PPAR-γ Agonists for the Treatment of Major Depression: A Review

Authors

R. Colle[1, 2, 3, 4*], D. de Larminat[1, 2, 3, 4*], S. Rotenberg[1, 2, 3, 4], F. Hozer[1, 2, 3, 4], P. Hardy[1, 2, 3, 4], C. Verstuyft[1, 3, 5, 6], B. Fève[7, 8, 9#], E. Corruble[1, 2, 3, 4#]

Affiliations

1 University Paris-Sud, Le Kremlin Bicêtre, France
2 INSERM, UMRS 1178, Le Kremlin Bicêtre, France
3 Hôpital Bicêtre, Hôpitaux Universitaires Paris-Sud, Assistance Publique-Hôpitaux de Paris, Le Kremlin Bicêtre, France
4 Département de Psychiatrie, Le Kremlin Bicêtre, France
5 INSERM UMR_S1184, Centre IMVA
6 Service de Génétique moléculaire, Pharmacogénétique et Hormonologie
7 Sorbonne Universités, Université Pierre et Marie Curie, Centre de Recherche Saint-Antoine, INSERM UMR_S938, Paris, France
8 Institut Hospitalo-Universitaire ICAN, Paris, France
9 Service d'Endocrinologie, Assistance Publique des Hôpitaux de Paris, Hôpital Saint-Antoine, Paris, France

Key words

major depression, PPAR-γ agonists, pioglitazone, efficacy, safety

received 08.09.2016
revised 26.09.2016
accepted 25.10.2016

Bibliography

DOI http://dx.doi.org/10.1055/s-0042-120120
Published online: December 15, 2016
Pharmacopsychiatry 2017; 50: 49–55

ISSN 0176-3679

Correspondence

Romain Colle
CHU de Bicêtre
Département de Psychiatrie
78 Rue du Général Leclerc
Le Kremlin Bicêtre
France
romaincolle@hotmail.com

ABSTRACT

Introduction Selective agonists of the nuclear transcription factor peroxisome proliferator-activated receptor-gamma (PPAR-γ) are used for the treatment of type 2 diabetes. We reviewed their efficacy and safety for the treatment of major depression and the association of their potential antidepressant effects with changes in biomarkers of metabolism and inflammation.

Methods From 8 studies, 4 open-label trials, and 4 randomized controlled trials (RCT) (3 vs. placebo and 1 vs. metformin), 448 patients with major depression were included, of which 209 patients received PPAR-γ agonists (pioglitazone or rosiglitazone) for 6–12 weeks, either alone or in add-on therapy to conventional treatments.

Results PPAR-γ agonists have antidepressant effects in the 4 open-label studies and in 3 out of 4 RCT. No major adverse event was reported. Improvement in depression scores was associated with improvement in 3 biomarkers of insulin resistance (homeostatic model assessment [HOMA-IR], oral glucose tolerance test, and fasting plasma glucose) and 1 biomarker of inflammation (interleukin-6) among 21 biomarkers studied.

Conclusion PPAR-γ agonists may have antidepressant properties, which need to be assessed in further studies of major depressive episodes.

Introduction

Nowadays, more than 40 % of patients with a major depressive disorder (MDD) treated for a major depressive episode (MDE) with an adequate dosage and duration of antidepressant drug fail to respond to treatment [1]. Furthermore, approximately half of adults with an MDD do not achieve sustained remission [2]. The poor efficacy of conventional antidepressants in MDD is also shown in patients with bipolar disorder (BD) [3]. Thus, drugs with new mechanisms of action are needed to treat MDEs.

Selective agonists of the nuclear transcription factor peroxisome proliferator-activated receptor-gamma (PPAR-γ) [4] are ligand-dependent transcription factors that form heterodimers with the retinoid X receptors [5], bind to DNA in specific regions (PPAR response elements) [6], and finally regulate the transcription of target genes related to lipid and glucose metabolism, inflammatory processes, and cellular differentiation [5]. PPAR-γ agonists have both anti-inflammatory properties and efficacy in metabolic disorders (type 2 diabetes or polycystic ovary syndrome). Indeed, they can reduce hyperglycemia through enhanced free fatty acid uptake by adipose tissue and can improve beta-cell function and insulin sensitivity in type 2 diabetes mellitus (T2DM) [7]. Decreased free fatty acid plasma levels enhance insulin action in the liver and skeletal muscles [8]. By activating PPAR-γ in adipose tissue, PPAR-γ agonists decrease inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), while increasing circulating levels of adiponectin, an insulin-sensitizing adipokine [9].

PPAR-γ agonist drugs such as troglitazone, rosiglitazone, and pioglitazone have been used for the treatment of T2DM [4]. Due to hepatotoxicity, troglitazone was withdrawn from the market by the Food and Drug Administration (FDA) in 2000. Given the potential increased cardiovascular risk, the use of rosiglitazone was strictly limited by the FDA [10] and suspended by the European Medicine Agency in 2010 [11]. Pioglitazone has beneficial effects on cardiovascular diseases [12–18] and metabolic syndrome in patients with T2DM [19, 20] but can induce weight gain [21–23], congestive

[*] These authors contributed equally to this work.
[#] These authors co-directed this work.

heart failure [4, 24], peripheral edema, macular edema [25], and bone fractures [26].

Preliminary evidence of links between PPAR-γ and mood were drawn from behavioral studies in non-depressed animals. Indeed, the PPAR-γ agonist NP031115 induced an antidepressant-like effect in mice by enhancing PPAR-γ activity [27]. In the tail suspension test and the forced swimming test (2 animal models measuring the effectiveness of antidepressants), rosiglitazone showed an antidepressant-like activity, inducing a significant and dose-dependent decrease in immobility time in mice and rats [28]. Similarly, pioglitazone decreased the immobility time in the forced swimming test in mice [29], an effect that was reversed after administration of the PPAR-γ antagonist GW-9962. Recent data [56–58] suggest that serotonin could stimulate PPAR-γ activity. Indeed, in fat cells, serotonin leads to the activation of PPAR-γ responsive genes and enhances lipid accumulation [56–58].

Consequently, some effects of conventional antidepressants that influence the serotonin system functioning (selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and tricyclics) may involve the activity of the PPAR-γ pathway.

The first use of pioglitazone in MDE was published as a case report in 2009 [30]. A marked improvement of depression was evidenced in a 55-year-old woman treated with pioglitazone (30 mg/d for 12 weeks) for a metabolic syndrome and a resistant MDE. Insulin resistance improved concomitantly with the MDE in this woman. In 2014, a 24-week double-blind RCT in 145 patients with a metabolic syndrome [31] suggested a higher improvement of symptoms of depression and anxiety (assessed with the questionnaire Hospital Anxiety and Depression Scale) with pioglitazone (30 mg/d) than with placebo. However, these patients did not have a diagnosis of MDE.

Hence, we performed a review of the efficacy and safety of PPAR-γ agonists for the treatment of major depression and the association of their antidepressant effects with changes in biomarkers of metabolism and inflammation.

Material and Methods

A search was conducted on PubMed from January 1990 to August 2016 with the following keywords: (pioglitazone) OR (rosiglitazone) OR (thiazolidinedione) OR (troglitazone) [Title/Abstract] AND (depress *) [Title/Abstract] OR (bipolar) [Title/Abstract].

To be included in this review, studies had to fulfill the following criteria:

- Standardized diagnostic criteria for MDE (DSM-IV)
- Prospective treatment with PPAR-γ agonists
- Assessment of depression at baseline and follow-up using standardized depression rating scales

The following data were recorded from each study: sponsor, name of the study, registration trial number, design, number of patients, mean age, percentage of women, diagnosis criteria of MDE, drug, dosage and duration of treatment, concomitant use of psychotropic drugs, and standardized depression rating scale used to assess depression at baseline and follow-up (i. e., Hamilton Depression Rating Scale [HDRS] [32], Inventory for Depressive Symptomatology [IDS] [33], or Quick Inventory for Depressive Symptomatology [QIDS] [33]).

Studies including patients with metabolic comorbidities were not excluded.

Results

8 studies were identified: 4 open-label trials (▶ **Table 1**) and 4 RCT (▶ **Table 2**). Among the 348 patients included, 209 received PPAR-γ agonists. In the 4 open-label trials, patients received either rosiglitazone or pioglitazone. In the 4 double-blind RCT, pioglitazone was compared to a placebo (3 studies) or to metformin (1 study).

Efficacy

Open studies

In the 4 prospective open-label studies [34–37] (▶ **Table 1**), 118 patients with a current MDE and metabolic disorders were assessed before the beginning and after 8 or 12 weeks of treatment with PPAR-γ agonists (pioglitazone or rosiglitazone) and 59 by metformin. For rosiglitazone [34], the starting dose, 4 mg/d, was increased after 4 weeks at 8 mg/d. For pioglitazone, flexible dose designs were used with a starting dose of 15 mg/d possibly increased depending on response and tolerability at 30 mg/d (mean dose: 27.4 ± 5.8 mg/d) [35] or 45 mg/d (mean dose: 32.7 mg/d) [36] or was prescribed at fixed dose (30 mg/d) [37]. Concomitant psychotropic treatments were not described in 3 studies [34–36], but their dose changes were not allowed in 2 studies [35, 36]. Fluoxetine (fixed dose: 20 mg/d) was prescribed in the fourth one [37]. The main outcome was depression severity measured with the HDRS [34, 37] or IDS [35, 36] scales. In 3 studies, score changes from baseline were used to assess antidepressant effect of pioglitazone or rosiglitazone [34–36]. Of note, the outcome of the fourth study in post-stroke depression (i. e., the final HDRS score) [37] was unusual. Nonetheless, the 4 open studies converge to show that treatment with pioglitazone or rosiglitazone could induce a significant antidepressant effect (▶ **Table 1**).

Double-blind RCT

4 double-blind RCT of pioglitazone [38–41] are available for a total number of 161 patients with a diagnosis of MDE (MDD or BD) (▶ **Table 2**). Eighty-one patients received pioglitazone and 80 received a placebo (n = 60) [38, 40, 41] or metformin (n = 20) [37, 39]. The pioglitazone dose was 30 mg/d in 2 studies [38, 41] or began at 15 mg/d for the first week and 30 mg/d thereafter in fixed designs in the 2 others [39, 40]. The main statistical analysis was performed in intent-to-treat in only 2 studies [38, 39] and in per-protocol in the others [40, 41]. The main outcome measure was the mean HDRS score change (from baseline to follow-up), which was compared between pioglitazone and control groups. The HDRS score changes were higher in the pioglitazone group than in the control group in 3 double-blind RCTs [38–40] but were not different in 1 study [41]. However, in this study [41] with pioglitazone (30 mg/d), participants could benefit from their concomitant individualized treatment for depression. That could explain the absence of difference between pioglitazone and placebo. The HDRS score change differences between pioglitazone and controls that were reported in 3 double-blind RCT [38–41] were comprised between 2.3

▶ **Table 1** Open-label studies.

Studies	Rasgon 2010 [34]		Kemp 2012 [35]	Kemp 2014 [36]	Hu 2015 [37]
Trial registration number	No registration		No registration	NCT00835120	No registration
Sponsors	National Institutes of Health		National Institutes of Health, Takeda Pharmaceuticals	Brain and Behavior Research Foundation, National Institutes of Health, Takeda Pharmaceuticals	Chinese State Natural Science Fund
PPAR-γ agonist	Rosiglitazone		Pioglitazone	Pioglitazone	Pioglitazone Meformin
Dose (mg/d)	Fixed Starting: 4 After 4 weeks: 8		Flexible Starting: 15 After 4 weeks: 15–45	Flexible Starting: 15 After 4 weeks: 15–30	Pioglitazone: Fixed: 30 Meformin: Fixed: 1 000
Number of patients	12		23	34	118
Concomitant drug use	Add-on with antidepressants (all marketed)		Monotherapy	Add-on with mood stabilizers (all marketed)	Add-on with fluoxetine (20 mg/d)
Diagnosis	MDE-MDD MDE-BD		MDE-MDD	MDE-BD	Post-stroke depression
Age (years [m ± sd])	51.9 ± 5.6		44.6 ± 10.2	47.8 ± 10.9	64.6 ± 5.5
Women (%)	91		87	56	56.8
Metabolic status	Insulin resistance[b]		Metabolic syndrome[a] or abdominal obesity[a]	Metabolic syndrome[a] or insulin resistance[b]	Type 2 diabetes
Study duration (weeks)	12		12	8	12
Depression scales	HDRS	CGI-S	IDS	IDS	HDRS
Baseline score (m ± sd)	19.9 ± 5.0	4.0 ± 0.6	40.3 ± 1.8	38.7 ± 8.2	29.1 ± 12.8
Score change (m ± sd)	12.1 ± na *	2.9 ± na *	19.2 ± 1.8 *	21.9 ± 9.2 *	na
Response (n [%])	na	na	15 (65 %)	13 (38 %)	na
Remission (n [%])	na	na	5 (22 %)	8 (24 %)	na
Major adverse events	no		no	no	no

MDE: Major Depressive Episode; MDD: Major Depressive Disorder; BD: Bipolar Disorder; [a]: National Cholesterol Education Program's Adult Treatment Panel III definition; [b]: defined as 2 or more of the following criteria: body mass index (BMI) ≥ 28, fasting blood glucose (FPG) ≥ 100 mg/dl, triglycerides (TG) ≥ 150 mg/dl, or triglyceride/high-density lipoprotein (HDL)-cholesterol ratio (TG/HDL) ≥ 3.0); HDRS: Hamilton Depression Rating Scale; CGI-S: Clinical Global Impression - Severity; IDS: Inventory for Depressive Symptomatology; na: not available; * $p < 0.05$: comparison of score changes; Response: ≥ 50 % reduction in HDRS or IDS total score from baseline to endpoint; Remission: HDRS total score < 8 or IDS total score ≤ 12

and 4.2 HDRS points. In 1 study [38] but not the others, higher rates of remitters were shown with pioglitazone than with placebo.

Safety

In the 8 studies, there were no deaths, no major adverse events, no clinically significant weight gain (≥ 7 % increase in basal weight), and no significant difference in weight change.

The common side effects reported with pioglitazone were the following: increased appetite (15–25 %), headache (5–26 %), nausea (8.7–25 %), sexual dysfunction (20 %), abdominal pain (20 %), muscular pains (10–17.4 %), blurred vision (13–15 %), irritability (11.7 %), insomnia (8.7–10 %), decreased appetite (5 %), and edema (11.7 %). In 1 RCT with pioglitazone (30 mg/d) [41], 1 patient (4.7 %) discontinued because of an edema. In another RCT with pioglitazone (30 mg/d) [37], 3 (5.1 %) patients discontinued because of mild adverse events (not described) [37]. The 2 studies in which patients discontinued because of adverse events were the 2 longer (12 weeks). Of note, these studies did not stratify on the presence or absence of metabolic comorbidities. Thus, the safety of these drugs in patients with major depression without comorbidities remains poorly known.

Association of improvement of depression and improvement of biomarkers of metabolism/inflammation

Several markers of metabolism were studied in 5 different studies [35–37, 39, 41] but detailed in only 2 studies [35, 36]. Some of them were clinical: weight, waist circumference, body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP). Others were biological: total-cholesterolemia (TC), triglyceridemia (TG), low-density lipoprotein cholesterolemia (LDL-C), high-density lipoprotein cholesterolemia (HDL-C), TG/HDL-C ratio, fasting plasma glucose (FPG), fasting plasma insulinemia (FPI), Homeostatic Model Assessment (HOMA-IR) (fasting insulin [μU/mL]) × ((fasting glucose [mg/dL]) ÷ 22.5), insulin sensitivity index (ISI), oral glucose tolerance test (OGTT), and adiponectin.

Some inflammatory biomarkers were studied in 2 studies [35, 36]: high-sensitivity C-reactive protein (hsCRP); IL-1, IL-6, and IL-10; and TNF-α.

Table 2 Double-blind randomized controlled trials.

Studies	**Sepanjnia 2012 [38]**		**Kashani 2013 [39]**		**Zeinoddini 2015 [40]**		**Lin 2015 [41]**	
Trial registration number	**NCT01109030**		**IRCT201106081556N23**		**IRCT201211211556N46**		**NCT01559857**	
Sponsor	**Tehran University of Medical Sciences**		**Tehran University of Medical Sciences**		**Tehran University of Medical Sciences**		**National Institutes of Health**	
Drugs	Pioglitazone	Placebo	Pioglitazone	Metformin	Pioglitazone	Placebo	Pioglitazone	Placebo
Dose (mg/d)	Fixed: 30	–	Fixed: 1st week: 15 Later: 30	1st week: 500 2nd week: 1 000 Later: 1 500	Fixed: 1st week: 15 Later: 30	–	Fixed: 30	–
Number of patients	40		40		44		37	
Diagnosis	MDE-MDD		MDE-MDD		MDE-BD		MDE-MDD or BD	
Age (years [m ± sd])	32.1 ± 5.4		20.8 ± 4.0		32.7 ± 4.7		46.4 ± 13.8	
Women (%)	72.5		100		34.1		na	
Metabolic comorbidities	no		Polycystic Ovary Syndrome: 100 %		no		Insulin resistance[a]: 54 %	
Concomitant drug (Dose [mg/d])	Citalopram (30)		no		Lithium salts (serum: 0.6–0.8 mEq/L)		Marketed antidepressant [b]	
Duration (weeks)	6		6		6		12	
Depression scale	HDRS		HDRS		HDRS		HDRS	
Baseline score (m ± sd)	25.4 ± 3.4		15.1 ± 1.8		23.1 ± 1.7		15.6 ± 5.1	
Score change (m ± sd)	**16.7 ± 3.5** *	**13.4 ± 3.5** *	**5.6 ± 2.1** *	**1.3 ± 0.9** *	**14.0 ± 3.2** *	**11.7 ± 2.3** *	4.1 ± na	3.2 ± na
Response rates (n [%])	**19 (95 %)** *	**8 (40 %)** *	na	na	19 (86 %)	16 (73 %)	na	na
Remission rates (n [%])	**9 (45 %)** *	**3 (15 %)** *	4 (20 %)	0 (0 %)	5 (23 %)	1 (4 %)	na	na
Major Adverse Event	no	no	no	no	no	no	na	na
Adverse Events (difference between groups)	No difference		Increased appetite	Decreased appetite	No difference		na	na

MDE: Major Depressive Episode; MDD: Major Depressive Disorder; BD: Bipolar Disorder; [a]: at least 3 of the following criteria: FPG ≥ 100 mg/dL, Fasting plasma insulin ≥ 15 ml U/ml, Oral Glucose Tolerance Test (OGGT at 120 min ≥ 140 mg/dL); na: not available; [b]: at least 8 weeks of stable antidepressant treatment before inclusion; HDRS: Hamilton Depression Rating Scale; Response: ≥ 50 % reduction in HDRS score from baseline to endpoint; Remission: HDRS < 8; * $p < 0.05$ for comparison of treatment efficacy rates between pioglitazone and control treatment

For metabolism, an association between depression score improvement and HOMA-IR score decrease was observed with pioglitazone (30 mg/d) in 2 studies [35, 39]. HDRS score decreases were associated with FPG and OGTT decreases [41]. No significant difference was observed for the other 15 biomarkers studied in all the studies.

For inflammation, a significant association was observed between decrease in IL-6 and the improvement of depression score in 1 study [36] but not in the other one [35]. No significant association was found with the other 5 inflammatory biomarkers studied in all the studies.

Thus, there are positive results with 4 biomarkers out of the 21 studied. They may suggest a link between the antidepressant response to PPAR-γ agonists and metabolism (insulin resistance) and inflammation (IL-6 serum levels).

Ongoing registered double-blind RCT

2 other double-blind RCT of pioglitazone are currently ongoing for the treatment of BD. The first ongoing study (NCT01717040, Calabrese, clinicaltrials.gov) compares pioglitazone (first week at 15 mg/d then flexible 15–45 mg/d) vs. placebo for 8 weeks in 36 patients with bipolar depression (inclusion completed). The first objective of this study is to assess the efficacy of pioglitazone in bipolar depression, and its second objective is to assess changes in insulin resistance (HOMA-IR and fasting lipid profile). The second ongoing study (2014-003803-31, clinicaltrialsregisters.ue) compares pioglitazone to placebo for 3 months in 60 patients with bipolar depression. The first objective of this study is to assess the efficacy and safety of pioglitazone in bipolar depression. Its second aims are to determine the effects of pioglitazone on remission rates and to assess the association of antidepressant effects with the pro/anti-inflammatory status, BDNF levels, and cognitive functioning.

Discussion

This work highlights the potential relevance of PPAR-γ agonists for the treatment of MDE. From the 8 available studies, 4 open-label trials and 3 out of the 4 double-blind RCT, PPAR-γ agonists, either alone or in add-on therapy, may have significant antidepressant properties with no significant adverse events in patients with MDE. These effects may be associated with improvement of insulin resistance (HOMA-IR, OGTT, and FPG) and inflammation (IL-6), but this point should be further studied because only 4 biomarkers out of 21 were positively associated with depression improvement.

Some limits have to be emphasized for this review. First, the efficacy and safety of pioglitazone are assessed in short-term (6–12 weeks) but not in long-term studies. This point should be further studied because antidepressant treatments are usually needed for several months or years. Second, the effects of the inclusion criteria in terms of diagnoses of mood disorder (MDD, BD, or post-stroke depression) and concomitant psychotropic treatments were not studied here. This heterogeneity may also influence the results. Third, the number of studies available is low and the number of patients treated with PPAR-γ is relatively low (n = 209). Fourth, the current review is vulnerable to publication bias. Hence, these findings should be considered as preliminary. Fifth, association is not causation; thus, it cannot be stated that clinical and biomarkers changes are due to PPAR-γ agonists effects. They could be independent from the PPAR-γ mechanism of action. Indeed, rosiglitazone and pioglitazone have been reported to have off-target effects such as partial glucocorticoid receptor agonism leading to anti-steroid properties [42] or retinoic acid receptor agonism [43, 44], which may contribute to their potential antidiabetic and antidepressant effects. Of note, anti-steroid drugs with PPAR-γ properties (such as aminoglutethimide, for example [45, 46]) could be considered for the treatment of T2DM and major depression.

The 2 registered ongoing studies in larger samples will enable to confirm or not the effects of pioglitazone in MDE and to explore the mechanisms of action of PPAR-γ agonists in MDE. Furthermore, further research is warranted to validate the benefits of pioglitazone in the specific diabetic subpopulation to treat major depression. In line with recent data showing a high comorbidity between MDD and metabolic syndrome [47–49] and that conventional antidepressant medication could induce or worsen metabolic syndromes [50], PPAR-γ agonists could combine beneficial effects on mood and metabolic disorders. The insulin-sensitizing and anti-inflammatory effects of PPAR-γ agonists could act in interaction and convergence to improve major depression. In this context, anti-inflammatory approaches may be promising approaches to treat both diabetes [51] and major depression [52, 53].

Furthermore, the neuroprotective effects of PPAR-γ agonists, shown in a variety of pre-clinical models of neurological disorders [54–64], could be useful for the treatment of mood disorders.

Conclusion

The present review argues for significant antidepressant properties of PPAR-γ agonists, especially pioglitazone, in the treatment of MDE in patients with MDD or BD, with or without concomitant metabolic comorbidities. It should be further studied whether these antidepressant effects are associated with improvement of insulin resistance and inflammation.

Conflicts of Interest

Romain Colle, Delphine de Larminat, Samuel Rotenberg, Franz Hozer, Patrick Hardy, Céline Verstuyft, and Emmanuelle Corruble declare no potential conflict of interest. Bruno Fève has received conference fees for Astra-Zeneca, Sanofi, NovoNordisk, and MSD and consulting fees from Sanofi.

References

[1] Thomas SJ, Shin M, McInnis MG et al. Combination therapy with monoamine oxidase inhibitors and other antidepressants or stimulants: strategies for the management of treatment-resistant depression. Pharmacotherapy 2015; 35: 433–449

[2] McIntyre RS, Filteau MJ, Martin L et al. Treatment-resistant depression: definitions, review of the evidence, and algorithmic approach. J Affect Disord 2014; 156: 1–7

[3] Perlis RH, Ostacher MJ, Patel JK et al. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 2006; 163: 217–224

[4] Consoli A, Formoso G. Do thiazolidinediones still have a role in treatment of type 2 diabetes mellitus? Diabetes Obes Metab 2013; 15: 967–977

[5] Kapadia R, Yi JH, Vemuganti R. Mechanisms of anti-inflammatory and neuroprotective actions of PPAR-gamma agonists. Front Biosci 2008; 13: 1813–1826

[6] Garcia-Bueno B, Perez-Nievas BG, Leza JC. Is there a role for the nuclear receptor PPARgamma in neuropsychiatric diseases? Int J Neuropsychopharmacol 2010; 13: 1411–1429

[7] Lincoff AM, Tardif JC, Schwartz GG et al. Effect of aleglitazar on cardiovascular outcomes after acute coronary syndrome in patients with type 2 diabetes mellitus: the AleCardio randomized clinical trial. JAMA 2014; 311: 1515–1525

[8] Kovacs P, Stumvoll M. Fatty acids and insulin resistance in muscle and liver. Best Pract Res Clin Endocrinol Metab 2005; 19: 625–635

[9] Tontonoz P, Spiegelman BM. Fat and beyond: the diverse biology of PPARgamma. Annu Rev Biochem 2008; 77: 289–312

[10] Loke YK, Kwok CS, Singh S. Comparative cardiovascular effects of thiazolidinediones: systematic review and meta-analysis of observational studies. BMJ 2011; 342: d1309

[11] Rosen CJ. Revisiting the rosiglitazone story – lessons learned. N Engl J Med 2010; 363: 803–806

[12] Dormandy JA, Charbonnel B, Eckland DJ et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005; 366: 1279–1289

[13] Dormandy JA, Betteridge DJ, Schernthaner G et al. Impact of peripheral arterial disease in patients with diabetes – results from PROactive (PROactive 11). Atherosclerosis 2009; 202: 272–281

[14] Erdmann E, Dormandy JA, Charbonnel B et al. The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) Study. J Am Coll Cardiol 2007; 49: 1772–1780

[15] Erdmann E, Charbonnel B, Wilcox RG et al. Pioglitazone use and heart failure in patients with type 2 diabetes and preexisting cardiovascular disease: data from the PROactive study (PROactive 08). Diabetes Care 2007; 30: 2773–2778

[16] Mazzone T, Meyer PM, Feinstein SB et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. JAMA 2006; 296: 2572–2581

[17] Nissen SE, Nicholls SJ, Wolski K et al. Comparison of pioglitazone vs. glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA 2008; 299: 1561–1573

[18] Wilcox R, Bousser MG, Betteridge DJ et al. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). Stroke 2007; 38: 865–873

[19] Schernthaner G, Currie CJ, Schernthaner GH. Do we still need pioglitazone for the treatment of type 2 diabetes? A risk-benefit critique in 2013. Diabetes Care 2013; 36 (Suppl 2): S155–S161

[20] van Wijk JP, de Koning EJ, Martens EP et al. Thiazolidinediones and blood lipids in type 2 diabetes. Arterioscler Thromb Vasc Biol 2003; 23: 1744–1749

[21] Doehner W, Erdmann E, Cairns R et al. Inverse relation of body weight and weight change with mortality and morbidity in patients with type 2 diabetes and cardiovascular co-morbidity: an analysis of the PROactive study population. Int J Cardiol 2012; 162: 20–26

[22] Domecq JP, Prutsky G, Leppin A et al. Clinical review: Drugs commonly associated with weight change: a systematic review and meta-analysis. J Clin Endocrinol Metab 2015; 100: 363–370

[23] Jacob AN, Salinas K, Adams-Huet B et al. Weight gain in type 2 diabetes mellitus. Diabetes Obes Metab 2007; 9: 386–393

[24] Lincoff AM, Wolski K, Nicholls SJ et al. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA 2007; 298: 1180–1188

[25] Idris I, Warren G, Donnelly R. Association between thiazolidinedione treatment and risk of macular edema among patients with type 2 diabetes. Arch Intern Med 2012; 172: 1005–1011

[26] Zhu ZN, Jiang YF, Ding T. Risk of fracture with thiazolidinediones: an updated meta-analysis of randomized clinical trials. Bone 2014; 68: 115–123

[27] Rosa AO, Kaster MP, Binfare RW et al. Antidepressant-like effect of the novel thiadiazolidinone NP031115 in mice. Prog Neuropsychopharmacol Biol Psychiatry 2008; 32: 1549–1556

[28] Eissa Ahmed AA, Al-Rasheed NM, Al-Rasheed NM. Antidepressant-like effects of rosiglitazone, a PPARgamma agonist, in the rat forced swim and mouse tail suspension tests. Behav Pharmacol 2009; 20: 635–642

[29] Sadaghiani MS, Javadi-Paydar M, Gharedaghi MH et al. Antidepressant-like effect of pioglitazone in the forced swimming test in mice: the role of PPAR-gamma receptor and nitric oxide pathway. Behav Brain Res 2011; 224: 336–343

[30] Kemp DE, Ismail-Beigi F, Calabrese JR. Antidepressant response associated with pioglitazone: support for an overlapping pathophysiology between major depression and metabolic syndrome. Am J Psychiatry. 2009; 166: 619

[31] Roohafza H, Shokouh P, Sadeghi M et al. A possible role for pioglitazone in the management of depressive symptoms in metabolic syndrome patients (EPICAMP Study): A double blind, randomized clinical trial. Int Sch Res Notices 2014; 2014: 697617

[32] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23: 56–62

[33] Trivedi MH, Rush AJ, Ibrahim HM et al. The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. Psychol Med. 2004; 34: 73–82

[34] Rasgon NL, Kenna HA, Williams KE et al. Rosiglitazone add-on in treatment of depressed patients with insulin resistance: a pilot study. Scientific World Journal 2010; 10: 321–328

[35] Kemp DE, Ismail-Beigi F, Ganocy SJ et al. Use of insulin sensitizers for the treatment of major depressive disorder: a pilot study of pioglitazone for major depression accompanied by abdominal obesity. J Affect Disord 2012; 136: 1164–1173

[36] Kemp DE, Schinagle M, Gao K et al. PPAR-gamma agonism as a modulator of mood: proof-of-concept for pioglitazone in bipolar depression. CNS Drugs 2014; 28: 571–581

[37] Hu Y, Xing H, Dong X et al. Pioglitazone is an effective treatment for patients with post-stroke depression combined with type 2 diabetes mellitus. Exp Ther Med 2015; 10: 1109–1114

[38] Sepanjnia K, Modabbernia A, Ashrafi M et al. Pioglitazone adjunctive therapy for moderate-to-severe major depressive disorder: randomized double-blind placebo-controlled trial. Neuropsychopharmacology 2012; 37: 2093–2100

[39] Kashani L, Omidvar T, Farazmand B et al. Does pioglitazone improve depression through insulin-sensitization? Results of a randomized double-blind metformin-controlled trial in patients with polycystic ovarian syndrome and comorbid depression. Psychoneuroendocrinology 2013; 38: 767–776

[40] Zeinoddini A, Sorayani M, Hassanzadeh E et al. Pioglitazone adjunctive therapy for depressive episode of bipolar disorder: a randomized, double-blind, placebo-controlled trial. Depress Anxiety 2015; 32: 167–173

[41] Lin KW, Wroolie TE, Robakis T et al. Adjuvant pioglitazone for unremitted depression: Clinical correlates of treatment response. Psychiatry Res 2015; 230: 846–852

[42] Matthews L, Berry A, Tersigni M et al. Thiazolidinediones are partial agonists for the glucocorticoid receptor. Endocrinology 2009; 150: 75–86

[43] Kotake D, Hirasawa N. Activation of a retinoic acid receptor pathway by thiazolidinediones induces production of vascular endothelial growth factor/vascular permeability factor in OP9 adipocytes. Eur J Pharmacol 2013; 707: 95–103

[44] Iqbal S, Naseem I. Role of vitamin A in type 2 diabetes mellitus biology: effects of intervention therapy in a deficient state. Nutrition 2015; 31: 901–907

[45] Lu JM, Li JY, Pan CY et al. Changes in pituitary-adrenal function in diabetics and their response to aminoglutethimide. Chin Med J (Engl) 1988; 101: 587–590

[46] Sonino N, Fava GA. Erratum to "CNS drugs in Cushing's disease: pathophysiological and therapeutic implications for mood disorders" [Prog Neuro-Psycol Biol Psychiatry, 26, 763 (2002)]. Prog Neuropsychopharmacol Biol Psychiatry 2002; 26: 1011–1018

[47] Pan A, Keum N, Okereke OI et al. Bidirectional association between depression and metabolic syndrome: a systematic review and meta-analysis of epidemiological studies. Diabetes Care 2012; 35: 1171–1180

[48] Vancampfort D, Correll CU, Wampers M et al. Metabolic syndrome and metabolic abnormalities in patients with major depressive disorder: a meta-analysis of prevalences and moderating variables. Psychol Med 2014; 44: 2017–2028

[49] Rhee SJ, Kim EY, Kim SH et al. Subjective depressive symptoms and metabolic syndrome among the general population. Prog Neuropsychopharmacol Biol Psychiatry 2014; 54: 223–230

[50] Corruble E, El Asmar K, Trabado S et al. Treating major depressive episodes with antidepressants can induce or worsen metabolic syndrome: results of the METADAP cohort. World Psychiatry 2015; 14: 366–367

[51] Bellucci PN, Gonzalez Bagnes MF, Di Girolamo G et al. Potential effects of nonsteroidal anti-inflammatory drugs in the prevention and treatment of type 2 diabetes mellitus. J Pharm Pract 2016 [Epub ahead of print]

[52] Kohler O, Benros ME, Nordentoft M et al. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. JAMA Psychiatry 2014; 71: 1381–1391

[53] Kohler O, Krogh J, Mors O et al. Inflammation in Depression and the Potential for Anti-Inflammatory Treatment. Curr Neuropharmacol 2016; 14: 732–742

[54] Chen YC, Wu JS, Tsai HD et al. Peroxisome proliferator-activated receptor gamma (PPAR-gamma) and neurodegenerative disorders. Mol Neurobiol 2012; 46: 114–124

[55] Moreno S, Farioli-Vecchioli S, Ceru MP. Immunolocalization of peroxisome proliferator-activated receptors and retinoid X receptors in the adult rat CNS. Neuroscience 2004; 123: 131–145

[56] Skerrett R, Pellegrino MP, Casali BT et al. Combined Liver X Receptor/Peroxisome Proliferator-activated Receptor gamma Agonist Treatment Reduces Amyloid beta Levels and Improves Behavior in Amyloid Precursor Protein/Presenilin 1 Mice. J Biol Chem 2015; 290: 21591–21602

[57] Carta AR. PPAR-gamma: therapeutic prospects in Parkinson's disease. Curr Drug Targets 2013; 14: 743–751

[58] Lecca D, Nevin DK, Mulas G et al. Neuroprotective and anti-inflammatory properties of a novel non-thiazolidinedione PPARgamma agonist in vitro and in MPTP-treated mice. Neuroscience 2015; 302: 23–35

[59] Gold PW, Licinio J, Pavlatou MG. Pathological parainflammation and endoplasmic reticulum stress in depression: potential translational targets through the CNS insulin, klotho and PPAR-gamma systems. Mol Psychiatry 2013; 18: 154–165

[60] Wu JS, Tsai HD, Cheung WM et al. PPAR-gamma Ameliorates Neuronal Apoptosis and Ischemic Brain Injury via Suppressing NF-kappaB-Driven p22phox Transcription. Mol Neurobiol 2016; 53: 3626–3645

[61] Cimini A, Ceru MP. Emerging roles of peroxisome proliferator-activated receptors (PPARs) in the regulation of neural stem cells proliferation and differentiation. Stem Cell Rev 2008; 4: 293–303

[62] Sato T, Hanyu H, Hirao K et al. Efficacy of PPAR-gamma agonist pioglitazone in mild Alzheimer disease. Neurobiol Aging 2011; 32: 1626–1633

[63] Brundin P, Wyse R. Parkinson disease: laying the foundations for disease-modifying therapies in PD. Nat Rev Neurol 2015; 11: 553–555

[64] Pershadsingh HA, Heneka MT, Saini R et al. Effect of pioglitazone treatment in a patient with secondary multiple sclerosis. J Neuroinflammation 2004; 1: 3