The role of oxidative stress in the pathomechanism of major mood disorders: a narrative review with a special focus on uric acid

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Major mood disorder (i.e. major depressive disorder [MDD] and bipolar disorders [BPDs]) are among the most prevalent and disabling mental illnesses. Several, frequently intertwining theories (such as the monoamine, neuroinflammatory and neurotrophic theories) exist to explain the etiopathogenic background of mood disorders. A lesser-known hypothesis addresses the role of oxidative stress (OS; i.e. the overproduction and accumulation of free radicals) in the pathogenesis of these mental disorders. Free radicals are capable of damaging phospholipids, polyunsaturated fatty acids, proteins and nucleic acids. In the brain, OS impairs inter alia synaptic signalling and neuroplasticity. In the current paper, in addition to a brief description of the aforementioned pathophysiological processes involved in mood disorders (with a special focus on OS), we discuss in detail the results of studies on changes in non-enzymatic antioxidant uric acid (UA) levels in major mood disorders. Findings to date indicate that UA - a routinely measured laboratory parameter - may be a candidate biomarker to distinguish between MDD and BPD. Since the diagnostic criteria are identical for major depressive episodes regardless of whether the episode occurs in the context of MDD or BPD and also bearing in mind that the treatment for those two disorders is different, we may conclude that the identification of biomarkers to enable MDD to be distinguished from BPD would be of great clinical relevance.
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INTRODUCTION

According to the typical approach, the category of mood disorders consists of unipolar depressive disorders (major depressive disorder [MDD] and dysthymia/persistent depressive disorder) and bipolar disorders (including bipolar I and bipolar II disorders, as well as cyclothymia) (e.g. Akiskal, 2017; Kessler et al., 2022). Although bipolar disorders (BPDs) are typically characterized by alternating (hypo)manic episodes and major depressive episodes (MDE) (Carvalho et al., 2020), according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the diagnosis of bipolar I only requires the presence of manic episode(s) but does not require the presence of a major depressive episode throughout the course of the disease. However, the diagnosis of bipolar II requires the lifetime occurrence of at least one hypomanic (but no manic) episode and at least one episode of major depression (American Psychiatric Association, 2013; McIntyre et al., 2020). By contrast, the diagnosis of MDD requires at least one major depressive episode without prior (hypo)manic episode(s) (American Psychiatric Association, 2013). While DSM-IV addressed MDD and BPD in the same section entitled "Mood Disorders", DSM-5 handles these two major mood disorders in separate chapters (the reasons for this change are detailed later) (American Psychiatric Association, 1994, 2013). In this paper, we only deal with "major" mood disorders, namely MDD and BPD (Zwicker et al., 2023).

The lifetime prevalence and 12-month prevalence of MDD are 11-18% and 6%-7.7%, respectively (Kessler et al., 2022; Malhi et al., 2021; Malhi and Mann, 2018). The lifetime prevalence and 12-month prevalence for BPD (bipolar I and II disorders combined) is about 1-2.1% and 0.7%, respectively (Kessler et al., 2022; McIntyre et al., 2020). Those figures mean that mood disorders (MDD + dysthymia and bipolar disorders) - alongside anxiety disorders - are the most prevalent mental disorders worldwide (GBD 2019 Mental Disorders Collaborators, 2022). Gender distribution in MDD (where the female-to-male ratio is about 2:1) differs from BPD, where the corresponding figure is closer to 1:1 (especially in BPD-I [whereas BPD-II is somewhat more frequent in women]) (Carvalho et al., 2020; Malhi et al., 2021). On average MDD begins later (in the mid-20s) than BPD, which has a mean age-at-onset in the late teen years or in the early 20s (Carvalho et al., 2020; Malhi et al., 2021; Malhi and Mann, 2018).

MDD and BPD are heritable conditions with an estimated heritability of approximately 30-45% and 55-75%, respectively (Berrettini, 2022; Kelsoe and Greenwood, 2017; Malhi et al., 2021; Sullivan et al., 2012). First-degree family members of bipolar probands have a 7-times higher risk of having BPD than members of the general population. With regard to MDD, the first-degree relatives of subjects with MDD have a 2-3-times higher risk of having MDD than members of the general population (Kelsoe and Greenwood, 2017). There is a considerable genetic correlation between BPD (especially BPD I) and schizophrenia (the strength of the corresponding correlations between MDD and BPD, as well as between MDD and schizophrenia, are much weaker). The discovery of this overlap justifies BPD being discussed separately from MDD in DSM-5 (unlike in DSM-5, in the fourth edition of DSM MDD and BPD were discussed together in the chapter entitled Mood disorders). The new chapter on BPD in DSM-5 is placed between the chapters on schizophrenia spectrum disorders and depressive disorders, reflecting the fact that BPD is currently considered a bridge between MDD and schizophrenia in terms of clinical symptomatology, genetics and family history (American Psychiatric Association, 1994, 2013; Berrettini, 2022; Kelsoe and Greenwood, 2017; Malhi et al., 2021; Mullins et al., 2021; Stahl et al., 2019).

Major mood disorders represent a serious burden to patients, as well as to society. For instance, depressive disorders (MDD and dysthymia) and BPDs were ranked 13th and 67th among the leading causes of disability-adjusted life-years (DALY) in 2019 (GBD 2019 Mental Disorders Collaborators, 2022). With regard to years lived with disability (YLD), depressive disorders (MDD and dysthymia) and BPDs were ranked 2nd and 28th, respectively (GBD 2019 Mental Disorders Collaborators, 2022). In addition, subjects with MDD or BPD have shortened life expectancies by about 10-20 years and the all-cause mortality of these individuals is about 2-times higher than that of members of the general population. Natural causes (i.e. comorbid physical diseases) rather than unnatural causes (e.g. suicide) are responsible for the excess mortality of individuals with major mood disorders (Carvalho et al., 2020; Laursen et al., 2016; McIntyre et al., 2020). Completed suicide is about 6-60-times more frequent in subjects with mood disorders than among normal controls (Carvalho et al., 2020;

Malhi et al., 2021; Moitra et al., 2021; Rihmer and Döme, 2016). Finally, several aspects of personal life are impaired in subjects with major mood disorders. Accordingly, early-onset mood disorder is associated with an elevated risk of not completing secondary school or high school, as well as with a lower probability of ever marrying. Furthermore, the marriages of individuals with mood disorders with premarital onset frequently end in divorce and marital dissatisfaction (Kessler et al., 2022).

Although several antidepressants (ADs) with somewhat different modes-of-action are available, the main effects of the majority of them can be interpreted in the context of the monoaminergic theory. We should highlight that, although all ADs are more effective than placebo, the number-needed-to-treat (NNT) for ADs is estimated at between 3 and 7, thus the efficacy of these agents is far from perfect (it is worth noting that these figures are no worse than the corresponding figures for ACE-inhibitors for the treatment of hypertension and chronic heart failure or for metformin for the treatment of diabetes) (Bauer et al., 2017; Cipriani et al., 2018; Royal College of Psychiatrists, 2019; Stahl, 2021). Currently, due to definitional difficulties, there are no exact prevalence data for treatment-resistant BPD (Howes et al., 2022). However, about 25% of depressive episodes in the context of BPD are considered refractory to treatment (Diaz et al., 2022). Furthermore, residual/subsyndromal symptoms between episodes of major depression or (hypo) mania are quite frequent in BPD (Diaz et al., 2022; Grover et al., 2021). In other words, the treatment of BPD, like that of MDD, cannot be considered completely resolved. In order to be able to develop more effective treatment modalities for major mood disorders, more detailed knowledge is needed of the possible pathomechanisms of these disorders, as well as the interactions between them. The current paper discusses the relevance of one such - lesser-known - mechanism, namely the role of oxidative stress (with a special focus on the role of uric acid) in the pathomechanism of major mood disorders. By reviewing the results of investigations examining urate level alterations in major mood disorders, we also seek to reveal whether measuring urate levels can help clinicians to decide whether a patient presenting with a major depressive episode (and without a (hypo)manic episode in his/her medical history) has BPD or MDD.

MAIN NEUROBIOLOGICAL THEORIES FOR MOOD DISORDERS

Over time, several interconnected neurobiological theories have been established to explain the development of mood disorders (Filatova et al., 2021). In the following, we briefly discuss the most common such theories, as well as some of their interrelationships.

The discovery of the depressogenic effect of reserpine (a monoamine store depleting agent), as well as the mood-improving effects of iproniazid (an antitubercular medication with monoamine oxidase inhibitory properties) and both amphetamine and cocaine (both of which increase the levels of extracellular noradrenaline and dopamine) led to the first neurobiological explanation (namely the monoamine hypothesis) of mood disorders in the modern era. In its primordial form this hypothesis posits that dysfunctions of the monoaminergic (i.e. serotonergic, dopaminergic, noradrenenergic) systems result in affective disorders (Gillespie, 2022; Moncrieff et al., 2022; Owens and Nemeroff, 1994; Rihmer et al., 2017; Thase, 2017). It should be noted that the monoaminergic theory and other theories discussed below that potentially explain the development of mood disorders are intertwined. For instance, the cholinergic-monoaminergic interaction theory posits that the central predominance of cholinergic to catecholaminergic tone causes depression, while pathologically elevated mood results from the converse (Dulawa and Janowsky, 2019; Filatova et al., 2021; Rihmer et al., 2017). Furthermore, the interrelationship between the inflammation hypothesis and the monoaminergic hypothesis of mood disorders is also supported by several facts (e.g. pro-inflammatory cytokines can decrease the availability of monoamine neurotransmitters by increasing the expression of their presynaptic reuptake transporters, as well as by reducing their synthesis) (Miller et al., 2013; Miller and Raison, 2016).

Cholinergic neurotransmission is also proposed to be implicated in the etiopathogenesis of major mood disorders. This hypothesis is based on several findings, for instance that the administration of acetylcholinesterase inhibitors may cause depression-like symptoms while muscarinic acetylcholine receptor antagonists (such as scopolamine) have antidepressive properties. Furthermore, elevated choline (the rate-limiting precursor to acetylcholine) levels were found in the brains of patients with

depression. The amalgamation of cholinergic and monoaminergic theories to explain pathological mood states was already mentioned in the previous paragraph (Dome et al., 2010; Dulawa and Janowsky, 2019; Rihmer et al., 2017).

Implication of the GABAergic system in the pathophysiology of MDD is supported by several lines of evidence. For instance, various studies of depressed patients or suicide victims have reported findings of fewer GABAergic neurons in the cortex, decreased GABA levels in the cerebrospinal fluid (CSF) and plasma, decreased GABA levels in several cortical areas, reduced expression levels of mRNA of some $GABA_A$ receptor subunits and diminished levels of GABA-synthesizing enzymes in the brain (Filatova et al., 2021; Fogaça and Duman, 2019; Gonda et al., 2023; Gunduz-Bruce et al., 2019; Li, 2020; Ragguett et al., 2019). There are also some hints that alterations of the GABAergic system are also implicated in the pathogenesis of BPD (Gillespie, 2022; Simmonite et al., 2023; Young and Juruena, 2021). There is a connection between the GABAergic and stress-induced hypotheses of mood disorders, since the hypothalamic-pituitary-adrenal axis (HPA) is under GABAergic signalling control at the level of the paraventricular nucleus of the hypothalamus (Gonda et al., 2023; Meltzer-Brody and Kanes, 2020). The GABAergic hypothesis is also interrelated with the monoaminergic theory of depression since serotonergic and noradrenergic neurons of the raphe nuclei and locus coeruleus are under GABAergic control (Gonda et al., 2023; Luscher et al., 2011; Ragguett et al., 2019).

There is ample evidence to suggest that disruption of glutamatergic transmission is also implicated in the pathophysiology of mood disorders (glutamate is the main excitatory neurotransmitter in the brain). For instance, higher and higher/lower glutamate levels have been found in the plasma and in the frontal cortex of depressed patients, respectively. In addition, in subjects with MDD, postmortem studies have identified altered expression levels of ionotropic and metabotropic glutamate receptors in depression-relevant brain areas (Gillespie, 2022; Gonda et al., 2023). Similarly, results of several studies suggest that the glutamatergic system is also involved in the pathophysiology of BPD (Li et al., 2018). Unsurprisingly, the glutamatergic system is interconnected with other systems that are also assumed to play a role in the pathophysiology of mood disorders. For instance, the stress hypothesis of depression is linked to the glutamatergic system since acute stress results in cortisol release, which in turn increases the release of glutamate in several brain areas (hippocampus, amygdala, prefrontal cortex) (Gonda et al., 2023; Mikasova et al., 2017). Furthermore, the "excitatory-inhibitory (E/I) imbalance theory" of depression supposes that dysfunction of both the glutamatergic (excitatory) and the GABAergic (inhibitory) systems is present in various brain areas in MDD. Accordingly, glutamatergic and GABAergic explanations for depression are also interconnected (Hu et al., 2023; Page and Coutellier, 2019). Furthermore, as glutamatergic (and probably also some GABAergic) neurons of the frontal/prefrontal cortices (PFC) project to the raphe nuclei and in turn the serotonergic neurons of the raphe project to the glutamatergic and GABAergic neurons of the PFC, there is a neuroanatomical link between the relatively novel "E/I imbalance" theory and the prevailing monoamine theory of MDD (Li, 2020; Melzer and Monyer, 2020).

The stress theory of depression postulates that stress, and the consequential malfunctioning of the hypothalamic–pituitary–adrenal (HPA) axis, is associated with mood disorders (Filatova et al., 2021; Thase, 2017). Several clinical findings support the validity of that theory, the most important being that activity of the HPA axis is increased in 20-60% of depressed subjects (Thase, 2017; Watson and Mackin, 2009). Furthermore, it is also known that elevated levels of cortisol associated with activation of the HPA axis, as well as activation of corticotropin-releasing hormone (CRH)-positive neurons - which project to different brain areas - during the stress-response are proposed to be responsible for depressive symptoms (Bao and Swaab, 2019; Filatova et al., 2021; Kovács, 2013; Watson and Mackin, 2009). The HPA axis is under the control of GABAergic (see discussed above), serotonergic and noradrenergic neurotransmitter systems. Furthermore, CRH increases the activity of the noradrenergic locus coeruleus (Bao and Swaab, 2019; Thase, 2017). In addition, there is a bidirectional link between the stress and inflammatory hypotheses of depression, since

1) pro-inflammatory cytokines promote activation of the HPA axis and finally the release of glucocorticoids from the adrenal cortex;

2) glucocorticoids regulate the immune response since they have both anti-inflammatory and pro-inflammatory effects (Benedetti et al., 2020; Mazza et al., 2022; Troubat et al., 2021). The stress theory is therefore related to several other theories of mood disorders.

Furthermore, inflammation is also suggested as a mechanism that may play a role in the pathophysiology of major mood disorders. This assumption is supported by several findings, for instance: the levels of some proinflammatory cytokines (e.g. IL-6) and acute phase proteins (e.g. C-reactive protein; CRP) are increased in MDD patients compared to healthy controls; subjects with severe infections and autoimmune diseases are more likely to have depression; the therapeutic administration of proinflammatory cytokines (e.g. IFN-γ) causes depression (it should be noted that, despite the functioning of the blood-brain barrier [BBB], pro-inflammatory cytokines may enter the brain by various mechanisms); elevated levels of IL-6 and CRP are associated with an increased risk of developing depression later in life; signs of microglial activation and neuroinflammation in subjects with MDD. Finally, inflammation may be linked to various other systems and mechanisms proposed to play a role in the pathophysiological background of depression (the relationships between the inflammatory theory and the monoaminergic and stress hypotheses were discussed above) (Benedetti et al., 2020; Beurel et al., 2020; Çakici et al., 2020; Cecerska-Heryć et al., 2022; Dantzer et al., 2008; Malhi and Mann, 2018; Mazza et al., 2022; Serafini et al., 2023; Zainal and Newman, 2021). With regard to BPD, the levels of some inflammatory cytokines (e.g. IL-1β, IL-6 and TNF-α) and acute-phase proteins (CRP) are elevated in manic episodes and/or in euthymic states (Benedetti et al., 2020; Beurel et al., 2020; Himmerich et al., 2019; McIntyre et al., 2020; Toups and Nemeroff, 2022). Furthermore, microglia activation was also found in subjects with BPD (Benedetti et al., 2020). In line with the above, there is some evidence for the efficacy of anti-inflammatory agents in the treatment of major mood disorders (Beurel et al., 2020; Carvalho et al., 2020; Marwaha et al., 2023).

Neurotrophic factors (such as brain-derived neurotrophic factor [BDNF], neurotrophin-3 and -4 [NT-3, NT-4], glial cell line-derived neurotrophic factor [GDNF] and nerve growth factor [NGF]) and their receptors (such as tropomyosin receptor kinases [i.e. Trk-A, Trk-B and Trk-C] and p75 neurotrophin receptor [p75NTR]) are also proposed to be implicated in the pathophysiology of mood disorders. Accordingly, several lines of evidence support the role of neurotrophic factors in the genesis of MDD. For instance, lower peripheral levels of BDNF were found in subjects with MDD (it should be noted that BDNF and other neurotrophins are able to cross the BBB, so peripheral levels of them may mirror their central levels in a feasible manner). Furthermore, decreased BDNF levels in several brain areas (e.g. hippocampus, prefrontal cortex, anterior cingulum) of subjects with MDD and/or suicide victims have also been demonstrated. Finally, the use of antidepressants and other treatments for mood disorders (e.g. ECT) are associated with an elevation in BDNF levels (Amidfar et al., 2021; Ding et al., 2023; László et al., 2019; Luan et al., 2020; Nikolac Perkovic et al., 2021; Pan et al., 1998; Pelosof et al., 2023; Petersen et al., 2021; Porter and O'Connor, 2022; Seney and Lewis, 2022; Vega-Núñez et al., 2022). Furthermore, a new hypothesis has emerged recently which states that all antidepressant agents (including ketamine and psychedelics with antidepressive properties) have a common mode-of-action, namely they sensitize the Trk-B receptor to BDNF (Castrén, 2023). The role played by neurotrophins with regard to the pathophysiology of BPD has also emerged. For instance, BDNF levels were reported to be lower in subjects with BPD when they are depressed or manic, but BDNF levels returns to normal during euthymia (Baykara et al., 2021; Chiou and Huang, 2019; Petersen et al., 2021; Vega-Núñez et al., 2022). The neurotrophic hypothesis of mood disorders is interconnected with other theories of affective disorders. For instance, HPA axis hyperactivity with increased levels of cortisol and CRH inhibits the synthesis of BDNF (Filatova et al., 2021; Thase, 2017). Furthermore, inflammation has been shown to decrease the expression of BDNF; on the other hand BDNF may play an important negative regulatory role on inflammation within the central nervous system (Porter and O'Connor, 2022).

OXIDATIVE STRESS (OS) IN THE BRAIN

Free radicals are highly reactive molecules because they contain at least one unpaired electron in the outer electron shell. Oxidative stress (OS) is a pathological state, where the production of free radicals (primarily reactive oxygen and nitrogen species [ROS and RNS, respectively] in biological systems) exceeds the ability of the antioxidant systems to detoxify them (Cecerska-Heryć et al., 2022; Jelinek et al., 2021). In the central nervous system, superoxide is considered the most important ROS. Other kinds of ROSs include, for instance, hydrogen peroxide, hydroxyl radical and hypochlorous acid, while nitric oxide (NO) and peroxynitrite are examples of the most important

RNSs (Jelinek et al., 2021). The major sources of intracellular ROS production are the mitochondria, where about 90% of cellular ROS is generated as a by-product of the oxidative phosphorylation process (peroxisomes, the endoplasmatic reticulum, cell membrane and cytoplasm are responsible for the remaining 10% of ROS production) (Correia et al., 2023; Jelinek et al., 2021; Salim, 2017; Tirichen et al., 2021). Extracellular free radicals are released from immune cells as part of their response to invading pathogens (Jelinek et al., 2021; Rosen et al., 1995). In the human body, non-enzymatic and enzymatic protective systems operate to eliminate free radicals. Non-enzymatic elements operate either within the cells (for example, in the case of glutathione [GSH], melatonin, ferritin and Coenzyme Q10) or in the extracelullar fluids (e.g. uric acid, bilirubin, albumin and ceruloplasmin). Glutathione reductase (GR), glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase (CAT) are the most important enzymatic antioxidants (Cecerska-Heryć et al., 2022; Correia et al., 2023; Jelinek et al., 2021; Lu et al., 2022; Mirończuk-Chodakowska et al., 2018; Salim, 2017).

Although ROSs have physiological functions in low concentrations - for instance in metabolic processes and the immune response - and are considered important for the appropriate development and functioning of neurons (for instance, NO is a retrograde neurotransmitter), their presence in high concentrations is malignant (Ait Tayeb et al., 2023; Correia et al., 2023; Jelinek et al., 2021; Massaad and Klann, 2011; Salim, 2017; Tirichen et al., 2021). Accordingly, free radicals may evoke DNA/RNA damage, protein oxidation and lipid peroxidation, resulting in functional decline of cells (Cecerska-Heryć et al., 2022; Jelinek et al., 2021; Salim, 2017; Tirichen et al., 2021).

The brain is extremely vulnerable to OS for several reasons. First of all, due to its enormous oxygen consumption (the human brain consumes 20% of the total oxygen intake) free radicals form at a high rate in the brain. Furthermore, the brain has a limited endogenous antioxidant defence capacity (Brand-Yavin and Yavin, 2009; Cecerska-Heryć et al., 2022; Cobley et al., 2018; Jelinek et al., 2021; Lu et al., 2022; Salim, 2017). In addition, since the brain is rich in phospholipids and polyunsaturated fatty acids (PUFA), this organ is particularly vulnerable to the attack of free radicals (Brand-Yavin and Yavin, 2009; Gong et al., 2022; Jelinek et al., 2021). In addition, free radicals in excess are able to increase the permeability of the blood-brain barrier, thus putting the central nervous system (CNS) at higher risk of tissue damage (Banks and Rhea, 2021; Jelinek et al., 2021; Salim, 2017). Several other consequences of OS are also known, such as influencing the synaptic transmission and long-term potentiation (LTP) due to the oxidation of N-methyl-D-aspartate (NMDA) receptors (Ait Tayeb et al., 2023; Cecerska-Heryć et al., 2022; Correia et al., 2023; Salim, 2017). Not only NMDA receptors, but also some types of acetylcholinergic receptors are sensitive to OS (Guan, 2008). The discussion of other detrimental effects of OS in the brain may be found in several excellent review papers (e.g. Cecerska-Heryć et al., 2022; Cobley et al., 2018; Jelinek et al., 2021).

OXIDATIVE STRESS (OS) IN MOOD DISORDERS AND THE LINKS BETWEEN OS AND OTHER THEORIES OF MOOD DISORDERS

Given that the brain is highly vulnerable to OS, it is not surprising that great research efforts have been made to identify the possible role of OS in the pathophysiological background of neuropsychiatric disorders (such as Alzheimer's disease, schizophrenia and mood disorders) (Cecerska-Heryć et al., 2022). A recently published narrative review summarized the results on the association between OS-related biomarkers and MDD. According to the main findings of that paper, higher H_2O_2 plasma levels, elevated CAT and decreased GPx levels and increased levels of biomarkers of oxidative damage of lipids are associated most consistently with MDD. Considering that the effects of antioxidants and pro-oxidants are additive, a joint evaluation of them could be useful. In depression, the total antioxidant status (TAS) is reduced, as opposed to the total oxidant status (TOS), which is increased in MDD (Ait Tayeb et al., 2023). A very recent meta-analysis (MA) found that the level of oxidative damage of nucleic acids is higher in blood cells, plasma and serum of subjects with MDD (Jorgensen et al., 2022a). With regard to MDD, a bidirectional Mendelian randomization study (BMRS) was unable to prove that any of the investigated biomarkers of oxidative stress have a causal effect on the risk of MDD. On the other hand, the study found that genetically predicted MDD was significantly associated with decreased levels of total bilirubin (a non-enzymatic antioxidant) (Lu et al., 2022). In addition, results of another Mendelian randomization study do not support the existence of significant causal associations between genetically determined diet-derived circulating antioxidants

and the risk of MDD. Accordingly, the authors of that paper concluded that the efficacy of simply taking antioxidants to increase blood antioxidant levels in order to prevent major mental disorders (including MDD) in healthy, well-nourished adults is questionable (Zhao et al., 2023). Finally, it is worth noting that some behaviours that favour the development of oxidative stress (e.g. smoking, alcohol consumption and/or a lower intake of antioxidants like vitamins A and C) occur more often in MDD and also in BPD (Cecerska-Heryć et al., 2022; Correia et al., 2023; Levit et al., 2023; Vermeulen et al., 2021).

With regard to BPD, elevated levels of malondialdehyde (MDA; an oxidative damage product of lipids) were found by an MA in subjects with unmedicated BPD. Authors of that MA also found that especially those studies enrolling more older euthymic female subjects with BPD are more likely to find higher malondialdehyde levels (Ait Tayeb et al., 2023; Capuzzi et al., 2022). Another MA confirmed that MDA levels are higher in all BPD subjects (but not in BPD subjects in euthymia) than in healthy controls (Jiménez-Fernández et al., 2021). The same MA also found that levels of thiobarbituric acid reactive substances (TBARS; another marker of oxidative damage of lipids) were also higher in subjects with any phases (i.e. depression, mania, euthymia) of BPD than in healthy controls (Jiménez-Fernández et al., 2021, 2022). Changes in other factors associated with OS in BPD (vs. healthy controls) are also described in that MA, for instance elevated levels of CAT, GST and lower levels of GSH (Jiménez-Fernández et al., 2021). According to the results of a study, total bilirubin and albumin (both of which are non-enzymatic antioxidants) levels were higher and lower, respectively in subjects with (hypo)manic, mixed or depressive phases of BPD (vs healthy controls) (Gong et al., 2022). Another study from China also found lower levels of albumin in subjects with bipolar disorder. However, unconjugated bilirubin levels did not differ between bipolar patients and healthy controls (Xu et al., 2023). By contrast, a previous study did not find significant differences between subjects with BPD and healthy controls with regard to their albumin and total bilirubin levels (De Berardis et al., 2008). A MA investigating damage to DNA/RNA due to OS across various neuropsychiatric diagnoses found the third highest level of oxidative damage of nucleic acids (after dementias and psychotic disorders) in BPD (Jorgensen et al., 2022a). Similarly, a very recent study identified higher levels of RNA damage due to OS in newly diagnosed BPD subjects and their unaffected relatives (vs. healthy controls) (Coello et al., 2023). The previously mentioned BMRS could not prove that any of the investigated biomarkers of OS have a causal effect on the risk of BPD or, vice versa, that BPD has a causal effect on any investigated biomarker of oxidative stress injury (Lu et al., 2022). Furthermore, the results of another Mendelian randomization study do not support the existence of significant causal associations between genetically determined diet-derived circulating antioxidants and the risk of BPD. Accordingly, the authors of that paper concluded that the efficacy of simply taking antioxidants to prevent BPD in healthy adults is doubtful (Zhao et al., 2023).

Oxidative stress is related to other theories of mood disorders (which were discussed above). For instance, OS is associated with induction of the synthesis of pro-inflammatory cytokines. Furthermore, the excess synthesis of inflammatory cytokines is linked to reduced antioxidant activity and neuroinflammation induces excess ROS generation. Accordingly, there is bidirectional link between the oxidative stress theory and the inflammatory theory of mood disorders (Ait Tayeb et al., 2023; Cecerska-Heryć et al., 2022; Correia et al., 2023; Ji et al., 2023; Salim, 2017). OS is also associated with the neurotrophic theory of mood disorders, since the overproduction of ROS inhibits expression of the BDNF gene and protein (Ji et al., 2023). Further information on the relationships between OS and other theories of mood disorders (e.g. the HPA axis dysregulation theory and the monoaminergic theory) can be found in the relevant literature (see, for instance, Correia et al., 2023; Ji et al., 2023; Madireddy and Madireddy, 2022; Prevatto et al., 2017).

Although it is unclear whether the link between OS and major mood disorders is of a causal nature (see, for instance, the results of the previously cited bidirectional Mendelian randomization study), the findings on elevated levels of markers of OS in mood disorders raise the question as to whether antioxidant supplementation may be beneficial in treating these conditions. Several studies have been carried out to assess the efficacy of primary antioxidants (e.g. vitamin E, vitamin C) or herbs with antioxidative properties (e.g. saffron and turmeric [the source of curcumin]) and other molecules that are protective against OS (e.g. N-Acetylcysteine [NAC], S-Adenosyl-L-Methionine [SAM] and Zinc) in the treatment of mood disorders. Unfortunately, the results are inconclusive for the majority of

these agents; accordingly, treatment guidelines recommend the use of only a few of them to treat mood disorders (Bradlow et al., 2022; Cecerska-Heryć et al., 2022; Dome et al., 2019; Gabriel et al., 2023; Lee et al., 2022; Malhi et al., 2021; Marreiro et al., 2017; Sarris et al., 2022).

Another relevant question is that of whether the treatment of mood disorders is associated with the normalization of altered OS parameters associated with these disorders. With regard to both MDD and BPD, in short, it can be said that some (but not all) markers show a tendency to be restored during treatment (or in remitted MDD) (Ait Tayeb et al., 2023; Capuzzi et al., 2022; Gong et al., 2022; Jiménez-Fernández et al., 2021, 2022; Jorgensen et al., 2022b).

ALTERATIONS OF URIC ACID LEVELS IN MDD AND BPD

Uric acid (UA) is the end product of purine (i.e. adenine and guanine) metabolism in humans. Intriguingly, the majority of mammals are able to convert UA to allantoin since they possess the enzyme uricase (urate oxidase) while humans (and other primates) are unable to do so. Allantoin is more soluble than UA and easily eliminated by urine. De novo purine synthesis, the catabolism of DNA, RNA and ATP, as well as dietary intake (especially with the consumption of for instance liver, kidney and anchovy), are considered the main sources of purines. UA is produced in the organs (primarily the liver and the small intestines) expressing xanthine oxidase, the enzyme that is responsible for catalysing the final step [i.e. the xanthine→UA transformation] of the purine catabolism. Approximately 300-400 mg of UA is produced in the human body per day. Kidneys, and to a lesser degree, the intestinal system are responsible for the elimination and excretion of UA from the human body (Furuhashi, 2020; Hyndman et al., 2016; Ishikawa et al., 2013; Kaur and Bhatt, 2023; Maiuolo et al., 2016; Mecchella and Burns, 2022; Mijailovic et al., 2022). It should be noted that, besides its role in the synthesis of UA, the byproduct of the operation of the enzyme xanthine oxidase is a ROS (hydrogen peroxide) (Aziz and Jamil, 2022; Correia et al., 2023; Jelinek et al., 2021).

As has already been mentioned, UA is a non-enzymatic antioxidant. The relevance of UA as an antioxidant is underscored by the fact that this agent is accountable for up to 60% of the antioxidant capacity of the human plasma (Bartoli et al., 2016b; Bartoli et al., 2018; Cecerska-Heryć et al., 2022; Fang et al., 2013; Lu et al., 2022; Maiuolo et al., 2016). According to a popular evolutionary hypothesis, the increase in the levels of antioxidant UA in primates due to their lack of the expression of uricase (as discussed above) compensates for the loss of their ability to synthesize ascorbic acid (i.e. vitamin C, another antioxidant agent) (Cecerska-Heryć et al., 2022; Furuhashi, 2020; Li et al., 2022b). Several underlying mechanisms are responsible for the antioxidant properties of UA. For instance, UA is a scavenger of singlet oxygen, hydroxyl and peroxyl radicals and also defends the cell from oxidative damage by chelating metal ions (Fang et al., 2013; Maiuolo et al., 2016; Mijailovic et al., 2022). Nevertheless, it should be noted that UA also has some pro-oxidant and pro-inflammatory properties (Fang et al., 2013; Kang and Ha, 2014; Maiuolo et al., 2016; Mijailovic et al., 2022). The expression of xanthine oxidase is very limited in the brain tissue, thus very small amounts of UA may be synthesized in the brain *in situ* (Bowman et al., 2010; Otani et al., 2023). In line with that, UA levels in the CSF are at least 10-times lower than its plasma levels (Bowman et al., 2010; Otani et al., 2023; Yuan et al., 2023). An intact blood-brain barrier (BBB) impedes UA from getting from the blood to the brain but injured BBB is associated with higher UA levels in the CSF (Mijailovic et al., 2022; Otani et al., 2023; Yuan et al., 2023). Despite the fact that access of UA to the brain is limited by an intact BBB, there is a strong positive correlation between peripheral and central (CSF) UA levels (Bartoli et al., 2016b; Bowman et al., 2010). Since it is unknown for many other markers of OS whether their peripheral levels are reflective of their CNS levels, the strong positive correlation between its peripheral and CSF concentrations makes UA particularly interesting among antioxidant agents (Black et al., 2018; Mijailovic et al., 2022).

The potential relevance of UA in the etiological background of mood disorders may be supported by the fact that OS plays a role in the pathogenesis of mood disorders (see Chapter 4 for discussion of this issue) and also that UA has antioxidant effects. In addition, UA is the final product of purine metabolism and purinergic neurotransmission is intricately implicated in the molecular background of mood disorders. In other words, UA reflects the activity of a transmitter system (namely the purinergic system) that is involved in mood regulation (Bartoli et al., 2016b; Cheffer et al., 2018; Gonçalves et al., 2022; He et al., 2020; Lorenzi et al., 2010; Maiuolo et al., 2016; Ortiz et al., 2015; Szopa et al., 2021).

Intriguingly, the history of the uric acid hypothesis of mood disorder dates back to the second half of the 19th century. At that time British physicians Alfred Garrod and Alexander Haig, as well as Armand Trousseau from France, proposed that uric acid pathology may play a role in the etiologic background of mood disorders ("cerebral gout"). Since lithium salts were frequently prescribed for patients with gout at that time, Garrod raised the possibility that lithium treatment may also be effective for the treatment of the "cerebral forms" of gout. Accordingly, some physicians (such as William Hammond in the USA and the Lange brothers in Denmark) began to use lithium salts to treat mania and depression. Emil Kraepelin, a leading psychiatrist of the early 20th century, also addressed the possible association between abnormal UA metabolism and mania. The investigations of the Australian psychiatrist John Cade in 1949 on the toxicity of urine of manic patients in guinea pigs and the discovery that lithium is able to reduce that toxicity has led to the modern revival of lithium (Cade used lithium because he knew of Garrod's findings on the role of this agent in treating gout). Accordingly, the UA hypothesis of mood disorders was closely related to the discovery of lithium treatment for these disorders (Baldessarini, 2013; Dos Santos Oliveira et al., 2019; Draaisma, 2019; Fountoulakis, 2015; Hidvégi et al., 2016; Maletzky and Blachly, 1971; Pacholko and Bekar, 2021; Shorter, 2009).

Results of various studies indicate that UA levels are altered in subjects with BPD in comparison to healthy controls. For instance, drug-naïve subjects with a first manic episode have higher UA levels than those of matched healthy controls (Chen et al., 2019; Salvadore et al., 2010). Similarly, in a recent study, drug-naïve subjects diagnosed with BPD for the first time have higher UA levels than those of matched healthy controls (the majority [63.4 %] of BPD patients were in a depressive episode) (Li et al., 2023). Results of a study of bipolar patients with a current episode of mania (33% of them were drug-free) and matched healthy controls corroborated that UA levels are significantly higher in the patient group (Dessoki et al., 2019). Gong et al. found that UA levels in the BPD group (consisting of subjects with manic or hypomanic or mixed or depressed episodes) were higher than those in the healthy control group (Gong et al., 2022). Results of a study suggest that both subjects in acute stages of BPD or remitted BPD have higher UA levels than healthy controls (Lu et al., 2021). In a recent study from Poland, authors found that females (but not males) with BPD in remission after a depressive or manic episode have higher UA levels than healthy controls (though, in both genders, neither acute depressive or manic episodes were associated with significantly altered UA levels) (Malewska-Kasprzak et al., 2022). However, findings of some other studies (e.g. Meng et al., 2020) suggest that the UA levels of bipolar individuals with a depressive episode do not differ from the UA levels of normal controls. Furthermore, a study from Egypt was also unable to identify a significant difference between the UA levels of subjects with BPD and healthy controls (the authors did not characterize their BPD sample in terms of episode type(s) of participants, but since all patients had moderate or severe manic symptoms according to the Young Mania Rating Scale [YMRS] it may be presumed that all subjects had a current manic episode). In addition, authors described a significant inverse correlation between the severity of manic symptoms and UA levels (Shaker et al., 2023). Similarly, a study from China did not detect significant differences in UA level between subjects with bipolar mania or bipolar depression and healthy controls (Xu et al., 2023). At the same time, findings of a meta-analysis (MA) corroborated that individuals with BPD may have higher UA levels than healthy controls (subjects with BPD could be in any phase of the disorder) (Bartoli et al., 2016b). A more recent MA corroborated that, compared to healthy controls, BPD is associated with higher levels of UA. The same MA found that BPD subjects with a manic episode or in euthymia, but not depressed BPD subjects, have higher UA levels than healthy controls (Jiménez-Fernández et al., 2021). Similarly, findings of a very recent MA, including only studies from China, indicated that UA levels are higher in subjects with BPD than in healthy controls (there were BPD subjects with manic or mixed or depressed episodes in studies that were included into that MA) (Chen et al., 2023). At the same time, results of a recent MA suggest that the UA levels of adult subjects with bipolar *depression* do not differ from those of healthy controls (Jiménez-Fernández et al., 2022). The fact that patients with BPD are at higher risk of the development of gout may also underpin the intimate link between BPD and uric acid (Chung et al., 2010).

Another line of research focused on the differences in UA levels between the two major mood disorders (e.g. BPD and MDD). For instance, results of a study indicate that bipolar subjects with mania (but not with depression) have higher UA levels than subjects with MDD (Bartoli et al., 2017b). Lu et al. found

higher UA levels 1) in bipolar depressive episodes than in unipolar depressive episodes, and 2) in subjects with BPD in remission than in subjects with MDD in remission (Lu et al., 2021). Results of two other studies also indicated that UA levels are higher in bipolar depressive episodes than in unipolar depressive episodes (Liu et al., 2022; Meng et al., 2020). By contrast, Gong et al. did not find a significant difference between bipolar depressed subjects and individuals with MDD with regard to their UA levels (however, it is unclear whether only currently depressed subjects or only remitted subjects were included in their MDD cohort or perhaps that cohort contained both currently depressed patients as well as patients in remission) (Gong et al., 2022). In the case of at least one study, UA levels were found to be higher in bipolar depression than in unipolar depression but that difference was not statistically significant (Tan et al., 2023). Furthermore, in three studies UA levels were also found to be higher in the BPD group than in the MDD group (Albert et al., 2015; Gong et al., 2022; Wu et al., 2022). In one of those studies, the BPD group consisted of subjects with depressive/manic episodes or in euthymia while patients with MDD were in euthymia (Albert et al., 2015). In another study (Gong et al., 2022), the BPD group consisted of patients with (hypo)manic or mixed or depressed episodes and it is unclear whether the presence of a current depressive episode at the time of inclusion was a requirement for the MDD subjects or not. In the case of the final study, MDD subjects probably had a *current* depressive episode (since they were required to meet the inclusion criteria of the F32 ICD-10 code), but the current state (i.e. depression vs. mania vs. euthymia) of the BPD members is not clearly described (Wu et al., 2022). Partly in line with the results discussed above, findings of a recent MA suggest that although the UA levels of subjects with bipolar depression do not differ from those of subjects with unipolar depression, after excluding a study of young subjects, UA levels in the unipolar depressed group were significantly lower than in the bipolar depressed group (Jiménez-Fernández et al., 2022). A recently published MA of studies exclusively from China, indicated that UA levels are higher in BPD than in MDD (unfortunately, BPD studies were included in the MA irrespective of the current state [i.e. mania, depression, mixed state] of the participants in them and it is also not entirely clear from the text whether MDD patients of the included studies were exclusively currently depressed or not) (Chen et al., 2023). Finally, a MA found that UA levels are higher in subjects with BPD than in subjects with MDD, but the differences between the members of the two groups with regard to their age and gender may partially affect this result (subjects with BPD could be in any phase of the disorder and it is unclear whether participants with MDD were exclusively in a current depressive episode or they were exclusively euthymic or both currently depressed and currently euthymic MDD subjects were included in the final samples of that MA) (Bartoli et al., 2016b).

Results of other investigations also indicated that UA levels may differ between different phases of BPD. Accordingly, some studies found that manic phases are more frequently associated with hyperuricaemia (or higher levels of UA) than other phases of BPD (i.e. euthymia and depression) (De Berardis et al., 2008; Gong et al., 2022; Li et al., 2022a; Lu et al., 2021; Muti et al., 2015). However, another study found that there are no relevant differences in UA levels between different phases of BPD (i.e. mania, euthymia, depression); to be more precise, only drug-naïve subjects with a first episode (hypo)mania (FEDN) have higher levels of UA compared to either UA levels of all bipolar subjects or to all manic subjects (of course subjects with FEDN were excluded from both comparison groups) (Albert et al., 2015). Although, a recent study from China detected higher mean UA levels in bipolar mania than in bipolar depression, the difference between them was insignificant (Xu et al., 2023). Results of a MA indicate that although manic/mixed episodes (compared to depressive episodes) are associated with increased UA levels, this difference has a small effect size and might be explained by between-study heterogeneity (Bartoli et al., 2016b). Similarly, findings of a very recent MA, including only studies conducted in Chinese patients, indicated that within the BPD group manic episodes are associated with higher UA levels than depressive episodes (Chen et al., 2023). Similarly, a third MA found that UA levels are higher in bipolar mania than in bipolar depression (however, there were no significant differences between the UA levels of BPD subjects with mania vs BPD subjects in euthymia) (Jiménez-Fernández et al., 2021). The finding that the add-on administration of the xanthine oxidase inhibitor allopurinol (compared to placebo) may improve the symptoms of patients with pure mania (but not with mixed episodes) may further support the notion that increased UA levels are intimately linked to the manic phases of BPD (Bartoli et al., 2021; Bartoli et al., 2017a).

Furthermore, some studies have found that UA levels decreased during the successful treatment of mania. Accordingly, an investigation among drug-naïve BPD subjects with mania found that both YMRS scores and UA levels were significantly lower than their corresponding baseline values after an 8-week pharmacological treatment of a manic episode. In addition, UA levels were significantly lower at baseline (and also after the 8-week treatment) in remitter subjects compared to non-remitter subjects (Chen et al., 2019). Results of another study also indicate that treatment is associated with a decrease of UA levels in subjects with BPD (the sample of that study consisted of subjects with manic or hypomanic or mixed or depressed episodes) (Gong et al., 2022). By contrast, a third study found that UA levels are non-significantly different in drug-treated vs. drug-free BPD subjects irrespective of the polarity of their current episode (i.e. mania or depression) (Lu et al., 2021).

It is not entirely clear whether the association between altered UA levels and BPD is causal or not. Results of a related study indicated that "most of the effect of BPD on UA levels was direct and only partially mediated by relevant metabolic parameters" (Bartoli et al., 2016a). Nevertheless, a bidirectional Mendelian randomization study found no convincing evidence for significant causal effects of UA levels on BPD or *vice versa* (Lu et al., 2022).

UA levels have also been intensively investigated in subjects with MDD. In some of these studies, UA levels of individuals with MDD were compared to those of subjects with BPD. The results of those studies were discussed above. Below we discuss only the findings of studies in which the UA levels of subjects with MDD were compared to those of normal subjects. Lower levels of UA in MDD subjects compared to normal controls have been identified by several studies (e.g. Dessoki et al., 2019; Meng et al., 2020). One of those studies found that only current (but not remitted) MDD and/or anxiety disorders are associated with lower UA levels than those of healthy controls (Black et al., 2018). However, a recent study did not detect differences in UA level between subjects with MDD in a current depressive episode or in remission and healthy controls (Lu et al., 2021). Unlike the aforementioned results, a study found that UA levels among MDD subjects were higher than those of healthy controls (and even higher UA levels were measured after the treatment of MDD) (Gong et al., 2022). Furthermore, in some other studies the levels of UA were found not to differ between healthy controls and subjects with MDD (Ait Tayeb et al., 2023; Kotan et al., 2011; Mondin et al., 2016; Shaker et al., 2023; Sohn et al., 2018; Wiener et al., 2014). Of course, the findings of meta-analyses (MA) are more relevant than the results of single studies. For instance, after excluding a study of young subjects, the results of a MA indicate that the UA levels of unipolar depressed persons are lower than those of healthy controls (Jiménez-Fernández et al., 2022). A previous MA had come to the same conclusion, having found that subjects with MDD have lower UA levels than those of healthy controls. That study also revealed that this association was significant only when untreated (drug-naïve) subjects were compared to healthy controls. However, no significant differences were detectable between treated MDD subjects and controls (Bartoli et al., 2018). A third MA corroborated that serum UA levels are negatively correlated with MDD. At the same time, that study, using the Mendelian randomization technique, came to the conclusion that there is scant evidence that the negative association between serum UA levels and MDD is causal (Chen et al., 2022). Another bidirectional Mendelian randomization study did not find significant causal effects of UA levels on the risk of MDD or significant causal effects of MDD on UA levels (Lu et al., 2022). Finally, in line with the prevailing view that MDD is associated with lower UA levels, a study of 96,989 subjects from the Danish general population showed that higher levels of UA were associated - even after controlling for potential confounders - with a decreased risk of hospitalization for depression and lower likelihood of antidepressant use (Wium-Andersen et al., 2017).

Several investigations and also MAs have been conducted to assess the effect of treatment on UA levels in MDD. Although the majority of those studies found an elevation in UA levels as a result of the treatment of MDD (Bartoli et al., 2018; Chaudhari et al., 2010; Gong et al., 2022; Jiménez-Fernández et al., 2015; Soliman and Mahdy, 2018; Wen et al., 2012), a few studies (e.g. Kotan et al., 2011) were unable to corroborate this finding.

BPD frequently begins with depressive episodes and the diagnostic criteria are identical for unipolar depressive episodes and bipolar depressive episodes. Taking into consideration these facts and also that the treatment of BPD differs from that of MDD, we may conclude that identification of the correct diagnosis of a patient with a first depressive episode (in other words, the ability to decide whether the correct diagnosis of a patient with his/her first depressive episode is BPD or MDD) would be of paramount

importance (American Psychiatric Association, 2013; Cardoso de Almeida and Phillips, 2013; Dos Santos Oliveira et al., 2019; Fountoulakis, 2015; Goldberg et al., 2001; Jiménez-Fernández et al., 2022; Wu et al., 2022). Unfortunately, there are not yet any reliable biomarkers available to help identify those subjects with their first depressive episode who later convert to BPD (Dos Santos Oliveira et al., 2019; Jiménez-Fernández et al., 2022). Due to the above discussed results on the possible differences in UA levels between BPD and MDD *in genere* and between their depressive phases *in specie*, the question may arise as to whether UA would be a possible biomarker for differentiation of BPD and MDD in subjects with a depressive episode. A retrospective study found that patients hospitalized for a depressive episode with higher UA levels at admission are at elevated risk of subsequent (hypo)manic episode(s) and, accordingly, to bipolar conversion (Dos Santos Oliveira et al., 2019). Another study found that UA level was able to significantly distinguish MDD from BPD in subjects with acute depressive stages and also in remitted individuals (Lu et al., 2021). Furthermore, several studies by the same Chinese research group investigated whether UA, as one element in a larger set of biochemical markers, is able to differentiate BPD from MDD (due to space limitations we have not discussed their results; interested readers are referred to the original papers) (Niu et al., 2022; Wu et al., 2022; Zhu et al., 2022a; Zhu et al., 2022b).

Affective temperaments measured by Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A) are considered subsyndromal manifestations and harbingers of major mood disorders. Subjects with MDD typically have a depressive (DE) temperament, while patients with BPD exhibit higher scores on cyclothymic (CT), hyperthymic (HT) and irritable temperament (IT) subscales of TEMPS-A than subjects with MDD (Belteczki et al., 2021; Karam et al., 2023; Rihmer et al., 2010). In line with the above discussed results on higher UA levels in BPD and lower UA levels in MDD, a study found that high UA levels are associated with HT and IT scores, whereas low UA levels are associated with DT scores (Kesebir et al., 2014). Furthermore, an earlier study using a different scale for the assessment of affective temperaments from TEMPS-A found a trend-level correlation between UA levels and HT and IT among males and found that women in the higher tertile of UA levels more often have HT and IT than those with lower UA levels (Lorenzi et al., 2010).

DISCUSSION

Major mood disorders (i.e. MDD and BPD) represent a considerable public health burden worldwide. In the current paper we have discussed various neurobiological theories of mood disorders with a special focus on the oxidative stress (OS) hypothesis and, related to that, have reviewed investigations on alterations of uric acid (UA; a non-enzymatic antioxidant agent) levels in mood disorders. According to our review of relevant papers, results so far suggest that, compared to healthy controls, subjects with BPD (especially if they are not in a depressive phase) have higher levels of UA. On the other hand, subjects with MDD seem to have lower UA levels than those of healthy controls. Furthermore, findings also indicate that subjects with BPD have higher UA levels than individuals with MDD. It is worth noting that results point to the direction that UA levels of unipolar depressed subjects are significantly lower than among bipolar depressed individuals. In that context, some findings also suggest that depressed subjects with higher UA levels are at elevated risk of bipolar conversion. If future studies confirm that major depressive episodes in the context of BPD (vs major depressive episodes in the context of MDD) are associated with higher UA levels, it would mean that an easily measurable biomarker would become available to help distinguish MDD from BPD. This would be of particular importance, since the symptoms of a major depressive episode are the same in both diseases, but their therapy is different.

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Az oxidatív stressz szerepe a major hangulatzavarok patomechanizmusában: narratív review különös tekintettel a húgysav szerepére

A súlyos hangulatzavarok (azaz a major depresszív zavar [MDD] és a bipoláris zavarok [BPD]) a leggyakoribb, súlyos funkciókárosodással együtt járó mentális betegségek közé tartoznak. Ezen kórképek etiopatogenezisét számtalan – egymással gyakran összefonódó – teória (pl. a monoamin-, a neuroinflammációs és a neurotrofikus elméletek) igyekszik megmagyarázni. Egy kevésbé ismert elmélet az oxidatív stressz (OS; azaz a szabadgyökök túltermelődése és felhalmozódása) szerepét veti fel eme betegségek kialakulásában. A szabadgyökök képesek károsítani a foszfolipideket, a többszörösen telítetlen zsírsavakat, a fehérjéket és a nukleinsavakat. Az agyban az OS károsítja, többek között, a szinaptikus jelátvitelt és a neuroplaszticitást. Áttekintő tanulmányunkban vázlatosan tárgyaljuk a hangulatzavarok fő patofiziológiai elméleteit, majd ezt követően részletekbe menően diszkutáljuk az OS hipotézist. Ezután áttekintjük egy non-enzimatikus antioxidáns, a húgysav, szintjének a súlyos hangulatzavarokban való változásairól szóló tanulmányok eredményeit. Az eddig történt ezirányú vizsgálatok alapján úgy tűnik, hogy a húgysavszint – mely egy egyszerű rutinlabor-vizsgálat során is beszerezhető –egy potenciális biomarker lehet az MDD és a BPD elkülönítésére. Mivel az MDD és a BPD depressziós epizódjainak a diagnosztikai kritériumai azonosak, de a két kórkép kezelése eltérő, így az olyan biomarkerek azonosítása, melyek képesek elkülöníteni az MDD-t a BPD-től nagy klinikai jelentőséggel bírhat.

Kulcsszavak: major depressziós zavar, bipoláris zavar, agy, oxidatív stressz, húgysav