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REVIEW ARTICLE

Why Should Psychiatrists and Neuroscientists Worry about Paraoxonase 1?

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Abstract: ***Background*:** Nitro-oxidative stress (NOS) has been implicated in the pathophysiology of psychiatric disorders. The activity of the polymorphic antioxidant enzyme paraoxonase 1 (PON1) is altered in diseases where NOS is involved. PON1 activity may be estimated using different substrates some of which are influenced by PON1 polymorphisms.

***Objectives*:** 1) to review the association between PON1 activities and psychiatric diseases using a standardized PON1 substrate terminology in order to offer a state-of-the-art review; and 2) to review the efficacy of different strategies (nutrition, drugs, lifestyle) to enhance PON1 activities.

***Methods*:** The PubMed database was searched using the terms paraoxonase 1 and psychiatric diseases. Moreover, the database was also searched for clinical trials investigating strategies to enhance PON1 activity.

***Results*:** The studies support decreased PON1 activity as determined using phenylacetate (*i.e.*, arylesterase or AREase) as a substrate, in depression, bipolar disorder, generalized anxiety disorder (GAD) and schizophrenia, especially in antipsychotic-free patients. PON1 activity as determined with paraoxon (*i.e.*, POase activity) yields more controversial results, which can be explained by the lack of adjustment for the Q192R polymorphism. The few clinical trials investigating the influence of nutritional, lifestyle and drugs on PON1 activities in the general population suggest that some polyphenols, oleic acid, Mediterranean diet, no smoking, being physically active and statins may be effective strategies that increase PON1 activity.

***Conclusion*:** Lowered PON1 activities appear to be a key component in the ongoing NOS processes that accompany affective disorders, GAD and schizophrenia. Treatments increasing attenuated PON1 activity could possibly be new drug targets for treating these disorders.

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1. INTRODUCTION

Psychiatric disorders have a significant social and economic impact. It is estimated that one in five adults (17.6%) experienced a common mental disorder within the past year, with a lifetime prevalence of 29.2% [1]. Psychiatric disorders frequently co-exist with metabolic syndrome and cardiovascular diseases [2, 3], suggesting that shared pathophysiological mechanisms underpin these comorbidities. Nitro-oxidative stress is a biological condition accompanying many mental disorders [4] and it may link psychiatric disorders with some of these comorbidities [5].

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Paraoxonases (PON) are a family of detoxifying enzymes composed of three members: PON1, PON2 and PON3. PON1 and PON3 are expressed mainly in the liver and are secreted into the blood where they are associated with serum high-density lipoproteins (HDLs), whereas PON2 is expressed in nearly all tissues [6]. PON2 is the ancient member, but the name of the family (*i.e.*, paraoxonases) is derived from the ability of PON1, the most studied PON, to hydrolyze the pesticide paraoxon [6]. The primary physiological role of PON1 is still debated, but PON1 has important antioxidant properties [7, 8] and therefore was examined in disorders involving an oxidative imbalance.

Considering that nitro-oxidative stress with consequent lipid peroxidation may play a role in psychiatric disorders [9-12] and that PON1 has peroxidase properties, the associa-

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tion of PON1 with different psychiatric diseases is the main core of this review. Additionally, we will review that lowered PON1 activity is one of the key components in the ongoing immune-inflammatory and nitro-oxidative processes that accompany those psychiatric diseases. Finally, we will review different strategies that may enhance PON1 activities.

1.1. Determination of PON1 Activity and Genotyping

The biological hydrolytic activity of PON1 can be described as a lipolactonase activity, which encompasses arylesterase, phosphotriesterase and lactonase activities [13]. As revised by Ceron *et al* [14], PON1 activity may be evaluated using different substrates resulting in the determination of paraoxonase/phosphotriesterase activity (paraoxon or 4-chloromethyl phenol acetate as substrates), arylesterease activity (phenylacetate or 4 (p)-nitrophenyl acetate as substrates) or lactonase activity (5-thiobutil butyrolactone or dihydrocoumarin as substrates). Paraoxonase and arylesterase are the activities that are most frequently investigated although the lactonase activity is considered by some authors as the main physiological activity [14, 15]. However, the range of physiologically relevant substrates remains an open question [16].

PON1 is polymorphic and more than 160 single nucleotides polymorphisms (SNPs) have been described in the coding or in introns and regulatory regions of the *PON1* gene [17, 18]. The majority of these polymorphisms have not been characterized, but may affect splicing efficiency, message stability or efficiency of polyadenylation [19]. The most studied polymorphisms in the coding region are Q192R (rs 662), which entails a substitution of glutamine by arginine at position 192, and L55M (rs 854560), which entails a substitution of leucine by methionine at position 55.

The Q192R polymorphism influences the catalytic activity of PON1, but the direction of this change is substrate-dependent [20, 21]. The R allozyme is more efficient to detoxify substrates such as paraoxon, 4-chloromethyl phenol acetate (CMPA) and 5-thiobutil butyrolactone (TBBL) even though the influence on TBBL (*i.e*., lactonase activity) is lower (30-50% higher in RR) than paraoxon (100-200% higher in RR) [22]. The Q allozyme is more efficient to detoxify substrates such as diazoxon. Based on this knowledge it was concluded that the assessment of PON1 total plasmatic activity should be based on the use of a substrate with a detoxifying rate that is not influenced by Q192R, *e.g*., phenylacetate or 4-nitrophenyl acetate [14, 23, 24]. In order to estimate PON1 total activity many studies measured the detoxifying rate of paraoxon, however, without adjusting the results for the Q192R genotype results may be very difficult to interpret.

The L55M polymorphism does not affect PON1 catalytic activity, but has been associated with plasma PON1 protein levels. PON1M55 is associated with low plasma PON1 [25]. However, this appears to result primarily from a linkage disequilibrium with a polymorphism located in the promoter region, *i.e*., the C(-108)T (rs 705379). The -108C allele provides higher levels of PON1 (approximately twice) than the -108T allele [26].

Another point that needs to be taken into consideration when examining the association between PON1 status and medical disorders is that, PON1 activity may vary up to 50-fold and the PON1 protein levels up to 15-fold within the same genotype [27, 28]. Therefore, it is suggested that on the top of genotyping, PON1 total plasmatic activity should be measured in order to interpret the data. Based on the above considerations, a reliable strategy to measure PON1 as a marker of disease susceptibility is to assay total PON1 plasmatic activity using phenylacetate or 4-nitrophenyl acetate (and not paraoxon or CMPA) associated or not with genotyping [29].

Due to the different terminologies used in the literature denoting different PON1 activities, we will always specify the type of PON1 activity as defined by the specific substrate that was used in the study. All in all, readers should be aware that PON1 activities determined using paraoxon (POase) and CMPA (CMPAase) are influenced by the Q192R polymorphism and do not reflect total PON1 activity. The latter may be measured using AREase activity with phenylacetate as substrate and determined under low salt conditions [17].

2. METHODS

In this narrative review, the primary sources were identified by a Medline (PubMed) search and were limited to the English language. There was no date limit and the last search update was conducted on February 2018. For the investigation of the associations between PON1 and psychiatric disorders, the following search terms were used: “paraoxonase” and “depressive disorder” or “depression” or “major depression disorder”; “paraoxonase” and “bipolar disorder” or “bipolar”; “paraoxonase” and “anxiety”; “paraoxonase” and “psychosis” or “schizophrenia”; “paraoxonase” and “obsessive compulsive disorder”. A total of 52 manuscripts were retrieved but 18 were excluded. The exclusion criteria were: 1) animal data; 2) toxicological studies; and 3) the above disorders were not the main diagnoses. The retrieved manuscripts were cross-referenced for additional ones. For the review on therapeutic strategies enhancing PON1 activity, clinical trials investigating the impact of nutrition (*i.e*., polyphenols, lipids, vitamins), lifestyle (smoking, drinking, exercising) and drugs (hypolipidemics, hypoglycemics, anticoagulants) were reviewed.

3. RESULTS IN PSYCHIATRIC DISORDERS

3.1. PON1 and Anxiety Disorders

Studies investigating the association of PON1 activity and anxiety are summarized in Table **1**. Adult patients diagnosed with general anxiety disorder (GAD) and without other psychiatric comorbidities showed increased levels of hydroperoxides, decreased POase activity (no adjustment for Q192R genotype) and unaltered AREase activity [30]. There was no correlation between the severity of GAD and the observed results.

In children and teenagers diagnosed with anxiety disorders, hydroperoxides levels were increased, while there were no significant changes in POase or AREase PON1 activities

Table 1. PON1 activity in patients diagnosed with an anxiety disorder or obsessive compulsive disorder (OCD).

Subjects	N	Genotyped for PON1?	PON1 Activity Substrate	Exclusion Criteria	Statistical Adjustment of the Data	Results	Refs.
Adults with GAD	CON: 40 Cases: 40	No	PO PA	Comorbid axis I or II DSM-IV condition, DM, epilepsy, hypertension, SD, pregnancy, drug dependence, use of vitamin or fish oil	NI	↓ POase Normal AREase	[30]
Adults with GAD comorbid or not with other anxiety disorder, MDD, BD, TUD	CON: 126 Cases: 46	Q192R	PA	Comorbid axis I DSM-IV condition, pregnancy, neurodegenerative or immune-inflammatory disorders, use of immunoregulatory drugs	Sex, age, BMI, education, smoking, mood disorders, PON1 genotype	↓ AREase	[9]
Children and teenagers (6-16 years) with any anxiety disorder	CON: 36 Cases: 37	No	PO PA	Comorbid psychiatric, neurological or genetic disorders, chronic SD, use of psychotropic drug	NI	Normal POase Normal AREase	[31]
Subjects from the HERITAGE study	461	Q192R L55M C(-108)T A(-162)G G(-126)C	PO	Not applicable	NI	Inverse association POase X anxiety state 192RR more frequent in high trait anxiety C(-108)T more frequent in lower trait anxiety	[32]
Children and teenagers (8-17 years) with OCD	CON: 36 Cases: 28	No	PO PA	Chronic SD, comorbid psychiatric disorder, mental retardation, use of psychotropic or antioxidant drugs in the previous 6 months	NI	↓ POase Normal AREase	[33]

Abbreviations: BD: bipolar disorder; BMI: body mass index; CMPA: 4-(chloromethyl)phenyl acetate; CON: control group; DM: diabetes mellitus; GAD: general anxiety disorder; MDD: major depressive disorder; NI: not informed; PA: phenyl acetate; PO: paraoxon; SD: systemic disease; TUD: tobacco use disorder.

[31]. Recently, Maes *et al*. [9] reported that AREase activity is significantly lower in patients with GAD than in those without GAD and that this activity was significantly and positively associated with HDL-cholesterol and inversely with lipid hydroperoxide levels. Moreover, a composite index of combined PON1 activity and HDL-cholesterol levels was highly significantly decreased in GAD whilst predicting different indices indicating increased oxidative and nitro-oxidative stress, increased aldehyde production (malondialdehyde) and protein oxidation as assessed with advanced oxidation protein products [9]. A study investigating the role of diverse risk factors and responses to regular exercise in healthy subjects [32] showed that POase activity (no adjustment for Q192R genotype) was inversely associated with anxiety state (*i.e*., experienced at a certain time). Moreover, genotyping for PON1 polymorphisms revealed that there was a significant association between high trait anxiety and PON1 192R homozygotes, whereas in the patients with lower trait anxiety heterozygotes to C(-108)T were more frequently observed.

3.2. PON1 and Obsessive Compulsive Disorders

The only study reporting results in obsessive compulsive disorder (Table **1**) was conducted with children and teenagers (8-17 years). This study reported that POase activity is decreased (data not adjusted for Q192R genotype) and is accompanied by a lowered total antioxidant status and increased oxidative stress. AREase activity was not significantly different between the groups [33].

3.3. PON1 and Major Depression

Table **2** summarizes studies, which reported PON1 activity in major depressive disorder (MDD). The first study, which investigated a possible association between PON1 and MDD, reported no association [34] between MDD and POase or AREase activities as well as Q192R functional genotype even though a lipid peroxidation marker (malondialdehyde) was increased in MDD. In the latter study, patients were free of antidepressants for at least 3 weeks when blood was sampled. Lack of altered AREase activity has also been reported in antidepressant-naive women diagnosed with MDD [35]. There are, however, studies reporting significant lower AREase, but not POase, activity in MDD patients [36-38] including in patients who were drug-free for at least 3 months [37].

Regarding the effects of antidepressant treatments on PON1, one study reported reduced POase and AREase ac-

Table 2. PON1 activity in major depressive disorder (MDD).

Subjects	N	Genotyped for PON1?	PON1 Activity Substrate	Exclusion Criteria	Statistical Adjustment of the Data	Results	Refs.
Adults drug-free for at least 3 weeks	CON: 36 Cases: 86	Q192R	PO PA	Comorbid axis I or II DSM-IV condition, significant suicide risk, other diseases judged from clinical and laboratory examination	Smoking	Normal POase Normal AR-Ease	[34]
Women antidepressant-naive	CON: 35 Cases: 35	No	PA	History of CV and cerebrovascular diseases, DM, hepatic and/or renal diseases, hypothyroidism, malignancies, macroalbuminuria, excessive alcohol consumption, use of hypolipidemic, polyunsaturated fatty acids, vitamins, antioxidants	NI	Normal AR-Ease	[35]
Adults	CON: 22 Cases: 24	No	PO PA	Use of alcohol, smoking, GI disease or operation, walking >1 km/ day, health complaints in the previous month, follicular phase	NI	Normal POase ↓ AREase	[36]
Adults drug-free for 3 months	CON: 44 Cases: 73	No	PO PA	Comorbid axis I or II DSM-IV condition, use of alcohol or other substances, diagnosis of a physical disease or syndrome, presence of early CVD in first-degree relatives, pregnancy, BMI>30, regular drug treatment, heavy smokers	NI	Normal POase ↓ AREase	[37]
Adults	CON: 199 Cases: 91	Q192R	PO PA	Comorbid axis I DSM-IV condition, any major medical illness, use of immunoregulatory drugs, acute inflammatory or infective reactions the month prior to the study	Sex, age, BMI, education, smoking, PON1 genotype	↓ AREase	[38]

Abbreviations: BMI: body mass index; CON: control group; CVD: cardiovascular disease; DM: diabetes mellitus; GI: gastrointestinal; NI: not informed; PA: phenyl acetate; PO: paraoxon.

tivities 6 weeks after starting treatment [34], whereas 3 studies reported increased activities. Kodydková *et al*. [35] found increased AREase and POase activities 24 weeks after starting antidepressant treatment (drug and dose adjusted for each patient). Barim *et al*. [36] reported increased AREase activity, but not POase, 3 months after citalopram treatment, while Kotan *et al*. [37] reported that both AREase and POase activities were increased 24 weeks after starting antidepressant treatment.

In a recent meta-analysis study [39], the authors reported that serum PON1 activity was lower in patients with acute episodes than controls (studies used were [36-38]), but PON1 activity was not increased following antidepressant therapy (studies used were [36, 37]). The lack of significance regarding antidepressant therapies may be ascribed to lower statistical power (only 2 studies and a total of 67 patients were included) or to a misunderstanding of the nomenclature of PON1 activities. In fact, if the authors considered paraoxonase activity as activity obtained with paraoxon, we would have a negative [36] and a positive [37] study. However, in this case, the work of Bortolasci *et al*. [30] could not have been included in the analysis because these authors considered total paraoxonase activity which was obtained with phenylacetate as substrate and is equivalent to what Barim *et al*. [36] and Kotan *et al*. [37] are considering AR-Ease activity. And if we consider AREase activity, both the Barim *et al*. [36] and Kotan *et al*. [37] studies reported increased activity following antidepressant treatment. There is also some evidence that lowered PON1 activity may be related with severity of depression. Thus, Oglodek [40] divided his study sample into mild, moderate and severe depression groups and found that patients with MDD had lower PON1 blood concentrations as depression became more severe.

Besides the association of MDD with PON1 activity, there are also studies reporting on the association of these mood disorders and PON1 polymorphisms. Lawlor *et al*. [41] examined data obtained by the British Women's Heart and Health (BWHH) study and reported that in women aged 60-79 years, the 192R genotype was associated with clinical depression. This observation was not corroborated by two other studies, which employed DNA methodology [42] or functional genotyping [34]. Rice *et al*. [42] examined two independent samples of elderly people (the ELSA and InCHIANTI studies) and found no significant associations between Q192R polymorphism and current depressive symptoms or history of diagnosed depression in both study samples separately or combined (3919 people aged 60-79 years).

Table 3. PON1 activity in bipolar disorder (BD).

Subjects	N	Genotyped for PON1?	PON1 Activity Substrate	Exclusion Criteria	Statistical Adjustment of the Data	Results	Refs.
Adults	CON: 64 Cases: 66	No	PO	Other psychiatric illnesses, epilepsy, mental retardation	Gender, BMI, alcoholic intake	↓ POase	[46]
Adults	CON: 58 Cases: 59	Q192R	CMPA* PA	Comorbid axis I DSM-IV condition, cognitive impairment, neurodegenerative and neuro-inflammatory disorders, inflammatory or (auto)immune disorder, use of immunoregulatory drugs, pregnancy	PON1 genotype, age, sex, BMI, smoking, mood stabilizer, education, income, MS	↓ CMPAase* ↓ AREase	[47]
Adults	CON: 199 Cases: 45	Q192R	PO PA	Comorbid axis I DSM-IV condition, any major medical illness, inflammatory or infective reactions the month prior to the study, use of immunoregulatory drugs	Sex, age, BMI, education, smoking, PON1 genotype	Unaltered AREase	[38]

Abbreviations: *CMPAase activity is equivalent to POase activity. BMI: body mass index; CMPA: 4-(chloromethyl)phenyl acetate; CON: control group; MS: metabolic syndrome; NI: not informed; PA: phenyl acetate; PO: paraoxon.

In summary, the studies seem to support decreased AREase PON1 activity in MDD patients which may play a role in its pathophysiology for example by exacerbating the activated nitro-oxidative stress pathways [5, 43]. Moreover, lowered PON1 activities may also lead to activated immune-inflammatory pathways, which is another hallmark of MDD [44]. Since PON1 hepatic synthesis is inhibited by inflammatory stimuli [45] the lower depression-associated PON1 activity may at least in part result from inflammation-induced decreases in plasma PON1 concentrations [40]. These reciprocal relationships between PON1 activity and neuro-immune and neuro-oxidative pathways will be discussed in section 5.2.

3.4. PON1 and Bipolar Disorder

Compared to MDD, fewer studies investigated the association between PON1 and bipolar disorder (BD). Table **3** summarizes the studies which measured PON1 activity in BD. Decreased POase/CMPAase [46, 47] and AREase activities [47] as well as a lack of association between AREase activity and BD [38] were reported. Moreira *et al*. [47] reported an inverse association between CMPAase (equivalent to POase) as well as AREase activities and the number of depressive and manic episodes. Moreover, they also report an association between lower CMPAase activity and worse quality of life and disability scores, reflecting worse outcomes in mood disorders (both BD and MDD).

Measurements of PON1 Q192R polymorphism showed a positive association between the R allele and BD in a Tunisian population [48]. These findings were in part corroborated by Kuçukali *et al*. [49], who reported a lower frequency of QQ genotype in BD in a Turkish population, although these differences did not reach statistical significance. PON1 L55M studies are controversial with Ezzaher *et al*. [48] reporting a higher frequency and Kuçukali *et al*. [49] reporting a lower frequency of the MM genotype in BD. Both studies, however, found a higher frequency of the heterozygous LM genotype in BD. It was expected that MM genotype individuals would express lower PON1 levels and therefore it is difficult to understand how they would be protected from BD if we consider the antioxidant and anti-inflammatory roles of PON1.

3.5. PON1 and Schizophrenia

Table **4** summarizes the results of studies on PON1 activity in patients with drug naïve first episode psychosis (FEP) and chronic schizophrenia (SCZ). In FEP, decreased AREase [11, 50, 51] and unaltered POase [51] activities were reported. Recovery of the AREase activity was observed 11 weeks after starting risperidone treatment [43, 45], but not 6 weeks after treatments with diverse antipsychotic drugs [51]. AREase activity did not predict treatment outcome in remitted patients following treatment with risperidone [52].

The results obtained in SCZ patients are more diverse. In polymedicated SCZ patients, most studies report normal AREase [12, 53] and POase [53-56] activities. Lower AREase activity was reported by Paval *et al*. [57], who also reported lowered POase activity in QQ patients taking olanzapine, but not other atypical antipsychotics. Ünsal *et al*. [58] found lower POase activity in patients who were taking olanzapine (data not adjusted for PON1 Q192R genotype), but not quetiapine. Noteworthy, in both studies, the statistical significance disappeared when patients with the diverse treatments were lumped together into one schizophrenia group. There is only one study reporting lower POase activity in chronic SCZ patients regardless of drug treatment [59]. Sarandol *et al*. [60] evaluated POase and AREase activities in drug naïve patients or after a 3 week washout period and reported both activities to be lower than in controls (*i.e*., similar to what is generally observed in drug naive FEP patients). Six weeks after the drugs were reintroduced, there was a partial recovery of enzyme activities (*i.e*., the post-treatment values were not statistically significant when compared to either pre-treatment or control values). Only one

Table 4. PON1 activity in first episode psychosis (FEP) and schizophrenia (SCZ).

Subjects	N	Genotyped for PON1?	PON1 Activity Substrate	Exclusion Criteria	Statistical Adjustment of the Data	Results	Refs.
16-40 years, FEP	CON: 61 Cases: 51	No	PA	Prior use of AP, acute intoxication, psychotic episodes due to a general medical condition or drug abuse, intellectual disability, immune-inflammatory disorders, pregnancy, postpartum period, use of antioxidants or immunoregulatory drugs	Age, sex, BMI, smoking, education, income	↓ AREase	[11] [50]
Adults, FEP	CON: 25 Cases: 29	No	PO PA	Mental retardation, neurological disorders, history of head trauma, other concomitant illnesses, use of anti-inflammatory drugs, pregnancy, breast-feeding	NI	Unaltered POase ↓ AREase	[51]
Adults, SCZ, chronically treated	CON: 118 Cases: 125	No	PA	Immune-inflammatory disorders, pregnancy, postpartum period, use of immunoregulatory drugs	Age, sex, use of AP, income, smoking	Unaltered AREase	[12]
Adults, males, SCZ, chronically treated	CON: 30 Cases: 30	No	PO PA	Comorbid axis I DSM-IV condition, history of alcohol or substance abuse; use of antioxidants in the previous year; concomitant or past SD; inability to provide informed consent	NI	Unaltered POase Unaltered AREase	[53]
Adults, SCZ, chronically treated	CON: 61 Cases: 64	No	PO	Substance abuse, hypertension, heart disease, DM, hepatic or renal failure, active or chronic immune-inflammatory diseases, heavy smoking (>15 cigarettes/ day), obesity, use of immune-inflammatory modulators or antioxidants	NI	Unaltered POase	[54]
Adults, SCZ, chronically treated	CON: 119 Cases: 140	No	PO	Other psychiatric illness, epilepsy, mental retardation, endocrinological or CV diseases	Age, sex, BMI, smoking and alcohol consumption	Unaltered POase	[55]
Adults, SCZ, chronically treated	CON: 43 Cases: 41	No	PO PA	Comorbid psychiatric or medical condition	NI	Unaltered POase Unaltered AREase (all patients X CON or patients taking typical AP X CON) ↑ AREase (patients taking atypical AP X CON)	[56]
Adults, SCZ treated with atypical AP	CON: 34 Cases: 60	Q192R L55M C-108T	PO PA	Genetic, metabolic or neurologic condition, acute or chronic inflammatory disease, use of long-term medication other than AP	Sex, age, treatment, polymorphisms	Unaltered POase (all patients X CON) ↓ POase (QQ patients taking olanzapine X CON) ↓ AREase	[57]
Adults, SCZ, treated with olanzapine or quetiapine for at least 1 year	CON: 32 Cases: 64	No	PO	History of alcohol or drug dependence; history of major medical illness; use of drug that might alter serum lipid or PON1; use of psychotropic drugs (except BZD); obesity; comorbid psychiatric disorder; mental retardation	NI	Unaltered POase (all patients X CON) ↓ POase (patients taking olanzapine X CON)	[58]

(Table 4) contd….

Subjects	N	Genotyped for PON1?	PON1 Activity Substrate	Exclusion Criteria	Statistical Adjustment of the Data	Results	Refs.
Adults, SCZ, chronically treated	CON: 292 Cases: 267	Q192R L55M	PO	Comorbid neurological disease, mental retardation, history of substance abuse	NI	↓ POase	[59]
Adults, SCZ, drug naïve or drug free for 3 weeks	CON: 35 Cases: 40	No	PO PA	Endocrine, metabolic or autoimmune disorders; use of depot AP in the previous 6 months; regular drinking; use of drugs that might affect the parameters of the study	NI	↓ POase ↓ AREase	[60]
Adults, SCZ, treated with clozapine or risperidone for at least 1 year	CON: 19 Cases: 66	No	PO PA DHC	Acute or chronic illness known to affect the immune, endocrine, or metabolic systems; use of chronic medications except for AP	Age, BMI	↑ POase ↑ AREase ↓ DHCase	[61]

Abbreviations: AP: antipsychotics; BMI: body mass index; CON: control group; CV: cardiovascular; DHC: dihydrocoumarin; DM: diabetes mellitus; NI: not informed; PA: phenyl acetate; PO: paraoxon; SD: systemic severe disease.

study, which was conducted on patients taking clozapine or risperidone for at least 1 year, reported increased POase and AREase activities [61]. These results are partially corroborated by those of Gunes *et al* [56] who observed increased AREase, but not POase, activities in patients taking atypical antipsychotics, but not in those taking typical or typical + atypical antipsychotics. Gilca *et al* [61] measured the lactonase activity of PON1 using dihydrocoumarin as substrate and found that this activity was decreased in SCZ patients.

Regarding PON1 polymorphisms, neither Matsumoto *et al* [62] or Paval *et al* [57] found an association between the Q192R polymorphism and SCZ. On the other hand, Kuçukali *et al*. [59] reported that the RR genotype was more prevalent in SCZ patients than controls, whilst Paval *et al* [57] reported that the LL genotype was more prevalent in SCZ.

All in all, the studies suggest that in the first episode of schizophrenia, PON1 activity is lowered and that it may normalize upon treatment with appropriate antipsychotic drugs. It should be noted, however, that this may not be the case with olanzapine, because POase activity was not normalized in chronic SCZ patients taking this drug.

3.6. PON1 in Psychiatric Disorders Comorbid with Smoking or Tobacco use Disorder

There is a strong comorbidity between psychiatric disorders, including depression, and tobacco use disorder. As illustrated in Fig. **1**, smoking has been reported to be negatively associated with PON1 activities [63] and these lower catalytic activities may result both from a structural modification (*i.e.*, reduced number of free sulfhydryl groups) induced by smoking [64] or decreased protein concentrations, as observed in smokers with coronary artery disease [65]. Moreover, PON1 is susceptible to free radical attack [66] and in situations where there is a generalized pro-oxidant status, as in tobacco use disorder, PON1 is expected to be less effective.

Few studies have investigated the influence of smoking or tobacco use disorder on PON1 activities in psychiatric patients and the results are diverse. Recently, we reported a significant interaction between diagnosis of mood disorders (MDD or BD) and tobacco use disorder on AREase and CMPAase PON1 activities [47]. In patients without mood disorders there was an important effect of tobacco use reducing PON1 activities, while in the presence of mood disorders, smoking did not induce an extra decrease in PON1 activities. Similar observations were made by Ezzaher *et al*. [46] who examined POase activity in BD patients, but not by Bortolasci *et al* [38] and Nunes *et al*. [67]. Bortolasci *et al*. [38] reported that smoking decreases AREase activity independently of a mood disorder diagnosis, and Nunes *et al*. [67] reported a synergism between mood disorder diagnosis and tobacco use disorder in lowering AREase activity. Smoking did not influence AREase [12, 50] or POase [55, 58] activities in patients with a SCZ diagnosis or FEP.

4. TREATMENTS INCREASING PON1 ACTIVITIES

4.1. Vitamins E and C

Since oxidative stress can disrupt PON1 activity, many antioxidant compounds were evaluated as positive modulators of PON1. Rafraf *et al*. [68] evaluated the influence of 400 IU/day vitamin E (α-tocopherol) supplementation on AREase activity in 42 patients with type 2 diabetes mellitus, comparing the parameters to placebo group. After 8 weeks, PON1 AREase activity increased about 9.4% in the supplemented group. Wade *et al*. [69] found that 6 weeks treatment with vitamin E (400 IU / day) reduced AREase activity by 8.9% and inversely affected both HDL 2 and 3 thereby favoring an oxidation state. Sánchez-Muniz *et al*. [70] investigated whether the PON1 polymorphisms would affect the effects of low-fat meat or walnut-enriched meat consumption (5 weeks) on the metabolic response of volunteers (n=22) at high cardiovascular risk. Interestingly, QQ individuals showed increments in POase activity after the intake of 300g/week walnut-enriched meat, whereas such effects were not observed in the low-fat meat group independently of PON1 genotype.

Although vitamin C was previously thought to augment PON1 POase activity [71], Boaventura *et al*. [72] did not find a significant association between ascorbic acid serum levels and POase activity in dyslipidemic patients receiving

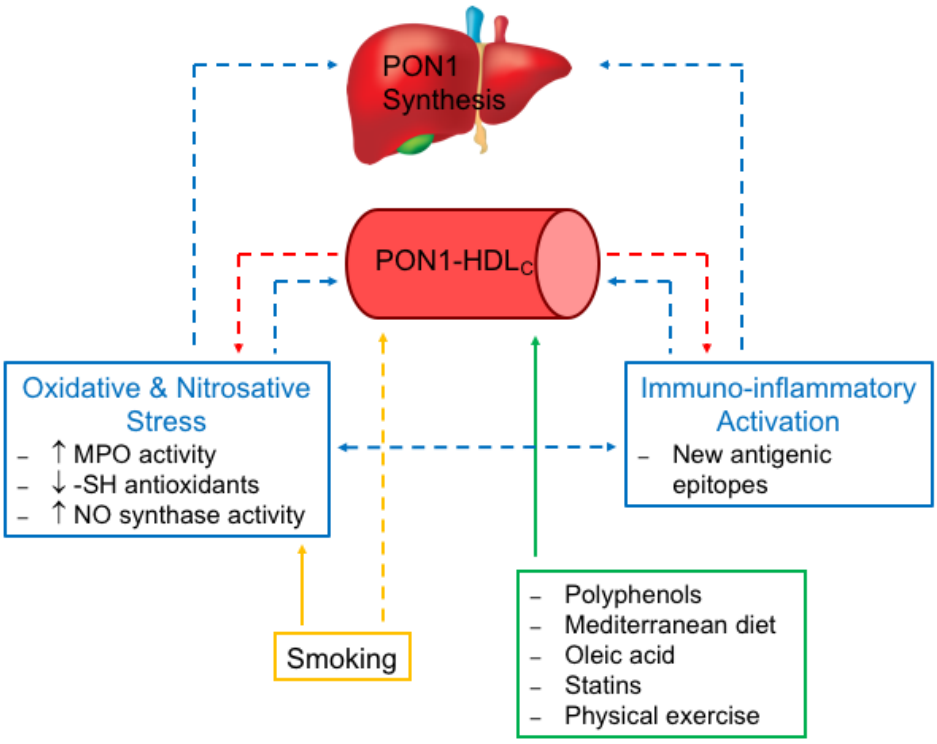

Fig. (1). Factors that may influence PON1 activity and/or expression relevant in the context of mood disorders (major depressive and bipolar disorders). Mood disorders are associated with lowered antioxidants and increased inducible nitric oxide synthase resulting in increased markers of oxidative and nitrosative stress. Oxidized lipids as well as proteins that were hypernitrosylated may form antigenic epitopes and trigger immune-inflammatory activation. Both oxidative stress and immune-inflammatory activation may inhibit PON1 activity as well as its expression. Decreased PON1 function further increases oxidative and nitrosative stress as well as the formation of new antigenic epitopes. Smoking is associated with decreased PON1 activity through direct effects inactivating PON1 as well as through indirect effects increasing oxidative stress. Polyphenols, Mediterranean diet, oleic acid, statins and physical exercise may increase PON1 activity. MPO: myeloperoxidase activity, -SH: sulfhydryl containing, NO: nitric oxide. Dashed lines: inhibition, solid lines: stimulation. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

1L/day of mate tea and ingesting vitamin C during 3 months. Ingestion of vitamin C, however, was positively associated with reduced glutathione levels, an antioxidant marker. Although concentrated orange juice intake (750 ml/day during 60 days) did not increase POase activity, it augmented cholesterol transference to HDL in hypercholesterolemic patients by 22% [73].

4.2. Polyphenols

Polyphenols encompass a variety of substances (*e.g.*, resveratrol, quercetin and gallic acid) found in many plants as well as in its derivatives. Important sources of flavonoid and non-flavonoid polyphenols are chokeberry, blueberry, pomegranate and olive oil [74]. Due to their known antioxidant activity, polyphenols were evaluated as modulators of PON1 activity, but also this research yielded contradictory results. Kardum *et al*. [75] reported an increment in PON1 activity towards diazoxon (17.5%) after 20 weeks of 100 ml/day chokeberry juice supplementation in 29 healthy women, which was accompanied by decreased lipoperoxidation (as measured using the thiobarbituric acid reactive substances assay). Parsaeyan *et al*. [76] reported increments of 33% and 40% in AREase and POase activities, respectively, following 6 weeks 200 ml/day pomegranate juice intake by diabetic patients. Noteworthy, Loued *et al*. [77] evaluated the influence of 25 ml/day extra virgin olive oil consumption in volunteers stratified in two groups based on age (20-30 and 65-85 years). Twelve weeks supplementation did not influence PON1 in the younger subjects, but enhanced AREase activity in elderly individuals, with their AREase activity approximating the levels observed in the younger subjects.

The beneficial effects of polyphenols on PON1 may at least in part be explained by the knowledge that flavonoids may induce PON1 transcription through the peroxisome proliferator-activator receptors (PPAR) pathway [78, 79]. Moreover, the PPAR-δ response is attenuated by oxidized lipids and free radicals [22]. As a consequence, polyphenols may positively modulate PON1 by increasing its transcription or indirectly by providing an antioxidant environment favoring both PON1 activity and PPAR response.

It is noteworthy, however, that some authors were unable to detect positive correlations between polyphenols ingestion and PON1 activity [80-82], which could be explained by differences in dosage, the type of polyphenol sources, duration of treatment and differences in possible interactions between PON1 polymorphisms and polyphenols. In this respect, Rizzi *et al*. [83] reported in a nutrigenetic study performed in an Italian healthy population that high polyphenol

consumption was effective in improving cardiovascular markers only in individuals carrying some alleles of PON1 SNPs (5 out a total of 18 analyzed SNPs).

4.3. Dietary Lipids

The content of lipids in meals influences PON1 activity, and the understanding of this influence is of major interest due to its possible application to reduce oxidative PON1 inactivation in patients with diverse illnesses, such as dyslipidemia, diabetes type 2, and possibly psychiatric disorders. Mediterranean diet, which comprises high concentration of monounsaturated fatty acids, was associated with higher AREase activity, elevated cholesterol efflux from macrophages and lower levels of oxidized lipids in 296 volunteers who ingested either Mediterranean diet enriched with virgin olive oil or with great amounts of nuts [84]. However, these results must be interpreted with caution because Mediterranean diet possesses more components that may enhance PON1 activity, including polyphenols and vitamin C and E. Kim *et al*. [85] studied the effects of saturated, monounsaturated or polyunsaturated fatty acids (PUFAs) in 1.548 volunteers on AREase activity to better characterize the individual effects of these fatty acids. These authors reported that both saturated fatty acids (represented by myristic acid) and monounsaturated fatty acids (represented by gadoleic acid) were positively associated with higher AREase activity, an effect that may be due to the ability of these substances to attach to PON1 molecule thereby protecting PON1 against oxidation, although the binding tends to reduce PON1 activity [85]. In the same study, PUFAs (represented by arachidonic and eicosapentaenoic acids) were negatively associated with PON1 activity, while oleic acid did not reach significant effects. This negative association may be ascribed to the oxidized lipids, which are produced during the peroxidation process [86]. Furthermore, 2g/day supplementation with omega-3 PUFAs (both docosahexaenoic and eicosapentaenoic acids) during 6 weeks did not alter significantly the postprandial levels of PON1 POase and AREase activities, adiponectin, and leptin in 34 diabetic patients [87]. Higher PON1 protein expression was detected following 28 days omega-3 supplementation in overweight/class I obesity volunteers [88]. On the other hand, saturated lipids as well as oleic acid were identified to augment AREase activity from PON1 attached to chylomicrons in blood samples from diabetic patients [89]. These differences may be explained by effects on PON1 genotypes because individuals who are R carriers for the Q192R polymorphism appear to benefit more from oleic acid and walnut supplementation [90, 91]. In patients recovering from stroke, α-lipoic acid, linoleic and γ-linolenic acids as well as α-tocopherol supplementation improved PON1 lactonase activity by approximately 58% [92]. This is of major importance, considering that PON1 lactonase activity is emerging as one of the main endogenous activities of PON1 [6].

4.4. Lifestyle

Lifestyle characteristics including smoking, alcohol consumption and physical exercise may also modulate PON1 activities [93]. In section 3.6 we have reviewed the effects of comorbid tobacco use disorder on PON1 activities. Already in 1997, it was shown that PON1 is inhibited by smoking extracts *in vitro* [64] and these findings were corroborated by *in vivo* studies [94, 95]. Smoking can disrupt PON1 functions through interactions between smoking-derived metabolites (such as heavy metals and ROS) and free thiol groups present in the PON1 molecule [96].

Alcohol consumption appears to augment PON1 activity in individuals whose alcohol intake is moderate, whereas heavy drinkers show the reverse outcome [97, 98]. However, alcohol-induced PON1 overexpression is accompanied by a reduced enzymatic activity [99, 100]. This observation may explain the lack of any correlation between alcohol consumption and PON1 AREase or POase activities reported by some authors [71, 101].

Regarding physical activity, PON1 activity may be decreased after acute exercise due to increased ROS production, an effect that is partially reversed by vitamin E supplementation [102]. On the other hand, in patients with metabolic syndrome, walk / run exercises for 10 weeks may increase PON1 activity *via* higher HDL antioxidant and anti-inflammatory capacity rather than by increasing its synthesis [103]. Moreover, since obesity and sedentarism are accompanied by higher oxidative stress biomarkers [104], which are associated with lower PON1 levels [105], the weight loss induced by physical activity is beneficial in many ways. Aerobic activity appears to enhance PON1 synthesis more than anaerobic resistance training [106]. However, the effects of physical exercise on PON1 levels or activity is not unanimous and, therefore, more data are needed to firmly establish these associations [107].

4.5. Pharmacological Modulation

Reduced PON1 activity has been described in many disorders and therefore drugs that are used to treat these diseases have been evaluated as modulators of PON1. Importantly, some of those drugs were also described as potential treatments for affective disorders or the comorbidity between cardiovascular disease/metabolic syndrome and affective disorders, including statins and various antioxidants [43, 108]. Statins inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), reducing the hepatic synthesis of cholesterol due to decreased mevalonate production from HMG-CoA, being widely employed to treat patients at high cardiovascular risk [109]. Statins are believed to positively modulate PON1 activity thereby decreasing oxidative stress through lowered production of oxidized lipids [110]. Samy *et al*. [111] evaluated the influence of 40 mg/day atorvastatin treatment in patients with non-alcoholic fatty liver disease and found that, after 8 months, POase activity was enhanced by 30%. In the latter study, the levels of glucose were negatively correlated with POase activity, an effect that may be explained by the direct non-enzymatic glycation of PON1 molecule because similar results were reported in diabetic patients [112]. Moreover, the combination of statins (atorvastatin 10 mg) with angiotensin receptor blockers with different PPAR-γ agonist capacities (namely partial activator, weak partial activator and non-activator) was investigated [113]. No significant changes were observed for POase and AREase activities as

well as for HDL-C after a 12 week intervention. Recently, one meta-analysis performed on 25 studies identified a positive association between statin treatment and both PON1 POase and AREase activities, although no association was found with PON1 serum concentrations [114]. The latter authors reported that the PON1-enhancing effects of statins were robust in sensitivity analyses and were independent of statin dose, treatment duration and changes in plasma low-density lipoprotein cholesterol concentration. Noteworthy, Q192R polymorphism may play an important role regarding statins pharmacodynamics. In this respect, Sumi *et al*. [110] reported that QQ diabetes type 2 individuals presented higher insulin secretion than RR carriers under statin therapy.

Only a few papers examined the association between fibrates and PON1 expression and one of these reported that fenofibric acid augmented PON1 AREase activity by approximately 70% as well as its mRNA concentrations in HuH7 cells [115], whereas gemfibrozil did not significantly alter PON1 activity. Paragh *et al*. [116] reported similar results showing that ciprofibrate treatment in patients with metabolic syndrome increased both AREase and POase activities 3 months after starting treatment. These effects were ascribed to effects on HDL-C levels. Fibrates act *via* PPAR-α to induce lipoprotein lipase transcription and augment HDL-C, but PPAR-α did not seem to be involved in PON1 overexpression following fibrate treatment [115]. Neither the association of bezafibrate (400 mg/day) with simvastatin (40 mg/day) nor the use of fibrates alone increased AREase or POase activity when used to treat diabetic patients during 8 weeks [117].

Other lipid-lowering agents with different mechanisms of action than statins and fibrates were correlated to either presence or absence of changes on PON1 activity. Rosiglitazone, a thiazolidinedione that activates PPAR-γ, was investigated in three studies and it was found that POase increased by around 9.3% to 22.8% [118-120]. Metformin administration for 1 year (850 mg/day) resulted in a 59% increase in POase activity in patients with metabolic syndrome [121], although treatment for 3 months (1.000 mg/day) did not have significant effects in patients with diabetes type 2 [122]. Lastly, ezetimibe and orlistat, both drugs that prevent intestinal cholesterol absorption, did not modify PON1 AREase and POase activities either in monotherapy or in combination, although they reduced LDL levels, leading to an improved PON1 activity / LDL-C ratio and, consequently, decreased atherogenic risk in diabetic patients [123].

Other classes of drugs have been minimally investigated. Acetylsalicylic acid was identified to induce PON1 activity *in vitro* [124], but clinical trials did not establish these effects. Ames *et al*. [125] assessed the influence of 7 days (100 or 325 mg/day) aspirin administration on nitro-oxidative stress markers (NO_2^-, NO_3^-, POase activity, serum soluble P-selectin, and 8-iso-prostaglandin-F2α) in type 2 diabetic patients and no changes were noticed on POase activity. Moreover, diabetic patients tended to have higher nitrite, nitrate, and 8-iso-prostaglandin-F2α levels when compared to the control group, suggesting higher reactive oxygen and nitrogen species in this group. In diabetic patients with comorbid hypertension, anti-hypertensives, including olmesartan and amlodipine, did not enhance POase activity when administered alone, but increased POase activity by 16.5% when used in combination for 1 year [126]. Barnidipine and lercanidipine increased POase activity by 13.7% and 12.8%, respectively, after 6 months of treatment with losartan [127]. The beta-blocker carvedilol was also associated with higher POase (19.8%) and AREase (8.2%) activities in mild to moderate hypertensive patients [128].

5. DISCUSSION

5.1. General Considerations

There are not many studies investigating the association of PON1 with psychiatric disorders especially with obsessive compulsive disorder. The great diversity of terminology regarding PON1 activity used by different authors can certainly hamper interpretation of the results. In general, the studies seem to support a decreased AREase PON1 activity in mood disorders, both MDD and BD. In SCZ, AREase PON1 activity is also decreased but mainly in antipsychotics-free patients. In chronic polymedicated patients, AREase activity is usually not different from control values, indicating that antipsychotic treatments or the chronicity of the disease are associated with a normalization of AREase activity. Regarding POase activity, results are more contradictory, which could partially be explained by the knowledge that this activity is influenced by the Q192R polymorphism and that most of the authors did not adjust the POase activity for this polymorphism. It is interesting to note that even though lactonase activity is considered by some authors as PON1 most important physiological activity [6, 14, 15], only one study investigated this activity [61].

5.2. PON1 and the Pathophysiology of Psychiatric Disorders

There is abundant evidence that MDD, BD and SCZ are accompanied by activated immune-inflammatory and nitro-oxidative pathways. Thus mood disorders, including MDD and BD, are characterized by increased M1 macrophage cytokines, including interleukin-6 (IL-6), IL-1 and tumor necrosis factor (TNF)-α, T helper (Th)-1 activation and elevated T regulatory functions [44]. Both mood disorders are also characterized by reduced lipid-associated antioxidant defenses including lowered levels of lecithin-cholesterol acyltransferase (LCAT), vitamin E, HDL-cholesterol, coenzyme Q10 and PON1 [10]. These deficits in antioxidant defenses are associated with many indicants of nitro-oxidative stress in MDD and BD, including increased reactive oxygen production, lipid peroxidation, damage to cell membranes and increased production of aldehydes, including malondialdehyde, and generation of advanced oxidation protein products [10].

Recently, it was shown that GAD is also characterized by similar immune-inflammatory and nitro-oxidative pathways [9]. In fact, GAD is adequately predicted by using two composite biomarkers, namely lowered AREase + HDL-cholesterol and increased nitro-oxidative stress (as measured with superoxide dismutase 1, lipid hydroperoxides and nitric oxide metabolites) [9]. Furthermore, the comorbidity between GAD and MDD is characterized by higher indices of

nitro-oxidative stress and lowered lipid-associated antioxidant defenses as compared with BD, GAD alone and controls [9]. Also, acute episodes of SCZ are accompanied by activated immune-inflammatory pathways, such as M1, Th-1, Th-2 and T regulatory, and by enhanced nitro-oxidative stress pathways, including lowered PON1 AREase activity [11, 129, 130].

As described in the Introduction, there is a strong comorbidity between cardio-vascular disorders (CVD) and affective disorders (MDD/BD/GAD) reviewed by [131-133]. There is also a strong comorbidity between CVD and SCZ, which in part can be explained by lifestyle factors, including substance abuse, smoking, metabolic syndrome, use of psychotropic medications and physical inactivity [134]. Nevertheless, these lifestyle factors alone cannot explain the comorbidity of SCZ with CVD [134]. Recently, we reviewed that shared pathways may contribute to the comorbidity between CVD and affective disorders, including activated immune-inflammatory pathways (such as increased levels of pro-inflammatory cytokines, complement factors, acute phase proteins), increased lipid peroxidation (including formation of aldehydes and autoimmune responses to oxidized LDL), protein oxidation, oxidative damage to DNA and mitochondria, translocation of Gram-negative bacteria *via* leaky gut, increased production of tryptophan catabolites, lowered levels of ω3 polyunsaturated fatty acids (PUFAs) and antioxidants (like zinc, coenzyme Q10, glutathione and glutathione peroxidase) [135-137]. Also, the strong comorbidity between GAD and CVD may be explained by lowered antioxidant defenses, and elevated nitro-oxidative and immune-inflammatory pathways [133]. Lowered levels of HDL-cholesterol and PON1 activities are other factors that may underpin staging of affective disorders, GAD as well as CVD [133]. Atherogenic pathways that may underpin the comorbidity between CVD/metabolic syndrome and SCZ comprise activated immune and oxidative stress pathways and lowered antioxidant defenses including PON1 [11, 138].

As illustrated in Fig. **1**, PON1 is produced in the liver and upon secretion in the peripheral blood is integrated into HDL molecules [66, 136]. This functional PON1-HDL binding explains the significant positive correlations between HDL-cholesterol levels and PON1 activities observed in many studies. Moreover, the anchored PON1 activity stimulates HDL to enhance cholesterol efflux from macrophages to the liver and protects against macrophage-mediated lipid oxidation, including that of LDL [66, 137]. It follows that lowered PON1 activities are accompanied by increased lipid peroxidation and activated immune-inflammatory pathways, explaining the association between PON1 activity and CVD. There are many published reviews on the pathophysiological role of PON1 in CVD [23, 138-142]. One mechanism that may be important in the context of psychiatric diseases is that PON1 detoxifies oxidized low density lipoprotein (oxLDL) and degrades homocysteine thiolactone, an intermediate that can induce protein N-homocysteinylation [143]. Homocysteinylation occurs when there is an interaction between the free thiol group of homocysteine with a free thiol derived from a protein cysteine residue (N-homocysteinylation) or an acylation of the free protein amino group (N-homocysteinylation) [144]. The former process alters the thiol-dependent redox status of functional proteins resulting in oxidative stress whereas the latter results in protein adducts and immune activation, autoimmune and inflammatory responses and cellular toxicity [144]. Such processes are considered risk factors for cardiovascular, neurological and autoimmune diseases and, certainly, for psychiatric diseases.

As a consequence, the loss of antioxidant defenses in mood disorders and GAD through lowered levels of PON1 + HDL-cholesterol may explain the inverse associations between the latter and indices of nitro-oxidative stress including lipid peroxidation and aldehyde and advanced oxidation protein products formation [10,44]. Moreover, MDD and BD are accompanied by increased immune responses to a number of neoepitopes, including malondialdehyde and azelaic acid and oxidized LDL, as well as nitrosylated proteins [145, 146]. The formation of these neoepitopes may further aggravate immune-inflammatory responses [147].

Interestingly, in first episode psychosis (FEP), lowered PON1 AREase activity is associated with increased levels of IL-6, IL-10 and IL-4, but not TNF-α [11]. Moreover, FEP patients with PON1 activity lower than the 25th quartile show significantly elevated levels of those M1, Th-2 and T regulatory cytokines as compared with patients with higher PON1 AREase activity [11]. Previously, it had been shown that increased PON1 activity has anti-inflammatory properties, for example by inhibiting macrophage activities, production of monocyte chemoattractant protein-1 and LPS-induced pro-inflammatory cytokines through regulation of MAPK and NF-κB pathways [11]. These findings suggest that lowered PON1 activity in FEP patients may be linked to the immune-inflammatory responses observed during that condition.

As illustrated in Fig. **1**, PON1 activity and the PON1-HDL complex are downregulated by nitro-oxidative and immune-inflammatory processes including activated macrophages producing oxygen radicals and nitric oxide and polymorphonuclear cells producing myeloperoxidase. Firstly, the PON1-HDL complex is damaged by peroxynitrite formed by reactive oxygen species and nitric oxide [66]. Secondly, myeloperoxidase may oxidize PON1 thereby attenuating its binding to HDL and thus inactivating this complex and PON1 activity as well [66]. Such a process may in turn inactivate the inhibitory effects of PON1 on myeloperoxidase activity thereby causing more protein oxidation, nitration and formation of peroxynitrite (*via* hydroxyl radicals) [66]. Thirdly, pro-inflammatory cytokines such as IL-1 and TNF-α, inhibit the hepatic synthesis of PON1, as part of the acute phase response, thereby downregulating PON1 expression and activity [45, 148]. Such findings indicate that the associations between PON1-HDL and increased nitro-oxidative stress may be explained by reciprocal relationships between lowered lipid-associated antioxidant defenses and increased nitro-oxidative stress and inflammation. As a consequence, lowered PON1 activity may be a key factor in the neuro-immune and neuro-oxidative pathophysiology of psychiatric disorders including MDD, BD, GAD and SCZ, and therefore it is safe to posit that lowered PON1 is a new drug target in these disorders.

5.3. PON1 as a Novel Target in Psychiatric Disorders

Increments in both PON1 serum concentration and activity are assumed to be advantageous in reducing the negative effects of immune-inflammatory responses present in many conditions. Considering that lowered PON1 activity seems to be a key factor in the neuro-immune and neuro-oxidative pathophysiology of psychiatric disorders, it is safe to posit that increasing PON1 activity could be a therapeutic strategy in these disorders. As reviewed in section 4.5, some drugs and natural products may increase PON1 expression and / or activity. Nevertheless, the investigation of the pharmaceutical effects on PON1 activities is not an easy task because PON1 possesses intrinsic genotypic variability as well as a known tendency to interact with many exogenous compounds, which hinders the full understanding of how new therapies could modulate PON1 expression. Rainwater *et al*. [149] estimated that only 1 to 6% of PON1 activity is determined by external factors and that genotype could influence even this external effect. Recently, Ruiz *et al* [150] revised the role of several nuclear receptors on the modulation of PON1 expression.

CONCLUSION

To date, most data covering new treatments that may enhance PON1 expression originated from *in vitro* or animal studies. Clinical trials are scarce and focused mainly in the fields of diet (*i.e*., consumption of antioxidant compounds and lipids), lifestyle characteristics and pharmacological modulation. The few clinical trials conducted to date point that the ingestion or supplementation with some polyphenols or fatty acids, not smoking, being physically active and statins might be effective strategies for this purpose. Here we reviewed different strategies to enhance PON1 activities, including administration of vitamin E/C, polyphenols, Mediterranean diet, oleic acid, statins, fibrates and physical exercise. It is interesting to note that some of these treatments are advocated or trialed as putative treatments for depression including polyphenols, Mediterranean diet, statins and physical exercise (*e.g*., [43, 108, 151-154]). We reviewed that these treatments may have a clinical efficacy in affective disorders *via* their antioxidant and anti-inflammatory properties [43, 108], whist the current review suggests that increasing PON1 activity is another mechanism underpinning the putative clinical activity of these compounds. Future research should examine whether the working mechanisms of these treatments and perhaps antidepressants and antipsychotic agents may be associated with effects on PON1 activities.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Steel, Z.; Marnane, C.; Iranpour, C.; Chey, T.; Jackson, J.W.; Patel, V.; Silove, D. The global prevalence of common mental disorders: a systematic review and meta-analysis 1980-2013. *Int. J. Epidemiol.,* **2014**, *43*(2), 476-493. [http://dx.doi.org/10.1093/ije/dyu038] [PMID: 24648481]

[2] Merikangas, K.R.; Kalaydjian, A. Magnitude and impact of comorbidity of mental disorders from epidemiologic surveys. *Curr. Opin. Psychiatry,* **2007**, *20*(4), 353-358. [http://dx.doi.org/10.1097/YCO.0b013e3281c61dc5] [PMID: 17551350]

[3] Kessler, R.C.; Merikangas, K.R.; Wang, P.S. Prevalence, comorbidity, and service utilization for mood disorders in the United States at the beginning of the twenty-first century. *Annu. Rev. Clin. Psychol.,* **2007**, *3*, 137-158. [http://dx.doi.org/10.1146/annurev.clinpsy.3.022806.091444] [PMID: 17716051]

[4] Ng, F.; Berk, M.; Dean, O.; Bush, A.I. Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. *Int. J. Neuropsychopharmacol.,* **2008**, *11*(6), 851-876. [http://dx.doi.org/10.1017/S1461145707008401] [PMID: 18205981]

[5] Maes, M.; Kubera, M.; Obuchowiczwa, E.; Goehler, L.; Brzeszcz, J. Depression's multiple comorbidities explained by (neuro) inflammatory and oxidative & nitrosative stress pathways. *Neuroendocrinol. Lett.,* **2011**, *32*(1), 7-24. [PMID: 21407167]

[6] Bar-Rogovsky, H.; Hugenmatter, A.; Tawfik, D.S. The evolutionary origins of detoxifying enzymes: the mammalian serum paraoxonases (PONs) relate to bacterial homoserine lactonases. *J. Biol. Chem.,* **2013**, *288*(33), 23914-23927. [http://dx.doi.org/10.1074/jbc.M112.427922] [PMID: 23788644]

[7] Mackness, M.I.; Arrol, S.; Abbott, C.; Durrington, P.N. Protection of low-density lipoprotein against oxidative modification by high-density lipoprotein associated paraoxonase. *Atherosclerosis,* **1993**, *104*(1-2), 129-135. [http://dx.doi.org/10.1016/0021-9150(93)90183-U] [PMID: 8141836]

[8] Watson, A.D.; Berliner, J.A.; Hama, S.Y.; La Du, B.N.; Faull, K.F.; Fogelman, A.M.; Navab, M. Protective effect of high density lipoprotein associated paraoxonase. Inhibition of the biological activity of minimally oxidized low density lipoprotein. *J. Clin. Invest.,* **1995**, *96*(6), 2882-2891. [http://dx.doi.org/10.1172/JCI118359] [PMID: 8675659]

[9] Maes, M.; Bonifacio, K.L.; Morelli, N.R.; Vargas, H.O.; Moreira, E.G.; St Stoyanov, D.; Barbosa, D.S.; Carvalho, A.F.; Nunes, S.O.V. Generalized anxiety disorder (GAD) and comorbid major depression with GAD are characterized by enhanced nitro-oxidative stress, increased lipid peroxidation, and lowered lipid-associated antioxidant defenses. *Neurotox. Res.,* in press [PMID: 29736827]

[10] Maes, M.; Bonifacio, K.; Vargas, H.; Barbosa, D.; Carvalho, A.; Nunes, S. Major differences in neuro-oxidative and neuro-nitrosative stress pathways between major depressive disorder and types I and II bipolar disorders. *Mol. Neurobiol.,* **in press**.

[11] Brinholi, F.F.; Noto, C.; Maes, M.; Bonifácio, K.L.; Brietzke, E.; Ota, V.K.; Gadelha, A.; Cordeiro, Q.; Belangero, S.I.; Bressan, R.A.; Vargas, H.O.; Higachi, L.; de Farias, C.C.; Moreira, E.G.; Barbosa, D.S. Lowered paraoxonase 1 (PON1) activity is associated with increased cytokine levels in drug naïve first episode psychosis. *Schizophr. Res.,* **2015**, *166*(1-3), 225-230. [http://dx.doi.org/10.1016/j.schres.2015.06.009] [PMID: 26123170]

[12] Boll, K.M.; Noto, C.; Bonifácio, K.L.; Bortolasci, C.C.; Gadelha, A.; Bressan, R.A.; Barbosa, D.S.; Maes, M.; Moreira, E.G. Oxidative and nitrosative stress biomarkers in chronic schizophrenia. *Psychiatry Res.,* **2017**, *253*, 43-48. [http://dx.doi.org/10.1016/j.psychres.2017.03.038] [PMID: 28346888]

[13] Moya, C.; Máñez, S. Paraoxonases: metabolic role and pharmacological projection. *Naunyn Schmiedebergs Arch. Pharmacol.,* **2018**, *391*(4), 349-359. [http://dx.doi.org/10.1007/s00210-018-1473-9] [PMID: 29404699]

[14] Ceron, J.J.; Tecles, F.; Tvarijonaviciute, A. Serum paraoxonase 1 (PON1) measurement: an update. *BMC Vet. Res.,* **2014**, *10*, 74. [http://dx.doi.org/10.1186/1746-6148-10-74] [PMID: 24666514]

[15] Menini, T.; Gugliucci, A. Paraoxonase 1 in neurological disorders. *Redox Rep.,* **2014**, *19*(2), 49-58. [http://dx.doi.org/10.1179/1351000213Y.0000000071] [PMID: 24225313]

[16] Furlong, C.E.; Marsillach, J.; Jarvik, G.P.; Costa, L.G. Paraoxonases-1, -2 and -3: What are their functions? *Chem. Biol. In-*

teract., **2016**, *259*(Pt B), 51-62. [http://dx.doi.org/10.1016/j.cbi.2016.05.036] [PMID: 27238723]

[17] Richter, R.J.; Jarvik, G.P.; Furlong, C.E. Determination of paraoxonase 1 status without the use of toxic organophosphate substrates. *Circ Cardiovasc Genet,* **2008**, *1*(2), 147-152. [http://dx.doi.org/10.1161/CIRCGENETICS.108.811638] [PMID: 20031556]

[18] Jarvik, G.P.; Jampsa, R.; Richter, R.J.; Carlson, C.S.; Rieder, M.J.; Nickerson, D.A.; Furlong, C.E. Novel paraoxonase (PON1) nonsense and missense mutations predicted by functional genomic assay of PON1 status. *Pharmacogenetics,* **2003**, *13*(5), 291-295. [http://dx.doi.org/10.1097/00008571-200305000-00009] [PMID: 12724622]

[19] Mackness, M.; Mackness, B. Human paraoxonase-1 (PON1): Gene structure and expression, promiscuous activities and multiple physiological roles. *Gene,* **2015**, *567*(1), 12-21. [http://dx.doi.org/10.1016/j.gene.2015.04.088] [PMID: 25965560]

[20] Li, W.F.; Costa, L.G.; Richter, R.J.; Hagen, T.; Shih, D.M.; Tward, A.; Lusis, A.J.; Furlong, C.E. Catalytic efficiency determines the in-vivo efficacy of PON1 for detoxifying organophosphorus compounds. *Pharmacogenetics,* **2000**, *10*(9), 767-779. [http://dx.doi.org/10.1097/00008571-200012000-00002] [PMID: 11191881]

[21] Mackness, B.; Davies, G.K.; Turkie, W.; Lee, E.; Roberts, D.H.; Hill, E.; Roberts, C.; Durrington, P.N.; Mackness, M.I. Paraoxonase status in coronary heart disease: are activity and concentration more important than genotype? *Arterioscler. Thromb. Vasc. Biol.,* **2001**, *21*(9), 1451-1457. [http://dx.doi.org/10.1161/hq0901.094247] [PMID: 11557671]

[22] Marsillach, J.; Camps, J.; Ferré, N.; Beltran, R.; Rull, A.; Mackness, B.; Mackness, M.; Joven, J. Paraoxonase-1 is related to inflammation, fibrosis and PPAR delta in experimental liver disease. *BMC Gastroenterol.,* **2009**, *9*, 3. [http://dx.doi.org/10.1186/1471-230X-9-3] [PMID: 19144177]

[23] Costa, L.G.; Cole, T.B.; Furlong, C.E. Paraoxonase (PON1): from toxicology to cardiovascular medicine. *Acta Biomed.,* **2005**, *76*(Suppl. 2), 50-57. [PMID: 16353344]

[24] Jarvik, G.P.; Rozek, L.S.; Brophy, V.H.; Hatsukami, T.S.; Richter, R.J.; Schellenberg, G.D.; Furlong, C.E. Paraoxonase (PON1) phenotype is a better predictor of vascular disease than is PON1(192) or PON1(55) genotype. *Arterioscler. Thromb. Vasc. Biol.,* **2000**, *20*(11), 2441-2447. [http://dx.doi.org/10.1161/01.ATV.20.11.2441] [PMID: 11073850]

[25] Mackness, B.; Mackness, M.I.; Arrol, S.; Turkie, W.; Durrington, P.N. Effect of the human serum paraoxonase 55 and 192 genetic polymorphisms on the protection by high density lipoprotein against low density lipoprotein oxidative modification. *FEBS Lett.,* **1998**, *423*(1), 57-60. [http://dx.doi.org/10.1016/S0014-5793(98)00064-7] [PMID: 9506841]

[26] Leviev, I.; James, R.W. Promoter polymorphisms of human paraoxonase PON1 gene and serum paraoxonase activities and concentrations. *Arterioscler. Thromb. Vasc. Biol.,* **2000**, *20*(2), 516-521. [http://dx.doi.org/10.1161/01.ATV.20.2.516] [PMID: 10669651]

[27] Richter, R.J.; Furlong, C.E. Determination of paraoxonase (PON1) status requires more than genotyping. *Pharmacogenetics,* **1999**, *9*(6), 745-753. [http://dx.doi.org/10.1097/00008571-199912000-00009] [PMID: 10634137]

[28] Costa, L.G.; Cole, T.B.; Jarvik, G.P.; Furlong, C.E. Functional genomic of the paraoxonase (PON1) polymorphisms: effects on pesticide sensitivity, cardiovascular disease, and drug metabolism. *Annu. Rev. Med.,* **2003**, *54*, 371-392. [http://dx.doi.org/10.1146/annurev.med.54.101601.152421] [PMID: 12525679]

[29] Li, W.F.; Costa, L.G.; Furlong, C.E. Serum paraoxonase status: a major factor in determining resistance to organophosphates. *J. Toxicol. Environ. Health,* **1993**, *40*(2-3), 337-346. [http://dx.doi.org/10.1080/15287399309531798] [PMID: 7693961]

[30] Bulut, M.; Selek, S.; Bez, Y.; Karababa, I.F.; Kaya, M.C.; Gunes, M.; Emhan, A.; Aksoy, N.; Sir, A. Reduced PON1 enzymatic activity and increased lipid hydroperoxide levels that point out oxidative stress in generalized anxiety disorder. *J. Affect. Disord.,* **2013**, *150*(3), 829-833. [http://dx.doi.org/10.1016/j.jad.2013.03.011] [PMID: 23706841]

[31] Ceylan, M.F.; Guney, E.; Alisik, M.; Ergin, M.; Dinc, G.S.; Goker, Z.; Eker, S.; Kizilgun, M.; Erel, O. Lipid peroxidation markers in children with anxiety disorders and their diagnostic implications. *Redox Rep.,* **2014**, *19*(2), 92-96. [http://dx.doi.org/10.1179/1351000213Y.0000000082] [PMID: 24520970]

[32] Sklan, E.H.; Lowenthal, A.; Korner, M.; Ritov, Y.; Landers, D.M.; Rankinen, T.; Bouchard, C.; Leon, A.S.; Rice, T.; Rao, D.C.; Wilmore, J.H.; Skinner, J.S.; Soreq, H. Acetylcholinesterase/paraoxonase genotype and expression predict anxiety scores in health, risk factors, exercise training, and genetics study. *Proc. Natl. Acad. Sci. USA,* **2004**, *101*(15), 5512-5517. [http://dx.doi.org/10.1073/pnas.0307659101] [PMID: 15060281]

[33] Kandemir, H.; Abuhandan, M.; Aksoy, N.; Savik, E.; Kaya, C. Oxidative imbalance in child and adolescent patients with obsessive compulsive disorder. *J. Psychiatr. Res.,* **2013**, *47*(11), 1831-1834. [http://dx.doi.org/10.1016/j.jpsychires.2013.08.010] [PMID: 24011862]

[34] Sarandol, A.; Sarandol, E.; Eker, S.S.; Karaagac, E.U.; Hizli, B.Z.; Dirican, M.; Kirli, S. Oxidation of apolipoprotein B-containing lipoproteins and serum paraoxonase/arylesterase activities in major depressive disorder. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2006**, *30*(6), 1103-1108. [http://dx.doi.org/10.1016/j.pnpbp.2006.04.012] [PMID: 16716479]

[35] Kodydková, J.; Vávrová, L.; Zeman, M.; Jirák, R.; Macásek, J.; Stanková, B.; Tvrzická, E.; Zák, A. Antioxidative enzymes and increased oxidative stress in depressive women. *Clin. Biochem.,* **2009**, *42*(13-14), 1368-1374. [http://dx.doi.org/10.1016/j.clinbiochem.2009.06.006] [PMID: 19527700]

[36] Barim, A.O.; Aydin, S.; Colak, R.; Dag, E.; Deniz, O.; Sahin, I. Ghrelin, paraoxonase and arylesterase levels in depressive patients before and after citalopram treatment. *Clin. Biochem.,* **2009**, *42*(10-11), 1076-1081. [http://dx.doi.org/10.1016/j.clinbiochem.2009.02.020] [PMID: 19272368]

[37] Kotan, V.O.; Sarandol, E.; Kirhan, E.; Ozkaya, G.; Kirli, S. Effects of long-term antidepressant treatment on oxidative status in major depressive disorder: a 24-week follow-up study. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2011**, *35*(5), 1284-1290. [http://dx.doi.org/10.1016/j.pnpbp.2011.03.021] [PMID: 21515329]

[38] Bortolasci, C.C.; Vargas, H.O.; Souza-Nogueira, A.; Barbosa, D.S.; Moreira, E.G.; Nunes, S.O.V.; Berk, M.; Dodd, S.; Maes, M. Lowered plasma paraoxonase (PON)1 activity is a trait marker of major depression and PON1 Q192R gene polymorphism-smoking interactions differentially predict the odds of major depression and bipolar disorder. *J. Affect. Disord.,* **2014**, *159*, 23-30. [http://dx.doi.org/10.1016/j.jad.2014.02.018] [PMID: 24679385]

[39] Liu, T.; Zhong, S.; Liao, X.; Chen, J.; He, T.; Lai, S.; Jia, Y. A Meta-Analysis of Oxidative Stress Markers in Depression. *PLoS One,* **2015**, *10*(10), e0138904. [http://dx.doi.org/10.1371/journal.pone.0138904] [PMID: 26445247]

[40] Ogłodek, E.A. The role of PON-1, GR, IL-18, and OxLDL in depression with and without posttraumatic stress disorder. *Pharmacol. Rep.,* **2017**, *69*(5), 837-845. [http://dx.doi.org/10.1016/j.pharep.2017.03.015] [PMID: 28623707]

[41] Lawlor, D.A.; Day, I.N.M.; Gaunt, T.R.; Hinks, L.J.; Timpson, N.; Ebrahim, S.; Davey, S.G. The association of the paraoxonase (PON1) Q192R polymorphism with depression in older women: findings from the British Women's Heart and Health Study. *J. Epidemiol. Community Health,* **2007**, *61*(1), 85-87. [http://dx.doi.org/10.1136/jech.2006.049247] [PMID: 17183021]

[42] Rice, N.E.; Bandinelli, S.; Corsi, A.M.; Ferrucci, L.; Guralnik, J.M.; Miller, M.A.; Kumari, M.; Murray, A.; Frayling, T.M.; Melzer, D. The paraoxonase (PON1) Q192R polymorphism is not associated with poor health status or depression in the ELSA or INCHIANTI studies. *Int. J. Epidemiol.,* **2009**, *38*(5), 1374-1379. [http://dx.doi.org/10.1093/ije/dyp265] [PMID: 19651761]

[43] Maes, M.; Fišar, Z.; Medina, M.; Scapagnini, G.; Nowak, G.; Berk, M. New drug targets in depression: inflammatory, cell-mediated immune, oxidative and nitrosative stress, mitochondrial, antioxidant, and neuroprogressive pathways. And new drug candidates--Nrf2 activators and GSK-3 inhibitors. *Inflammopharmacology,* **2012**, *20*(3), 127-150. [http://dx.doi.org/10.1007/s10787-011-0111-7] [PMID: 22271002]

[44] Maes, M.; Carvalho, A.F. The compensatory immune-regulatory reflex system (CIRS) in depression and bipolar disorder. *Mol. Neurobiol,* **2018**. epub ahead

[45] Feingold, K.R.; Memon, R.A.; Moser, A.H.; Grunfeld, C. Paraoxonase activity in the serum and hepatic mRNA levels decrease during the acute phase response. *Atherosclerosis,* **1998**, *139*(2), 307-315. [http://dx.doi.org/10.1016/S0021-9150(98)00084-7] [PMID: 9712337]

[46] Ezzaher, A.; Mouhamed, D.H.; Mechri, A.; Araoud, M.; Neffati, F.; Douki, W.; Gaha, L.; Najjar, M.F. Lower paraoxonase 1 activity in Tunisian bipolar I patients. *Ann. Gen. Psychiatry,* **2010**, *9*, 36. [http://dx.doi.org/10.1186/1744-859X-9-36] [PMID: 20964824]

[47] Moreira, E.G.; Correia, D.G.; Bonifácio, K.L.; Moraes, J.B.D.; Cavicchioli, F.L.; Nunes, C.S.; Nunes, S.O.V.; Vargas, H.O.; Barbosa, D.S.; Maes, M. Lowered PON1 activities are strongly associated with depression and bipolar disorder, recurrence of (Hypo)mania and depression, increased disability and lowered quality of Life *World J. Biol. Psychiatry,* **2017**. epub ahead

[48] Ezzaher, A.; Mouhamed, D.H.; Mechri, A.; Neffati, F.; Rejeb, J.; Omezzine, A.; Douki, W.; Bouslama, A.; Gaha, L.; Najjar, M.F. Association between bipolar I disorder and the L55M and Q192R polymorphisms of the paraoxonase 1 (PON1) gene. *J. Affect. Disord.,* **2012**, *139*(1), 12-17. [http://dx.doi.org/10.1016/j.jad.2011.06.029] [PMID: 21783258]

[49] Küçükali, C.I.; Ulusoy, C.; Özkan, Ö.; Orhan, N.; Güleç, H.; Erdaı, E.; Buker, S.; Tüzün, E. In: *Evaluation of Paraoxonase 1 Polymorphisms in Patients with Bipolar Disorder. In Vivo (Brooklyn)*; **2015**, 29, pp. 103-108.

[50] Noto, C.; Ota, V.K.; Gadelha, A.; Noto, M.N.; Barbosa, D.S.; Bonifácio, K.L.; Nunes, S.O.; Cordeiro, Q.; Belangero, S.I.; Bressan, R.A.; Maes, M.; Brietzke, E. Oxidative stress in drug naïve first episode psychosis and antioxidant effects of risperidone. *J. Psychiatr. Res.,* **2015**, *68*, 210-216. [http://dx.doi.org/10.1016/j.jpsychires.2015.07.003] [PMID: 26228421]

[51] Sarandol, A.; Sarandol, E.; Acikgoz, H.E.; Eker, S.S.; Akkaya, C.; Dirican, M. First-episode psychosis is associated with oxidative stress: Effects of short-term antipsychotic treatment. *Psychiatry Clin. Neurosci.,* **2015**, *69*(11), 699-707. [http://dx.doi.org/10.1111/pcn.12333] [PMID: 26172069]

[52] Noto, C.; Ota, V.K.; Gouvea, E.S.; Rizzo, L.B.; Spindola, L.M.N.; Honda, P.H.S.; Cordeiro, Q.; Belangero, S.I.; Bressan, R.A.; Gadelha, A.; Maes, M.; Brietzke, E. Effects of risperidone on cytokine profile in drug-naïve first-episode psychosis. *Int. J. Neuropsychopharmacol.,* **2014**, *18*(4), 1-8. [PMID: 25522386]

[53] Yegin, A.; Ay, N.; Aydin, O.; Yargici, N.; Eren, E.; Yilmaz, N. Increased oxidant stress and inflammation in patients with chronic schizophrenia. *Int. J. Clin. Med.,* **2012**, *3*, 368-376. [http://dx.doi.org/10.4236/ijcm.2012.35070]

[54] Kulaksizoglu, B.; Kulaksizoglu, S. Relationship between neutrophil/lymphocyte ratio with oxidative stress and psychopathology in patients with schizophrenia. *Neuropsychiatr. Dis. Treat.,* **2016**, *12*, 1999-2005. [http://dx.doi.org/10.2147/NDT.S110484] [PMID: 27574431]

[55] Mabrouk, H.; Mechria, H.; Mechri, A.; Azizi, I.; Neffati, F.; Douki, W.; Gaha, L.; Najjar, M.F. Paraoxonase 1 activity and lipid profile in schizophrenic patients. *Asian J. Psychiatr.,* **2014**, *9*, 36-40. [http://dx.doi.org/10.1016/j.ajp.2013.12.019] [PMID: 24813034]

[56] Güneş, M.; Camkurt, M.A.; Bulut, M.; Demir, S.; İbiloğlu, A.O.; Kaya, M.C.; Atlı, A.; Kaplan, İ.; Sir, A. Evaluation of paraoxonase, arylesterase and malondialdehyde levels in schizophrenia patients taking typical, atypical and combined antipsychotic treatment. *Clin. Psychopharmacol. Neurosci.,* **2016**, *14*(4), 345-350. [http://dx.doi.org/10.9758/cpn.2016.14.4.345] [PMID: 27776386]

[57] Pavăl, D.; Nemeş, B.; Rusu, R.L.; Dronca, E. Genotype-phenotype analysis of paraoxonase 1 in schizophrenic patients treated with atypical antipsychotics. *Clin. Psychopharmacol. Neurosci.,* **2018**, *16*(1), 32-38. [http://dx.doi.org/10.9758/cpn.2018.16.1.32] [PMID: 29397664]

[58] Unsal, C.; Albayrak, Y.; Albayrak, N.; Kuloglu, M.; Hashimoto, K. Reduced serum paraoxonase 1 (PON1) activity in patients with schizophrenia treated with olanzapine but not quetiapine. *Neuropsychiatr. Dis. Treat.,* **2013**, *9*, 1545-1552. [PMID: 24143103]

[59] Kucukali, C.I.; Aydin, M.; Ozkok, E.; Orhan, N.; Cakir, U.; Kilic, G.; Ozbek, Z.; Ince, N.; Kara, I. Paraoxonase-1 55/192 genotypes in schizophrenic patients and their relatives in Turkish population. *Psychiatr. Genet.,* **2008**, *18*(6), 289-294. [http://dx.doi.org/10.1097/YPG.0b013e3283060f94] [PMID: 19018234]

[60] Sarandol, A.; Kirli, S.; Akkaya, C.; Ocak, N.; Eroz, E.; Sarandol, E. Coronary artery disease risk factors in patients with schizophrenia: effects of short term antipsychotic treatment. *J. Psychopharmacol. (Oxford),* **2007**, *21*(8), 857-863. [http://dx.doi.org/10.1177/0269881107077609] [PMID: 17715203]

[61] Gilca, M.; Piriu, G.; Gaman, L.; Delia, C.; Iosif, L.; Atanasiu, V.; Stoian, I. A study of antioxidant activity in patients with schizophrenia taking atypical antipsychotics. *Psychopharmacology (Berl.),* **2014**, *231*(24), 4703-4710. [http://dx.doi.org/10.1007/s00213-014-3624-0] [PMID: 24871701]

[62] Matsumoto, C.; Ohmori, O.; Hori, H.; Shinkai, T.; Nakamura, J. Analysis of association between the Gln192Arg polymorphism of the paraoxonase gene and schizophrenia in humans. *Neurosci. Lett.,* **2002**, *321*(3), 165-168. [http://dx.doi.org/10.1016/S0304-3940(02)00049-6] [PMID: 11880198]

[63] Haj, M.D.; Ezzaher, A.; Mechri, A.; Neffati, F.; Omezzine, A.; Bouslama, A.; Gaha, L.; Douki, W.; Najjar, M.F. Effect of cigarette smoking on paraoxonase 1 activity according to PON1 L55M and PON1 Q192R gene polymorphisms. *Environ. Health Prev. Med.,* **2012**, *17*(4), 316-321. [http://dx.doi.org/10.1007/s12199-011-0256-4] [PMID: 22205545]

[64] Nishio, E.; Watanabe, Y. Cigarette smoke extract inhibits plasma paraoxonase activity by modification of the enzyme's free thiols. *Biochem. Biophys. Res. Commun.,* **1997**, *236*(2), 289-293. [http://dx.doi.org/10.1006/bbrc.1997.6961] [PMID: 9240427]

[65] James, R.W.; Leviev, I.; Righetti, A. Smoking is associated with reduced serum paraoxonase activity and concentration in patients with coronary artery disease. *Circulation,* **2000**, *101*(19), 2252-2257. [http://dx.doi.org/10.1161/01.CIR.101.19.2252] [PMID: 10811591]

[66] Gugliucci, A.; Menini, T. Paraoxonase 1 and HDL maturation. *Clin. Chim. Acta,* **2015**, *439*, 5-13. [http://dx.doi.org/10.1016/j.cca.2014.09.016] [PMID: 25261854]

[67] Vargas Nunes, S.O.; Pizzo de Castro, M.R.; Moreira, E.G.; Guembarovski, R.L.; Barbosa, D.S.; Vargas, H.O.; Piccoli de Melo, L.G.; Bortolasci, C.C.; Watanabe, M.A.E.; Dodd, S.; Berk, M.; Maes, M. Association of paraoxonase (PON)1 activity, glutathione S-transferase GST T1/M1 and STin.2 polymorphisms with comorbidity of tobacco use disorder and mood disorders. *Neurosci. Lett.,* **2015**, *585*, 132-137. [http://dx.doi.org/10.1016/j.neulet.2014.11.002] [PMID: 25445355]

[68] Rafraf, M.; Bazyun, B.; Sarabchian, M.A.; Safaeiyan, A.; Gargari, B.P. Vitamin E improves serum paraoxonase-1 activity and some metabolic factors in patients with type 2 diabetes: No effects on nitrite/nitrate levels. *J. Am. Coll. Nutr.,* **2016**, *35*(6), 521-528. [http://dx.doi.org/10.1080/07315724.2015.1116896] [PMID: 26886716]

[69] Wade, L.; Nadeem, N.; Young, I.S.; Woodside, J.V.; McGinty, A.; McMaster, C.; McEneny, J. α-Tocopherol induces proatherogenic changes to HDL2 & HDL3: An *in vitro* and *ex vivo* investigation. *Atherosclerosis,* **2013**, *226*(2), 392-397. [http://dx.doi.org/10.1016/j.atherosclerosis.2012.11.032] [PMID: 23287638]

[70] Sánchez-Muniz, F.J.; Canales, A.; Nus, M.; Bastida, S.; Guillén, M.; Corella, D.; Olmedilla-Alonso, B.; Granado-Lorencio, F.; Benedí, J. The antioxidant status response to low-fat and walnut paste-enriched meat differs in volunteers at high cardiovascular Risk carrying different PON-1 polymorphisms. *J. Am. Coll. Nutr.,* **2012**, *31*(3), 194-205. [http://dx.doi.org/10.1080/07315724.2012.10720027] [PMID: 23204156]

[71] Jarvik, G.P.; Tsai, N.T.; McKinstry, L.A.; Wani, R.; Brophy, V.H.; Richter, R.J.; Schellenberg, G.D.; Heagerty, P.J.; Hatsukami, T.S.; Furlong, C.E. Vitamin C and E intake is associated with increased paraoxonase activity. *Arterioscler. Thromb. Vasc. Biol.,* **2002**, *22*(8), 1329-1333. [http://dx.doi.org/10.1161/01.ATV.0000027101.40323.3A] [PMID: 12171796]

[72] Boaventura, B.C.B.; Di Pietro, P.F.; Stefanuto, A.; Klein, G.A.; de Morais, E.C.; de Andrade, F.; Wazlawik, E.; da Silva, E.L. Association of mate tea (Ilex paraguariensis) intake and dietary intervention and effects on oxidative stress biomarkers of dyslipidemic subjects. *Nutrition,* **2012**, *28*(6), 657-664. [http://dx.doi.org/10.1016/j.nut.2011.10.017] [PMID: 22578980]

[73] Cesar, T.B.; Aptekmann, N.P.; Araujo, M.P.; Vinagre, C.C.; Maranhão, R.C. Orange juice decreases low-density lipoprotein cholesterol in hypercholesterolemic subjects and improves lipid transfer to high-density lipoprotein in normal and hypercholesterolemic subjects. *Nutr. Res.,* **2010**, *30*(10), 689-694. [http://dx.doi.org/10.1016/j.nutres.2010.09.006] [PMID: 21056284]

[74] García-Conesa, M-T.; Chambers, K.; Combet, E.; Pinto, P.; Garcia-Aloy, M.; Andrés-Lacueva, C.; de Pascual-Teresa, S.; Mena, P.; Konic Ristic, A.; Hollands, W.; Kroon, P.; Rodríguez-Mateos, A.;

Istas, G.; Kontogiorgis, C.; Rai, D.; Gibney, E.; Morand, C.; Espín, J.; González-Sarrías, A. Hollands, W.; Kroon, P.; Rodríguez-Mateos, A.; Istas, G.; Kontogiorgis, C.; Rai, D.; Gibney, E.; Morand, C.; Espín, J.; González-Sarrías, A. Meta-Analysis of the Effects of foods and drdiometabolic biomarkers: Analysis of factors influencing variability of the individual responses, **2018**, *19,* 694.

[75] Kardum, N.; Konić-Ristić, A.; Šavikin, K.; Spasić, S.; Stefanović, A.; Ivanišević, J.; Miljković, M. Effects of polyphenol-rich chokeberry juice on antioxidant/pro-oxidant status in healthy subjects. *J. Med. Food,* **2014**, *17*(8), 869-874. [http://dx.doi.org/10.1089/jmf.2013.0135] [PMID: 24650155]

[76] Parsaeyan, N.; Mozaffari-Khosravi, H.; Mozayan, M.R. Effect of pomegranate juice on paraoxonase enzyme activity in patients with type 2 diabetes. *J. Diabetes Metab. Disord.,* **2012**, *11*(1), 11. [http://dx.doi.org/10.1186/2251-6581-11-11] [PMID: 23497651]

[77] Loued, S.; Berrougui, H.; Componova, P.; Ikhlef, S.; Helal, O.; Khalil, A. Extra-virgin olive oil consumption reduces the age-related decrease in HDL and paraoxonase 1 anti-inflammatory activities. *Br. J. Nutr.,* **2013**, *110*(7), 1272-1284. [http://dx.doi.org/10.1017/S0007114513000482] [PMID: 23510814]

[78] Pallauf, K.; Duckstein, N.; Hasler, M.; Klotz, L.O.; Rimbach, G. Flavonoids as putative inducers of the transcription factors Nrf2, FoxO, and PPARγ. *Oxid. Med. Cell. Longev.,* **2017**, *2017*, 4397340. [http://dx.doi.org/10.1155/2017/4397340] [PMID: 28761622]

[79] Khateeb, J.; Gantman, A.; Kreitenberg, A.J.; Aviram, M.; Fuhrman, B. Paraoxonase 1 (PON1) expression in hepatocytes is upregulated by pomegranate polyphenols: a role for PPAR-γ pathway. *Atherosclerosis,* **2010**, *208*(1), 119-125. [http://dx.doi.org/10.1016/j.atherosclerosis.2009.08.051] [PMID: 19783251]

[80] Deáková, Z.; Országhová, Z.; Andrezálová, L.; Slezák, P.; Lehotay, J.; Muchová, J.; Bürki, C.; Ďuračková, Z. Influence of oak wood polyphenols on cysteine, homocysteine and glutathione total levels and PON1 activities in human adult volunteers - a pilot study. *Gen. Physiol. Biophys.,* **2015**, *34*(1), 73-80. [http://dx.doi.org/10.4149/gpb_2014029] [PMID: 25367762]

[81] Huebbe, P.; Giller, K.; de Pascual-Teresa, S.; Arkenau, A.; Adolphi, B.; Portius, S.; Arkenau, C.N.; Rimbach, G. Effects of blackcurrant-based juice on atherosclerosis-related biomarkers in cultured macrophages and in human subjects after consumption of a high-energy meal. *Br. J. Nutr.,* **2012**, *108*(2), 234-244. [http://dx.doi.org/10.1017/S0007114511005642] [PMID: 22011640]

[82] Strunz, C.C.; Oliveira, T.V.; Vinagre, J.C.M.; Lima, A.; Cozzolino, S.; Maranhão, R.C. Brazil nut ingestion increased plasma selenium but had minimal effects on lipids, apolipoproteins, and high-density lipoprotein function in human subjects. *Nutr. Res.,* **2008**, *28*(3), 151-155. [http://dx.doi.org/10.1016/j.nutres.2008.01.004] [PMID: 19083402]

[83] Rizzi, F.; Conti, C.; Dogliotti, E.; Terranegra, A.; Salvi, E.; Braga, D.; Ricca, F.; Lupoli, S.; Mingione, A.; Pivari, F.; Brasacchio, C.; Barcella, M.; Chittani, M.; D'Avila, F.; Turiel, M.; Lazzaroni, M.; Soldati, L.; Cusi, D.; Barlassina, C. Interaction between polyphenols intake and PON1 gene variants on markers of cardiovascular disease: a nutrigenetic observational study. *J. Transl. Med.,* **2016**, *14*(1), 186. [http://dx.doi.org/10.1186/s12967-016-0941-6] [PMID: 27338244]

[84] Hernáez, Á.; Castañer, O.; Elosua, R.; Pintó, X.; Estruch, R.; Salas-Salvadó, J.; Corella, D.; Arós, F.; Serra-Majem, L.; Fiol, M.; Ortega-Calvo, M.; Ros, E.; Martínez-González, M.Á.; de la Torre, R.; López-Sabater, M.C.; Fitó, M. Mediterranean diet improves high-density lipoprotein function in high-cardiovascular-risk individuals clinical perspective. *Circulation,* **2017**, *135*, 633-643. [http://dx.doi.org/10.1161/CIRCULATIONAHA.116.023712] [PMID: 28193797]

[85] Kim, D.S.; Maden, S.K.; Burt, A.A.; Ranchalis, J.E.; Furlong, C.E.; Jarvik, G.P. Dietary fatty acid intake is associated with paraoxonase 1 activity in a cohort-based analysis of 1,548 subjects. *Lipids Health Dis.,* **2013**, *12*, 183. [http://dx.doi.org/10.1186/1476-511X-12-183] [PMID: 24330840]

[86] Ferretti, G.; Bacchetti, T. Effect of dietary lipids on paraoxonase-1 activity and gene expression. *Nutr. Metab. Cardiovasc. Dis.,* **2012**, *22*(2), 88-94. [http://dx.doi.org/10.1016/j.numecd.2011.08.011] [PMID: 22118836]

[87] Stirban, A.; Nandrean, S.; Götting, C.; Stratmann, B.; Tschoepe, D. Effects of n-3 polyunsaturated fatty acids (PUFAs) on circulating adiponectin and leptin in subjects with type 2 diabetes mellitus. *Horm. Metab. Res.,* **2014**, *46*(7), 490-492. [PMID: 24356795]

[88] Lambert, C.; Cubedo, J.; Padró, T.; Sánchez-Hernández, J.; Antonijoan, R.M.; Perez, A.; Badimon, L. Phytosterols and Omega 3 Supplementation Exert Novel Regulatory Effects on Metabolic and Inflammatory Pathways: A Proteomic Study. *Nutrients,* **2017**, *9*(6), 599. [http://dx.doi.org/10.3390/nu9060599] [PMID: 28608804]

[89] Manning, P.J.; Jong, S.A.; Ryalls, A.R.; Sutherland, W.H.F. Paraoxonase 1 activity in chylomicrons and VLDL: The effect of type 2 diabetes and meals rich in saturated fat and oleic acid. *Lipids,* **2012**, *47*(3), 259-267. [http://dx.doi.org/10.1007/s11745-011-3640-3] [PMID: 22160450]

[90] Tomás, M.; Sentí, M.; Elosua, R.; Vila, J.; Sala, J.; Masià, R.; Marrugat, J. Interaction between the Gln-Arg 192 variants of the paraoxonase gene and oleic acid intake as a determinant of high-density lipoprotein cholesterol and paraoxonase activity. *Eur. J. Pharmacol.,* **2001**, *432*(2-3), 121-128. [http://dx.doi.org/10.1016/S0014-2999(01)01482-0] [PMID: 11740946]

[91] Nus, M.; Frances, F.; Librelotto, J.; Canales, A.; Corella, D.; Sánchez-Montero, J.M.; Sánchez-Muniz, F.J. Arylesterase activity and antioxidant status depend on PON1-Q192R and PON1-L55M polymorphisms in subjects with increased risk of cardiovascular disease consuming walnut-enriched meat. *J. Nutr.,* **2007**, *137*(7), 1783-1788. [http://dx.doi.org/10.1093/jn/137.7.1783] [PMID: 17585031]

[92] Manolescu, B.N.; Berteanu, M.; Cintezã, D. Effect of the nutritional supplement ALAnerv® on the serum PON1 activity in post-acute stroke patients. *Pharmacol. Rep.,* **2013**, *65*(3), 743-750. [http://dx.doi.org/10.1016/S1734-1140(13)71054-5] [PMID: 23950599]

[93] Ferré, N.; Camps, J.; Fernández-Ballart, J.; Arija, V.; Murphy, M.M.; Ceruelo, S.; Biarnés, E.; Vilella, E.; Tous, M.; Joven, J. Regulation of serum paraoxonase activity by genetic, nutritional, and lifestyle factors in the general population. *Clin. Chem.,* **2003**, *49*(9), 1491-1497. [http://dx.doi.org/10.1373/49.9.1491] [PMID: 12928230]

[94] Aslan, R.; Kutlu, R.; Civi, S.; Tasyurek, E. The correlation of the total antioxidant status (TAS), total oxidant status (TOS) and paraoxonase activity (PON1) with smoking. *Clin. Biochem.,* **2014**, *47*(6), 393-397. [http://dx.doi.org/10.1016/j.clinbiochem.2013.10.002] [PMID: 24440837]

[95] Ramanathan, G.; Araujo, J.A.; Gornbein, J.; Yin, F.; Middlekauff, H.R. Cigarette smoking is associated with dose-dependent adverse effects on paraoxonase activity and fibrinogen in young women. *Inhal. Toxicol.,* **2014**, *26*(14), 861-865. [http://dx.doi.org/10.3109/08958378.2014.965559] [PMID: 25472476]

[96] Milnerowicz, H.; Kowalska, K.; Socha, E. Paraoxonase activity as a marker of exposure to xenobiotics in tobacco smoke. *Int. J. Toxicol.,* **2015**, *34*(3), 224-232. [http://dx.doi.org/10.1177/1091581815584624] [PMID: 25953737]

[97] Rao, M.N.; Marmillot, P.; Gong, M.; Palmer, D.A.; Seeff, L.B.; Strader, D.B.; Lakshman, M.R. Light, but not heavy alcohol drinking, stimulates paraoxonase by upregulating liver mRNA in rats and humans. *Metabolism,* **2003**, *52*(10), 1287-1294. [http://dx.doi.org/10.1016/S0026-0495(03)00191-4] [PMID: 14564680]

[98] Roest, M.; van Himbergen, T.M.; Barendrecht, A.B.; Peeters, P.H.M.; van der Schouw, Y.T.; Voorbij, H.A.M. Genetic and environmental determinants of the PON-1 phenotype. *Eur. J. Clin. Invest.,* **2007**, *37*(3), 187-196. [http://dx.doi.org/10.1111/j.1365-2362.2007.01769.x] [PMID: 17359486]

[99] Osaki, F.; Ikeda, Y.; Suehiro, T.; Ota, K.; Tsuzura, S.; Arii, K.; Kumon, Y.; Hashimoto, K. Roles of Sp1 and protein kinase C in regulation of human serum paraoxonase 1 (PON1) gene transcription in HepG2 cells. *Atherosclerosis,* **2004**, *176*(2), 279-287. [http://dx.doi.org/10.1016/j.atherosclerosis.2004.05.029] [PMID: 15380450]

[100] Arii, K.; Suehiro, T.; Ikeda, Y.; Kumon, Y.; Inoue, M.; Inada, S.; Takata, H.; Ishibashi, A.; Hashimoto, K.; Terada, Y. Role of protein kinase C in pitavastatin-induced human paraoxonase I expression in Huh7 cells. *Metabolism,* **2010**, *59*(9), 1287-1293. [http://dx.doi.org/10.1016/j.metabol.2009.12.003] [PMID: 20092859]

[101] Schwedhelm, C.; Nimptsch, K.; Bub, A.; Pischon, T.; Linseisen, J. Association between alcohol consumption and serum paraoxonase and arylesterase activities: a cross-sectional study within the Bavar-

ian population. *Br. J. Nutr.,* **2016**, *115*(4), 730-736. [http://dx.doi.org/10.1017/S0007114515004985] [PMID: 26769660]

[102] Tsakiris, S.; Karikas, G.A.; Parthimos, T.; Tsakiris, T.; Bakogiannis, C.; Schulpis, K.H. Alpha-tocopherol supplementation prevents the exercise-induced reduction of serum paraoxonase 1/arylesterase activities in healthy individuals. *Eur. J. Clin. Nutr.,* **2009**, *63*(2), 215-221. [http://dx.doi.org/10.1038/sj.ejcn.1602918] [PMID: 17882129]

[103] Sang, H.; Yao, S.; Zhang, L.; Li, X.; Yang, N.; Zhao, J.; Zhao, L.; Si, Y.; Zhang, Y.; Lv, X.; Xue, Y.; Qin, S. Walk-run training improves the anti-inflammation properties of high-density lipoprotein in patients with metabolic syndrome. *J. Clin. Endocrinol. Metab.,* **2015**, *100*(3), 870-879. [http://dx.doi.org/10.1210/jc.2014-2979] [PMID: 25514103]

[104] Heymsfield, S.B.; Wadden, T.A. Mechanisms, pathophysiology, and management of obesity. *N. Engl. J. Med.,* **2017**, *376*(3), 254-266. [http://dx.doi.org/10.1056/NEJMra1514009] [PMID: 28099824]

[105] Kota, S.K.; Meher, L.K.; Kota, S.K.; Jammula, S.; Krishna, S.V.; Modi, K.D. Implications of serum paraoxonase activity in obesity, diabetes mellitus, and dyslipidemia. *Indian J. Endocrinol. Metab.,* **2013**, *17*(3), 402-412. [http://dx.doi.org/10.4103/2230-8210.111618] [PMID: 23869295]

[106] Mahdirejei, T.A.; Razi, M.; Barari, A.; Farzanegi, P.; Mahdirejei, H.A.; Shahrestani, Z.; Ahmadi, M. A Comparative study of the Effects of endurance and resistance exercise training on PON1 and lipid profile levels in obese men. *Sport Sci. Health,* **2015**, *11*, 263-270. [http://dx.doi.org/10.1007/s11332-015-0232-2]

[107] Aicher, B.O.; Haser, E.K.; Freeman, L.A.; Carnie, A.V.; Stonik, J.A.; Wang, X.; Remaley, A.T.; Kato, G.J.; Cannon, R.O., III Diet-induced weight loss in overweight or obese women and changes in high-density lipoprotein levels and function. *Obesity (Silver Spring),* **2012**, *20*(10), 2057-2062. [http://dx.doi.org/10.1038/oby.2012.56] [PMID: 22402736]

[108] de Melo, L.G.P.; Nunes, S.O.V.; Anderson, G.; Vargas, H.O.; Barbosa, D.S.; Galecki, P.; Carvalho, A.F.; Maes, M. Shared metabolic and immune-inflammatory, oxidative and nitrosative stress pathways in the metabolic syndrome and mood disorders. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2017**, *78*, 34-50. [http://dx.doi.org/10.1016/j.pnpbp.2017.04.027] [PMID: 28438472]

[109] Schachter, M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. *Fundam. Clin. Pharmacol.,* **2005**, *19*(1), 117-125. [http://dx.doi.org/10.1111/j.1472-8206.2004.00299.x] [PMID: 15660968]

[110] Sumi, A.; Nakamura, U.; Iwase, M.; Fujii, H.; Ohkuma, T.; Ide, H.; Jodai-Kitamura, T.; Komorita, Y.; Yoshinari, M.; Hirakawa, Y.; Hirano, A.; Kubo, M.; Kitazono, T. The gene-treatment interaction of paraoxonase-1 gene polymorphism and statin therapy on insulin secretion in Japanese patients with type 2 diabetes: Fukuoka diabetes registry. *BMC Med. Genet.,* **2017**, *18*(1), 146. [http://dx.doi.org/10.1186/s12881-017-0509-1] [PMID: 29233102]

[111] Samy, W.; Hassanian, M.A. Paraoxonase-1 activity, malondialdehyde and glutathione peroxidase in non-alcoholic fatty liver disease and the effect of atorvastatin. *Arab J. Gastroenterol.,* **2011**, *12*(2), 80-85. [http://dx.doi.org/10.1016/j.ajg.2011.04.008] [PMID: 21684478]

[112] Abdin, A.A.; Hassanien, M.A.; Ibrahim, E.A.; El-Noeman, Sel-D. Modulating effect of atorvastatin on paraoxonase 1 activity in type 2 diabetic Egyptian patients with or without nephropathy. *J. Diabetes Complications,* **2010**, *24*(5), 325-333. [http://dx.doi.org/10.1016/j.jdiacomp.2009.04.001] [PMID: 19553142]

[113] Rizos, C.V.; Liberopoulos, E.N.; Tellis, K.; DiNicolantonio, J.J.; Tselepis, A.D.; Elisaf, M.S. Combining rosuvastatin with angiotensin-receptor blockers of different PPARγ-activating capacity: effects on high-density lipoprotein subfractions and associated enzymes. *Angiology,* **2015**, *66*(1), 36-42. [http://dx.doi.org/10.1177/0003319713512556] [PMID: 24288364]

[114] Ferretti, G.; Bacchetti, T.; Sahebkar, A. Effect of statin therapy on paraoxonase-1 status: A systematic review and meta-analysis of 25 clinical trials. *Prog. Lipid Res.,* **2015**, *60*, 50-73. [http://dx.doi.org/10.1016/j.plipres.2015.08.003] [PMID: 26416579]

[115] Gouédard, C.; Koum-Besson, N.; Barouki, R.; Morel, Y. Opposite regulation of the human paraoxonase-1 gene PON-1 by fenofibrate and statins. *Mol. Pharmacol.,* **2003**, *63*(4), 945-956. [http://dx.doi.org/10.1124/mol.63.4.945] [PMID: 12644596]

[116] Paragh, G.; Seres, I.; Harangi, M.; Erdei, A.; Audikovszky, M.; Debreczeni, L.; Kovácsay, A.; Illyés, L.; Pados, G. Ciprofibrate increases paraoxonase activity in patients with metabolic syndrome. *Br. J. Clin. Pharmacol.,* **2006**, *61*(6), 694-701. [http://dx.doi.org/10.1111/j.1365-2125.2006.02565.x] [PMID: 16722831]

[117] Dullaart, R.P.F.; de Vries, R.; Voorbij, H.A.M.; Sluiter, W.J.; van Tol, A. Serum paraoxonase-I activity is unaffected by short-term administration of simvastatin, bezafibrate, and their combination in type 2 diabetes mellitus. *Eur. J. Clin. Invest.,* **2009**, *39*(3), 200-203. [http://dx.doi.org/10.1111/j.1365-2362.2009.02090.x] [PMID: 19260949]

[118] Atamer, Y.; Atamer, A.; Can, A.S.; Hekimoğlu, A.; Ilhan, N.; Yenice, N.; Koçyiğit, Y. Effects of rosiglitazone on serum paraoxonase activity and metabolic parameters in patients with type 2 diabetes mellitus. *Braz. J. Med. Biol. Res.,* **2013**, *46*(6), 528-532. [http://dx.doi.org/10.1590/1414-431X20132818] [PMID: 23802228]

[119] Coll, B.; van Wijk, J.P.H.; Parra, S.; Castro Cabezas, M.; Hoepelman, I.M.; Alonso-Villaverde, C.; de Koning, E.J.P.; Camps, J.; Ferre, N.; Rabelink, T.J.; Tous, M.; Joven, J. Effects of rosiglitazone and metformin on postprandial paraoxonase-1 and monocyte chemoattractant protein-1 in human immunodeficiency virus-infected patients with lipodystrophy. *Eur. J. Pharmacol.,* **2006**, *544*(1-3), 104-110. [http://dx.doi.org/10.1016/j.ejphar.2006.06.014] [PMID: 16843455]

[120] van Wijk, J.; Coll, B.; Cabezas, M.C.; Koning, E.; Camps, J.; Mackness, B.; Joven, J.; Joven, J. Rosiglitazone modulates fasting and post-prandial paraoxonase 1 activity in type 2 diabetic patients. *Clin. Exp. Pharmacol. Physiol.,* **2006**, *33*(12), 1134-1137. [http://dx.doi.org/10.1111/j.1440-1681.2006.04505.x] [PMID: 17184491]

[121] Meaney, E.; Sierra-Vargas, P.; Meaney, A.; Guzmán-Grenfell, M.; Ramírez-Sánchez, I.; Hicks, J.J.; Olivares-Corichi, I.; Ceballos, G. Does metformin increase paraoxonase activity in patients with the metabolic syndrome? Additional data from the MEFISTO study. *Clin. Transl. Sci.,* **2012**, *5*(3), 265-268. [http://dx.doi.org/10.1111/j.1752-8062.2012.00391.x] [PMID: 22686204]

[122] Esteghamati, A.; Eskandari, D.; Mirmiranpour, H.; Noshad, S.; Mousavizadeh, M.; Hedayati, M.; Nakhjavani, M. Effects of metformin on markers of oxidative stress and antioxidant reserve in patients with newly diagnosed type 2 diabetes: a randomized clinical trial. *Clin. Nutr.,* **2013**, *32*(2), 179-185. [http://dx.doi.org/10.1016/j.clnu.2012.08.006] [PMID: 22963881]

[123] Nakou, E.S.; Filippatos, T.D.; Kiortsis, D.N.; Derdemezis, C.S.; Tselepis, A.D.; Mikhailidis, D.P.; Elisaf, M.S. The effects of ezetimibe and orlistat, alone or in combination, on high-density lipoprotein (HDL) subclasses and HDL-associated enzyme activities in overweight and obese patients with hyperlipidaemia. *Expert Opin. Pharmacother.,* **2008**, *9*(18), 3151-3158. [http://dx.doi.org/10.1517/14656560802548430] [PMID: 19040336]

[124] Jaichander, P.; Selvarajan, K.; Garelnabi, M.; Parthasarathy, S. Induction of paraoxonase 1 and apolipoprotein A-I gene expression by aspirin. *J. Lipid Res.,* **2008**, *49*(10), 2142-2148. [http://dx.doi.org/10.1194/jlr.M800082-JLR200] [PMID: 18519978]

[125] Ames, P.R.J.; Batuca, J.R.; Muncy, I.J.; De La Torre, I.G.; Pascoe-Gonzales, S.; Guyer, K.; Matsuura, E.; Lopez, L.R. Aspirin insensitive thromboxane generation is associated with oxidative stress in type 2 diabetes mellitus. *Thromb. Res.,* **2012**, *130*(3), 350-354. [http://dx.doi.org/10.1016/j.thromres.2012.03.025] [PMID: 22521214]

[126] Derosa, G.; Mugellini, A.; Pesce, R.M.; D'Angelo, A.; Maffioli, P. Olmesartan combined with amlodipine on oxidative stress Parameters in Type 2 Diabetics, compared with single therapies: A randomized, controlled, clinical trial. *Medicine (Baltimore),* **2016**, *95*(13), e3084. [http://dx.doi.org/10.1097/MD.0000000000003084] [PMID: 27043671]

[127] Derosa, G.; Mugellini, A.; Pesce, R.M.; D'Angelo, A.; Maffioli, P. Barnidipine compared to lercanidipine in addition to losartan on endothelial damage and oxidative stress parameters in patients with hypertension and type 2 diabetes mellitus. *BMC Cardiovasc. Disord.,* **2016**, *16*, 66. [http://dx.doi.org/10.1186/s12872-016-0237-z] [PMID: 27068332]

[128] Ayashi, S.; Assareh, A.R.; Jalali, M.T.; Olapour, S.; Yaghooti, H. Role of antioxidant property of carvedilol in mild to moderate hypertensive patients: A prospective open-label study. *Indian J. Pharmacol.,* **2016**, *48*(4), 372-376. [http://dx.doi.org/10.4103/0253-7613.186206] [PMID: 27756946]

[129] Noto, C.; Maes, M.; Ota, V.K.; Teixeira, A.L.; Bressan, R.A.; Gadelha, A.; Brietzke, E. High predictive value of immune-inflammatory biomarkers for schizophrenia diagnosis and associa-

tion with treatment resistance. *World J. Biol. Psychiatry,* **2015**, *16*(6), 422-429. [http://dx.doi.org/10.3109/15622975.2015.1062552] [PMID: 26212792]

[130] Noto, C.; Ota, V.K.; Santoro, M.L.; Gouvea, E.S.; Silva, P.N.; Spindola, L.M.; Cordeiro, Q.; Bressan, R.A.; Gadelha, A.; Brietzke, E.; Belangero, S.I.; Maes, M. Depression, cytokine, and cytokine by treatment interactions modulate gene expression in antipsychotic naïve first episode psychosis. *Mol. Neurobiol.,* **2016**, *53*(8), 5701-5709. [http://dx.doi.org/10.1007/s12035-015-9489-3] [PMID: 26491028]

[131] Maes, M.; Ruckoanich, P.; Chang, Y.S.; Mahanonda, N.; Berk, M. Multiple aberrations in shared inflammatory and oxidative & nitrosative stress (IO&NS) pathways explain the co-association of depression and cardiovascular disorder (CVD), and the increased risk for CVD and due mortality in depressed patients. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2011**, *35*(3), 769-783. [http://dx.doi.org/10.1016/j.pnpbp.2010.06.008] [PMID: 20561554]

[132] Vaccarino, V.; McClure, C.; Johnson, B.D.; Sheps, D.S.; Bittner, V.; Rutledge, T.; Shaw, L.J.; Sopko, G.; Olson, M.B.; Krantz, D.S.; Parashar, S.; Marroquin, O.C.; Merz, C.N. Depression, the metabolic syndrome and cardiovascular risk. *Psychosom. Med.,* **2008**, *70*(1), 40-48. [http://dx.doi.org/10.1097/PSY.0b013e31815c1b85] [PMID: 18158378]

[133] Roomruangwong, C.; Simeonova, D.S.; Stoyanov, D.S.; Anderson, G.; Carvalho, A.; Maes, M. Common Environmental Factors May Underpin the Comorbidity between Generalized Anxiety Disorder and Mood Disorders *via* Activated Nitro-Oxidative Pathways *Curr. Top. Med. Chem,* **2018**. epub ahead [http://dx.doi.org/10.2174/1568026618666181115101625]

[134] Azad, M.C.; Shoesmith, W.D.; Al Mamun, M.; Abdullah, A.F.; Naing, D.K.S.; Phanindranath, M.; Turin, T.C. Cardiovascular diseases among patients with schizophrenia. *Asian J. Psychiatr.,* **2016**, *19*, 28-36. [http://dx.doi.org/10.1016/j.ajp.2015.11.012] [PMID: 26957335]

[135] Koola, M.M.; Raines, J.K.; Hamilton, R.G.; McMahon, R.P. Can anti-inflammatory medications improve symptoms and reduce mortality in schizophrenia? *Curr. Psychiatr.,* **2016**, *15*(5), 52-57. [PMID: 27274712]

[136] Huang, Y.; Wu, Z.; Riwanto, M.; Gao, S.; Levison, B.S.; Gu, X.; Fu, X.; Wagner, M.A.; Besler, C.; Gerstenecker, G.; Zhang, R.; Li, X-M.; DiDonato, A.J.; Gogonea, V.; Tang, W.H.W.; Smith, J.D.; Plow, E.F.; Fox, P.L.; Shih, D.M.; Lusis, A.J.; Fisher, E.A.; DiDonato, J.A.; Landmesser, U.; Hazen, S.L. Myeloperoxidase, paraoxonase-1, and HDL form a functional ternary complex. *J. Clin. Invest.,* **2013**, *123*(9), 3815-3828. [http://dx.doi.org/10.1172/JCI67478] [PMID: 23908111]

[137] Efrat, M.; Aviram, M. Paraoxonase 1 interactions with HDL, antioxidants and macrophages regulate atherogenesis - a protective role for HDL phospholipids. *Adv. Exp. Med. Biol.,* **2010**, *660*, 153-166. [http://dx.doi.org/10.1007/978-1-60761-350-3_14] [PMID: 20221878]

[138] Mackness, M.I.; Mackness, B.; Durrington, P.N. Paraoxonase and coronary heart disease. *Atheroscler. Suppl.,* **2002**, *3*(4), 49-55. [http://dx.doi.org/10.1016/S1567-5688(02)00046-6] [PMID: 12573363]

[139] Aviram, M.; Rosenblat, M. Paraoxonases 1, 2, and 3, oxidative stress, and macrophage foam cell formation during atherosclerosis development. *Free Radic. Biol. Med.,* **2004**, *37*(9), 1304-1316. [http://dx.doi.org/10.1016/j.freeradbiomed.2004.06.030] [PMID: 15454271]

[140] Chistiakov, D.A.; Melnichenko, A.A.; Orekhov, A.N.; Bobryshev, Y.V. Paraoxonase and atherosclerosis-related cardiovascular diseases. *Biochimie,* **2017**, *132*, 19-27. [http://dx.doi.org/10.1016/j.biochi.2016.10.010] [PMID: 27771368]

[141] Kunutsor, S.K.; Bakker, S.J.L.; James, R.W.; Dullaart, R.P.F. Serum paraoxonase-1 activity and risk of incident cardiovascular disease: The PREVEND study and meta-analysis of prospective population studies. *Atherosclerosis,* **2016**, *245*, 143-154. [http://dx.doi.org/10.1016/j.atherosclerosis.2015.12.021] [PMID: 26724525]

[142] Kowalska, K.; Socha, E.; Milnerowicz, H. Review: The role of paraoxonase in cardiovascular diseases. *Ann. Clin. Lab. Sci.,* **2015**, *45*(2), 226-233. [PMID: 25887882]

[143] Billecke, S.; Draganov, D.; Counsell, R.; Stetson, P.; Watson, C.; Hsu, C.; La Du, B.N. Human serum paraoxonase (PON1) isozymes Q and R hydrolyze lactones and cyclic carbonate esters. *Drug Metab. Dispos.,* **2000**, *28*(11), 1335-1342. [PMID: 11038162]

[144] Petras, M.; Tatarkova, Z.; Kovalska, M.; Mokra, D.; Dobrota, D.; Lehotsky, J.; Drgova, A. Hyperhomocysteinemia as a risk factor for the neuronal system disorders. *J. Physiol. Pharmacol.,* **2014**, *65*(1), 15-23. [PMID: 24622826]

[145] Maes, M.; Mihaylova, I.; Kubera, M.; Uytterhoeven, M.; Vrydags, N.; Bosmans, E. Increased plasma peroxides and serum oxidized low density lipoprotein antibodies in major depression: markers that further explain the higher incidence of neurodegeneration and coronary artery disease. *J. Affect. Disord.,* **2010**, *125*(1-3), 287-294. [http://dx.doi.org/10.1016/j.jad.2009.12.014] [PMID: 20083310]

[146] Maes, M.; Kubera, M.; Mihaylova, I.; Geffard, M.; Galecki, P.; Leunis, J.C.; Berk, M. Increased autoimmune responses against auto-epitopes modified by oxidative and nitrosative damage in depression: implications for the pathways to chronic depression and neuroprogression. *J. Affect. Disord.,* **2013**, *149*(1-3), 23-29. [http://dx.doi.org/10.1016/j.jad.2012.06.039] [PMID: 22898471]

[147] Maes, M.; Mihaylova, I.; Kubera, M.; Leunis, J-C.; Geffard, M. IgM-mediated autoimmune responses directed against multiple neoepitopes in depression: New pathways that underpin the inflammatory and neuroprogressive pathophysiology. *J. Affect. Disord.,* **2011**, *135*(1-3), 414-418. [http://dx.doi.org/10.1016/j.jad.2011.08.023] [PMID: 21930301]

[148] Kumon, Y.; Suehiro, T.; Ikeda, Y.; Hashimoto, K. Human paraoxonase-1 gene expression by HepG2 cells is downregulated by interleukin-1beta and tumor necrosis factor-alpha, but is upregulated by interleukin-6. *Life Sci.,* **2003**, *73*(22), 2807-2815. [http://dx.doi.org/10.1016/S0024-3205(03)00704-5] [PMID: 14511766]

[149] Rainwater, D.L.; Rutherford, S.; Dyer, T.D.; Rainwater, E.D.; Cole, S.A.; Vandeberg, J.L.; Almasy, L.; Blangero, J.; Maccluer, J.W.; Mahaney, M.C. Determinants of variation in human serum paraoxonase activity. *Heredity (Edinb),* **2009**, *102*(2), 147-154. [http://dx.doi.org/10.1038/hdy.2008.110] [PMID: 18971955]

[150] Ponce-Ruiz, N.; Murillo-González, F.E.; Rojas-García, A.E.; Mackness, M.; Bernal-Hernández, Y.Y.; Barrón-Vivanco, B.S.; González-Arias, C.A.; Medina-Díaz, I.M. Transcriptional regulation of human Paraoxonase 1 by nuclear receptors. *Chem. Biol. Interact.,* **2017**, *268*, 77-84. [http://dx.doi.org/10.1016/j.cbi.2017.02.005] [PMID: 28223025]

[151] Fracassi, A.; Marangoni, M.; Rosso, P.; Pallottini, V.; Fioramonti, M.; Siteni, S.; Segatto, M. Statins and the brain: More than lipid lowering agents? *Curr. Neuropharmacol,* **2019,** *17*(1),59-83.

[152] Köhler-Forsberg, O.; Gasse, C.; Berk, M.; Østergaard, S.D. Do Statins Have Antidepressant Effects? *CNS Drugs,* **2017**, *31*(5), 335-343. [http://dx.doi.org/10.1007/s40263-017-0422-3] [PMID: 28303466]

[153] Lassale, C.; Batty, G.D.; Baghdadli, A.; Jacka, F.; Sánchez-Villegas, A.; Kivimäki, M.; Akbaraly, T. Healthy dietary indices and risk of depressive outcomes: A systematic review and meta-analysis of observational studies. *Mol. Psychiatry,* **2018**. Epub ahead.

[154] Godos, J.; Castellano, S.; Ray, S.; Grosso, G.; Galvano, F. Dietary polyphenol intake and depression: Results from the mediterranean healthy eating, lifestyle and aging (MEAL) study. *Molecules,* **2018**, *23*(5), 1-15. [http://dx.doi.org/10.3390/molecules23050999] [PMID: 29695122]