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Mini review

Malondialdehyde and bipolar disorder: A short comprehensive review of available literature

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ABSTRACT

Background: The pathogenetic mechanisms of Bipolar Disorder (BD) have not been totally clarified. Oxidative stress seems to be involved in the etiology of BD, and malondialdehyde (MDA) represents a candidate biomarker for monitoring this aspect in different medical conditions including mood disorders. This article has the objective to critically summarize the available data about the association between MDA and BD.
Methods: A research in Pubmed, PsycINFO and Isi Web of Knowledge was fulfilled to identify studies in which MDA levels were measured in BD patients for the purpose of securing a comprehensive review concerning the issue.
Results: We detected 20 articles that satisfied the inclusion criteria: most of them observed higher MDA levels (or Thiobarbituric acid-reactive substances-TBARS) in BD patients compared to healthy controls (HC), although there are some contrasting results, depending in particular on the phase of illness or the inclusion criteria or the methodological differences.
Limitations: We included studies, exclusively in English, that used different laboratory methods to measure MDA.
Conclusions: The analysed articles suggest that MDA or TBARS are increased in BD patients with respect to HC, thus supporting the hypothesis that MDA may be a promising and potential biomarker to monitor the course of BD, although further studies are needed to confirm this hypothesis.

1. Introduction

Even though the biological mechanisms underlying Bipolar Disorder (BD) have not been completely clarified till now, there is evidence about the involvement of oxidative stress in its etiology (Siwek et al., 2016).

Oxidative stress induces an overproduction of reactive nitrogen species (RNS) or reactive oxygen species (ROS), which can react with other biomolecules, such as lipids, to generate different compounds including Malondialdehyde (MDA). This phenomenon is known as lipid peroxidation, which represents, in turn, one of the major sources of ROS. MDA plasma levels, therefore, reflect the magnitude of lipid peroxidation, but also the severity of oxidative stress (Tsikas, 2017). These aspects are consistent with the observed increased inflammation in BD as showed by higher C-Reactive Protein (CRP) and abnormal total cholesterol plasma levels in bipolar patients than healthy controls (De Berardis et al., 2006; De Berardis et al., 2008; De Berardis et al., 2009).

In physiologic conditions, there is an equilibrium between free radicals and antioxidant defences, whereas in case of oxidative stress there is a persistent imbalance, and abnormally increased ROS induce lipid peroxidation in cell membranes (Tsikas, 2017). The damage of cell membranes may induce the constitution of neoantigens that trigger autoimmune responses and consequently cell death (Maes et al., 2011).

Lipids are the major constitutive elements of myelin and neuronal membranes (Joshi and Praticò, 2014) and the nervous system seems to be particularly vulnerable to the oxidative damage, both for its high request of oxygen and as the result of lack of antioxidant defences (Liu et al., 2015). Lipid peroxidation, as well as free radicals formation, may be involved in neurodegeneration inducing loss of membranes fluidity and membrane rupture, thus leading to potential neuronal death (Bilici et al, 2001).

Of note, MDA has different targets: it can damage mitochondria by reducing complex I activity with consequent ROS increase. Moreover, it can alter the dopaminergic metabolism and eventually may interact with cellular repair proteins, thus compromising the base excision re-

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pair system and promoting mutagenesis (Maes et al., 2011). The magnitude of brain lipid peroxidation cannot be directly assessed. However, the levels of MDA in different biological fluids (Cui et al., 2018) reflect the antioxidant capability and the degree of cellular damage caused by ROS (Oglodek, 2018). Different analytical methods are used to measure MDA including high-performance liquid chromatography (HPLC); chemical analysis of MDA usually starts with its measurement as a component of the so-called thiobarbituric acid-reactive substances (TBARS) (Tsikas, 2017).

Several studies demonstrated that lipid peroxidation is involved in different psychiatric disorders, such as Schizophrenia (Wu et al., 2013; Zhang et al., 2010), Major Depressive Disorder (MDD), Substance Misuse Disorders (Ng et al., 2008), Attention Deficit and Hyperactivity Disorder (ADHD) (Alvarez-Arellano et al., 2020), Anxiety Disorders (Krolow et al., 2014) and Obsessive-Compulsive Disorder (OCD) (Maia et al., 2019). With regard to MDD, a meta-analysis confirmed that patients with depression show higher concentrations of MDA than healthy controls (HC) (Mazereeuw et al., 2015). On the other hand, less data have been published concerning BD.

This review aims to gather the current evidence about the relation between blood MDA levels and BD, to better explore the involvement of oxidative stress in the etiology of BD and the potential role of MDA as biomarker.

2. Methods

To accomplish this purpose, a research on Pubmed, PsycINFO and Isi Web of Knowledge was fulfilled crossing the words "bipolar", "malondialdehyde" and "thiobarbituric acid-reactive substance (TBARS)" with last check on 15th December 2019. Articles having as main outcome the measurement of MDA levels in patients with a BD diagnosis, defined according to the Diagnostic and Statistical Manuals of Mental Disorders, fourth edition Text-Revised and fifth edition (DSM-IV-TR and DSM-5) criteria, were selected and included. Exclusion criteria consisted of animal studies, articles in a language different from English or off-topic articles. In this way, 146 articles were initially identified, of which 45 were included after restriction criteria were applied. The text of these 45 articles was fully screened. Then, 2 were excluded as duplicates, whereas 2 were inserted from biography. Finally, 20 articles were included as they satisfied the inclusion criteria (Figure 1).

3. Results

Table 1 summarizes the results of the included studies.

A first small sample study showed that patients with BD, independently from the phase of illness, had higher MDA plasma levels with respect to controls (Kuloglu et al., 2002). These results were confirmed in larger samples by five independent studies that assessed serum TBARS levels in subjects with BD versus HC (Andreazza et al., 2007; Banerjee et al., 2012; Chowdhury et al., 2016; Kapczinski et al., 2011; Kunz et al., 2008). MDA plasma levels were found to be higher in BD than in HC even in case of remission of symptoms (Aydemir et al., 2014). Furthermore, a recent article reported higher TBARS serum levels in patients affected by mood disorders than HC, although no statistically significant differences were observed between MDD and BD (Sowa-Kućma et al., 2018). Similar findings were pre-

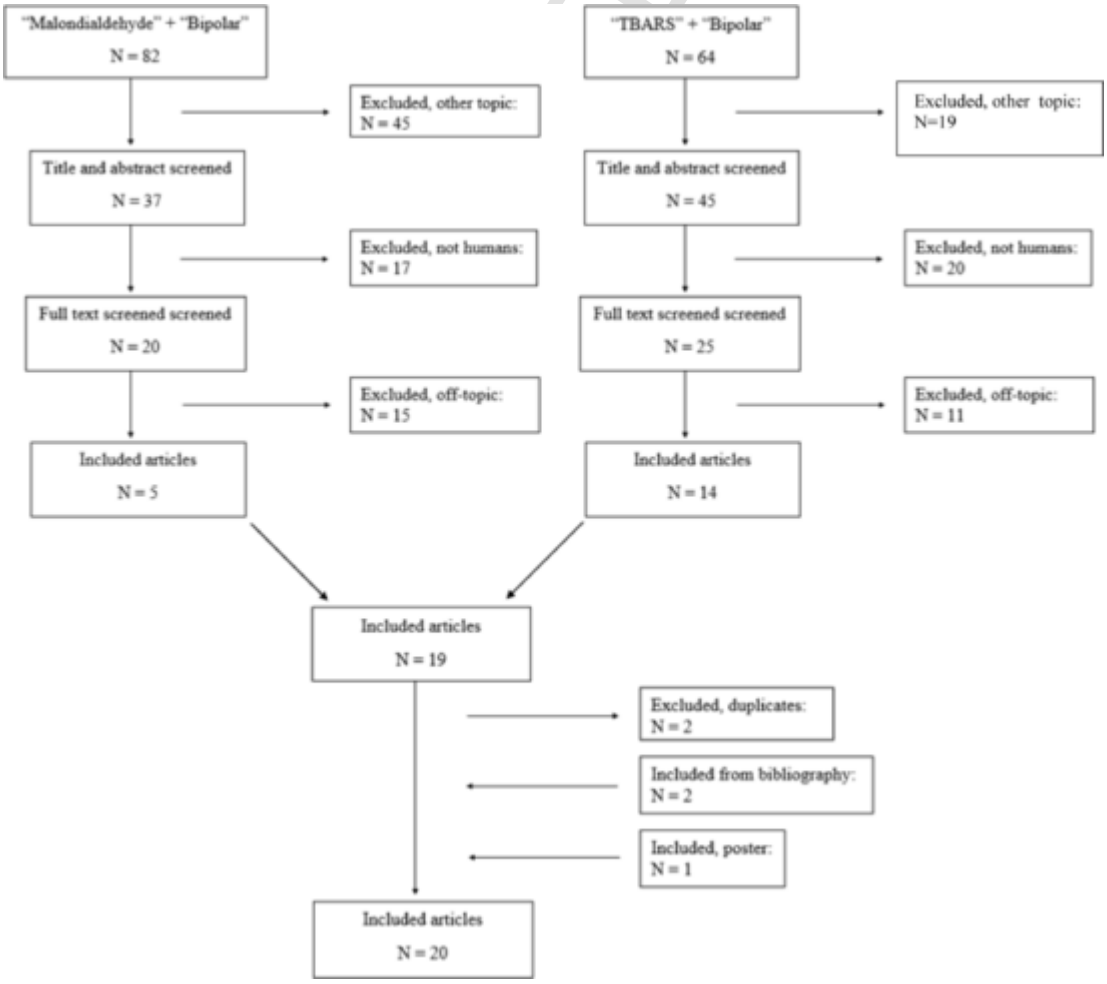

Fig. 1. Prisma diagram for systematic reviews.

Table 1
Summary of the results of the included studies

Study	N (BD/ C)	Type / phase	Scales	Method	Treatment	Results
De La Fuente et al., 2019	101	Early stage: 20 Intermediate stage: 50 Late stage: 31	n/a	MDA, blood	n/a	No significant difference between stages ($p = 0.445$)
Sowa-Kućma et al., 2018	BD: 133 MDD: 114 C: 50	I: 69 II: 64	SCID-I HDRS	TBARS, nMol/ mL, serum	yes: AD, AP-I, AP-II, Li, AC	Differences between groups: $p < 0.001$ (↓ TBARS in C group) MDD VS BD: $p = 0.851$
Valvassori et al., 2018	BD 51	I D: 17 E: 34	SCID-I YMRS HDRS	TBARS, peripheral blood mononuclear cells	yes: Li, AC, AP, AD, BZD, anti-cholinergics	Differences between groups: $p < 0.001$ (TBARS in D > E)
Chowdhury et al., 2017	BD: 55 C: 55	n/a	n/a	TBARS, µg/ mL, serum	n/a	Differences between groups: $p = 0.003$ (TBARS in BD > C)
Siwek et al., 2016	BD: 129 C: 50	I: 69 II: 60 D: 58 M/H: 23 R: 48 Early: 53 Late: 76	MADRS HDRS YMRS	TBARS, nMol/ mL, serum	yes: Li, AC, AP-II, AD	Differences between groups (BD versus C): D > C ($p<0.0001$), M/H > C ($p=0.04$), D > R ($p<0.0001$). No differences between R and C ($p=0.53$), M/H and D ($p=0.38$), M/H and R ($p=0.29$) Differences between groups in BD I: D > R ($p = 0.014$) and C ($p < 0.001$) Differences between groups in BD II: D > R ($p = 0.002$) e C ($p < 0.001$) Differences between groups in early-stage BD: D > R ($p < 0.001$) e C ($p < 0.001$) Difference between groups in late-stage BD: D > C ($p < 0.0001$), R > C ($p \leq 0.05$)
Bengesser et al., 2015	BD: 113 C: 78	I: 62,9% II: 35,3% E: 100%	SCID-I YMRS HDRS	TBARS, µMol/ L serum MDA (GCMS), µMol/L, serum	yes: Li, AP-II, AC	No differences in TBARS between euthymic bipolar patients and C MDA: E < C ($p <0.01$)
Panizzutti et al., 2015	BD: 31 C: 27	I, E Early stage: 17 Late stage: 14	SCID-I YMRS HDRS FAST	TBARS, µM MDA, serum	yes: Li, AC, AP-I, AP-II, AD, BZD	No differences between patients and controls both in early stage ($p = 0.683$) and in late stage ($p = 0.650$)
Tsai et al., 2015	BD: 23 C: 40	I, M	SCID-I YMRS	TBARS, µMol/ L, serum	No	M > C ($p = 0.006$)
Aydemir et al., 2014	BD: 51 C: 50	I: 33 II: 18 R	SCID-CV HDRS YMRS	MDA, HPLC, mMol/L, plasma	yes: mood stabilizers, AP-II	R > C ($p < 0.001$)
De Sousa et al., 2014	BD: 29 C: 28	I: 11 II: 18 D	SCID-I HDRS YMRS	TBARS, nMol/ mL, plasma	yes: 3 no: 26	No differences between groups ($p = 0.95$)
Gubert et al., 2013	BD: 12 C: 30	I E	HDRS YMRS	TBARS, µM of MDA, plasma	yes: mood stabilizers, AP-I, AP-II	No differences between groups ($p=0.26$)
Banerjee et al., 2012	BD: 73 C: 35	n/a	n/a	TBARS, nMol/ mL, serum	yes: 48 Li no: 25 drug-naïves	BD > C ($p < 0.001$)
Magalhães et al., 2012	BD: 55 C: 94	I: 33 II: 22 Early stage	MINI SCID-I ASSIST	TBARS, nMol/ mg of protein	yes: 9,6%	No differences between BD and C ($p = 0.397$)
Kapczinski et al., 2011	BD: 60 C: 80 Sepsis: 15	I D: 20 M :20 E: 20	SCID-NP SCID-I	TBARS, nMol/ mL, serum	yes: Li, AC, AP, AD, BZD	BD > C ($p < 0.001$) D > C ($p < 0.001$) M > C ($p < 0.001$) D > E ($p < 0.001$) M > E ($p < 0.001$) M > D ($p < 0.001$)
Kunz et al., 2008	BD: 83 C: 32	D: 21 M: 32 E: 31	YMRS HDRS	TBARS, nMol/ mL, serum	yes	D > C ($p=0.028$) M > C ($p < 0.001$) E > C ($p < 0.01$) M > E / D / C ($p < 0.01$) D VS E: NS
Andreazza et al., 2007	BD: 84 C: 32	D: 21 M: 32 E: 31	SCID-I YMRS HDRS	TBARS, nMol/ mL, serum	yes: Li, AC	D > C ($p=0.022$) M > C ($p < 0.001$) E > C ($p < 0.01$)

Table 1 (*Continued*)

Study	N (BD/C)	Type / phase	Scales	Method	Treatment	Results
Machado-Vieira et al., 2007	BD: 35 C: 30	I, M	SCID-I YMRS	TBARS, nMol/mL, plasma	yes: 15 Li no: 30	Non-treated patients > treated and C ($p < 0.001$)
Ozcan et al., 2004	BD: 18 rMDD: 6 SZA: 6 C: 21	I M: 16 D: 2	n/a	MDA, μMol/gHb, RBC	yes	Increased MDA in all patients vs C ($p < 0.002$)
Ranjekar et al., 2003	BD: 10 C: 10	Psychotic	SCID-P SCID-NP HDRS BPRS	TBARS, nMol/mL, plasma	yes	No differences between groups
Kuloglu et al., 2002	BD: 23 C: 20	n/a	n/a	MDA, nMol/mL, plasma	n/a	BD > C ($p < 0.05$)

Legend:
I = Bipolar Disorder type 1
II = Bipolar Disorder type 2
AC = anticonvulsants
AD = antidepressants
AP-I = first generation antipsychotics
AP-II = second generation antipsychotics
ASSIST = Alcohol, Smoking and Substance Involvement Screening Test
BZD = benzodiazepines
BPRS = Brief Psychiatric Rating Scale
C = controls
D = depressed
E = euthymic
FAST = Functioning Assessment Short Test
GCMS = gas chromatography–mass spectrometry
gHB = gram of haemoglobin
H = hypomanic
HDRS = Hamilton Depression Rating Scale
HPLC = high performance liquid chromatography
Li = lithium
M = manic
MADRS = Montgomery–Åsberg Depression Rating Scale
MDA = malondialdehyde
MDD = Major Depressive Disorder
MINI = Mini-International Neuropsychiatric Interview
N = sample size
n/a = not applicable
NS = not significant
p = p value
R = remission
RBC = red blood cells
rMDD = Recurrent Major Depressive Disorder
SCID = Structured Clinical Interview for DSM-IV
SCID-NP = Structured Clinical Interview-Non-Patient Edition
SCID-P = Structured Clinical Interview-Patient Edition
SCID-CV = Structured Clinical Interview-Clinician Version
SD = standard deviation
SZA = Schizoaffective Disorder
TBARS = Thiobarbituric Acid-Reactive Substances
VS = versus
YMRS = Young Mania Rating Scale

viously published by other researchers who compared the MDA levels in red cells of a small sample of patients affected by Schizoaffective Disorder, MDD and BD than HC (Ozcan et al., 2004).

Other authors reported data about TBARS serum levels during specific phases of illness. Siwek and co-authors (Siwek et al., 2016) reported higher serum TBARS in patients with bipolar depression versus bipolar subjects in remission, but no statistically significant differences between remitted subjects versus HC or between patients with mania/hypomania than remitted ones. In agreement with these findings, TBARS levels in lymphocytes were found to be higher in subjects with bipolar depression than those in euthymia (Valvassori et al., 2018). Also patients with mania were reported to show higher TBARS serum levels than HC (Tsai et al., 2015).

One article specifically focused on the effect of treatment and the authors reported more oxidative stress (higher TBARS plasma levels) in non-treated than in treated patients with BD (Machado-Vieira et al., 2007), while another study failed to find difference in MDA blood levels according to the stage of BD (early versus intermediate versus advanced stage) (De La Fuente et al., 2019).

Six studies reported no differences in serum/plasma TBARS levels in patients with BD than HC (Bengesser et al., 2015; De Sousa et al., 2014; Gubert et al., 2013; Magalhães et al., 2012; Panizzuti et al., 2015; Ranjekar et al., 2003). However, these studies assessed TBARS in specific subgroups of BD, and in particular in euthymic bipolar patients (Gubert et al., 2013; Bengesser et al., 2015; Panizzuti et al.,

2015), in a small sample of patients with bipolar depression (De Sousa et al., 2014), in 55 young patients with BD 1 and 2 (Magalhães et al., 2012) and in a small sample of subjects affected by psychotic BD (Ranjekar et al., 2003).

4. Discussion

Even though several articles have been published till now about the association between MDA and a number of mental conditions, oxidative stress markers, particularly MDA/TBARS, have been less investigated in BD. A first meta-analysis was published about oxidative stress markers in BD, reporting the few available data regarding lipid peroxidation in patients with BD measured by TBARS (Brown et al., 2014). In our knowledge, this is the first systematic review specifically focused on MDA among oxidative stress markers in BD.

Most of studies for a total of 581 subjects with BD and 394 HC (Andreazza et al., 2007; Aydemir et al., 2014; Banerjee et al., 2012; Chowdhury et al., 2016; Kapczinki et al., 2011; Kuloglu et al., 2002; Kunz et al., 2008; Siwek et al., 2016; Tsai et al., 2015) showed that oxidative stress (MDA or TBARS) is increased in BD than HC independently from the phases of illness. As mentioned above, the negative studies (Bengesser et al., 2015; De Sousa et al., 2014; Gubert et al., 2013; Panizzuti et al., 2015; Ranjekar et al., 2003) for a total of 195 bipolar patients and 173 HC assessed oxidative stress in specific subgroup of patients with BD, especially euthymic ones.

With regard to the phase of bipolar illness, euthymia would seem to be characterized by less oxidative stress than mania or depression (Kapczinski et al., 2011; Kunz et al., 2008; Valvassori et al., 2018). The negative impact of acute phases of BD on biological markers such as MDA/TBARS is consistent with the data published by Kapczinki and collaborators who observed that TBARS levels were negatively correlated with Brain-Derived Neurotrophic Factor (BDNF) (Kapczinski et al., 2008). In contrast, available data do not show significant differences in MDA/TBARS levels between patients with mania or depression (Kunz et al., 2008; Siwek et al., 2016).

Preliminary available data do not seem to indicate that progression of illness (early versus late stage of BD) may be associated with more oxidative stress as showed by increased MDA blood levels (De la Fuente et al., 2019) or TBARS serum levels (Panizzuti et al., 2015; Siwek et al., 2016).

These findings need to be compared with what emerged in other psychiatric disorders. To date, most of the studies in this field were conducted on schizophrenia and MDD. In particular, meta-analyses showed increased MDA levels in patients with both schizophrenia (Ciobica et al., 2011; Wu et al., 2013) and MDD (Liu et al., 2015; Mazereeuw et al., 2015) when compared to healthy subjects, similarly to what happens in BD according to the results presented in this manuscript. A recent meta-analysis, which included the results of 5 studies, reported increased MDA plasma levels in OCD (Maia et al., 2019) similarly to other psychiatric conditions including BD.

On the other hand, MDA/TBARS levels in anxiety disorders were little investigated in humans (Krolow et al., 2014). Recently, a review explored the link between anxiety disorders and oxidative stress, without specifically focusing on MDA (Fedoce et al., 2018). Similarly, available data about MDA levels in ADHD are contrasting and further research is needed with regard the role of oxidative stress in this disorder (Alvarez-Arellano et al., 2020).

Globally the available literature highlights that patients with BD show more oxidative stress than healthy controls, but scanty or no data have been published about outcome predictors of BD such as psychotic symptoms or rapid-cycling (Buoli et al., 2017). Also the effect of pharmacotherapy has been poorly investigated; most of the published data include patients under treatment and only few studies have reported that non-treated patients show more oxidative stress than treated ones (Machado-Vieira et al., 2007; Banerjee et al., 2012; de Sousa et al., 2014; Tsai et al., 2015), while Ozcan and colleagues (2004) did not find differences between treated and untreated groups. Finally, other factors may influence MDA levels including Body Mass Index (BMI), smoking status and substances abuse. For example, cholesterol plasma levels seem to be influenced by the acute mood state in bipolar disorder (De Berardis et al., 2009) and one animal study demonstrated that cholesterol enriched diet increases MDA modification of proteins in cerebral microvessels of rabbits (Mooradian et al., 1995). All these aspects should be studied in deep by future research.

5. Limitations

Limits of the present article include the exclusive selection of manuscripts in English and the heterogeneity of the laboratory methods used to measure MDA in the described articles. The most-frequently used is TBARS: the reaction between TBA and MDA produces a pink pigment, detected by ultraviolet spectrophotometry or fluorescence assays (Seljeskog et al., 2006). However, this method has poor reproducibility, lack of specificity, with consequent risk of MDA overestimation since TBA also reacts with other substances (Tsikas, 2016). Moreover, this laboratory technique may be biased by the interaction with EthyleneDiamineTetra-acetic Acid (EDTA) and by storage conditions (Khoubnasabjafari et al., 2015). Other analytical methods have superior specificity and sensitivity, such as high-performance liquid chromatography (HPLC) (Mosehly et al., 2013). The use of reliable laboratory methods may improve the robustness of published data about this topic.

6. Conclusions

From the examined papers emerges that MDA or TBARS levels are higher in patients with BD than in HC, suggesting that MDA may be a useful potential biomarker to monitor the progression of the disorder, even though further studies are needed to confirm this hypothesis.

Contributors

Drs Caldiroli and Capuzzi wrote the first draft of the manuscript and supervised the research of articles. Dr Auxilia performed the research of articles. Prof. Clerici revised the manuscript. Dr Buoli revised the manuscript, contributed to the final version of the manuscript and suggested the topic of the article.

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Declaration of Conflict of Interests

Dr. Buoli reports personal fees from Mylan, outside the submitted work. The other authors have no potential conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.05.001.

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