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SCIENTIFIC REVIEW

The Toxicological Evaluation of Rimonabant, Taranabant, Surinabant and Otenabant In The Treatment of Obesity: Why The Trials On Endocannabinoid Receptor Antagonists and Inverse Agonists Are Suspended?

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The Toxicological Evaluation of Rimonabant, Taranabant Surinabant and Otenabant in the Treatment of Obesity: Why the Trials on Endocannabinoid Receptor Antagonists and Inverse Agonists are Suspended?

Summary

Obesity is a condition in which excess body fat has accumulated to the high extent that may have adverse effects on health. Obesity may lead to reduced life quality and expectancy. Besides, it may cause serious health problems. Several anorectic anti-obesitic drugs have been developed with quite a few entering clinical trials. Currently, there are only two drugs (sibutramine and orlistat) commercially available. Drugs acting on endocannabinoid system (EC) were expected to be successful on preventing weight gain. Rimonabant was the first to be on market in 2006. However, the drug's approval has been withdrawn in 2008 due to its adverse effects, especially of its potential to cause psychiatric disorders. Other trials on EC inverse agonists or antagonists have also been suspended for now mostly for regulatory issues. This review will focus on anti-obesitic drugs affecting on EC and their toxicological outcomes. The suspension of clinical trials on these drugs will also be discussed.

Key Words: *obesity, endocannobinoid antagonists, endocannobinoid partial agonists, rimonabant, taranabantKeywords: Zingiber officinalis, HeLa, L929, anticancer effect, antimicrobial activity.*

Obezite Tedavisinde Kullanılan Rimonabant, Taranabant Surinabant ve Otenabant'ın Toksikolojik Açıdan Değerlendirilmesi: Endocannabinoid Reseptör Antagonistleri ve Ters Agonistler Üzerindeki Denemeler Neden Durduruldu?

Özet

Obezite, vücut yağının sağlık üzerine olumsuz etkiler yaratabilecek şekilde yüksek miktarda birikmesidir. Hayat kalitesinin ve beklentisinin azalmasına yol açabilir. Ayrıca, ciddi sağlık problemlerine neden olabilir Birçok anorektik anti-obezitik ilaç geliştirilmiş, bunların çok azı klinik çalışmalara girebilmiştir. Obezite tedavisinde kullanılan iki ilacın (sibutramin ve orlistat) satışı hali hazırda mevcuttur. Endokannabinoid sistem (EC) üzerine etki eden ilaçların da kilo alımını önlemede başarılı olabilecekleri düşünülmüştür. Rimonabant, 2006'da satışa sunulan ilk ürün olmuştur. Ancak, özellikle psikiyatrik bozukluklar başta olmak üzere ters etkilere neden olduğu için 2008'de ilacın satışı durdurulmuştur. EC ters agonistleri veya antagonistleri ile olan diğer çalışmalar da özellikle regulatör nedenlerle askıya alınmıştır. Bu derlemede EC'yi etkileyen anti-obezitik ilaçlardan ve toksikolojik etkilerinden söz edilecektir. Ayrıca bu ilaçlar üzerine yapılan klinik araştırmaların neden durdurulduğundan bahsedilecektir.

Anahtar Kelimeler: *obezite, endokannobinoid antagonistler, endokannobinoid parsiyel agonistler, rimonabant, taranabant*

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INTRODUCTION

World Health Organization (WHO) defines overweight as body mass index (BMI) of at least 25 kg/m^2 and obesity as BMI of at least 30 kg/m^2 (1). However, health authorities and researchers in the field started to give the overweight limit as 27 kg/m^2 according to increase in BMI throughout the

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world. More than 1.1 billion people in the world are estimated to be overweight, around 320 million of which are calculated to be obese. It is predicted that 1.7 billion people may be exposed to weight-related health problems while 2.5 million of them die of problems related to high BMI. These numbers are expected to be doubled by the year 2030 (2). The rising prevalence of obesity and obesity-related comorbities elevate the health costs and reduce the quality of life (3). The currently available drugs (sibutramine, orlistat) with Food and Drug Administration (FDA) approval have limited efficiency (4). New drugs are needed with high efficiency and low toxicity in the treatment of obesity.

This review will focus on the newly developed drugs with anti-obesitic mode of action, why they were suspended when they were on the market or on clinical trials, and the potential toxicological outcomes in the usage of these drugs.

Endocannabinoid System

The mood altering effects of *Cannabis sativa* are well-recognized and the plant has been used therapeutically and recreationally for centuries for different medical reasons. Marijuana is the illegal drug made from mature flowers and leaves of the plant. The use of marijuana has stimulant, depressant, hallucinogenic and antiphysicotic effects. Besides, it stimulates appetite. The active compounds of the plant are tetrahydrocannabinol (Δ^9-tetrahydrocannabinol; THC; (–) – (6a*R*,10a*R*) – 6,6,9 – trimethyl – 3 – pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromen-1-ol) and cannabidiol (2-((1S,6S)-3-methyl-6-(prop-1-en-2-yl) cyclohex-2-enyl)-5-pentylbenzene-1,3-diol). Synthetic Δ^9 THC (dronabinol) is approved in the United States for the treatment of nausea and vomiting associated with chemotherapy as well as appetite stimulate in AIDS (5).

The pharmacological actions of THC result from its binding to the cannabinoid receptor-1 (CB-1) (6). Cannabidiol does not bind to CB-1 or cannabinoid receptor-2 (CB-2) receptors but it does block the effects of cannabinoid agonists by an unknown indirect way (7). CB-1s are coupled through $G_{i/o}$ proteins and inhibit adenylate cyclase and activate mitogen-activated protein (MAP) kinase. In addition, activation of CB_1s inhibit presynaptic N- and P/Q-type calcium channels and activate rectifying potassium channels inwardly (5, 8, 9). CB-1 antagonists produce inverse cannabimimetic effects that are opposite in direction from those produced by agonists for these receptors (5, 10, 11). This caused an interest in the use of endogenous cannabinoid receptor agonists and antagonists for weight-related disorders.

Endocannabinoids are polyunsaturated phospholipids - derived from eicosanoids produced on demand from arachidonic acid that elicit many biological responses, including counteracting stimuli such as food deprivation, aversive memories and pain. In brain they act in a retrograde manner (moving from posynaptic neurons to presynaptic CB-1 receptors) and are rapidly cleared (12). The endocannabinoid system (EC) has two major receptors: CB-1 and CB-2 and two major ligands, anadamide and 2-arachidonylglycerol (2-AG). CB-1 has a location in several areas of brain, including hypothalamus. It is also located in adipocytes, muscles and gastrointestinal tract (13-15). Endocannabinoid passage across membranes is a passive and transporter dependent issue. This transporter is called "endocannabinoid membrane transporter (EMT)" (5, 16). Stimulation of this receptor in fat cells gives signal to lipogenesis, and inhibits adipokin. As adipokin has antidiabetic and antiatherosclerotic effects, these effects are also inhibited by this stimulation (17). Additional endocannabinoids include virodhamine (O-arachidonoyl ethanolamine), noladin ether (2-arachidonoyl glyceryl ether) and N-arachidonoyl dopamine (NADA) (18). Cannabinoid receptor-related processes are involved in cognition, memory, anxiety, control of appetite, emesis, motor behavior, sensory, autonomic and neuroendocrine responses, immune responses and inflammatory effects (19).

The EC was found to be overactive in obese animals in both genetic and diet-induced obesity. As a result, research began to develop a potential antagonist of CB-1s (20, 21). The rationale of using CB-1 receptor antagonist was very simple: If the receptor agonist cannabis enhanced appetite, blockage of the receptor would lead to appetite loss anecdotally

(22). Of potential drugs affecting the EC system, CB-1 antagonists received the most attention. The primary indication is obesity and the secondary indications are disorders that have a prominent craving component. However, clinical studies suggested that CB-1 antagonists have significant metabolic effects that are beyond decreasing caloric intake merely (23).

The first approach to develop CB-1 antagonists in the late 1980´s was to modify the structure of THC but the results were disappointing. In the early 1990´s a new family of cannabinoid agonists was discovered from the non-steroidal anti-inflammatory drug pravadoline, which led to the discovery of aminoalkyl indole antagonists with some but limited success. As the search based on the structure of agonists was disappointing, it was no surprise that the first potent and selective CB-1 antagonist belonged to an entirely new chemical family. In 1994 the first selective cannabinoid antagonist, rimonabant, was introduced to the market. It belonged to a family of 1,5-diarylpyrazoles (24, 25).

Though the early discovered CB antagonists were not a big success, the researchers are still going on to synthesize new compounds related to EC as the problem with the synthesized drugs is not a problem of efficacy but a problem of safety. The effects of CB-1 antagonists and inverse agonists are given in the **Figure 1.**

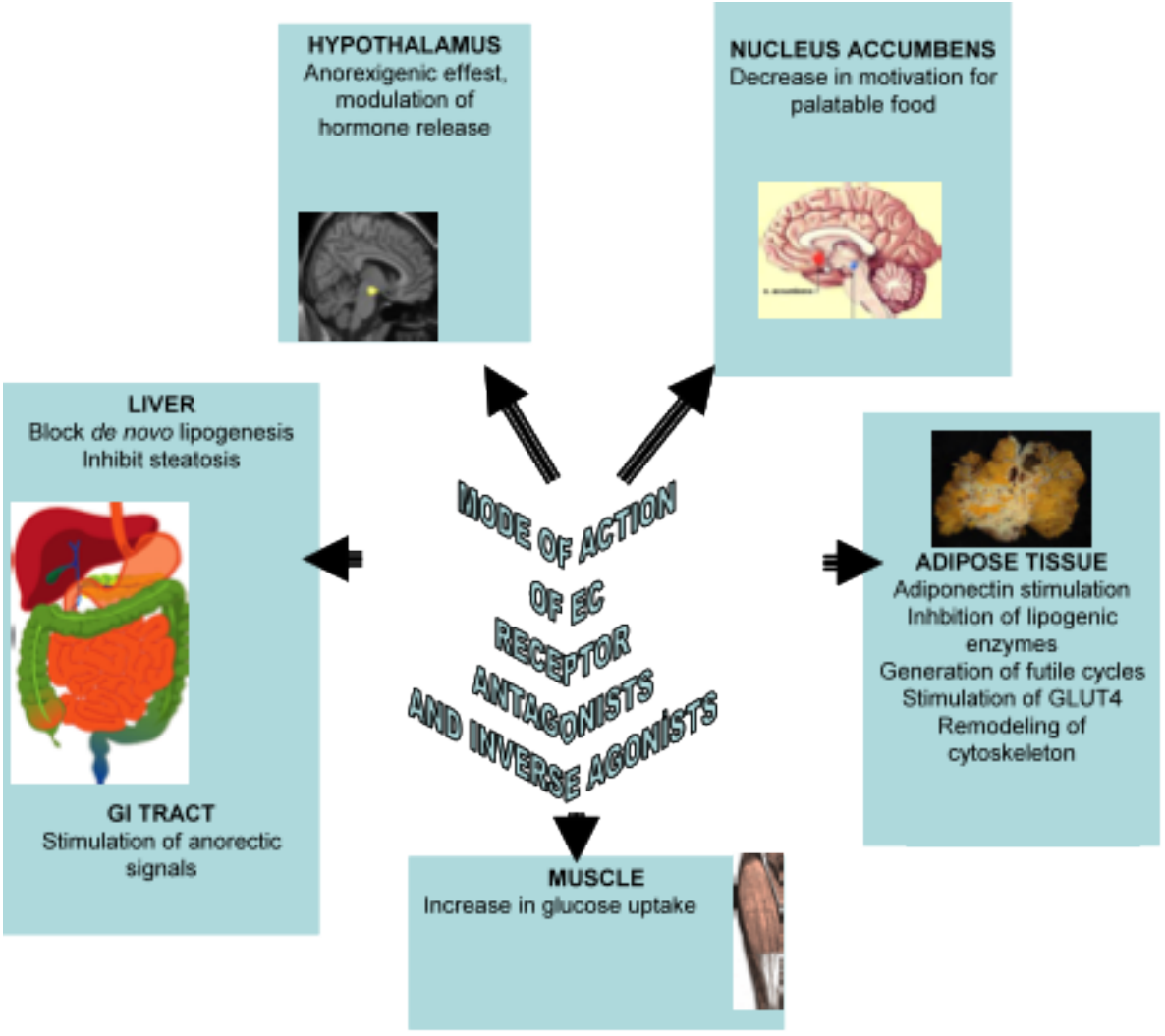

Figure 1: Mode of Action of Endocannabinoid Antagonists

A. Rimonabant

The potential antiobesity drug that was released and had the most success in clinic as a CB-1 antagonist was rimonabant (5-(4-Chlorophenyl) - 1 - (2,4-dichlorophenyl)-4-methyl-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide, SR141716A). Rimonabant is a potent CB-1 ligand, with 1000-fold affinity for CB-1 than CB-2 (26). Rimonabant was also found to be effective in smoking cessation, in cocaine addiction, memory loss due to THC and in the blockade of cannabis effects (27-29). Studies with "Rimonabant and Tobacco Use (STRATUS) Program" involved more than 6000 subjects. STRATUS was designed to explore two smoking-related therapies: first, to use rimonabant directly to aid in smoking cessation; second, to help preventing weight gain in former smokers. Initial results suggested that rimonabant was effective for both uses. However, the FDA had explicitly stated to the manufacturing company that without additional studies rimonabant could not be approved in the United States for smoking cessation therapy (30).

Among other drugs developed, rimonabant was considered to be the most promising one. However, FDA rejected the use of rimonabant for safety reasons (31). The drug was released in European Union (EU) with European Commission's approval. The EU's approval was not a blanket approval, nor did it approve the drug for non-obesity related problems such as smoking cessation, although off-label use of the drug was possible before the drug was withdrawn from the market. The approval was in combination with diet and exercise for the treatment of obese patients (BMI greater than or equal to 30), or overweight patients (BMI greater than 25) with associated risk factors, such as type 2 diabetes or dyslipidaemia. In October 23, 2008, the European Medicines Agency recommended that doctors not prescribe the drug due to the risk of serious psychiatric problems and even suicide (32).

The adverse effects of rimonabant are summarized in the Table 1 (27, 33-38). Adverse reactions not observed in clinical studies, but seen in rodent studies at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were convulsions, tactile hyperesthesia, liver steatosis, centrilobular necrosis, abnormal oestrous cyclicity, decrease in corpora lutea and fertility index and sporadic malformations (anencephaly, micro-ophthalmia, widened brain ventricles and omphalocele) (33). The drug was subsequently suspended in UK and it was also suspended in other European countries in January 19, 2009 (39).

Biotransformation of Rimonabant

Rimonabant displays high in vitro permeability and is not a substrate of P-glycoprotein. Rimonabant shows linear pharmacokinetics in doses up to 20 mg. Maximum plasma concentrations of rimonabant is achieved in ~2 hours and steady state plasma level is achieved within 13 days. The drug shows similar pharmacokinetics between healthy non-smoking subjects and patients who smoke (40).

Human plasma protein binding of rimonabant is high (>99.9%). The apparent peripheral volume of distribution of rimonabant appears to be related to body weight. Rimonabant is metabolized by both CYP3A and amidohydrolase (predominantly hepatic) pathways in vitro (39, 41). This may lead to the potential for drug interactions with common CYP3A inhibitors and inducers (42). Circulating metabolites do not contribute to its pharmacologic activity. Rimonabant is mainly eliminated by metabolism and subsequent biliary excretion of metabolites. ~3% of the dose of rimonabant is eliminated in the urine, while ~86% of the dose is excreted in the faces as unchanged drug and metabolites. The half life of rimonabant is 6–9 days in non-obese subjects; in obese subjects the half-life is ~16 days due to a larger area of distribution. Non-obese patients have a half-life of 9 days (39, 41).

Gender does not affect pharmacokinetics. Elderly patients have slightly higher exposure than young patients. Mild hepatic impairment and mild renal impairment do not alter rimonabant exposure. Data are insufficient to draw conclusions regarding pharmacokinetics in moderate hepatic impairment (39, 41).

Animal Studies on Rimonabant

Animal studies with rimonabant were successful

and research showed that rimonabant suppressed food intake and the drug was also effective on increasing the energy metabolism in peripheral organs (31). Ravinet Trillou et al. (2003) performed a study on mice with diet induced obesity and treated the animals with 5 weeks of rimonabant. The results showed that rimonabant receiving group was 20% lighter than those receiving placebo. In addition, the weight loss in response to a 24-hour fast was greater in animals treated with rimonabant, suggesting that metabolic effects other than simple reduction of caloric intake made a contribution to the weight loss. The rimonabant treated mice also showed a 50% decrease in plasma insulin levels, a 53% decrease in leptin levels, a statistically significant decrease in non-esterified fatty acids, and statistically significant improvement in insulin sensitivity (43).

When these experiments were performed on CB-1 knockout mice, rimonabant had no effect, indicating that the beneficial effect of rimonabant was mediated entirely through the CB-1. Interestingly, CB-1 knockout mice also appeared to have a greater tendency towards anxiety-like responses and an hedonic state (44).

In an obese rat model, Vickers et al. (2003) demonstrated that 4 weeks of treatment with rimonabant decreased food intake and weight. Discontinuation of rimonabant led to increased food intake and significant weight regain (45). These findings suggested that the effects of rimonabant on weight were reversible upon cessation of treatment.

Leptin is a beneficial adipose tissue derived neuropeptide that appears to be strongly associated with weight and metabolism (46). Rats with genetically deficient leptin signaling are obese and are used as a research model of obesity. It appears that leptin modulates appetite at least in part by reducing levels of endocannabinoids in the hypothalamus (47). Adiponectin is a protein product of white adipose tissue and is beneficial in lipid and glucose metabolism. Some of the known effects of adiponectin include increasing skeletal muscle fatty acid transport and oxidation, improvement of hepatic insulin sensitivity, and decreasing vascular inflammation (48). Bensaid et al. (2003) demonstrated that blockade of CB-1 by rimonabant increased levels of adiponectin in wild type mice and in obese rats with defective leptin signaling (49). Together these animal studies demonstrated that by blocking CB-1, administration of rimonabant led to sustained weight loss, decreased free fatty acid levels, and improvement in insulin sensitivity that is reversible upon the discontinuation of the drug. These effects were likely to be mediated through multiple mechanisms including decreased energy intake and changes in metabolism related to increases in circulating levels of leptin and adiponectin (50).

Clinical Trials on Rimonabant

After Phase II trials brought success for rimonabant, four large multicenter, international, randomized, double-blind, placebo-controlled Phase III trials were initiated. The anti-obesitic effects of rimonabant has been extensively investigated in the Rimonabant in Obesity (RIO) programme, comprising four 1-2 year placebo-controlled randomized clinical trials recruiting more than 6600 overweight/obese patients with or without co-morbidities. They were four groups of RIO trials: RIO-Europe (RIO-EU), RIO-Lipids, RIO-North America (RIO-NA) and RIO-Diabetes (RIO-DM) (50, 51).

The results obtained from these studies are as follows:

1. In RIO-EU 1507 obese patients (BMI ≥30 kg/m^2, the mean baseline weight 101 kg) or overweight patients (BMI ≥27 kg/m^2) with either hypertension or dyslipidemia were randomized to placebo, 5 mg or 20 mg of rimonabant daily. Only 61% of participants completed the trial. The body weights (3.4 kg vs. 6.6 kg) and waist circumferences decreased significantly in both groups. When compared with placebo, only 20 mg rimonabant led to statistically significant improvement in lipid profile, fasting glucose, fasting insulin, and insulin resistance (15).

2. In RIO-Lipids 1036 obese or overweight patients (BMI 27– 40 kg/m^2, mean weight 96 kg) with dyslipidemia were randomized to placebo, 5 mg

or 20 mg of rimonabant daily for 1 year. 62% of the participants completed the study. The body weight (3.1 kg. vs 6.4 kg), waist circumferences and C-reactive protein (CRP) decreased significantly in both groups. Only 20 mg group showed significant beneficial changes in lipid profile and fasting insulin levels. A modest statistically significant decrease in systolic and diastolic blood pressure was observed in the 20 mg group compared with placebo. Besides, 20 mg rimonabant receiving group also demonstrated beneficial effects on leptin and adiponectin levels that were not seen with placebo (14).

3. In RIO-NA 3045 obese or overweight subjects (BMI ~38 kg/m^2, baseline average weight ~105 kg) were randomized to placebo, 5 mg rimonabant or 20 mg rimonabant daily. Only 52.6% of participants completed the first year of the study. Unique to RIO-NA following the first year of treatment, patients who received rimonabant were re-randomized to receive the same dose of rimonabant or placebo for a second year; subjects initially randomized to placebo remained on placebo for the full two years. The body weights (1.3 kg vs. 4.7 kg) decreased significantly in both groups. Besides, waist circumferences showed a significant decrease and a significant improvement in lipid profile was observed in the 20 mg rimonabant group. The changes in lipid profile and insulin levels were twice that is attributable to the weight loss alone, once again pointing to a weight-independent effect of CB-1 blockade. During the second year of the study, only subjects who continued to receive 20 mg of rimonabant maintained the weight loss achieved during the first year (placebo subtracted mean loss of 7.4 kg) and continued to show significant beneficial changes in lipid profile, waist circumference, fasting insulin, and insulin resistance. Based on these results, it was clear that chronic administration of rimonabant, at least longer than 1 year, might be necessary in order to maintain the beneficial clinical effect over the long term (34).

4. In RIO-DM 1045 overweight or obese patients (average baseline weight 98 kg, mean baseline glycosylated hemoglobin (HbA1c) 7.3%) with diabetes mellitus were randomized to daily doses of placebo, 5 mg, or 20 mg of rimonabant for 1 year in a fashion similar to the above-mentioned trials. Additional inclusion criteria for RIO-DM included monotherapy with oral hypoglycemic treatment either with metformin or a sulfonylurea for at least 6 months. The majority of patients were on metformin monotherapy at baseline. 60% of patients completed the 1-year follow-up. The body weights (2.3 kg vs. 5.3 kg) and waist circumferences decreased significantly in both groups. Beneficial effects were also seen in fasting glucose, insulin resistance, lipid profile, and systolic BP blood pressure. However, after adjusting for weight loss, the residual effects on triglycerides and systolic BP blood pressure were not significant. Like in RIO-Lipids, all three randomized groups showed an increase in LDL-C of ~7%. Unlike the other studies, RIO-DM also examined change in placebo subtracted HbA1C. After one year of therapy, in the 20 mg group a two-fold decrease in HbA1C, which was attributable to weight loss, was observed (52).

The results of these studies showed that rimonabant 20 mg daily consistently reduced body weight, waist circumference, triglycerides, blood pressure, insulin resistance and CRP levels, and increased HDL cholesterol concentrations in both non-diabetic and type-2 diabetic overweight/obese patients (53). However, rimonabant's beneficial role on reduction of blood glucose and blood pressure in type II diabetes patients and elevation of HDL cholesterol is independent of its effect of weight loss (54-56).

B. Taranabant

Similar drugs acting on CB-1 were also developed by several companies. Taranabant (MK-0364, N-[(1S,2S)-3-(4-Chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-methyl-2-((5-(trifluoromethyl) pyridin-2-yl)oxy)propanamide) is a CB-1 inverse agonist being investigated as a potential treatment for obesity due to its anorectic effects (57, 58). It works by blocking endogenous October 2, 2008 cannabinoid binding to neuronal CB-1 receptors (59, 60). Taranabant - which started out several years behind rimonabant - moved quietly through the clinical trial process (57). At 2nd October, 2008, the drug company that discovered taranabant decided not to seek regulatory approval to treat obesity

and to suspend its Phase III clinical development program for the time being. 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. Therefore, after careful consideration, the company determined that the overall profile of taranabant does not support further development for obesity (57). Considering that the drug is also effective in smoking cessation, whether these studies will go on or will be postponed or totally suspended is a compromise.

The adverse effects of taranabant experienced in different studies are given in **Table 1** (59).

Biotransformation of Taranabant

A study evaluating the safety, pharmacokinetics, and pharmacodynamics of taranabant (5, 7.5, 10, or 25 mg once daily for 14 days) in 60 healthy male subjects was performed by Addy et al. (2008). Taranabant was rapidly absorbed, with a median tmax of 1-2 hours and a half life of ~ 74-104 hours. Steady state was reached after 13 days. Taranabant was generally well tolerated up to doses of 10 mg and exhibited multiple-dose pharmacokinetics consistent with once-daily dosing (61).

Another double-blind, randomized, placebo-controlled, single oral dose study by the same

Table 1. Adverse Effects of Rimonabant and Taranabant

Drug	Psychiatric disorders	Nervous system disorders	Gastrointestinal disorders	Infections and infestations	Metabolism and nutrition disorders	Vascular disorders	Respiratory, thoracic and mediastinal disorders	Skin and subcutaneous tissue disorders	Musculoskeletal and connective tissue disorders	Injury, Poisoning and procedural complications	General disorders
Rimonabant	Depressive disorders Mood alterations Anxiety Irritability Nervousness Sleep disorders Insomnia Parasomnias Panic symptoms Anger Dysphoria Emotional disorder Suicidal ideation Aggressiveness Aggressive behaviour Hallucinations	Memory loss Dizziness Hypoaesthesia Paraesthesia Sciatica Paresthesia Lethargy Tremor	Nausea Diarrhoea Vomiting	Upper respiratory tract infection Gastroenteritis Influenza Nasopharyngiritis	Hypoglycaemia	Hot flush	Hiccups	Hyperhidrosis Night sweats Pruritus	Tendonitis Muscle cramp Muscle spasms	Fall Contusion Joint sprain	Headache Asthenia / fatigue
Taranabant	Mood change Depression Anxiety Irritability	Dizziness Drowsiness	Nausea Diarrhoea Vomiting Increased bowel movement Abdominal discomfort Abdominal pain Stomachache				Hiccups	Increased sweating			Headache Tiredness

	Psychiatric disorders	Nervous system disorders	Gastrointestinal disorders	Infections and infestations	Metabolism and nutrition disorders	Vascular disorders	Respiratory, thoracic and mediastinal disorders	Skin and subcutaneous tissue disorders	Musculoskeletal and connective tissue disorders	Injury, Poisoning and procedural complications	General disorders
Surinabant	Irritability		Nausea								
Otenabant	Imsomnia Irritability	Dizziness Headache	Diarrhea Nausea	Nasopharyngitis				Pruritus			

working group evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of taranabant (0.5-600 mg) in 24 healthy male volunteers. Plasma taranabant had a biphasic disposition, with a median tmax of 1 to 2.5 hours and a terminal elimination half life of 38 to 69 hours. From these studies the researchers reached to a point that the potential drug has pharmacokinetic characteristics suitable for a once-daily dosing regimen (61).

Animal Studies on Taranabant

There is one study on diet-induced obese (DIO) rats using taranabant as a CB-1 inverse agonist. Taranabant dose-dependently inhibited food intake and weight gain, with an acute minimum effective dose of 1 mg/kg in DIO rats. Chronic treatment of DIO rats with taranabant dose-dependently led to significant weight loss with a minimum effective dose of 0.3 mg/kg (p.o.), or a plasma C_{max} of 87 nM. Weight loss was accompanied by the loss of fat mass. Partial occupancy (30–40%) of brain CB-1 by MK-0364 was sufficient to reduce body weight. The magnitude of weight loss was correlated with brain CB1R occupancy. The partial receptor occupancy requirement for efficacy was also consistent with the reduced food intake of the heterozygous mice carrying one disrupted allele of CB1R gene compared with the wild-type mice. These studies demonstrated that taranabant was a highly potent and selective CB-1 inverse agonist and that it was orally active in rodent models of obesity (62).

Clinical Trials on Taranabant

The manufacturer company had demonstrated several trials on taranabant. Two one year early phase trials on taranabant have been completed. This worldwide study in patients with type 2 diabetes mellitus assessed the safety and tolerability as well as the effects of treatment with an investigational drug for weight loss on body weight. Taranabant was applied as 0.5 mg, 1 mg capsule, 2 mg capsule once daily for 52 weeks. The primary outcomes of the study were reduced body weight and HbA1c at 36 weeks. The secondary outcomes were the effects of the drug on the same parameters in 24 and 52 weeks (62). The other randomized, double-blind, placebo controlled one year study on obese and overweight patients with BMI=27-43 kg/m^2 has also been completed in January 2008. Taranabant was applied as 0.5 mg, 1 mg capsule, 2 mg capsule once daily for 52 weeks. The primary outcomes measured were reduced body weight and the secondary outcomes were reduced waist circumference, percent body fat, biochemical markers related with high body weight and blood pressure (63). An 18 month other randomized, double-blind, placebo controlled efficacy and safety study in obese patients with BMI=30-43 kg/m^2 has also been completed in November 2007. Primary outcome measures were reduced body weight, high safety, and high tolerability after 24 weeks. The secondary outcome measure was reduced body weight after 80 weeks. A two-year safety and efficacy study in obese patients with non recruiting patients was ongoing until October 2008 with 2, 4 and 6 mg daily doses of taranabant for 52 weeks. The primary outcome was decreased body weight. The secondary outcomes of the drug were decreased waist circumference and triglycerides with increases HDL-C and insulin sensitivity (62).

A two year safety and efficacy study in obese patients with non recruiting patients was ongoing until October 2008, with 2, 4 and 6 mg daily doses of taranabant for 2 years with obese patients (BMI=30-43 kg/m^2). 18 years and older. The study consisted of 1-year weight loss followed by 1-year prevention of regain to assess the safety, tolerability, and efficacy of taranabant in obese patients The primary outcome measures were the decreases in body weight; prevention of weight regain; safety and tolerability) and the secondary outcome measures were waist circumference, triglycerides, non-HDL-C, LDL-C, and fasting insulin with increases in HDL-C and insulin sensitivity) (64).

A randomized, double-blind, placebo controlled study to investigate a research drug as an aid for smoking cessation in chronic cigarette smokers has also been completed. The purpose of this study is to evaluate the safety and tolerability of an investigational drug that may help individuals to stop smoking. The primary outcome of the study was quitting smoking after 8 weeks of treatment by measuring lab values and expired breath CO levels (65).

The company did not give a press release for the results of all of these studies and declared that it would only share the results with the patients who contributed to these studies.

Surinabant and Otenabant

Surinabant (SR-147,778; 5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethyl-N-(1-piperidinyl)-1H-pyrazole-3-carboxamide) is a second generation CB-1 antagonist (66). It was being investigated as a potential treatment for nicotine addiction, to assist smoking cessation. Besides, surinabant was also assessed to be used as in the treatment of other addictive disorders such as alcoholism and as an anorectic drug to aid weight loss. (67-70). Other potential applications such as treatment of attention deficit hyperactivity disorder (ADHD) have also been proposed (71). Surinabant has a longer duration of action than rimonabant and enhanced oral activity. This enhanced duration of action is probably due to the presence of the more metabolically stable ethyl group at the 4-position of its pyrazole ring. Another change is the replacement of the 5-phenyl chlorine substitute by bromine (72, 73). The manufacturer company has also suspended development of surinabant for smoking cessation at October 31, 2008. Though there are limited number of reports in literature concerning the side effects of surinabant, patients with a limited level of motivation, patients dependent to alcohol or illicit drugs, patients with a diagnosis of psychotic disorder or currently presenting with a depressive episode, patients who have suffered from a myocardial infarction, unstable angina or other major cardiovascular event within the past 6 months prior to screening and pregnant or breast-feeding women were not taken in the clinical trials of surinabant. The side effects observed in clinical trials with surinabant are given in the Table 1 (74, 75).

Another pharmaceutical company terminated the Phase III development program for its obesity compound otenabant (CP-945,598; 1-[8-(2-chlorophenyl)-9-(4-chlorophenyl)-9H-purin-6-yl]-4-(ethylamino) piperidine-4- carboxamide), a selective antagonist of the CB-1. According to the manufacturer company their decision was based on changing regulatory perspectives on the risk/benefit profile of the CB-1 class and likely new regulatory requirements for approval. Though the company was confident in the safety of the compound, they believed that this was the appropriate decision based on all available information regarding this class of agents, as well as recent discussions with regulatory authorities (76). There are limited number of reports in literature concerning the efficiency and side effects of otenabant. Patients with serious medical or psychiatric conditions were excluded from the clinical trials due to the potential of CB-1 antagonists to induce psychiatric disorders. The side effects observed in Phase III studies are given in the Table (77, 78).

Current Status of Endocannabinoid Receptor Antagonists and Inverse Agonists

Though the trials on rimonabant, taranabant and surinabant seem to be suspended for now, there are still new molecules to be discovered that will act on EC system and can be a hope in the treatment of obesity. The therapeutic and research goal to develop safe and effective drugs that act on EC system is still ongoing.

Considering the risk/benefit ratio and the toxicological outcomes of the discovery of these drugs, new molecules with high efficiency and high safety and low toxicologic profile should be discovered in order not to waste the work of the discoverer companies and the hopes of people who are attending these studies or who are in wait of new drugs that will cure the epidemic. The drug companies are now refocusing on research and development of new molecules that act on EC system on high priority therapeutics for obesity that will address the medical need for this research area and have a high probability for success. Today, three other molecules are present that are candidates for the treatment of obesity and they will enter the clinical trials very soon. These molecules are named as rosonabant, ibipinabant (SLV-319, BMS-646256) and AVE1625 (75).

Furthermore, the physiological role of CB-2s remains to be fully defined. These receptors lack psychoreactivity. Research on selective CB-2 agonists

AM1241, HU308 and JWH133 showed that these receptors have a role in the maintenance of bone density and progression of atherosclerotic lesions. Several studies have demonstrated that CB-2 agonists are also effective in the chronic pain. CB-2 ligands may also have therapeutic utility in chronic inflammatory diseases. They may be a hope for the treatment of osteoporosis and cardiovascular diseases. It is still a research area whether these receptor partial agonists or antagonists have role in the treatment of obesity or not. Besides, the putative EMT also interacts with CB-1. There is strong evidence that may also have a role in the release of endocannabinoids. It is not clear that EMT inhibitors may have a role in the treatment of obesity and obesity-related disorders (79).

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