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SPECIAL REPORT

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Peripheral cannabinoid-1 receptor antagonists in clinical development: therapeutic potential for the management of obesity and related metabolic disorders

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ABSTRACT

Introduction: Obesity is a chronic metabolic disease associated with insulin resistance, cardiometabolic complications, and increased mortality. Limitations of existing therapies have driven interests in alternative biological targets, including the endocannabinoid system and the cannabinoid-1 receptor (CB1R) signaling pathway.

Areas covered: This review examines the rationale for targeting peripheral CB1R signaling and summarizes preclinical and clinical evidence supporting peripherally restricted CB1R antagonists and inverse agonists for obesity and related metabolic disorders. The metabolic effects of CB1R blockade in peripheral tissues are discussed, as well as distinctions between central and peripheral CB1R inhibition. The article also reviews the current development landscape of CB1R-targeted compounds, including agents evaluated in early-phase clinical trials. Literature was identified through PubMed, Embase, and Scopus, supplemented by ClinicalTrials.gov.

Expert opinion: Peripherally restricted CB1R antagonists aim to deliver the metabolic benefits of CB1R blockade while avoiding the toxicity that ended development of centrally acting agents such as rimonabant. Recent phase 2 data with monlunabant demonstrated dose-dependent psychiatric adverse events and high discontinuation rates. Nimacimab, an antibody-based approach, has shown only marginal efficacy. The future of this drug class will therefore likely depend on rigorous long-term safety evaluation, biased CB1R pharmacology, and multitarget strategies including combinations with incretin-based therapies.

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Peripheral CB1 receptor antagonists; endocannabinoid system; obesity pharmacotherapy; metabolic disease; obesity

1. Introduction

Obesity is a major public health challenge worldwide, contributing to increased morbidity, mortality, and healthcare costs [1]. The prevalence of obesity among adults in the US increased from 34.7% in 1990 to 42.5% in 2022 and is projected to reach 46.9% by 2035 [2]. Excess adiposity is associated with the development of insulin resistance, type 2 diabetes, dyslipidemia, cardiovascular disease, and depression, and is now recognized as a systemic disorder that affects multiple metabolic pathways rather than solely a condition of energy imbalance [3,4].

Lifestyle interventions remain the foundation of obesity management; however, long term weight loss management using these approaches alone is often challenging [5,6]. Bariatric surgery can achieve substantial and sustained weight loss, but its invasive nature, high cost, and limited accessibility limit its use as a population-level treatment [7,8]. Moreover, compensatory biological mechanisms to weight loss including reductions in energy expenditure and hormonal adaptations that promote increased appetite and weight regain, underscore the need for therapies that target underlying metabolic regulatory pathways [9]. While newer incretin-based anti-obesity medications have demonstrated large degrees of weight loss with added cardiovascular, glycemic, hepatic, and renal benefits, some patients cannot tolerate these medications or fail to achieve adequate benefit, and most patients experience significant weight regain after discontinuation of treatment [10–12]. Therefore, researchers continue to focus on developing alternative biological targets that modulate energy balance and metabolism.

The purpose of this review is to synthesize current evidence on the development of peripherally restricted cannabinoid-1 (CB1) receptor antagonists and to evaluate their therapeutic potential for the management of obesity and related metabolic disorders. This review builds on previous findings from centrally acting CB1 antagonists and focuses on the biological rationale and distinction between central and peripheral CB1 signaling, strategies aimed at minimizing central nervous system (CNS) adverse effects, and the current status of compounds in preclinical and clinical development.

2. Methodology

This article is a narrative review of the biological rationale, preclinical evidence, and clinical development of peripherally

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Article highlights

- Peripheral cannabinoid-1 (CB1) receptor antagonists represent a therapeutic strategy aimed at separating the metabolic benefits of CB1 blockade from the neuropsychiatric adverse effects that limited first-generation centrally acting agents.
- Preclinical and early clinical data suggest that peripherally restricted CB1 antagonists improve body weight, insulin sensitivity, hepatic steatosis, and cardiometabolic parameters without significant central nervous system penetration.
- Emerging peripherally restricted CB1 antagonists demonstrate promising efficacy and safety profiles in early-stage clinical trials, but durable weight loss and cardiometabolic benefits remain to be established.
- Securing approvals by regulatory agencies will require robust phase 3 data demonstrating sustained weight reduction and improvement in metabolic comorbidities, and an acceptable safety profile.
- Future research should clarify optimal patient selection and the broader role of peripheral CB1 modulation in disease.

restricted CB1R antagonists for obesity and related metabolic disorders. PubMed, Embase, and Scopus were searched using combinations of the terms 'cannabinoid receptor 1,' 'CB1R,' 'peripheral CB1 antagonist,' 'inverse agonist,' 'obesity,' 'insulin resistance,' 'metabolic syndrome,' 'MASH/NASH,' and the names of individual investigational agents. Reference lists of retrieved articles were hand-searched for additional sources. Because several agents discussed are early in clinical development, the search was supplemented with clinical-trial registry records (ClinicalTrials.gov), regulatory filings, and company disclosures where peer-reviewed publications were not yet available.

3. Endocannabinoid system and rationale for peripheral CB1 blockade

The endocannabinoid system (ECS) is now well recognized as an important regulator of energy balance and metabolic homeostasis. Early studies primarily focused on its role in appetite regulation and reward-related eating behaviors [13]. Later research showed that the ECS functions as a signaling network that integrates both central and peripheral pathways involved in nutrient intake, energy storage, and metabolic regulation [14].

ECS signaling is dysregulated in obesity and related metabolic disorders. Individuals with obesity often exhibit elevated circulating endocannabinoid levels, as well as changes in expression and activity of ECS components in metabolically relevant tissues, indicating a state of chronic ECS overactivation [15,16]. However, this relationship is not uniform across studies, reported circulating endocannabinoid concentrations in obesity have been inconsistent, and the apparent upregulation is influenced by both technical and biological factors, indicating the need for a more nuanced interpretation of these data [17]. This enhanced ECS activity has been linked to increased appetite and lipogenesis, impaired insulin sensitivity, and ectopic fat accumulation. ECS signaling network consists of the endogenous ligands anandamide, 2-arachidonoylglycerol (2-AG), the cannabinoid receptors CB1R and CB2R, and enzymes responsible for ligand synthesis and degradation [18]. Among these receptors, cannabinoid receptor type 1 (CB1R) plays a key role in metabolic control. CB1Rs are highly expressed in the CNS but are also functionally present in peripheral metabolic tissues, including the liver, pancreas, gastrointestinal tract, adipose tissue, and skeletal muscle, and their activation influences lipid metabolism, glucose homeostasis, and inflammatory signaling [14,18,19].

In the peripheral organs, CB1 signaling regulates key aspects of energy balance and substrate metabolism and has been linked to the metabolic and hormonal abnormalities associated with obesity [20]. Additionally, evidence indicates that dysregulated ECS signaling can impair insulin sensitivity and glucose homeostasis independently of changes in body weight via peripheral mechanisms, suggesting that peripheral CB1 activity contributes directly to metabolic disease rather than indirectly via appetite regulation [20,21]. In the skeletal muscle, CB1 signaling interferes with insulin-dependent glucose uptake by inhibiting key insulin signaling pathways required for glucose transporter translocation [20,21]. Beyond glucose regulation, skeletal muscle-specific CB1R deletion in Cre-Lox mouse models prevents both diet-induced and age-induced insulin resistance, enhances mitochondrial performance, and increases whole-body muscle energy expenditure and improves physical endurance, indicating that skeletal muscle CB1R regulates both energy expenditure and substrate handling [22]. In the liver, activation of hepatic CB1R has been shown to reduce systemic insulin sensitivity through impaired insulin signaling and increased hepatic glucose production, establishing a direct mechanistic link between ECS overactivity and obesity-associated metabolic disease [20,21]. Peripheral metabolic effects of CB1R overactivation and expected therapeutic benefits of peripheral CB1R blockade are further described in Figure 1. ECS activation in adipose tissue promotes *de novo* lipogenesis while downregulating adiponectin, impairing insulin sensitivity at distant organs, and may additionally promote local inflammation [23,24]. In brown adipose tissue (BAT), chronic CB1 antagonism activates thermogenesis with increased Ucp1 expression (mediates BAT thermogenesis) and BAT glucose uptake, contributing to the increase in energy expenditure that accompanies CB1 blockade independently of reduced food intake [25]. In the gastrointestinal tract, CB1 blockade reduces intestinal permeability, lowers circulating plasma LPS and metabolic endotoxemia, attenuates M1 macrophage trafficking into adipose tissue, and shifts gut microbiota composition; it notably increases the abundance of Akkermansia muciniphila (a beneficial gut bacterium), collectively strengthening the rationale for peripheral CB1 targeting beyond direct effects on individual metabolic organs [26].

Thus, it is apparent that excessive CB1 signaling in peripheral metabolic tissues contributes directly to the development of insulin resistance and obesity-associated metabolic dysfunction. Hence, pharmacologic strategies aimed at attenuating CB1 activity in peripheral organs represent a rational therapeutic approach for metabolic disease. However, given the presence of CB1R in both the CNS and peripheral organs, the clinical feasibility of this strategy depends on distinguishing the metabolic roles of peripheral CB1 signaling from the neuropsychiatric functions of CB1 in the CNS.

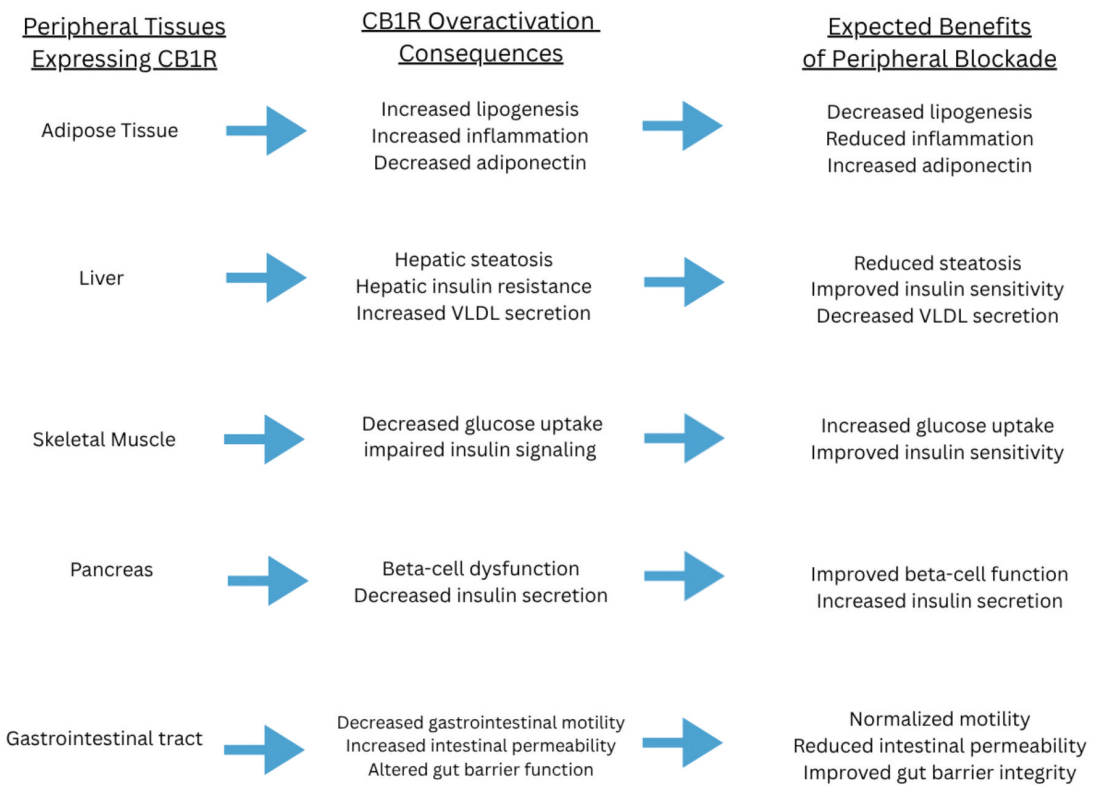

Figure 1. Peripheral metabolic effects of CB1R overactivation and expected therapeutic benefits of peripheral CB1R blockade.

One of the most significant conceptual advances of recent years is biased or functionally selective CB1R antagonism. The distinction between G-protein-coupled and β-arrestin-2-mediated CB1R signaling has profound therapeutic implications: preclinical work on MRI-1891 (also called INV-202) demonstrated that CB1R-induced anxiety-like behaviors are mediated exclusively via G-protein signaling, whereas obesity-associated insulin resistance in skeletal muscle is mediated via β-arrestin-2 [27]. A biased antagonist that preferentially inhibits β-arrestin-2 recruitment over G-protein activation can therefore dissociate metabolic benefit from CNS adverse effects by a mechanism entirely distinct from peripheral restriction *per se*.

Additionally, Cryo-EM structural studies have now illuminated how peripherally restricted compounds engage the CB1R orthosteric site with retained affinity despite their polar functionalities, and how differential engagement with transmembrane helices propagates to contribute to biased signaling [28]. These structural insights are highly relevant to the design of next-generation compounds.

4. CNS vs peripheral CB1R

CB1Rs play a critical role in maintaining emotional homeostasis and cognitive function within the CNS. They modulate synaptic transmission in key brain regions, including the hippocampus, amygdala, and prefrontal cortex [29]. Within the CNS, CB1R activation suppresses neurotransmitter release and fine-tunes the balance between excitatory glutamatergic and inhibitory GABAergic signaling. In this capacity, CB1 signaling acts as a stabilizing agent on neural circuits involved in stress responsiveness, emotional regulation, and reward processing [29].

Genetic or pharmacologic disruption of CB1 signaling in the brain has been shown to destabilize normal regulation between excitatory and inhibitory states, resulting in poor emotional and behavioral outcomes. CB1R blockade leads to heightened stress reactivity and increased anxiety and depression-like behaviors, consistent with a loss of endogenous mechanisms that normally regulate emotional responses [29]. Furthermore, mutant mice lacking CB1Rs (CB1KO) exhibited an anhedonic phenotype characterized by reduced sensitivity to rewarding stimuli, along with impairments in stress adaptation across multiple behavioral paradigms [30]. Together, these findings establish CB1 signaling in the CNS as essential for normal emotional regulation while providing a basis for psychiatric adverse effects observed following pharmacologic CB1 antagonism.

Early clinical trials targeting CB1R provided strong evidence that CB1 antagonism could lower body weight and improve cardiometabolic risk factors. Rimonabant, a central CB1R inverse agonist, demonstrated reductions in body weight, waist circumference, and improvements in glycemic control and lipid profiles across multiple large randomized trials [31]. However, rimonabant was later withdrawn from clinical use due to an increased incidence of psychiatric adverse events, including depression, anxiety, and suicidal ideation, which were attributed to its mechanism of action of CB1R blockade within the CNS [32]. Importantly, these adverse effects highlighted the risks associated with central CB1R inhibition rather

than CB1R antagonism *per se*. Further research led to the knowledge that CB1Rs are present in peripheral tissues and their selective blockade, independent of CNS signaling, can lower body weight and improve glycemic control with lower —though not absent — potential for side-effects [20,33,34]. As a result, there has been renewed interest in the development of peripherally restricted CB1 antagonists that retain metabolic efficacy while minimizing CNS adverse effects.

Building on the recognition that central CB1 blockade underlies psychiatric toxicity, Tam et al. investigated the metabolic effects of JD5037, a peripherally restricted CB1R inverse agonist, that does not cross the blood–brain barrier [33]. In a preclinical study, mice with diet-induced obesity (DIO), treated with this compound showed modest weight reduction, improved glycemic control and dyslipidemia, and reversal of hepatic steatosis. Mechanistically, JD5037 inhibits food intake by reversing hyperleptinemia and resensitizing the hypothalamus to endogenous leptin, with subsequent reactivation of melanocortin (MC4R-dependent) signaling in the arcuate nucleus and POMC neurons; the hypophagic effect is abolished in MC4R-deficient mice and by MC4R antagonism [35]. This demonstrated that the positive effects of CB1 antagonism, including restoration of an endogenous CNS satiety pathway from the periphery, could be retained in the context of weight loss while avoiding direct interference with CB1 in the CNS.

Preclinical evidence indicates that CB1R blockade exerts direct cardioprotective effects, independent of weight loss, including attenuation of diabetic cardiomyopathy, oxidative/nitrosative stress, myocardial inflammation, and improved ventricular function, as documented in multiple rodent studies. In a mouse model of type 1 diabetes cardiomyopathy, both pharmacological CB1R inhibition and genetic CB1R deletion attenuated myocardial dysfunction, oxidative/nitrosative stress, p38/JNK MAPK activation, advanced-glycation-end-product accumulation, and interstitial fibrosis [36]. Parallel findings in diabetic retinopathy, including reduced vascular oxidative stress, NF-κB activation, and endothelial cell death, indicate that the same upstream CB1R-driven signaling contributes broadly to diabetic end-organ damage [37]. These data are directly relevant to the cardiometabolic complications of obesity, although they have yet to be translated into long-term cardiovascular outcome trials in humans.

5. Pharmacologic strategies

CB1R-targeted compounds also differ in their intrinsic pharmacology, with important clinical consequences independent of peripheral restriction. Inverse agonists such as rimonabant and JD-5037 suppress ligand-independent constitutive CB1R signaling in addition to blocking agonist-evoked activity, whereas neutral antagonists such as AM-6545 bind to the receptor without eliciting changes in constitutive or intrinsic cellular endocannabinoid signaling [38]. Preclinical evidence indicates that inverse agonism but not neutral antagonism of CB1 receptors potentiates toxin-induced nausea [38]. A related design strategy is the dual-target approach exemplified by MRI-1867, a hybrid peripheral CB1R inverse agonist and inducible nitric oxide synthase (iNOS) inhibitor; in preclinical liver fibrosis models, this compound exceeded the antifibrotic efficacy of rimonabant by engaging profibrotic pathways uniquely driven by iNOS, slowing fibrosis progression and attenuating established fibrosis [39].

6. Clinical development

Monlunabant is the first peripherally selective CB1R antagonist to reach phase 2 level of clinical trial development. In a 16-week randomized controlled trial (RCT) among patients with obesity and metabolic syndrome, monlunabant 10, 20, and 50 mg were associated with placebo-subtracted weight changes of −5.9%, −6.3%, and −7.4% (−6.4, −6.9, and −8.0 kg), respectively [40]. It is important to note that the phase 2 monlunabant trial enrolled patients with obesity plus metabolic syndrome, which is relevant to interpreting the weight loss data in a broader obesity pharmacotherapy context.

Monlunabant was poorly tolerated, with both gastrointestinal adverse events (notably nausea and vomiting) and dose-dependent psychiatric adverse events, including anxiety, depressed mood, and irritability, contributing to early discontinuation. Overall, 31% and 43% of the study participants withdrew early in the 20 mg and 50 mg groups, respectively. The mixed model used for imputing missing data might have inflated effects as a more conservative jump-to-reference multiple imputation method attenuated the weight changes for monlunabant 10, 20, and 50 mg doses to −4.8, −4.6, and −4.8 kg, respectively. Despite exclusion of subjects with even mild depression or anxiety, psychiatric events occurred in 28%, 33%, and 42% of participants assigned to monlunabant 10, 20, and 50 mg. These findings may suggest that chronic dosing might have led to greater CNS penetrance and loss of its peripheral CB1 selectivity [41]. These findings were not entirely surprising because animal studies demonstrated increased central CB1R engagement with chronic dosing of monlunabant [27]. In another 16-week phase 2 RCT among patients with diabetic kidney disease, monlunabant 10 and 25 mg failed to demonstrate efficacy compared to placebo on the primary endpoint of change in urine albumin-to-creatinine ratio [42]. Placebo-subtracted average weight changes for monlunabant 10 and 25 mg were 2.6 and 3.2 kg, respectively. A total of 34% of the participants in the monlunabant 25 mg group withdrew early, with 23% discontinuing due to adverse events. Taken together, the results of these two clinical trials suggested that neuropsychiatric adverse events remain a major concern with monlunabant.

Nimacimab is a peripherally restricted IgG4 monoclonal antibody that acts as a negative allosteric modulator and inverse agonist at CB1 receptors, designed to avoid the neuropsychiatric adverse effects seen with brain-penetrant CB1 antagonists. However, in a phase 2a trial, 26-week treatment with nimacimab was associated with marginal efficacy of 1.26% weight loss vs placebo, and 2.95% greater weight loss for nimacimab plus semaglutide vs semaglutide monotherapy. These results must be interpreted with caution in the absence of a peer-reviewed publication [43].

Several peripherally selective CB1R antagonists and inverse agonists (Table 1) are in various phases of development, and

Table 1. Peripherally acting CB1 antagonists and inverse agonists in development.

Compound	Type	Indications	Development stage (mo/yr)	Source	Link to study	Key efficacy outcomes	Safety & withdrawal
Phase 3 — none to date							
Phase 2 — active or recently completed							
RYI-018 (Nimacimab)	Inverse agonist/ NAM (IgG4 mAb, ~150 kDa)	Obesity, MASH, diabetic kidney disease, FSGS, IgA nephropathy	Phase 2a completed in 2025.	Skye Bioscience 2025 [43]	NCT06577090	1.26% weight loss vs placebo (monotherapy, 26 wks) 2.95% weight loss in combination with semaglutide vs semaglutide monotherapy.	No peer-reviewed publication to date.
Monlunabant (INV202; MRI-1891)	Biased peripheral inverse agonist	Obesity + metabolic syndrome; diabetic kidney disease	Phase 2 trials in obesity and metabolic syndrome, and diabetic kidney disease completed in 2025.	Knop 2025 [40] Cherney 2026 [42]	Publications cited.	−5.9% to −7.4% vs placebo	Ph 2: dose-dependent neuropsychiatric AEs.
Phase 1 — completed or ongoing							
CRB-913	Inverse agonist (oral; reduced brain penetration)	Obesity, insulin resistance, MASH	Phase 1a complete; Phase 1b ongoing (CANYON-1, completion Summer 2026)	Morningstar 2023 [44]	NCT07310901 (CANYON-1, Ph 1b)	Ph 1a: −2.9% placebo adjusted at Day 14 (150 mg/d). CANYON-1: 16 wk, 240 non-diabetic obese, 20/40/60 mg. Additive with GLP-1 agonists (preclinical).	Ph 1a: daily C-SSRS, PHQ-9, GAD-7 negative; favorable safety.
GFB-024	Inverse agonist (mAb, once-monthly)	Diabetic nephropathy; overweight/T2D	Phase 1 complete	Bilic 2022 PMC9624947 https://academic.oup.com/jes/article/6/Supplement_1/A348/6787798	NCT04880291 PMCID 9624947	Ph 1: safety/PK established (overweight, T2D); efficacy NR.	No Phase 2 registered.
Preclinical							
JD-5037	Inverse agonist	MASLD/MASH, insulin resistance	Preclinical (planned Phase 1)	Tam 2012 [33] Tan 2020 [45]	PMCID 3832894	Reverses leptin resistance; reduces body weight, hepatic steatosis, insulin resistance (DIO mice).	Pivotal proof-of-concept agent. Worsened liver fibrosis in MDR2 deficient mice (PMID 38994954) may have delayed clinical entry; no human trials.
JD-5006	Inverse agonist	Obesity, insulin resistance, MASLD/MASH	Preclinical	O'Sullivan 2021 [34]	PMID 22959249	Reduces weight and glucose (rodent models).	No update; likely deprioritized for JD5037.
PMG-505-010/-013	Peripherally restricted antagonist/ inverse agonist	Obesity-associated NAFLD, hepatic fibrosis	Preclinical (2024)	Yang 2024 [46]	PMID 39366030; doi 10.1016/j.biopha.2024.117501	Improved fasting glucose and dyslipidemia; reduced hepatic steatosis, inflammation, fibrosis (NAFLD mice).	Reduced BBB penetration vs rimonabant; preclinical only.
RTI-348	Neutral antagonist	MASLD/MASH	Preclinical (2024)	Laudermilk 2024 [47]	PMID 39296275; doi 10.1021/acsptsci.4c00356	Reduces body/liver weight gain and steatosis; lowers ALP, AST, ALT, LDH; reduces profibrogenic gene expression (MASH mice).	Minimal brain exposure; no anhedonia (vs rimonabant); preclinical only.
AM-6545	Neutral antagonist	Hepatic steatosis, metabolic syndrome	Preclinical	Tam 2010 [48]	PMID 20664173	Reduces liver fat; improves glucose/lipid markers (mice).	Neutral antagonist; preclinical only.
AM-6527	Neutral antagonist	Obesity, opioid withdrawal, food-intake suppression	Preclinical	Soler-Cedeño 2022 [49]	PMID 36291128	Reduces food intake and body weight (rodents).	No trials registered; likely deprioritized (no sponsor).
URB447	Neutral antagonist	Obesity, glucose metabolism	Preclinical	LoVerme 2009 [50]	Bioorg Med Chem Lett 2009	Reduces feeding and weight gain; peripheral anti-obesity (mice).	Preclinical only.
LH-21	Neutral antagonist	Obesity	Preclinical	Pavon 2008 [51] Alonso 2012 [52]	PMID 18426510 PMID 21951309	Reduces feeding/weight; antihypertensive and metabolic effects (KKAy mice).	Low brain penetrant; preclinical only.

(*Continued*)

Table 1. (Continued).

Compound	Type	Indications	Development stage (mo/yr)	Source	Link to study	Key efficacy outcomes	Safety & withdrawal
TXX-522	Antagonist	Obesity, insulin resistance	Preclinical	Chen 2017 [53]	PMID 29051736	Reduces weight; improves insulin sensitivity (DIO mice).	Peripherally restricted; preclinical only.
BNS808	Neutral antagonist (tricyclic scaffold)	Obesity, liver health, cardiometabolic risk	Preclinical	Gammal 2025 [54]	PMID 40258217	Metabolic and hepatic benefits; minimal CNS penetration.	Early-stage investigation.
INV-101/ MRI-1867/ Zevaquenabant	Inverse agonist + iNOS dual inhibitor	Pulmonary/liver/ kidney fibrosis, MASH, systemic sclerosis	Preclinical	Zawatsky 2021 [55]	PMID 34650521	Antifibrotic across organ models; metabolic/liver benefit.	Second-generation antifibrotic candidate; no clinical trial.
PIMSR	Neutral antagonist	Substance use disorder	Preclinical	Soler-Cedeño 2022 [49]	PMID 36291128	Activity in substance-use models.	Limited brain penetration; no clinical development.
Discontinued/inactive							
TM-38837	Antagonist/inverse agonist	Obesity, MASLD/ MASH	Phase 1 complete; development halted	Klumpers 2013 [56]	PMID 23601084	Ph 1: peripheral selectivity confirmed (PK); efficacy NR.	Development halted (7TM Pharma dissolved).

they are being explored for conditions beyond obesity, including metabolic syndrome, metabolic dysfunction-associated steatotic liver disease (MASLD), and metabolic dysfunction-associated steatohepatitis (MASH), fibrotic disorders, and pain.

Beyond single-target CB1R blockade, dual proliferator-activated receptor-α (PPAR-α) agonist/CB1R antagonist scaffolds such as hydroxytyrosol linoleoyl ether (HTLE) reduced hepatic steatosis and body weight in obese Zucker rats [57], and a related dual agent (oleyl hydroxytyrosol ether) combined with the glucagon-like peptide-1 (GLP-1) agonist liraglutide produced greater weight loss and metabolic improvement than either drug alone in diet-induced obese rats [58]. These multitarget preclinical strategies have not yet entered clinical trials but signal a likely direction for next-generation development.

7. Expert opinion

Peripheral-restricted CB1R antagonists are an advancement in the field of obesity pharmacotherapy, providing metabolic benefits through CB1R blockade and the possibility of minimizing neuropsychiatric adverse events. However, significant challenges continue to limit clinical implementation.

The endocannabinoid system plays a key role in both central and peripheral metabolic regulation. Central CB1R activation regulates appetite, while CB1R activation in adipose, muscle, and liver results in peripheral insulin resistance and lipogenesis. Rimonabant, a central CB1R inverse agonist, developed for treatment of obesity and related metabolic disorders, failed to be translated into clinical practice, as it led to unacceptable psychiatric adverse effects including suicidality. In the past decade, considerable efforts have been made to develop truly peripherally restricted CB1R antagonists to achieve the metabolic benefits of CB1R blockade while avoiding the CNS adverse effects.

Monlunabant was the first peripherally restricted CB1R antagonist to advance into phase 2 clinical trials. However, phase 2 trials revealed a dose-dependent increase in psychiatric adverse events with monlunabant treatment, suggesting it carries the risk of some degree of CNS penetration with chronic dosing [41]. Thus, the challenge of achieving true peripheral restriction remains a hindrance to further clinical development of monlunabant and perhaps with other putative peripheral CB1R antagonists. Nimacimab, another peripherally selective CB1R antagonist, showed marginal weight loss efficacy in 26-week phase 2a trial. Thus, currently available efficacy and safety data are not sufficiently compelling to support the potential utility of peripherally restricted CB1R antagonists for treatment of obesity and related metabolic disorders. Long-term cardiovascular outcomes data are also missing for these investigational drugs.

The field of obesity therapeutics has moved beyond weight loss alone. With current gut hormone analogues achieving more than 15% weight loss, key priorities now include sustained and healthy weight reduction, preservation of lean and muscle mass, prevention of weight regain after discontinuation, and long-term tolerability [12]. Against this benchmark, the magnitude of weight loss reported for investigational peripheral CB1R antagonists has been modest. In the monlunabant 16-week phase 2 trial in obesity and metabolic syndrome, primary mixed-model analysis showed 5.9–7.4% placebo-subtracted weight loss across the 10, 20, and 50 mg doses, attenuating to 4.6–4.8 kg under more conservative jump-to-reference imputation [41]. In a separate 16-week phase 2 trial in diabetic kidney disease, monlunabant 10 and 25 mg failed to demonstrate efficacy on the primary endpoint of change in urine albumin-to-creatinine ratio, with placebo-subtracted weight loss of only 2.6 and 3.2 kg [42]. Monlunabant treatment-withdrawal rates reached 31–43% at the higher doses, driven by gastrointestinal and dose-dependent psychiatric adverse events [40,42]. To our knowledge, no randomized discontinuation studies have been conducted to evaluate weight regain after cessation of treatment with peripheral CB1R antagonists. Only 36 of 243 randomized subjects across 3 doses of monlunabant and placebo in the phase 2 trial had body composition assessment before and after 16-week treatment [40]; the sample sizes were too small to provide a meaningful interpretation whether weight loss associated peripheral CB1R antagonists might lead to more favorable body composition changes than weight loss achieved with other interventions. Rather than competing with GLP-1 receptor agonists like semaglutide and tirzepatide, peripheral CB1R antagonists are more likely to complement incretin-based therapies through their distinctive mechanism of action.

This difficulty in CB1R antagonists achieving true peripheral restriction reflects a class-wide pharmacokinetic limitation of this drug class. The blood–brain barrier's P-glycoprotein-mediated efflux is able to reliably restrict most compounds to remain outside of the CNS [59]. However, chronic exposure and the intrinsic lipophilicity required for CB1R binding allow for a gradual CNS accumulation of CB1R antagonists. Thus, other strategies may be required to ensure true, reliable peripheral restriction, including high plasma protein binding, large-molecule biologics, and conjugation of polar or charged moieties.

Moreover, in light of most recent developments in incretin-based therapies, the potential for clinical translation of CB1R antagonists becomes even more limited. GLP-1 agonists, such as semaglutide and tirzepatide, demonstrate a 15–22.5% weight loss, far exceeding the metabolic effects reported for CB1R antagonists. Hence, it is highly unlikely that CB1R antagonists will emerge as the dominant first-line monotherapy for treatment of obesity in the clinical setting. The primary strength of CB1R antagonism lies in its complementary metabolic effects beyond the appetite suppression provided by GLP-1 agonists. As such, it is feasible that CB1R antagonists are implemented in combination with incretin therapies or for patients who are unable to tolerate incretin therapies or in whom metabolic benefits beyond weight loss are desired. Thus, further development and implementation of this drug class depend on mechanistic specialization and combinatorial approaches, rather than acting as a standalone obesity monotherapy.

Among other investigational agents, JD-5037 is the best-characterized and has some significant metabolic effects,

demonstrating reversal of leptin resistance with concurrent improvement in steatosis, insulin resistance, and fibrosis [45]. TM-38837 has demonstrated preferential hematotropic distribution, while BNS808 has used a high plasma protein binding to reliably remain peripherally restricted [54,60]. CRB-913 is another peripheral CB1 antagonist that demonstrated an additive weight loss when combined with GLP-1 agonists in preclinical models, and is now progressing to early clinical trials [44]. Additionally, LH-21, a peripherally restricted triazole CB1 antagonist, has been reported to have a favorable adipokine profile, based on both in vitro and in vivo animal studies [51,52].

Currently, there is interest in developing peripheral CB1R antagonists for treatment of MASLD, MASH, and other fibrotic diseases. CB1R signaling has some contribution to hepatic lipogenesis, insulin resistance, inflammation, and fibrogenesis, making antagonism a favorable strategy. CB1R antagonists, such as JD-5037 and MRI-1867 have demonstrated antifibrotic effects in preclinical models, and TM-38837 has demonstrated reliable hematotropic distribution, suggesting these compounds may have the potential safety-efficacy profile required for clinical implementation in MASLD [45,55,60]. However, the full extent and relevance of CB1R expression in hepatocytes remain uncharacterized and must be better elucidated prior to clinical implementation.

Thus, the future of CB1R antagonists depends heavily on optimizing peripheral restriction, differentiating this drug class from incretin-based therapies, and identifying patient populations that will most benefit from its use. Practically, combination therapies, such as with incretin-based approaches, and tissue-targeted applications, such as in MASLD, MASH or other fibrotic diseases, may represent the most promising path forward for this drug class, although these approaches have not yet been clinically validated.

8. Conclusion

This review summarizes the biological rationale, preclinical evidence, and clinical status of peripherally restricted CB1R antagonism for obesity and related metabolic disorders. Excess CB1R activation across the liver, adipose tissue, skeletal muscle, gastrointestinal tract, and pancreas drives insulin resistance, hepatic steatosis, dyslipidemia, and impaired energy expenditure. Peripheral CB1R antagonism reverses these phenotypes in preclinical models. Among investigational agents, JD-5037 is the best-characterized for hepatic and metabolic effects, TM-38837 has demonstrated peripheral selectivity in healthy volunteers, MRI-1867 couples CB1R blockade with iNOS inhibition for fibro-metabolic indications, and BNS808 achieves peripheral restriction through high plasma protein binding. Clinically, Monlunabant produced gastrointestinal adverse events (notable nausea and vomiting) and dose-dependent psychiatric adverse events suggestive of CNS penetration, and nimacimab, another clinically advanced peripherally restricted agent, achieved only marginal placebo-subtracted weight loss. Future development is likely to focus on multitarget strategies, including CB1R combined with GLP-1 agonists or a dual PPAR-α/CB1R scaffold, and on fibro-metabolic indications such as MASH.

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Author contributions

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