

# A Clinical Update on Peroxisome Proliferator-Activated Receptors

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## ABSTRACT

The peroxisome proliferator-activated receptors (PPARs) belong to the group of nuclear receptor superfamily. There are three subtypes of these receptors, PPAR alpha, beta, and gamma. These receptors display differential tissue distribution and have specific functions. PPARs mainly regulate lipid and carbohydrate metabolism. These receptors are also involved in inflammatory process, reproduction, carcinogenesis, and other physiological processes in the body. Modulation of these receptors has wide therapeutic potential in diseases like diabetes mellitus, obesity, heart disease, atherosclerosis, cancer, inflammatory bowel disease, and many other conditions. In the last few decades, numerous agonists and antagonists of PPARs have been discovered some of which are now used in therapeutics. This review focuses mainly on the role of PPARs and their ligands under different clinical conditions.

## Introduction

The peroxisome is a subcellular organelle, helpful in the removal of molecular oxygen and in the breakdown of hydrogen peroxide in the cell. It is involved in processes like cholesterol synthesis, cholesterol breakdown, and in fatty acid oxidation. The proliferation of peroxisomes in experimental studies is associated with numerous biochemical changes. Till recently the underlying mechanism for the same was not known. The discovery of the peroxisome proliferator-activated receptors (PPARs) by Issemann and Green was the key in understanding the role of peroxisome proliferation in various diseases. The receptors were originally isolated from the *Xenopus* frog. PPARs are assigned to a group of nuclear receptor superfamily, which also include other receptors like thyroid hormone receptors and the retinoic acid receptors. PPARs normally function as transcription factors and help in regulating the expression of certain genes. These receptors have an impact on lipid and carbohydrate metabolism in the body and are concerned

with cellular differentiation and development.<sup>[1-3]</sup>

In the last decade, PPAR gamma agonists (thiazolidinediones group of drugs) have been used as insulin sensitizers in the treatment of diabetes mellitus; PPAR alpha agonists (fibrate group of drugs) are used as lipid-lowering drugs. Recently, a newer class of PPARs, the delta variety, has been discovered and its activation has shown beneficial effects in the treatment of obesity.<sup>[4-6]</sup>

The role of PPARs is complex in nature and involves many physiological processes in the body. Further study of these receptors will be of interest to the scientific community to develop new therapeutic targets for different diseases in the future.

## Types of PPARs

There are three types of PPARs PPAR  $\alpha$  (alpha), PPAR  $\gamma$  (gamma), and PPAR  $\delta$  (delta).<sup>[7]</sup>

### PPAR alpha

PPAR  $\alpha$  (alpha) is predominantly expressed in liver, kidney, heart muscle, vascular endothelial cells, smooth muscle, monocytes, and T lymphocytes. The PPAR alpha gene has been mapped on chromosome 22 in the region of 22q12-q13.1 and spans at least 80 kb with eight exons. These receptors are implicated in the regulation of expression of genes which encode proteins involved in cellular free fatty acid uptake,  $\beta$  oxidation, and cellular cholesterol trafficking. Natural ligands such as eicosanoids, mono- and polyunsaturated fatty acids, and long-chain fatty acyl-coenzyme A activate PPAR alpha in the body. PPAR alpha agonists drugs are used to decrease serum triglycerides and increase HDL synthesis in dyslipidemia.<sup>[2,7-9]</sup>

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## PPAR gamma

PPAR- $\gamma$  (gamma) is expressed in three isoforms. PPAR gamma 1 is present in the adipose tissue, heart, muscle, colon, kidney, pancreas, and spleen. PPAR gamma 2 is present mainly in the adipose tissue, liver, and heart. PPAR gamma 3 is present in the adipose tissue. The gene encoding PPAR gamma is located on chromosome 3 at position 3p25 and has six exons. PPAR gamma is activated by several naturally occurring compounds, such as the eicosanoids 9- and 13-hydroxyoctadecadienoic acids. Nitroated lipids known as nitroalkenes have been demonstrated to be potent, endogenous ligands of PPAR gamma. PPAR gamma promotes lipid storage and as a result improves insulin sensitivity and enhances glucose disposal in the adipose tissues and in skeletal muscles. These actions are beneficial in controlling blood sugar levels in diabetes mellitus. PPAR  $\gamma$  is also involved in the activation of glucose transporters (GLUT2) and glucokinase in  $\beta$  cells of pancreas and in the cells of liver, which also contributes to the beneficial effects of PPAR gamma in type 2 diabetes mellitus. The expression of these receptors is also implicated in other pathological conditions like metabolic syndrome and in cancers of breast, prostate, and colon.<sup>[10-16]</sup>

## PPAR delta

PPAR  $\delta$  (delta) are expressed in the adipose tissue, brain and skin. The gene encoding PPARs delta is present on Chromosome 6 in the region of 6p21.31 and spans about 85 kb of DNA consisting of nine exons and eight introns. Natural ligands of PPARs delta include fatty acids like bromopalmitate and prostanoid prostacyclin PGI<sub>2</sub>. PPARs delta regulates fatty acid metabolism in the skeletal muscle and adipose tissue. These receptors modulate the adaptive metabolic response of skeletal muscles to exercise. The activation of these receptors improves insulin sensitivity and elevates HDL levels in type 2 diabetes mellitus, dyslipidemia, and obesity. Treatment of obesity by PPAR delta agonists has shown to normalize various metabolic parameters related to obesity. These receptors are also implicated in several other diseases such as cancer and atherosclerosis. PPAR agonists have shown to enhance oligodendrocyte maturation and differentiation. It has also been demonstrated in animal experiments that PPAR delta regulates myelination of neurons.<sup>[6,15-19]</sup>

## Mechanism of PPAR activation

PPARs form heterodimers with retinoid X receptor (RXR) and then bind to specific consensus sequences (PPAR response elements, PPREs) in the enhancer regions of the related genes for gene regulation. PPREs consist of direct repeat (DR) of the nuclear receptor hexameric recognition sequence separated by one or two nucleotides. The protein structure of the PPAR isotypes reveals two domains: (1) DNA binding domain and (2) ligand-binding domain (LBD). The ligand binding domain is important for the activation of PPARs. In the absence of activation, PPAR-RXR heterodimers are bound to corepressor proteins such as HDACs and N-CoRs that maintain chromatin in the condensed state and inhibit the transcriptional apparatus from assembling. Upon activation, PPAR corepressor proteins dissociate. The activated PPARs form a complex with coactivator proteins such as p300 which leads to nucleosome remodeling and transcriptional preinitiation complex assembly on the target gene.<sup>[2,20-24]</sup>

## Therapeutic uses

### Type 2 diabetes mellitus

PPAR gamma enhances the expression of a number of gene-encoding proteins involved in glucose and lipid metabolism. The currently marketed PPAR gamma agonists for the treatment of diabetes mellitus type 2 are known as thiazolidinediones. The group includes drugs like pioglitazone and rosiglitazone. PPAR agonists are known to increase the sensitivity of the cells to the action of insulin.<sup>[25,26]</sup>

PPAR gamma activation with thiazolidinediones leads to an increase in c-Cbl-associating protein (CAP) expression and also increases insulin-stimulated c-Cbl phosphorylation in the cells. This increases the sensitivity of cells to insulin. It has been demonstrated in animal experiments that thiazolidinediones can prevent the onset of diabetes and its complications in rats and it also increases the expression of CAP protein in the adipose tissue. Insulin-sensitizing action of thiazolidinedione is synergistic when these drugs are given with other antidiabetic drugs like sulphonylurea, biguanides, and insulin. As an add-on therapy to the existing treatment of diabetes mellitus, thiazolidinediones seem to be very effective drugs.<sup>[27]</sup>

Diabetes mellitus type 2 and obesity are closely related. There is an increased frequency of obese individuals suffering from hyperlipidemia and related diseases like coronary artery disease, hypertension, stroke, etc. Beneficial action of the activation of PPARs on lipid and glucose metabolism has been established in various clinical trials. It has also been noted that new PPAR activators, having the capacity to activate both PPAR gamma and PPAR alpha, would not only help in sensitizing the body to insulin but would also have a beneficial effect on the lipid profile of the patient. This class of drug is called dual PPAR activator and includes recently developed drugs like muraglitazar and tesaglitazar. The drug development process for muraglitazar was abandoned recently, because of concerns about heart safety. Tesaglitazar did not appear to be more effective than the existing list of available antidiabetic mellitus drugs in various clinical trials [Table 1]. Other dual PPAR agonistic drugs are in various stages of development at this moment.<sup>[27]</sup>

### Atherosclerosis

PPARs are expressed in cells that make up atherosclerotic lesions.

**Table 1: List of PPAR drugs<sup>[27]</sup>**

Name of the drug	Receptor action	USA FDA	Current status
Troglitazone	PPAR gamma agonist	Initially approved	Withdrawn from market (Year 2000)
Pioglitazone	PPAR gamma agonist	Approved	Type 2 diabetes mellitus
Rosiglitazone	PPAR gamma agonist	Approved	Type 2 diabetes mellitus
Finofibrate, Clofibrate	PPAR alpha agonist	Approved	Dyslipidemia
Muraglitazar,	PPAR dual agonist (alpha and gamma)	Toxicity concerns	Type 2 diabetes mellitus and dyslipidemia
Tesaglitazar, Ragaglitazar, Naveglitazar	PPAR dual agonist (alpha and gamma)	Toxicity concerns	Type 2 diabetes mellitus and dyslipidemia

PPAR alpha activation regulates the genes involved in the transport and metabolic breakdown of cholesterol. PPAR alpha activation also decreases the levels of proatherosclerotic proteins (fibrinogen and C-reactive protein), inhibits foam cell formation, and increases plaque stability by reducing the expression of metalloproteinases involved in plaque destabilization. PPAR gamma also inhibits atherosclerosis by inducing the expression of a protein called ATP-binding cassette G1 (ABCG1) in macrophages and artery walls. This protein transfers cholesterol from cells to high-density lipoproteins (HDLs) and prevents the accumulation of cholesterol in the artery wall. PPAR gamma also inhibits the proliferation, hypertrophy, and migration of vascular smooth muscle cells in the vessel wall. The net effect is the inhibition in the progression of intima-media thickness in vessel walls. The activation of both PPAR alpha and gamma improves endothelial function by increasing nitric oxide expression as well as release from the vascular endothelial cells.<sup>[28-30]</sup>

### *Dyslipidemia*

The activation of PPAR alpha in the liver, and in the intestine, reduces the secretion of VLDLs. This decreases the formation of intravascular lipid remnants. PPAR alpha activation improves the process of lipolysis and helps in the removal of lipids by the liver via diminishing their apo CIII content. The activation of PPAR alpha also increases the expression of genes for extracellular heparan-containing proteoglycans that bind more efficiently to VLDL remnants. This is the first step in the hepatic uptake of lipids. In patients with dyslipidemia, PPAR alpha activation decreases triglycerides and VLDL levels and increased HDL levels. The drugs of the fibrate group are PPAR alpha activators. These drugs in addition to their antilipidemic action also inhibit the release of chemokines from the blood vessel walls which in turn inhibit the attraction of inflammatory cells toward the vessel wall and prevent atherosclerosis.<sup>[32,33]</sup>

### *Obesity and syndrome X*

Type 2 diabetes mellitus is associated with metabolic syndrome. This syndrome includes features like abdominal obesity, dyslipidemia, hypertension, and hyperglycemia. Recent evidence suggests the possibility of the role of PPARs in obesity and syndrome X. PPAR delta activation is a key regulator of lipid metabolism in the body and helps in burning fat and can protect the body against genetically acquired and dietary obesity. PPAR alpha participates in the beta oxidation of fatty acid in the liver and heart. PPAR delta is involved in fatty acid oxidation in muscles. PPAR gamma is available in the adipose tissue and it stimulates glucose and lipid uptake and their metabolism in the cells. Drugs which activate PPAR alpha and gamma such as fibric acid derivatives and thiazolidinediones, respectively, are in use for patients with type 2 diabetes mellitus and dyslipidemia. These drugs also improve insulin resistance in these patients. Dual PPAR agonist drugs help in improving lipid parameters, normalize blood pressure and endothelial function, as well as suppress atherosclerotic plaque formation.<sup>[33,34]</sup>

### *Cardiovascular diseases*

It is proved that the fibrate (PPAR alpha agonist) group of drugs reduces cardiovascular risks by altering the lipid profile of the

patient. It has also been noted that PPAR gamma ligands control blood pressure. However, the mechanism of this effect remains unknown.<sup>[35-36]</sup>

PPAR gamma is now recognized as a key player in the inflammatory cell response associated with cardiovascular diseases (CVDs) like coronary artery disease, stroke, etc. Genetic studies on PPAR gamma have revealed functional changes in these receptors in cases of CVDs. The PPAR gamma agonist reduces inflammatory markers and delays atherosclerosis progression in these patients. However, recent clinical studies suggest the deleterious action of PPAR activation on the cardiovascular system. This complex and paradoxical interaction needs to be studied more in the future.<sup>[37]</sup>

### *Inflammation and neurology*

PPAR activation inhibits inflammatory response genes and decreases the production of inflammatory mediators like IL-6, IL-2, TNF alpha, and cyclooxygenase-2, and also suppresses cells like T cell and macrophage. PPAR ligands have shown to have an anti-inflammatory activity in a variety of experimental and clinical studies of acute and chronic inflammation. PPAR alpha and gamma have been implicated in the regulation of endothelial cell inflammatory response and induction of apoptosis, and also decrease the formation of metalloproteinase.<sup>[38-39]</sup>

### *Alzheimer's disease*

The hallmark of Alzheimer's disease is the extracellular deposition of amyloid peptide in neuritic plaques and intracellular deposits of tau protein. This results in the formation of neurofibrillary tangles and finally neuronal death. It has been demonstrated that PPAR alpha activation inhibits amyloid peptide stimulated expression of tumor necrosis factor alpha and interleukin-6. PPAR gamma activation inhibits the  $\beta$ -amyloid stimulated expression of inflammatory cytokines. It also induces the clearance of  $\beta$ -amyloid peptide. The above-mentioned factors slow down the cognitive decline in Alzheimer's disease.<sup>[40]</sup>

### *Multiple sclerosis*

Neuroinflammation is the key to the pathophysiology of multiple sclerosis. PPAR gamma activation inhibits the production of nitric oxide, proinflammatory cytokines (tumor necrosis factor  $\alpha$ , interleukin- $1\beta$ , interleukin-6), and chemokine MCP-1 by microglia and astrocytes cells. PPAR  $\gamma$  activators also suppress T-cell proliferation by 40–50%. The above-mentioned mechanism supports the potential use of PPAR gamma as immunomodulatory drugs in multiple sclerosis.<sup>[41-42]</sup>

### *Parkinson's disease*

Oral administration of the PPAR gamma agonist pioglitazone attenuates MPTP-induced glial activation and prevents dopaminergic cell loss in the substantia nigra pars compacta as seen in various experiments conducted on different experimental animal models used to demonstrate PPAR gamma agonistic activity in Parkinson's disease. Pioglitazone also prevents MPTP-induced expression of inducible nitric oxide synthase. Thus PPAR activators can be one of the drugs to treat Parkinsonism in the future.<sup>[43]</sup>

### *Ischemic stroke*

PPAR activation protects the brain against toxic biological

reactions induced by cerebral ischemia. This neuroprotective effect of PPAR agonists is also related to the inhibition of ischemia-induced inflammatory markers in the brain cells.<sup>[11]</sup>

#### *Spinal cord Injury*

Traumatic spinal cord injury is accompanied by inflammatory response, which increases in the first week after injury and is responsible for the wide-spread damage associated with the spinal cord injury. PPAR activation decreases the inflammatory response in rodents with a spinal cord injury. PPAR agonist pioglitazone may be a treatment of future for limiting the functional damage associated with a spinal injury.<sup>[44]</sup>

#### *Psoriatic arthritis*

Psoriatic arthritis is a chronic disorder characterized by an inflammatory joint and skin condition. PPAR gamma activation significantly reduces inflammatory cytokine expression and neoangiogenesis in joints in various preclinical trials. Treatment with PPAR ligands may be useful in the treatment of psoriatic arthritis in the future.<sup>[45]</sup>

#### *Chronic obstructive pulmonary disease*

COPD is always associated with persistent inflammation. PPARs reduce the inflammatory response in the lung tissue and inhibit inflammatory signaling pathways, such as nuclear factor and AP-1 (activator protein). PPAR agonist can be of therapeutic potential in the treatment of COPD.<sup>[46]</sup>

#### *Cancers*

##### *Colon cancer*

PPAR delta is expressed in human colon cancer cells, where it regulates cell proliferation and differentiation. It is shown to down-regulate inflammation in some studies. In other studies it helps in the proliferation and differentiation of colon cancer cells. It remains unclear whether PPAR delta acts as oncogenes or as tumor suppressors. Ligand-activated PPAR gamma on the other hand interacts with beta-catenin and reduces beta-catenin transcriptional activity which is required for aberrant crypt foci formation. Short-term exposure to dietary PPAR gamma ligands such as linoleic acid has been shown to inhibit colon cancer metastasis.<sup>[11,47]</sup>

##### *Breast and prostate cancer*

PPAR gamma expresses itself in breast cancer cells and in prostate adenocarcinomas. The cancerous cells lose their malignant phenotype and show a decrease in the proliferation rate when PPAR gamma is activated. PPAR activation has a therapeutic role in the treatment of these cancers by acting as a biological modifier.<sup>[11]</sup>

##### *Lung cancer*

PPAR gamma ligands have been shown to decrease the proliferation of non-small-cell lung cancer cell lines.<sup>[11]</sup>

##### *Leukemia*

In T-cell leukemia, PPAR gamma ligands have shown antiproliferative effects.<sup>[11]</sup>

##### *Pituitary tumors*

PPAR gamma ligands induce cell-cycle arrest and apoptosis and

suppresses ACTH secretion in adrenocorticotrophic hormone-secreting pituitary tumors, in which morbidity is associated with excessive glucocorticoid production.<sup>[11]</sup>

#### *Gastric carcinoma*

PPAR gamma agonist inhibits the growth of cultured gastric cancer cells. Therefore, PPAR agonist can be of help in the treatment of gastric malignancies in the future.<sup>[48]</sup>

#### *Eye diseases*

Chronic inflammation is associated with diabetic retinopathy and with age-related macular degeneration. The anti-inflammatory role of PPARs, in particular PPAR gamma, can be of therapeutic benefit in the treatment of diabetic retinopathy and age-related macular degeneration.<sup>[49]</sup>

#### *Viral infections*

PPARs may have a role to play in various viral infections like HIV (human immunodeficiency virus), HCV (hepatitis C virus), and HBV (hepatitis B virus). Giralt *et al.* and Caron *et al.* showed the association of adipose tissue physiology with HIV infection and treatment. Doran and his colleagues stipulated the potential role of PPARs in the reduced bone mass associated with HIV-1 infection and treatment. Lemoine *et al.* stressed the role of PPARs in HIV and HCV-associated liver disease. These infections interfere with hepatic insulin signaling and down-regulate PPARs. Dubuquoy *et al.* showed the potential of PPARs in the modulation of HBV transcription and replication. Modulating of the PPAR/RXR heterodimer may be of therapeutic value to control HBV infection in the future.<sup>[50]</sup>

#### *Renal effect*

In a patient with diabetic nephropathy, PPAR gamma ligands ameliorate microalbuminuria, reduce urinary albumin excretion, and decrease the serum concentration of type IV collagen. PPAR gamma agonists cause reduction in glomerular cell proliferation. It also reduces glomerular macrophages and the drug confers some protection in cases of glomerulosclerosis. PPAR gamma in general reduces and delays renal fibrotic lesions in diabetic nephropathy and in nondiabetic chronic kidney diseases.<sup>[51-52]</sup>

### **Assisted reproductive technology**

Gametes, embryo and endometrium are essential for viable pregnancy. The outcome of assisted reproductive technology (ART) may be enhanced by improving any one or all of the above elements. Experimental studies have shown that PPAR delta ligands enhance embryo development. The application of PPAR delta ligands in the area of ART requires more research.<sup>[53]</sup>

#### *Polycystic ovarian disease*

Polycystic ovarian syndrome is the most frequent cause of female infertility. The treatment of polycystic ovarian syndrome with insulin sensitizers, such as thiazolidinediones, increases the ovulation rate and the number of successful pregnancies. The positive action of

the insulin-sensitizing treatments could be explained not only by a decrease in the peripheral insulin resistance but also by a direct action at the ovarian level.<sup>[54]</sup>

## Inflammatory bowel disease

PPAR gamma is expressed in the colon cells and is a key receptor in the regulation of intestinal inflammation. Therefore, greater knowledge of PPAR gamma expression and its function in intestinal inflammation will be of help in knowing the therapeutic potential of PPARs in inflammatory bowel disease. The discovery that 5-amino salicylic acid is a ligand for PPAR receptor (expressed by colonic epithelial cells) paves the way for the development of new molecules targeting inflammatory bowel disease.<sup>[55]</sup>

## Asthma

Bronchial asthma is associated with persistent inflammation of the airways. PPAR gamma has been shown to play an important role in the control of inflammatory responses within the lung, acting on both immune and nonimmune cells. It has also been demonstrated that inhaled agonistic ligands of PPAR gamma have therapeutic potential in bronchial asthma.<sup>[56]</sup>

## Diseases of the bone

All three isoforms of PPARs are expressed during the development and maturation of osteoclasts. PPAR agonists also have a strong influence on the bone resorption process and negatively regulate osteoblast differentiation of bone marrow stromal cells in unloading, resulting in bone loss. Evidence from ADOPT trial published in 2006 suggest that rosiglitazone and pioglitazone increase the fracture risk. It was also shown that women are more at risk of fractures as compared to men when on these therapies. Further exploration in this aspect needs to be studied. PPARs are also expressed in the synovial fluid in rheumatoid arthritis patients. Treatment with PPAR agonists has shown to improve symptoms in arthritic animal models. The precise mechanism of action of these agents is not known.<sup>[57-61]</sup>

## Aging and longevity

Calorie restriction is an effective way to delay aging process, and it also increases lifespan. Calorie restriction affects the same physiological functions of the body as PPAR activation does. It has been shown in animal experiments that aging alters the expression of PPARs in mice. There can be a possible role of PPARs in mediating the effects of longevity genes. The expression of PPARs change with age while calorie restriction appears to prevent these alterations. This phenomenon makes the relationship of PPARs, calorie restriction, and aging an important point of research for the future.<sup>[62]</sup>

## Drug metabolism

The cytosolic sulfotransferase and UDP-glucuronosyltransferase families of enzymes account for the majority of phase II metabolism in the process of drug metabolism. PPARs are important regulators

of sulfotransferase and UDP-glucuronosyltransferase gene transcription. It will be interesting to know about the relationship of PPAR activation and its effects on drug metabolism and to understand and minimize drug interactions in the future with the help of the same.<sup>[63]</sup>

## Wound healing

PPARs are expressed in the mouse epidermis during fetal development and they disappear progressively from the interfollicular epithelium after birth. PPAR alpha and beta express again in the adult epidermis after various stimuli, resulting in keratinocyte proliferation and differentiation in skin wound healing. All isoforms of PPARs are important for the rapid epithelialization of a skin wound. PPAR alpha is mainly involved in the early inflammatory phase of healing; PPAR beta is implicated in the control of keratinocyte proliferation. Thus PPAR ligands can be used as wound healing drugs in the future if tested positive in preclinical and clinical trials.<sup>[64]</sup>

## Acne

Acne vulgaris is a skin disorder and it has a pathological component of inflammation associated with it. Pemirolast (antiallergy drug) is a drug which has several antiacne actions, one of which is modulation of PPAR alpha and gamma. The activation of these receptors is associated with the reduced inflammation associated with acne. The drug can hold the key to the treatment of acne in a more effective way in the future.<sup>[65]</sup>

## Mitochondrial dysfunction diseases

There is no treatment for neuromuscular disorders with defects in the mitochondrial ATP generating system. It has been reported in various trials that PPAR gamma activation induces mitochondrial biogenesis. Pan-agonists of PPARs also show similar benefits. PPAR ligands successfully stimulate the residual respiratory capacity in the muscle tissue. Thus, the induction of mitochondrial biogenesis through PPAR pathway is an effective therapeutic approach for the treatment of mitochondrial disorders.<sup>[66]</sup>

## Newer PPAR approaches

### *PPAR coagonism (alpha and gamma)*

Dual PPAR activation showed significant improvement in lipid parameters in animal and clinical trials. Compounds with dual activities appear well suited for the treatment of diabetic patients with dyslipidemia. Most of these compounds are in a developmental stage at the moment.<sup>[67]</sup>

### *Pan-PPAR coagonism (alpha, gamma and delta)*

Pan-PPAR coagonism is an emerging concept and can reduce the severity of intermittent claudication, incidence of coronary events, or sudden death in old patients. Pan-PPAR drugs include experimental compounds like aleglitazar, muraglitazar, and tesaglitazar, which are in a developmental phase.<sup>[68-71]</sup>

### Limitations for use and discontinuation of various PPAR drug development projects

Many compounds are in the development process (more than 50), but safety issues are a major concern. Toxicities and side effects are observed in preclinical and clinical trials (cardiac, skeletal muscle, renal, bone marrow weight gain, fluid retention, brain hemorrhage, ventricular dilatation, sarcomatous tumors).<sup>[72]</sup>

### Conclusion

PPARs are interesting pharmaceutical targets. They have multiple beneficial effects. New PPAR drugs showing coagonism or pan-agonism are expected to show synergistic effects on various metabolic and inflammatory diseases. Long-term trials are needed to evaluate the efficacy and safety of these wonder agents.

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