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 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 (\textit{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 paraaxon (\textit{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.

Keywords: PON1, major depressive disorder, bipolar disorder, schizophrenia, inflammation, oxidative stress, PON1 modulators.

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].

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 (\textit{i.e.}, paraoxonases) is derived from the ability of PON1, the most studied PON, to hydrolyze the pesticide paraaxon [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-
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), arylesterase 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 diazoan. 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 “bi-polar”; “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, anti-coagulants) 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 | | | | 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 | | Q192R | | 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 | | No | | 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 | 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-
activities 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 AREase 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, Ogłodédek [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 another study, 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).
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3.5. PON1 and Schizophrenia

In summary, the studies seem to support decreased AR-

Ease PON1 activity in MDD patients which may play a role

in its pathophysiology for example by exacerbating the ac-

tivated nitro-oxidative stress pathways [5, 43]. Moreover, low-

ered PON1 activities may also lead to activated immune-

flammatory pathways, which is another hallmark of MDD
[44]. Since PON1 hepatic synthesis is inhibited by inflam-
matory 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

immune and neuro-oxidative pathways will be dis-
cussed in section 5.2.

3.4. PON1 and Bipolar Disorder

Compared to MDD, fewer studies investigated the asso-
ciation 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] re-
ported 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 out-
comes in mood disorders (both BD and MDD).

Measurements of PON1 Q192R polymorphism showed a
positive association between the R allele and BD in a Tun-

sian population [48]. These findings were in part corrobo-
rated by Kuçukali et al. [49], who reported a lower fre-
quency of QQ genotype in BD in a Turkish population,
although these differences did not reach statistical signifi-
cance. 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 het-
eurozygous 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 pro-
tected from BD if we consider the antioxidant and anti-

flammatory roles of PON1.

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; N: not informed; PA: phenyl acetate; PO: paraoxon.

The results obtained in SCZ patients are more diverse. In polymedicated SCZ patients, most studies report normal AREase [12, 53] and unaltered POase [51] 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 statisti-
cal 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 naïve 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 | 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 | 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 | 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 | 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....
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, Kuçukkili 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 CMPase 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. Rafaì 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

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**Table 1: Meta-analysis of PON1 Substrate Activity Studies**

| 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 | | | 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: paraxen; SD: systemic severe disease.
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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 AR-Ease 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/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 (NO₂⁻, NO³⁻, 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 co-morbid hypertension, anti-hypertensives, including olmesar-
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-homocysteinylated [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 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], whilst 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.

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CONFLICT OF INTEREST

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