignano A, Giustino A, Tattoli M, Palmery M, Cuomo V, Piomelli D. Modulation of anxiety through blockade of anandamide hydrolysis. Nat Med. 2003; 9:76–81. [PubMed: 12461523]

Le Foll B, Forget B, Aubin HJ, Goldberg SR. Blocking cannabinoid CB1 receptors for the treatment of nicotine dependence: insights from pre-clinical and clinical studies. Addict Biol. 2008; 13:239–52. [PubMed: 18482433]

Le Foll B, George TP. Treatment of tobacco dependence: integrating recent progress into practice. CMAJ. 2007; 177:1373–1380. [PubMed: 18025429]

Le Foll B, Goldberg SR. Cannabinoid CB_1 receptor antagonists as promising new medications for drug dependence. J Pharmacol Exp Ther. 2005; 312:875–883. [PubMed: 15525797]

Merck. Merck Discontinues Development of Investigational Medicine Taranabant for Obesity. 2008. http://www.merck.com/newsroom/press_releases/research_and_development/2008_1002.html

Nissen SE, Nicholls SJ, Wolski K, Rodes-Cabau J, Cannon CP, Deanfield JE, Despres JP, Kastelein JJ, Steinhubl SR, Kapadia S, Yasin M, Ruzyllo W, Gaudin C, Job B, Hu B, Bhatt DL, Lincoff AM, Tuzcu EM. Effect of rimonabant on progression of atherosclerosis in patients with abdominal

obesity and coronary artery disease: the STRADIVARIUS randomized controlled trial. JAMA. 2008; 299:1547–60. [PubMed: 18387931]

Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. JAMA. 2006; 295:1549–55. [PubMed: 16595758]

Pacher P, Batkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol Rev. 2006; 58:389–462. [PubMed: 16968947]

Pavon FJ, Serrano A, Perez-Valero V, Jagerovic N, Hernandez-Folgado L, Bermudez-Silva FJ, Macias M, Goya P, de Fonseca FR. Central versus peripheral antagonism of cannabinoid CB1 receptor in obesity: effects of LH-21, a peripherally acting neutral cannabinoid receptor antagonist, in Zucker rats. J Neuroendocrinol 20 Suppl. 2008; 1:116–23.

Reuter P, Pollack H. How much can treatment reduce national drug problems? Addiction. 2006; 101:341–7. [PubMed: 16499507]

Richardson D, Pearson RG, Kurian N, Latif ML, Garle MJ, Barrett DA, Kendall DA, Scammell BE, Reeve AJ, Chapman V. Characterisation of the cannabinoid receptor system in synovial tissue and fluid in patients with osteoarthritis and rheumatoid arthritis. Arthritis Res Ther. 2008; 10:R43. [PubMed: 18416822]

Rigotti NA, Gonzales D, Dale LC, Lawrence D, Chang Y. A randomized controlled trial of adding the nicotine patch to rimonabant for smoking cessation: efficacy, safety and weight gain. Addiction. 2009; 104:266–76. [PubMed: 19149823]

Rosenstock J, Hollander P, Chevalier S, Iranmanesh A. SERENADE: the Study Evaluating Rimonabant Efficacy in Drug-naive Diabetic Patients: effects of monotherapy with rimonabant, the first selective CB1 receptor antagonist, on glycemic control, body weight, and lipid profile in drug-naive type 2 diabetes. Diabetes Care. 2008; 31:2169–76. [PubMed: 18678611]

Rucker D, Padwal R, Li SK, Curioni C, Lau DC. Long term pharmacotherapy for obesity and overweight: updated meta-analysis. BMJ. 2007; 335:1194–9. [PubMed: 18006966]

Salamone JD, McLaughlin PJ, Sink K, Makriyannis A, Parker LA. Cannabinoid CB1 receptor inverse agonists and neutral antagonists: effects on food intake, food-reinforced behavior and food aversions. Physiol Behav. 2007; 91:383–8. [PubMed: 17521686]

Sanofi Aventis. Sanofi-Aventis to discountinue all clinical trials with Rimonabant. Paris: 2008.

Scheen AJ. CB1 receptor blockade and its impact on cardiometabolic risk factors: overview of the RIO programme with rimonabant. J Neuroendocrinol. 2008; 20(Suppl 1):139–46. [PubMed: 18426513]

Scherma M, Fadda P, Le Foll B, Forget B, Fratta W, Goldberg SR, Tanda G. The endocannabinoid system: a new molecular target for the treatment of tobacco addiction. CNS Neurol Disord Drug Targets. 2008a; 7:468–81. [PubMed: 19128204]

Scherma M, Panlilio LV, Fadda P, Fattore L, Gamaleddin I, Le Foll B, Justinova Z, Mikics E, Haller J, Medalie J, Stroik J, Barnes C, Yasar S, Tanda G, Piomelli D, Fratta W, Goldberg SR. Inhibition of anandamide hydrolysis by URB597 reverses abuse-related behavioral and neurochemical effects of nicotine in rats. J Pharmacol Exp Ther. 2008b; 327:482–90. [PubMed: 18725543]

Soyka M, Koller G, Schmidt P, Lesch OM, Leweke M, Fehr C, Gann H, Mann KF. Cannabinoid receptor 1 blocker rimonabant (SR 141716) for treatment of alcohol dependence: results from a placebo-controlled, double-blind trial. J Clin Psychopharmacol. 2008; 28:317–24. [PubMed: 18480689]

Sugamura K, Sugiyama S, Nozaki T, Matsuzawa Y, Izumiya Y, Miyata K, Nakayama M, Kaikita K, Obata T, Takeya M, Ogawa H. Activated endocannabinoid system in coronary artery disease and antiinflammatory effects of cannabinoid 1 receptor blockade on macrophages. Circulation. 2009; 119:28–36. [PubMed: 19103987]

Tanda G, Munzar P, Goldberg SR. Self-administration behavior is maintained by the psychoactive ingredient of marijuana in squirrel monkeys. Nat Neurosci. 2000; 3:1073–4. [PubMed: 11036260]

U.S. Department of Health and Human Services. The Health Consequences of Smoking: A Report of the Surgeon General. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; Atlanta, GA: 2004.

Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rossner S. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. Lancet. 2005; 365:1389–97. [PubMed: 15836887]

Van Gaal LF, Scheen AJ, Rissanen AM, Rossner S, Hanotin C, Ziegler O. Long-term effect of CB1 blockade with rimonabant on cardiometabolic risk factors: two year results from the RIO-Europe Study. Eur Heart J. 2008; 29:1761–71. [PubMed: 18417461]

Wiskerke J, Pattij T, Schoffelmeer AN, De Vries TJ. The role of CB1 receptors in psychostimulant addiction. Addict Biol. 2008; 13:225–38. [PubMed: 18482432]

Table 1

Possible therapeutic indications for cannabinoid CB_1 antagonists/inverse agonists

- Obesity (Christensen et al. 2007; Van Gaal et al. 2008)
- Dyslipidemia (Despres et al. 2008; Van Gaal et al. 2008)
- Metabolic syndrome (Despres et al. 2008; Van Gaal et al. 2008)
- Diabetes (Rosenstock et al. 2008)
- Coronary artery disease (Nissen et al. 2008; Sugamura et al. 2009)
- Tobacco dependence (Cahill and Ussher 2007; Le Foll et al. 2008)
- Other drug dependence (cannabis, alcohol, opiates, psychostimulants) (Le Foll and Goldberg 2005; Soyka et al. 2008; Wiskerke et al. 2008)
- Hypotension/shock (Batkai et al. 2004)
- Liver disease (Izzo and Camilleri 2008)
- Gastro-intestinal disease (Izzo and Camilleri 2008)
- Reproductive health (e.g., miscarriage) (Habayeb et al. 2008)
- Arthritis (Richardson et al. 2008)