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Review article

Medical comorbidity in bipolar disorder: The link with metabolic-inflammatory systems

Ana SayuriYamagata[a,b], Elisa Brietzke[b], Joshua D. Rosenblat[c], Ron Kakar[c], Roger S. McIntyre[c,*]

[a] University of São Paulo (USP), São Paulo, Brazil
[b] Research Group in Molecular and Behavioral Neuroscience of Bipolar Disorder, Federal University of São Paulo (Unifesp), São Paulo, Brazil
[c] Mood Disorders Psychopharmacology Unit (MDPU), University Health Network (UHN), University of Toronto, Toronto, Canada

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ABSTRACT

Background: Bipolar disorder (BD) is associated with chronic low-grade inflammation, several medical comorbidities and a decreased life expectancy. Metabolic-inflammatory changes have been postulated as one of the main links between BD and medical comorbidity, although there are few studies exploring possible mechanisms underlying this relationship. Therefore, the aims of the current narrative review were 1) synthesize the evidence for metabolic-inflammatory changes that may facilitate the link between medical comorbidity and BD and 2) discuss therapeutic and preventive implications of these pathways.
Methods: The PubMed and Google Scholar databases were searched for relevant studies.
Results: Identified studies suggested that there is an increased risk of medical comorbidities, such as autoimmune disorders, obesity, diabetes and cardiovascular disease in patients with BD. The association between BD and general medical comorbidities seems to be bidirectional and potentially mediated by immune dysfunction. Targeting the metabolic-inflammatory-mood pathway may potential yield improved outcomes in BD; however, further study is needed to determine which specific interventions may be beneficial.
Limitations: The majority of identified studies had cross-sectional designs, small sample sizes and limited measurements of inflammation.
Conclusions: Treatment and prevention of general medical comorbidities in mood disorders should include preferential prescribing of metabolically neutral agents and adjunctive lifestyle modifications including increased physical activity, improved diet and decreased substance abuse. In addition, the use of anti-inflammatory agents could be a relevant therapeutic target in future research.

1. Introduction

Bipolar disorder (BD) is associated with significant morbidity and mortality with an estimated reduction in life expectancy of 12–20 years for men and 11–17 years for women compared to the general population (Laursen et al., 2013). Although individuals with BD are at an elevated risk of suicide (Cassidy, 2011), elevated rates of medical comorbidities (primarily cardiovascular disease) is believed to be the primary reason for the observed decrease in life expectancy in BD (Kessing et al., 2015). Mortality secondary to cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease, influenza and pneumonia is more common in BD than in the general population (Crump et al., 2013). Cardiovascular disease is the leading cause of death in BD (Weiner et al., 2011) with a significantly increased prevalence in comparison with both matched healthy controls and subjects with other psychiatric illnesses (Parikh et al., 2010). Although iatrogenic metabolic effects of psychopharmacological treatment for BD can be partially responsible for the increase of cardiovascular disease and mortality (Kessing et al., 2015), they are not the sole cause of increased rates of metabolic and cardiovascular disease, as excessive weight gain and impairment in glucose metabolism may occur even in the absence of pharmacotherapy (Allison et al., 2009; Birkenaes et al., 2007).

General medical comorbidities (GMC) in BD also have a significant impact in morbidity, case complexity, cost of treatment and workplace disability. BD patients with three or more medical comorbidities have more rapid cycling, suicidal behavior, acute onset of mood episodes, poorer functioning, higher rates of anxiety disorder and treatment with anxiolytics and mood stabilizers compared with those with no history of medical illness (Forty et al., 2014). In addition, obesity, a chronic

* Correspondence to: Mood Disorders Psychopharmacology Unit (MDPU), University Health Network (UHN), University of Toronto, 399 Bathurst Street, MP 9-325, Toronto, ON, Canada M5T 2S8.
E-mail address: roger.mcintyre@uhn.ca (R.S. McIntyre).

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low-grade inflammatory disorder, is associated with cognitive dysfunction in BD with impairments in attention and psychomotor skills (Calkin et al., 2009; Goldstein et al., 2011; McIntyre et al., 2008; Yim et al., 2012); while type 2 diabetes mellitus (T2DM) is associated with higher frequency of the rapid cycling subtype, more chronic course, disability and impaired functionality in BD (Calkin et al., 2015; Hajek et al., 2005; Ruzickova et al., 2003).

Currently, several aspects of the pathophysiology of BD remain poorly understood, and possible reasons for the high prevalence of GMC are largely unknown. Several studies have shown increased inflammatory cytokines levels in the serum (Modabbernia et al., 2013) and neuroinflammatory markers in the cerebral spinal fluid (CSF) in BD patients (Söderlund et al., 2011; Rolstad et al., 2015) compared to healthy control as well as pathological evidence of inflammation in the frontal cortex in *post-mortem* samples of patients with BD (Rao et al., 2010; Bezchlibnyk et al., 2001). These observed alterations in inflammatory markers suggest that immune dysfunction may be an important mechanistic link between BD and metabolic/inflammatory comorbidities. Interestingly, Bond et al. (2016) observed that, besides indicating depressive relapse, BMI was a stronger predictor of inflammation than recent mood episodes. Additionally, factors of metabolic syndrome were accompanied by plasma levels of c-reactive protein (CRP) and transforming growth factor-beta (TGF-beta) after beginning of pharmacotherapy in BD-II (Lee et al., 2013). These studies have suggested that dysfunction of the immune system may be a key link between GMC and BD whereby immune dysfunction may be increasing the morbidity and mortality of BD (Rosenblat and McIntyre, 2015).

In addition, immune-inflammatory mediators seem to influence pathways involved in mood, motivation, psychomotor activity and cognition. In humans, tryptophan is an essential amino acid that is a required substrate for serotonin synthesis. However, about 95% of the tryptophan is metabolized via the kynurenine pathway and the limiting step of this reaction in the enzyme indoleamine 2,3-dioxygenase (IDO). Pro-inflammatory cytokines transcriptionally induce IDO in a variety of immune cells, including microglia, reducing the availability of tryptophan for serotonin synthesis. Because of this direct alteration of monoamine levels by inflammatory cytokines, inflammatory activation has been hypothesized as a possible contributor in mood disorders (Maes et al., 2011; Noto et al., 2014).

As the association between BD and GMC is a significant factor in morbidity and mortality, and immune dysfunction may mediate this association, it is important to understand the mechanisms involved in this interaction as well as the potential treatment implications these mechanisms may offer. Therefore, the aims of this narrative review were to 1) summarize and synthesize the role of metabolic-inflammatory abnormalities in GMC in BD and 2) discuss therapeutic and preventive implications of these mechanisms.

2. Methods

PubMed/Medline and Google Scholar databases used to search for relevant articles published from inception to August 2015. The keywords used to browse are related to the main topics and include combinations of the following: “bipolar disorder”, “metabolic syndrome”, “gene”, “autoimmunity”, “stress”, “allergy”, “inflammation”, “oxidative stress”, “obesity”, “diabetes”, “insulin resistance”, “gut microbiota”, “substance use disorder”, “childhood trauma”, “iatrogenic effects of atypical antipsychotics”, “exercise”. Reference lists for identified articles were manually searched for additional pertinent studies. Identified studies were synthesized to provide a meaningful narrative of the topic rather than provide an exhaustive review of the literature that systematically identified and described every potentially relevant study.

3. Results

3.1. Epidemiology of inflammatory comorbidities in BD

Several epidemiological studies have documented high rates of inflammatory comorbidities in BD (Rosenblat and McIntyre, 2015).

3.1.1. Auto-immunity

Bipolar Disorder is strongly associated with autoimmune diseases, including Guillain-Barré Syndrome (GBS), autoimmune hepatitis, multiple sclerosis (MS), rheumatoid arthritis, systemic lupus erythematosus, psoriasis and autoimmune thyroiditis (Hillegers, et al., 2007). Of these disorders, thyroid disease has the strongest association. Although lithium treatment was suspected to have created a bias in this observed association, given the potential effects of lithium on thyroid hormones (Myers et al., 1985; Wilson et al., 1991), several studies have shown that BD may also be associated with thyroid disease independent of lithium use (Haggerty et al., 1990; Kupka et al., 2002). Thyroid autoimmunity may contribute to rapid cycling and compromise treatment response (Hendrick et al., 1998; Oomen et al., 1996). Additionally, immune changes towards other various autoimmune diseases were reported, including inclination to Th1, low T regulatory cells, senescence-related cell types (do Prado et al., 2013) and higher titles of autoantibodies (Sidhom et al., 2012).

3.1.2. Hypersensitivity

Allergy is defined as elevated reactivity to innocuous antigens and may also contribute to increased risk of developing BD and worse course of disease or vice-versa. For example, hypersensitivity reaction during high pollen season worsens depressive symptoms in BD (Manalai et al., 2012; Postolache et al., 2007); and adolescents with asthma have 2.2 times greater risk to develop BD in adult life than healthy controls. In addition, occurrence of allergy increases the risk of metabolic syndrome in individuals with severe mental illnesses, including BD (Chen et al., 2014).

3.1.3. Chronic low-grade inflammation from metabolic syndrome

Inflammation can be understood as a reaction of tissue repair and protection and is engendered initially by the innate immune system. Metabolic syndrome has been defined by a cluster of metabolic risk factors for cardiovascular disease and insulin resistance, such as hypertension, hyperglycemia, dyslipidemia and obesity. A persistent low-grade level of inflammation is common among numerous medical conditions, including metabolic syndrome (MetS) (Ridker et al., 2003). Higher incidence of MetS in BD has been well-documented (Chauvet-Gelinier et al., 2012; Czepielewski et al., 2013; Fagiolini et al., 2008, 2005; McElroy and Keck, 2014; McIntyre et al., 2010; Sicras et al., 2008;)(Wysokinski et al., 2015). As shown by Sicras et al. (2008), 24.7% of individuals with BD have some form of metabolic disease, while the percentage for the general population is 14.4% (Sicras et al., 2008). Additionally, BD is more prevalent among individuals with obesity than without (Zhao et al., 2016). Patients with BD have higher blood glucose compared to healthy controls; and it rises progressively with age (Wysokinski et al., 2015). The risk of developing T2DM is three times higher in BD than in healthy controls (Cassidy et al., 1999; Lilliker, 1980; McIntyre et al., 2005).

3.2. Proposed mechanisms linking immune-inflammatory dysfunction and GMC in BD

Explanations for the persistent activation of the immune system in BD and in its impact on general health may involve several factors, both known and unknown. Inflammation induced by MetS may act synergistically with other factors and worsen the course of BD. In obesity, hypertrophied adipocytes produce more leptin and less adiponectin and have infiltration of macrophages leading to systemic

inflammation (Mathieu et al., 2010). High density lipoprotein (HDL) acts as anti-inflammatory agent, for example, by decreasing the secretion of TNF-α and IL-1β from activated monocytes (Rye and Barter, 2008); while HDL is low in dyslipidemia. Also, pro-inflammatory cytokines and high levels of free fatty acids promote insulin resistance (Chang-Chen et al., 2008). The inflammation present in BD may increase the risk of MetS. To date, it is unclear which exact mechanisms occur, although, several biologically plausible mechanisms have been elucidated. Indeed, BD may enhance immune dysfunction via several mechanisms; herein, mechanisms of greatest interest are discussed.

3.2.1. Genetics

Few studies have investigated genetic alterations in inflammation-related comorbidities and BD, but preliminary results suggest that BD patients might carry genotypes prone to inflammation. Compared to healthy individuals, BD patients have more genetic alterations in genes strictly related to pathways of IL-6, IL-8 and interferon (INF) (Drago et al., 2015). From 13 genes associated with BD, *CASP1* and *STAT* were highlighted. *CASP1* is responsible for the production of IL-1β (Vasilakos and Shivers, 1996); and *STAT* encodes for a transcriptional factor that takes part in inflammatory responses (Brierley and Fish, 2005). Genetic variations in receptors of innate immunity are also present in BD. The TLR-4 rs1927914 A and TLR-4 rs11536891 T alleles in homozygosity are more frequent in BD, especially in early onset, compared to controls; and such difference may be related to reduction in efficiency in defence against pathogens (Oliveira et al., 2014a). Additionally, there is low prevalence of *NOD2* rs2066482 polymorphism in BD (Oliveira et al., 2014b), which may explain an association between Crohn's Disease and BD and earlier onset of inflammatory bowel disease (IBD) in patients with BD compared with those IBD patients without lifetime history of a mood disorder (Walker et al., 2008). Interestingly, the Val66Met polymorphism in the BDNF gene, which is associated with suicidal ideation (Kim et al., 2008) and higher sensitiveness to stress (Hosang et al., 2010) in BD patients, is also correlated with increased body mass index (BMI) in individuals without mood disorders (Shugart et al., 2009).

3.2.2. Psychological stress

Dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis is frequent in BD (Taylor and MacQueen, 2006). Several studies have shown alterations in peripheral cortisol levels in BD subjects during periods of euthymia, depression and mania, compared to controls (Cervantes et al., 2001); and cortisol levels are higher in patients with rapid cycling (Havermans et al., 2011), suicidal behavior (Kamali et al., 2012) or multi-episodic course (Fries et al., 2015). Chronic HPA activation could lead to abnormal glucocorticoids signaling in BD patients (Spiliotaki et al., 2006) and blunted cortisol response has been reported in BD (Daban et al., 2005). Glucocorticoid receptor (GR) activation has anti-inflammatory effects; however, chronic stress can result in GR resistance preventing the negative feedback loop of the immune response (Cohen et al., 2012). Moreover, IL-1, IL-6, TNF-α and IFN-α, inflammatory cytokines leads to chronic hypercortisolemia by preventing the negative feedback loop, which usually decreases HPA activity when increased levels of cortisol is detected (Pace and Miller, 2009). Hypercortisolemia has been shown to have several endocrine and metabolic implications including weight gain (Gregoire et al., 1991), insulin resistance (Berrettini et al., 1985; Murphy, 1991) and hypothyroidism (Tsigos and Chrousos, 2002), with strong associations to BD (Cole et al., 2002).

Childhood maltreatment and early childhood adversity are considered significant risk factors for elevated inflammatory cytokines and BD. Within adult BD patients, more than half report experiences of severe abuse during their childhood (Garno et al., 2005); and these subpopulation seems to be more prone to early onset (Garno et al., 2005), rapid cycling (Garno et al., 2005; Leverich and Post, 2006), psychotic symptoms (Hammersley et al., 2003) and suicide attempts (Brown et al., 2005; Garno et al., 2005; Leverich and Post, 2006). The immune system and the brain are not yet fully developed and have the highest plasticity during early life and thus can be profoundly affected by psychological stress. Impairments in neuroplasticity resulting from epigenetic modifications (Klengel et al., 2013; Labonte et al., 2012; McGowan et al., 2009; Mehta et al., 2013; Perroud et al., 2011; Tyrka et al., 2012), could be responsible for maintained activation of inflammatory changes (Miller et al., 2009; Pace et al., 2007; Zunszain et al., 2011). In individuals with or without depression, childhood trauma is associated with increased inflammatory reactivity after psychological stress compared to individuals who did not have such experience (Pace et al., 2006; Carpenter et al., 2010). Moreover, childhood trauma could also lead to impairment in signaling of glucocorticoid receptor and HPA axis hyperactivity (Weaver et al., 2004; Klengel et al., 2013; Pervanidou, 2008; Trickett et al., 2010), which decreases the ability of cortisol to decrease inflammation.

Additionally, childhood trauma has been associated with factors that increase inflammation, such as gut microbiota imbalance, sleep disturbance, alcohol and substance use (Danese and Lewis, 2016), autoimmune diseases (Dube et al., 2009) and metabolic syndrome (De Bellis et al., 1994; Lee et al., 2014a; Pervanidou and Chrousos, 2012), including obesity (Gunstad et al., 2006; Midei et al., 2010; Noll et al., 2007; Thomas et al., 2008; Von Korff et al., 2009; Williamson et al., 2002) and diabetes (Goodwin and Stein, 2004).

3.2.3. Substance use

Comorbid substance use disorders (SUD) are highly prevalent in BD and are associated with a negative impact on the BD illness course. Approximately 58% of BD-I patients had alcohol use disorder (AUD) and 37.5% had drug use disorder (DUD) in a large-scale observational study (Grant et al., 2005). Rates of smoking is also elevated which further increases inflammation, oxidative and nitrosive stress (Chitty et al., 2014; Li and Wang, 2004; Mendez-Alvarez et al., 1998; Odebrecht Vargas Nunes et al., 2014; Zhang et al., 2007). The induced increase in IgE and the cytokines TNF-α, IL-1, IL-6 and IL-8 by tobacco promote conditions for both immunosuppression and autoimmune disorders (Arnson et al., 2010).

Bipolar disorder is metabolically affected by alcoholism. Alcohol misuse has been implied in reduced production of anti-inflammatory cytokines, such as IL-10 (Hill et al., 2002; Le Moine et al., 1995; McClain et al., 2002), which is correlated with elevated synthesis of TNF-α by monocytes (McClain and Cohen, 1989). Additionally, alcohol increases IL-6 and activation of Nuclear Factor Kappa B (NFκ-B), a transcription factor involved in maintenance of inflammatory response (Crews and Nixon, 2009). Alcohol abuse also causes higher central adiposity, contributing to maintaining a chronic pro-inflammatory state. Alcohol use also has significant effects on mood symptoms, even in the context of moderate consumption (Castaneda et al., 1996; Chitty et al., 2014). In addition, alcohol has the property to disrupt the blood-brain-barrier, allowing increased brain exposure to cellular mediators of inflammation, potentially contributing to the pathophysiology of mood disorders and suicide (Reeves et al., 2007).

3.2.4. Gut microbiota changes

Considering current information about the function of gut microbiota in neurobiology and metabolic health, it is possible that commensal bacteria may be a factor for activation of inflammation in BD and GMC. Penetration of bacteria across the gut epithelium may also result in chronic low-grade inflammation, which further induces MetS, as previously discussed by Chassaing and Gewirtz (2014) based on animal studies. “Leaky gut” was observed in MDD, with increased concentrations of IgM and IgA as a defence induced by the endotoxin lipopolysaccharide (LPS) (Maes et al., 2008); however, this has yet to be replicated in a BD sample. Alternatively, healthy humans have enhanced anxiety and depression, elevated plasma norepinephrine,

salivary cortisol and pro-inflammatory cytokines after administration of LPS (Grigoleit et al., 2011). In addition, dysfunction in gut microbiota may be associated with inflammation and metabolic syndrome in a bidirectional interaction (Ley et al., 2005; Turnbaugh et al., 2006). According to DiBaise et al. (2008), intestinal microbiota is the likely mediating factor between inflammation and MetS induced by a high fat diet (DiBaise et al., 2008). For example, *Escherichia coli* may infiltrate the intestinal barrier and lead to low-grade systemic inflammation (Devkota et al., 2012; Ding et al., 2010). Therefore, dysbiosis in the intestine is probably another relevant factor contributing to worse course of BD and GMC through inflammation.

3.2.5. Mood episodes as immune-inflammatory challenges

Recently, it was postulated by some authors that mood episodes may act as cause of toxicity and consequent inflammation (Kapczinski et al., 2010, 2011). This idea is supported by replicated evidence indicating a strong inflammatory state during mood episodes, especially during mania, compared to depressive states, and euthymia. Several original studies and some meta-analysis support the association between mania and a strong pro-inflammatory state, especially in unmedicated patients (Modabbernia et al., 2013). Euthymia and long-term treatment with lithium are associated with at least partial reversion of these abnormalities (Van Den Ameele et al., 2016).

While in the beginning of BD course, euthymia periods are putatively associated with reversion of immune-inflammatory changes, in multi-episodic illness there will be an accumulation of these effects with time (Kauer-Sant'Anna et al., 2009; Andreazza et al., 2009), imposing a permanent challenge for the immune system. A chronic immunological challenge can exhaust the ability to adapt to varying conditions and return to homeostasis. The result is, besides enduring inflammation, impaired functioning of the adaptive immune system including weak responses to vaccines and increased vulnerability to infections, usually found in aging. Interestingly, our group found preliminary evidences of accelerated aging of the immune system (immunosenescence) in BD (do Prado et al., 2013; Rizzo et al., 2013), which were more pronounced in individuals with a history of multiple mood episodes.

Interestingly, adipose tissue has been receiving attention recently in the field of inflammation in mood disorders. Adipokines, cytokines secreted by adipose tissue has been evaluated in BD, especially adiponectin, resistin and leptin. Barbosa and collaborators (2012) reported that patients with BD had increased plasma levels of adiponectin and leptin compared to healthy volunteers (Barbosa et al., 2012). In addition, in BD population, adiponectin levels were correlated with fasting glucose, fasting insulin, C-peptide, homeostatic model assessment-insulin resistance, HDL cholesterol levels, VLDL cholesterol levels and triglycerides levels. After adjustment for age, gender and BMI, individuals with BD and low adiponectin levels (i.e. < 7.5 μg/ml), had a significantly higher number of mood episodes, higher severity of depressive symptoms and lower levels of functioning. The authors concluded that, adiponectin levels, either directly or as a proxy of metabolic dysfunction, is independently associated with an unfavorable course of illness in BD (Mansur et al., 2016).

3.3. Targeting inflammation to treat and prevent GMC in BD

3.3.1. Prevention of iatrogenic metabolic dysfunction

Antipsychotic medication commonly used in the treatment of BD have been shown to have a deleterious impact in metabolic parameters causing higher risk of obesity (2.5 times) (Chagnon et al., 2004), glucose dysregulation (Hasnain et al., 2012), dyslipidemia (Newcomer, 2007), and weight gain (Allison et al., 1999; Hasnain et al., 2012). However, some authors suggest no contribution of psychotropic drugs to increase mortality in psychiatric patients (Khan et al., 2013). Metabolic effects of second generation anti-psychotics (SGAs) may be classified as high risk (clozapine and olanzapine), medium risk (iloperidone, paliperidone, quetiapine and risperidone) and low risk (aripiprazole, asenapine, lurasidone and ziprasidone) (Hasnain et al., 2012). Lithium and valproate are associated with weight gain as well (Chengappa et al., 2002); and obese patients have a higher risk of medication induced weight gain (Bowden et al., 2006; McIntyre et al., 2011; Sachs et al., 2006). Valproate may cause weight gain and possibly increased cravings for fatty foods (Martin et al., 2009; Bowden et al., 2000; Dinesen et al., 1984; Tohen et al., 2003). Nevertheless, metabolic side-effects are just one aspect that should be taken into account in medication choosing process in BD. In the risk-benefit analysis, balancing effectiveness with safety and tolerability, it could be justified to use a drug associated with metabolic side effects, such as the case of clozapine for treatment-resistant patients or lithium for its high efficacy and suicide prevention.

3.3.2. Treating BD and comorbidities simultaneously

The data obtained from the literature suggest the relevance of considering the diagnosis and treatment of GMC simultaneously with the management of psychiatric aspects of BD. This simultaneous treatment could not only improve the outcome of the treatment with psychotropic drugs, but probably also decelerate the progression of the disease, since GMCs were observed to be associated with chronic and progressive courses of BD.

Obesity is a predictor of inflammation and treatment resistance to mood stabilizers such as lithium and valproate (Kemp et al., 2010) (Calkin et al., 2009; Kemp et al., 2010). Resistance to lithium was also reported in diabetic and insulin resistant BD patients (Calkin et al., 2015); and there is a trend toward treatment resistance (Ruzickova et al., 2003). In this case, we can hypothesize that reducing BMI could potentially improve response to those mood stabilizers.

3.3.3. Anti-inflammatory medications

In a recent meta-analysis by our group, adjunctive anti-inflammatory agents were shown to have antidepressant effects in BD (Rosenblat et al., 2016). Eight RCTs (n=312) assessing adjunctive nonsteroidal anti-inflammatory drugs (n=53), omega-3 polyunsaturated fatty acids (n=140), N-acetylcysteine (n=76), and pioglitazone (n=44) in the treatment of BD were included in the quantitative analysis. The overall effect size of adjunctive anti-inflammatory agents on depressive symptom severity was −0.40 (95% confidence interval −0.14 to −0.65, p=0.002), indicative of a moderate and statistically significant antidepressant effect. Of note, most studies included in this meta-analysis had small sample sizes and short trial durations, a design that tends to overestimate treatment effects. Nevertheless, this meta-analysis provided a proof-of-concept that additional, more robust studies evaluating immune-modulating agents for BD were merited. Identification of subgroups that are more prone to respond to adjunctive anti-inflammatory treatments may also be of great value.

Some studies indicate improved efficacy of lithium or atypical antipsychotic when augmented by non-steroidal anti-inflammatory drugs (NSAIDs), Acetyl Salicylic Acid (ASA) and celecoxib (COX-2 inhibitor) in BD, with the potential for decreased depressive symptoms and decreased relapse and recurrence rates (Stolk et al., 2010; Nery et al., 2008). Interestingly, case-reports of BD patients treated for psoriasis with infliximab, a monoclonal anti-TNF-α antibody, show improvement in mood symptoms (Bassukas et al., 2008); and infliximab for Crohn's disease improved psychiatric symptoms in a patient with a psychotic episode (Reimer et al., 2009). Moreover, in a large cohort study, the use of sulfonylurea and metformin was associated with a decreased risk of T2D patients to develop an affective disorder (Wahlqvist et al., 2012). The antidepressant effect of rosiglitazone was reported in murine models (Eissa Ahmed et al., 2009; Sharma et al., 2012) and in humans with unipolar or bipolar depression (Rasgon et al., 2010). Likewise, pioglitazone was recently shown to have an antidepressant effect in MDD and BD with (Kemp et al., 2014a) or without MetS (Sepanjnia et al., 2012; Zeinoddini et al., 2015), without

any serious adverse effects. However, it is necessary to be aware of risks of combination of medications, such as lithium with NSAIDs (Sharma et al., 2014).

3.3.4. Physical exercise

BD patients usually have reduced frequency and intensity of physical activity (Elmslie et al., 2001; Janney et al., 2014; Kilbourne et al., 2007; Shah et al., 2007), although antidepressant properties of exercise might be beneficial in the management of BD, in addition to effects in improvement of metabolic parameters and cardiorespiratory status (Abdelhafiz and Sinclair, 2015; Church et al., 2007; Cornelissen and Fagard, 2005; Sari-Sarraf et al., 2015). Weight loss is generally associated with increased BDNF levels and decrease in depressive symptoms severity (Lee et al., 2014c). Subjects with BD, MDD and schizophrenia that underwent a program of dietary changes, exercise and modules of wellness had lower waist circumference and better mental health after the trial (Van Citters et al., 2010). Another study with a similar intervention reported reduction in weight, total cholesterol, triglycerides and glucose as well as improvement in depression in BD patients (Sylvia et al., 2013).

3.3.5. Balance in gut microbiota

It is possible that the gut microbiota has a role in the pathophysiology of BD, although research on the gut-brain-axis is in its infancy. Prebiotics increase expression of BDNF and NMDA (Savignac et al., 2013) and ameliorate characteristics of immune dysfunction in BD, for instance more self-tolerance and less hypersensitivity, by increase in Treg (van Vlies et al., 2012) and an improved immune response (Vulevic et al., 2008). The production of short chain fatty acids (SCFA) by symbiotic bacteria is important in reduction of inflammation (Hamer et al., 2008), insulin resistance (Brandsma et al., 2015) and protection of integrity of the blood-brain barrier in mice (Braniste et al., 2014). Moreover, administration of four probiotics (*Bifidobacterium animalis subsp. lactis*, *Streptococcus thermophiles*, *Lactobacillus bulgaricus*, and *Lactococcus lactis subsp. lactis*) improved brain connectivity and emotional processing in healthy women (Tillisch et al., 2013); two of those probiotics (*Lactobacillus and Bifidobacterium*) reduced stress and anxiety in healthy humans (Messaoudi et al., 2011); and *Bifidobacterium* reduced stress also in mice (Sudo et al., 2004).

4. Conclusion

General medical comorbidities in BD are not just a sum of different factors, but rather an intricate combination of pathways acting synergistically and redundantly making a negative effect in the course of BD. The role of inflammatory changes in GMC in BD could be causal (with BD leading to inflammation and these changes leading to GMC), consequential (with GMC, especially MetS, increasing vulnerability and impacting negatively the course of BD) or as two expressions of the same set of causes (with immune dysfunction leading to both BD and GMC).

Because of higher illness severity in BD patients with GMCs, it may be helpful to prioritize physical activity and the use of medications with less risk of MetS in order to avoid iatrogenic effects. Moreover, anti-inflammatory medications may be of benefit, however, more research is needed to confirm or refute their efficacy in BD. Finally, treating BD and GMCs simultaneously is merited to enhance treatment outcomes for both. Further study is merited to further the understanding of the underlying mechanisms and consequences of such interventions.

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