UPDATING

The psychiatric side-effects of rimonabant

Os efeitos-colaterais psiquiátricos do rimonabanto

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Abstract

Objective: *Experimental evidence has suggested that drugs that enhance cannabinoid type-1 (CB1) receptor activity may induce anxiolytic and antidepressant effects, whilst the opposite has been reported with antagonists. Thus, the objective of the present review is to discuss the potential psychiatric side-effects of CB1 receptor antagonists, such as rimonabant, which has been recently marketed in several countries for the treatment of smoking cessation, obesity and associated metabolic disorders.* ***Method****: Literature searches were performed in PubMed and SciELO databases up to February 2009. The terms searched were "*obesity*", "rimonabant", "cannabinoids", "unwanted effects", "diabetes", "smoking cessation" and "side-effects".* ***Results****: Clinical trials have revealed that rimonabant may promote weight loss in obese patients, although it may also induce symptoms of anxiety and depression.* ***Discussion****: Patients taking CB1 receptor antagonists should be carefully investigated for psychiatric side-effects. These drugs should not be prescribed for those already suffering from mental disorders. Nevertheless, the development of new compounds targeting the endocannabinoid system for the treatment of several conditions would be necessary and opportune.*

Descriptors*: Cannabinoids; Drug effects; Anxiety; Depression; Obesity*

Resumo

Objetivo: *Evidência experimental sugere que drogas que aumentam a atividade dos receptores canabinóides tipo 1 (CB1) podem induzir efeitos ansiolíticos ou antidepressivos, enquanto que o oposto tem sido relatado com antagonistas. Assim, o objetivo da presente revisão é discutir os potenciais efeitos-colaterais psiquiátricos de antagonistas do receptor CB1, como o rimonabanto, que foi recentemente liberado para comercialização em diversos países para o tratamento do tabagismo, obesidade e de desordens metabólicas associadas.* ***Método****: Foi realizada uma busca na literatura no PubMed e Scielo até fevereiro de 2009, com os termos* "obesity", "rimonabant", "cannabinoids", "unwanted effects", "diabetes" , "smoking cessation" e "side effects". ***Resultados:*** *Ensaios clínicos revelaram que o rimonabanto pode produzir perda de peso em pacientes obesos, embora também possa induzir sintomas de ansiedade e depressão.* ***Discussão****: Pacientes tomando antagonistas do receptor CB1 devem ser cuidadosamente examinados quanto aos efeitos-colaterais psiquiátricos. Estas drogas não devem ser prescritas a indivíduos que já sofrem de transtornos mentais. Entretanto, o desenvolvimento de novos compostos que atuem no sistema endocanabinóide para o tratamento das mais diversas condições parece necessário e oportuno.*

Descritores: *Canabinóides; Efeitos de drogas; Ansiedade; Depressão; Obesidade*

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Introduction

Rimonabant (Sanofi-Aventis®), a cannabinoid receptor antagonist/inverse agonist, has reached the market as a drug for the treatment of obesity in several countries. The approval for its use was based on few clinical trials claiming that it is an effective and safe anti-obesity drug[1-6] with a potential for aiding smoking cessation.[7] However, this should be interpreted with caution considering the limited information on the long-term effects. Furthermore, clinical studies have revealed that this drug may induce significant psychiatric side-effects, namely anxiety and depression. Actually, this was expected based on data available from animal models.

A license for rimonabant for weight reduction indication was received from the European Medicines Agency (EMEA) under the brand name Accomplia® in June 2006. In April 26th, 2007, the Brazilian Medicines Agency (*Agência Nacional de Vigilância Sanitária*, ANVISA) approved this compound for the same indication. In June 2007, the FDA refused to follow the EMEA and ANVISA and denied a license for weight reduction, as they had done a year earlier for smoking, until further trials gave positive assurances on side-effects.[8] In reviewing postmarketing surveillance data on the drug, the EU's Committee for Medicinal Products for Human Use found that rimonabant doubled the risk of psychiatric disorders in obese or overweight patients taking the drug, leading to an amendment to the Summary of Product Characteristics in August 2007. This fact culminated in the EMEA asking for rimonabant to be withdrawn from sale in October 2008, pending further trial results. An ANVISA resolution on November 3rd recommended that the company suspend sales and manipulation of the drug in Brazil due to safety concerns. Sanofi-Aventis® thus complied and withdrew rimonabant simultaneously from all other non-European Union (EU) markets, and on November 5th the manufacturer announced that they had discontinued all requested trial work on the drug.[9]

The withdrawal of rimonabant reflects the problems of premature approval of drugs. Obesity, associated metabolic disorders and tobacco dependence are major public health problems for which treatment options are limited. Particularly in this field, innovative pharmacological approaches often raise hopes in health professionals and in the general public, since they would have a huge impact in terms of public health and preventive medicine. However, novel drugs may not necessarily match such expectations, mainly due to low efficacy and poor safety profile. Thus, the objective of the present review is to discuss the side-effects and the psychiatric relevance of rimonabant and substances that act by similar mechanisms.

Method

For evaluating the psychiatric side-effects of rimonabant and cannabinoid receptor antagonists or inverse agonists, a literature search was performed in PubMed and SciELO up to February 2009. The terms entered were "obesity", "rimonabant", "cannabinoid", "unwanted effects", "diabetes", "smoking cessation", and "side-effects", which retrieved 71 articles. Inclusion criteria were usage of the English language and employing human beings as subjects, resulting in the inclusion of 49 studies. In addition, an extensive literature was consulted for the introduction on the endocannabinoid system and its role in anxiety and depression.

Results

1. The endocannabinoid system

The herb *Cannabis sativa* has been used for medical purpose, and as a drug of abuse, for 4000 years.[10-12] However, only in the middle of the 20th century its constituents were identified, with the chemical characterization of Δ^9-tetrahydrocannabinol (Δ^9-THC) and other substances. The pharmacology of Δ^9-THC has been largely elucidated and a specific receptor identified, the cannabinoid type 1 (CB1) receptor, responsible for the brain effects of cannabis.[13] The existence of receptors specific for cannabinoids suggested that endogenous cannabinoid-like substances should also be present in the brain. Accordingly, the arachidonic acid derivates 2-arachidonoyl ethanolamide (anandamide, after the Sanskrit word *ananda*, meaning "bliss") and 2-arachidonoyl glycerol (2-AG) were identified as endogenous agonists at the cannabinoid receptor, hence the name endocannabinoids.[14,15] In addition, a second receptor (CB2) has been characterized, mainly located in the immune system.[13]

Endocannabinoids are atypical neurotransmitters released from postsynaptic neurons and later re-internalized through a putative uptake process. This is followed by hydrolysis by the enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), which break down anandamide and 2-AG, respectively.[13] The endocannabinoids, their receptors and the enzymes for synthesis and hydrolysis constitute the endocannabinoid system (Figure 1).

This system is widely distributed in the brain. CB1 receptors are particularly enriched in regions possibly responsible for processing emotions, such as hippocampus, amygdala, periaqueductal gray, prefrontal cortex and hypothalamus.[16] This distribution provides a neuroanatomical basis for the effects of cannabis, which can induce states reported as relaxation, well-being and reduced anxiety.[17] Based on experimental evidence, other physiological functions have been attributed to the endocannabinoid system. For instance, this system seems to be relevant for motor responses, as revealed by the dense expression of CB1 receptors in the basal ganglia and cerebellum and by the sedative effects of cannabinoids. CB1 receptors also mediate analgesic effects, an anciently known property of cannabis.[18] Finally, endocannabinoids are also relevant

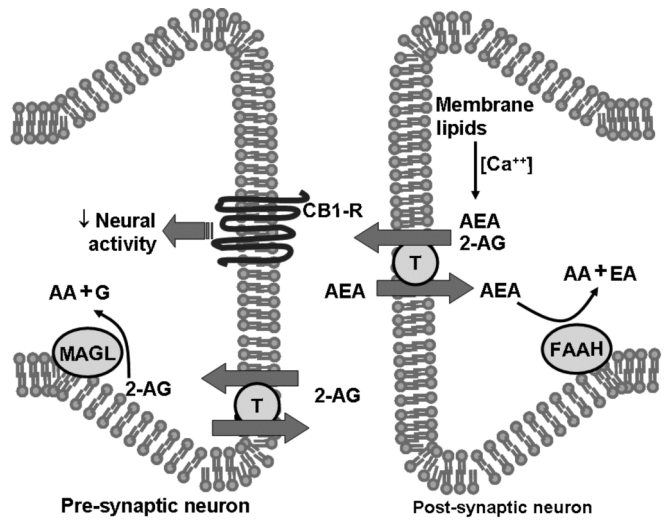

Figure 1 - Schematic representation of the endocannabinoid system at a synaptic cleft. Endogenous cannabinoids are synthesized from membrane lipids in postsynaptic neurons after calcium (Ca^{++}) increase. They diffuse and activate pre-synaptic CB1 receptors that induce intracellular cascades, inhibiting neural activity and neurotransmitter release. Anandamide (arachidonoyl ethanolamide, AEA) undergoes re-uptake and hydrolysis by fatty acid amide hydrolase (FAAH), whereas 2-arachidonoyl glycerol (2-AG) is broken down by monoacylglycerol lipase (MAGL). The existence of a membrane endocannabinoid-transporter (T) is controversial.

for motivation for food consumption, and an increase in appetite is a widely known effect of cannabis.[19,20]

These proposed functions of endocannabinoids were initially inferred from their distribution in the brain and from the effects of Δ^9-THC or its synthetic counterparts, such as nabilone. The relevance of the endocannabinoid system was further clarified after the synthesis of the first CB1 receptor antagonist, SR141716A or rimonabant.[21,22] This drug was developed by Sanofi-Aventis® and proved to be an invaluable pharmacological tool for studying the functions of endocannabinoids due to its selectivity and oral activity. Rimonabant was able to block the effects of cannabinoids *in vitro* and in experimental animals,[21,22] inducing behavioral effects that will be discussed later. In addition, a study with humans showed that it was able to block the psychological and cardiovascular effects of smoked marijuana.[23] Although it may have properties of inverse agonists *in vitro,*[24] the *in vivo* implications of this mechanism remain unknown. Thus, for the matter of simplicity, this review will refer to this and similar drugs as antagonists.

A well-known effect of cannabis is an increase in appetite. As a corollary, studies with laboratory animals revealed that rimonabant promote weight loss by reducing food intake and inducing peripheral and central effects on fat metabolism.[19,20] However, preclinical studies with this drug have also unveiled a tonic role for endocannabinoids in the modulation of anxiety and depression, as discussed below.

2. Role of the endocannabinoid system in anxiety and mood states

Cannabis smoking may induce a myriad of changes in mood and anxiety-related responses. This may depend on drug, individual and environmental factors such as dose, context and frequency of use, previous experience and emotional state.[25] Whilst variable, the effects of low doses are often described as rewarding and relaxing, with feelings of "high", relaxation, reduced anxiety and increased sociability.[11,17,26]

Several works have investigated the effects of Δ^9-THC or its synthetic counterparts administered to laboratory animals exposed to models predictive of anxiolytic-like activity. Obviously, animal models do not entirely mimic the complex features of psychiatric disorders. However, they can predict the clinical effects of substances and provide insights in the biological mechanisms of these diseases.[27] Generally, they are able to reproduce the effects of cannabinoids observed in humans. Thus, several authors have reported that, similarly to diazepam, Δ^9-THC and synthetic cannabinoids induced anxiolytic-like effects in laboratory rats and mice.[28-31] In addition, cannabinoids have also antidepressant-like properties.[32]

These data suggest that the CB1 receptor may restrain anxiety responses and prevent stress-induced alterations in mood states. Further supporting this notion are the effects of drugs that enhance the levels of endogenous cannabinoids. Two different processes have been explored to increase the brain levels of anandamide, namely membrane transport ("uptake") and hydrolysis. Inhibition of anandamide uptake induces anxiolytic- and antidepressant-like effects in rats,[30-35] although the later strategy has not been further developed due to the fact that the membrane transporter has not been characterized. More explored have been the effects on anandamide-hydrolysis. A specific FAAH inhibitor has been developed, called URB597. This drug also has anxiolytic- and antidepressant-like properties without the sedative effects seen with cannabinoids, which directly activate CB1 receptors.[30,36-38] Thus, endocannabinoids seems to modulate emotional responses and has emerged as a potential therapeutic target.

Experiments with rimonabant and other CB1 receptor antagonists have further consolidated this conclusion. Contrary to agonist, these drugs induce anxiogenic-like effects in laboratory animals[30,38-40] and aggravate the consequences of stress.[41] In addition, CB1 blockade impairs the extinction of fear conditioned to a tone previously paired with foot-shock, a model reminiscent of posttraumatic stress.[42] Thus, a set-point may exist in which endocannabinoid could keep emotional responses in a normal range and whose disruption may lead to anxiety and depression.[25]

Despite evidence that an endocannabinoid tonus should be maintained, rimonabant has reached the market as an alternative for the treatment of obesity. So far, the limited clinical information available on the efficacy and safety of this drug are in line with the results obtained from animal models.

3. Therapeutic potential and side-effects of CB1 receptor antagonists

CB1 receptors antagonists have been investigated mainly as a potential strategy for treating obesity and associated metabolic disorders.[19-20] Despite their putative clinical applications, the experimental evidence discussed above heralded the notion that rimonabant could induce psychiatric effects. This prediction has been confirmed by the clinical trials discussed below.

Apart from a few studies, information about the effects of rimonabant in humans is still scant. The first clinical trial with this drug aimed at assessing the antipsychotic efficacy of four investigational compounds.[43] Subjects were patients with schizophrenia or schizoaffective disorder who received placebo (n = 98), rimonabant 20mg (n = 72), a serotonin-2A/2C antagonist (n = 74), a neurokinin-3 antagonist (n = 70), a neurotensin-1 antagonist (n = 69), and haloperidol as a positive control (n = 98). Duration was 6 weeks. Only the serotonin-2A/2C and neurokinin-3 antagonists were better than placebo, though worse than haloperidol. No major psychiatric side-effects were reported.

As for the anti-obesity effects, the initial large multicenter, randomized, placebo-controlled clinical trials were the Rimonabant in Obesity Studies (RIO Studies), which have checked the effects of this drug on weight loss, waist circumference and metabolic parameters in diverse populations of overweight or obese patients.[1-5] In all cases, patients were also prescribed a hypocaloric diet and advised on increased physical activity. Psychiatric disorders were exclusion criteria, and side-effects were evaluated by the Hospital Anxiety and Depression Scale (HAD), which may be acceptable to screen for depression and anxiety in non-psychiatric patients, but it is not suitable as a primary outcome measure for depression.[44] Finally, it should be noticed that all the RIO-Studies were funded by Sanofi-Aventis®, which holds the patent for rimonabant. The company participated in the study design, data collection and analysis, and in manuscript preparations.[1-5] This company also funded the Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant – The Intravascular Ultrasound Study (STRADIVARIUS), which, contrary to the RIO Studies, did include psychiatric patients.[6] The main characteristics of these studies are summarized in Table 1. In the course of the treatments, many patients have abandoned both the RIO and STRADIVARIUS Studies due to general psychiatric side-effects, anxiety and depression. The absolute numbers and percentages for the groups placebo or rimonabant 20mg are presented in Table 2.

Table 1 - Main characteristics of the RIO, STRADIVARIUS, SERENADE, CIRRUS and ADAGIO-Lipids Studies (for further details, please see text)

Study	Population	Age of patients (years)	Duration (Months)	Groups	Psychiatric patients
RIO Europe[1] (Van Gaal et al., 2005)	1,507 obese patients with or without comorbidities (Europe)	18-76	12 months	Placebo and Rimonabant 5 or 20mg/day	Not included
RIO Europe, second year[5] (Van Gaal et al., 2008)			12 months		
RIO Lipids[2] (Després et al., 2005)	1,036 obese patients with untreated dyslipidemia (eight different countries)	20-70	12 months		
RIO North America[3] (Pi-Sunyer et al., 2006)	3,045 obese patients with or without co-morbidities (North America)	18-79	24 months		
RIO Diabetes[4] (Scheen et al., 2006)	1,047 obese type 2 diabetics treated with monotherapy (Europe, North and South America)	18-70	12 months		
STRADIVARIUS[6] (Nissen et al., 2008)	839 obese patients with metabolic syndrome/coronary disease (North America, Europe and Australia)	18-60	18 months	Placebo and Rimonabant 20mg/day	Included: 25% of patients in each group
SERENADE[51] (Rosenstock et al., 2008)	278 type 2 diabetics treated with monotherapy (Europe, North and South America)	≥ 18	6 months	Placebo and Rimonabant 20mg/day	Included: history of depression
CIRRUS[7] (Rigotti et al., 2009)	755 tobacco smokers (North America)	≥ 18	2 weeks	Rimonabant 20mg/day and placebo patch or nicotine patch	Included: history of depression or Anxiety
ADAGIO-Lipids[53] (Després et al., 2009)	799 abdominally obese patients with atherogenic dyslipidemia (Europe, Asia, Africa, Oceania, North and South America)	≥ 18	12 months	Placebo and Rimonabant 20mg/day	Included: history of depression

In the RIO-Europe Study, 1,507 obese patients have taken placebo, 5 or 20mg of the drug daily.[1] Both doses induced a reduction in body weight after one year of treatment, as compared to placebo. In addition, the higher dose induced greater improvements in several metabolic measures.[1] Despite these clinical improvements, the authors described psychiatric side-effects as detected by the HAD employed to evaluate mood. In some cases, the effects were severe, leading patients to abandon the trial (Table 2). An analysis of the second year of this study has been published with similar outcomes.[5] These data are summarized in Table 2.

Concerns on the safety of rimonabant have further increased after the RIO-Lipids Study, which for 1 year evaluated the effect on 1,036 overweight or obese patients with dyslipidemia taking placebo or daily doses of 5 or 20mg.[2] As in the RIO-Europe Study, the most common symptoms leading patients to drop out of the study were depression and anxiety (Table 2). Although the percentage of patients leaving the trial was similar among the groups, those taking 20mg attributed it more to adverse events, mainly anxiety and depression.[2]

The outcomes of these studies were replicated in the RIO-North America Study, which involved 3,045 subjects over 2 years. Rimonabant 20mg associated with hypocaloric diet induced a significant reduction in body weight in a population of obese patients.[3] However, the same side-effects present in the former studies were reported. Actually, the trial was limited by a high dropout rate (Table 2). The author stated that the overall incidence of adverse events leading to withdrawal was greater with 20mg, mainly due to anxiety and depression.[3]

Finally, in the RIO-Diabetes Study, 1,047 overweight or obese patients with type 2 diabetes were assigned to placebo or rimonabant 5 or 20mg/day. Weight loss and improvement of cardiovascular and metabolic risk factors were significantly greater after one year in both rimonabant groups as compared to placebo.[4] Discontinuation due to adverse effects was more common in rimonabant-treated patients, mainly due to depressed mood disorders (Table 2). However, the authors concluded that no serious adverse events linked to psychiatric disorders occurred.[4]

Thus, studies with different populations of obese subjects revealed that rimonabant has a potential to induce anxiety and depression. Actually, the assumptions of these studies may even be conservative. Since psychiatric patients were not included, these trials do not entirely mimic the clinical practice and underestimate the potential problems to be found with this drug, which might eventually be prescribed for patients already suffering from anxiety or depression, disorders commonly associated with obesity that could be aggravated by such compounds.[45,46] In fact, a remarkable report by the Advisory Committee of the US Food and Drug Administration (FDA) scrutinized the data from the RIO-Studies and raised even more concerns over this drug. This report indicated that rimonabant significantly increased risk of suicide attempts or ideation and that 26% of participants taking 20mg had some psychiatric side-effects compared to 14% taking placebo. In addition to depression and anxiety, there were more cases of irritability, insomnia, stress and panic attacks.[47] Accordingly, rimonabant has not been approved in the USA. In addition, Christensen et al. performed a meta-analysis of the four RIO studies, further unveiling that patients receiving 20mg were 2.5 and 3.0 times more likely to discontinue treatment because of depression or depressive symptoms and because of anxiety, respectively.[48] This meta-analysis also showed that, accordingly to the HAD Scale, rimonabant was associated with significant increases in anxiety.[48] An independent meta-analysis of diverse anti-obesity drugs pointed in the same direction.[49] Efficacy and safety were further analyzed pooling data obtained from a total of 5,580 non-diabetic and 1,047 diabetic patients from the RIO-Studies.[50] With the dose of 20mg, body weight reduction was

Table 2 - Absolute numbers (and percentages) of patients taking placebo or Rimonabant 20mg that abandoned the RIO, STRADIVARIUS, SERENADE, CIRRUS and ADAGIO-Lipids Studies due to diverse psychiatric disorders and specifically to anxiety or depression

Study	Group (n)	Psychiatric disorders	Anxiety	Depression
RIO Europe[1] (Van Gaal et al., 2005)	Placebo (305)	17 (5.6)	1 (0.3)	4 (1.3)
	Rimonabant (599)	47 (7.8)	6 (1.0)	14 (2.3)
RIO Europe second year[5] (Van Gaal et al., 2008)	Placebo (305)	1 (0.6)	0 (0)	1 (0.6)
	Rimonabant (599)	6 (1.7)	0 (0)	3 (0.8)
RIO Europe, first plus second year[5] (Van Gaal et al., 2008)	Placebo (305)	18 (5.9)	1 (0.3)	5 (1.6)
	Rimonabant (599)	53 (8.8)	6 (1.0)	17 (2.8)
RIO Lipids[2] (Després et al., 2005)	Placebo (342)	-	2 (0.6)	2 (0.6)
	Rimonabant (346)	-	6 (1.7)	10 (2.9)
RIO North America[3] (Pi-Sunyer et al., 2006)	Placebo (607)	14 (2.3)	2 (0.3)	8 (1.3)
	Rimonabant (1219)	76 (6.2)	12 (1.0)	27 (2.2)
RIO Diabetes[4] (Scheen et al., 2006)	Placebo (348)	-	0	3 (0.9)
	Rimonabant (339)	-	2 (0.6)	11 (3)
STRADIVARIUS[6]	Placebo (417)	13 (3.1)	3 (0.7)	5 (1.2)
(Nissen et al., 2008)	Rimonabant (422)	40 (9.5)	13 (3.1)	15 (3.6)
SERENADE[51] (Rosenstock et al., 2008)	Placebo (140)	0	0	0
	Rimonabant (138)	7 (5.1)	0	3 (2.2)
CIRRUS[7] (Rigotti et al., 2009)	Rimonabant plus placebo patch (362)	20 (5.5)	3 (0.8)	3 (0.8)
	Rimonabant plus nicotine patch (367)	19 (5.2)	5 (1.8)	4 (1.1)
ADAGIO-Lipids[53] (Després et al., 2009)	Placebo (395)	-	4 (1.0)	5 (1.3)
	Rimonabant (404)	-	9 (2.2)	8 (2.0)

6.5kg and waist circumference 6.4cm on average in the non-diabetic population. The authors stated that "serious adverse events were infrequent and almost equivalent to placebo". However, the rimonabant 20mg group (2,503 patients) was associated with a higher discontinuation due to depressive disorders (1.9%) and anxiety (1.0%) as compared to those receiving placebo (1,602 patients), whose rates of discontinuation were 0.8 and 0.3% for depressive and anxiety disorders, respectively.[50]

In addition to the RIO-Studies, Sanofi-Aventis® also funded the Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant – The Intravascular Ultrasound Study (STRADIVARIUS), a randomized, placebo-controlled clinical trial that enrolled 839 patients in North America, Europe and Australia[6] (Table 1). The authors described a significant effect of rimonabant 20mg on weight loss, though not in coronary artery disease progression. As for the adverse effects, an extremely relevant characteristic of this study was that psychiatric disorders were not exclusion criteria, contrary to the RIO-Studies. Thus, it detected alarming higher levels of psychiatric side-effects, namely anxiety and depression, and may reflect better the potential effects to be found in the routine clinical practice, further raising the concerns on the safety of rimonabant. Adverse effects for psychiatric disorders were statistically significant, 28.4 and 43.4% in the placebo and rimonabant 20mg groups, respectively. Anxiety and depression have accounted for this difference. Furthermore, the same factors significantly led to discontinuation, 3.1 and 9.5% of patients in placebo and drug groups, respectively (Table 2).

Recently, Sanofi-Aventis® funded the Study Evaluating Rimonabant Efficacy in Drug-Naive Diabetic Patients (SERENADE).[51] In this 6-month, randomized, double-blind, placebo-controlled trial of 20mg/day rimonabant, the glucose-lowering efficacy and safety of rimonabant monotherapy was assessed in 278 drug-naive type 2 diabetic patients (Table 1). The SERENADE study was the first trial to use A1C as the primary endpoint. Rimonabant monotherapy significantly improved glycemic control, body weight (waist circumference and weight loss), and lipid profile (triglycerides, and HDL cholesterol) in drug-naive type 2 diabetic patients. The safety profile of 20mg rimonabant in SERENADE was similar to that in the RIO-Diabetes study. The incidence of psychiatric disorders was higher with rimonabant versus placebo, and more patients receiving rimonabant experienced anxiety (5.8 *vs.* 3.6%, respectively) or depressed mood (5.8 *vs.* 0.7%, respectively) versus placebo (Table 2). One patient in the rimonabant group (0.7%) reported suicide ideation, judged by the investigator to be a symptom of depressed mood; although no cases of attempted or completed suicide were reported. The authors raised the need of further studies to better establish the benefit-to-risk profile of rimonabant.

Because obesity and tobacco dependence are the two major causes of preventable mortality and morbidity in many developed countries, a drug to treat both disorders was an exciting prospect.[52] Moreover, it is well-known that smoking cessation rates might be improved by combining drugs (such as bupropion or varenicline) with nicotine replacement and by reducing postcessation weight gain. Therefore, rimonabant was added on nicotine patch to test its smoking cessation efficacy in the CIRRUS study.[7] In a randomized, double-blind, placebo-controlled trial, 755 smokers (15 cigarettes/day) were given rimonabant (20mg daily) open-label for 9 weeks. The 735 participants who completed the first week of treatment

were randomized at day 8 (target quit day) to add a nicotine patch (n = 369) or placebo patch (n = 366) for 10 weeks (21mg daily for 8 weeks plus a 2-week taper). They also received weekly smoking counseling and were followed for 24 weeks. The authors observed that adding a nicotine patch to rimonabant increased smoking cessation rates over rimonabant alone (39.0 *vs.* 21.3%, respectively) in all other efficacy measures. Depression and anxiety-related adverse events occurred in 32 (4.2%) and 44 (5.8%) subjects, respectively; eight (1.1%) and nine (1.2%) subjects stopped the drug use due to depression and anxiety, respectively.

The most recently published clinical study with rimonabant is the ADAGIO-Lipids trial (An International Study of Rimonabant in Dyslipidemia with AtheroGenic Risk in Abdominally Obese Patients).[53] In this study the authors assessed the effect of rimonabant on cardiometabolic risk factors and intra-abdominal and liver fat. The ADAGIO-Lipids study was conducted in 799 patients with abdominal obesity and with the high triglyceride/low HDL-cholesterol dyslipidemia, who were randomized to placebo or rimonabant 20mg/day for 1 year. Rimonabant 20mg significantly improved multiple cardiometabolic risk markers and induced significant reductions in both intra-abdominal and liver fat. The safety profile of rimonabant was consistent and closely follows those from the previous studies. Anxiety and depression were again the most frequent psychiatric adverse events leading to premature treatment discontinuation: nine patients (2.2%) and four patients (1.0%) for anxiety; and eight patients (2.0%) and five patients (1.3%) for depression, in the rimonabant and placebo groups, respectively.

At the time of writing of this review, other clinical trials with rimonabant were being conducted (http://clinicaltrials.gov/ct2/results?term=rimonabant, accessed February 19th, 2009). Some of them are: Comprehensive Rimonabant Evaluation Study of Cardiovascular ENDpoints and Outcomes (CRESCENDO Study); Atherosclerosis Underlying Development Assessed By Intima-Media Thickness In Patients On Rimonabant (AUDITOR Study); Visceral Fat Reduction Assessed by CT-Scan on Rimonabant (VICTORIA Study); Study Evaluating Rimonabant Efficacy in Insulin-Treated Diabetic Patients (ARPEGGIO Study); Rimonabant In Prediabetic Subjects To Delay Onset Of Type 2 Diabetes (RAPSODI Study). However, the clinical relevance of these studies was passed when the benefit/risk ratio was evaluated by EMEA leading to the suspension of the drug from the market and also to the termination of the scientifically important and extensive research program by the manufacturer (www.sanofi-aventis.com). Another compound, taranabant, an inverse agonist at the CB1 receptor, has been developed by Merck® Research Laboratories and tested for the same purpose as rimonabant,[54-56] although outcomes seem to be similar. Taranabant is able to reduce body weight in obese subjects, though it may also induce psychiatric adverse effects. In the initial clinical study, 15% of patients experiencing psychiatric adverse effects, mainly anxiety, dropped out from the study[56] Both a single oral dose and a multiple administrations study in healthy volunteers reported anxiety and mood changes as adverse experiences.[54,55] However, it is still early for any meaningful analysis on the safety and efficacy of this drug. Considering that taranabant works by the same mechanism as rimonabant, more similarities than differences were expected. Thus, not surprisingly, Merck & Co announced the suspension of all research with this experimental obesity drug on October 2nd, 2008, since the available Phase III data showed that both efficacy and adverse events were dose related, with greater efficacy and more adverse events in the higher doses. In November 2008, Pfizer® did the same for another CB1 blocker, CP-945,598, which was also in Phase III trials for obesity.

Conclusion

The CB1 receptor antagonist rimonabant was approved for the treatment of obesity and soon removed from the market due to its psychiatric adverse effects. This drug has also been investigated for several other purposes such as treating diabetes, promoting smoking cessation and reducing alcohol consumption. So far, the data available are scant and have been compared to placebo, not with other active drugs. In any case, it already allows the conclusion that it may induce psychiatric side-effects, mainly anxiety and depression, though also agitation, eating disorders, irritability, aggression and insomnia. Possibly, the results discussed above may even be conservative and underestimate the problem, because in several studies psychiatric patients were not included and the scales used might not have detected all potential psychiatric adverse effects. Also, in some trials the exclusion criteria were vague, such as "severe psychological illness", which might have led to an over- or underestimation of the psychiatric adverse effects. Additionally, the endpoint reported in some studies was depressed mood disorders, an umbrella term consisting of depression, depressive mood, major depression, dysthymia and depressive symptoms, which are disorders with different severity and clinical implications. Finally, other psychiatric side-effects of rimonabant have not been completely well investigated yet, such as psychosis, other eating disorders, as well as the lo ng-term psychiatric effects of such compound.

The mechanisms through which CB1 receptor blockade increase anxiety and depression remain unclear. One possibility could be that endocannabinoids keep an appropriate neurochemical balance between glutamate and gamma-aminobutyric acid (GABA), in such a way that blocking CB1 receptor may disrupt this set-point and misbalance neurotransmitter activity, inhibiting GABA and favoring a glutamatergic tonus.[25] Another mechanism could involve the physiological activity of anandamide at CB1 or vanilloid (TRPV1) receptors. Preclinical data have shown that both receptors are activated by anandamide, although while CB1-mediated mechanisms may attenuate anxiety, TRPV1 may be aversive.[57] Thus, when CB1 receptors are blocked, anandamide would preferentially activate TRPV1 receptors inducing aversive reactions.

While rimonabant increases the likelihood of depressive and anxiogenic episodes, this effect is more pronounced in patients with a history of depression, suggesting that blocking CB1 receptor is more likely to exacerbate existing conditions rather than producing them in healthy individuals. In case CB1 receptor antagonists were to be prescribed, a careful selection of patients would be necessary and the presence of psychiatric disorders should be a formal contraindication. As in all cases of preventive medicine, health benefits would have been discounted heavily on the basis that the avoidance of death and disease in the future is less important to society than death and disease now.[52]

On the other hand, recent preclinical findings suggesting that cannabinoid CB1 receptor agonists and endocannabinoid enhancers possess antidepressant-like[58] and anti-addiction[59] properties, and the reported clinical evidence that the CB1 antagonist rimonabant increases the risk of depression and anxiety, support the notion that the endocannabinoid system represents a novel target in the treatment of mood disorders. Therefore, some researchers think

that abandoning this therapeutic avenue would be premature, as developing drugs that act in slightly different ways at the CB1 receptor would be a potential option to overcome the problems that have beset current endocannabinoid agents.[60] For instance, the non-psychomimetic major cannabis constituent, cannabidiol (CBD), has shown to be capable of antagonizing CB1/CB2 receptor agonists at reasonably low concentrations.[61] In spite of its low affinity for CB1 and CB2 receptors, CBD has shown several potential therapeutic properties, including antidepressive,[33] anxiolytic,[62] antipsychotic,[63] anti-diabetes[64] and motor diseases effects.[65] Studies of such compound in smoking cessation among other conditions are underway by our group.

To conclude, the CB1 receptor antagonist rimonabant may indeed increase anxiety and depression in humans. This is in accordance with preclinical experiments showing that endocannabinoids may mediate anxiolytic- and antidepressant-like effects in laboratory animals. From a clinical perspective, the advantages and restrictions of this drug must be critically questioned, although the study and development of new compounds targeting the endocannabinoid system for the treatment of obesity, diabetes, tobacco dependence and other conditions would be necessary and opportune.

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Disclosures

Writting group member	Employment	Research grant[1]	Other research grant or medical continuous education[2]	Speaker's honoraria	Ownership interest	Consultant/ Advisory board	Other[3]
Fabrício A. Moreira	ICB-UFMG	CAPES*	-	-	-	-	-
José Alexandre Crippa	FMRP-USP	FAPESP** CNPq*** CAPES** FAEPA*	FAEPA*	-	-	-	FUNPEC* Pfiser* Elli-Lilly* Bristol* THC-Pharm*

** Modest*
*** Significant*
**** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*
Note: ICB-UFMG = Instituto de Ciências Biológicas da Universidade Federal de Minas Gerais; FMRP-USP = Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo; CAPES = Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; FAPESP = Fundação de Amparo à Pesquisa do Estado de São Paulo; CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico; FAEPA = Fundação de Apoio ao Ensino, Pesquisa e Assistência do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo; FUNPEC = Fundação de Pesquisas Científicas de Ribeirão Preto.
For more information, see Instructions for authors.

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