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Bipolar disorder and the endocannabinoid system

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Perspective

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Abstract

Objective Bipolar disorder (BD) is a debilitating, lifelong neuropsychiatric illness characterised by unsteady mood states which vacillate from (hypo)mania to depression. Despite the availability of pharmaceutical agents which can be effective in ameliorating the acute affective symptoms and prevent episodic relapse, BD is inadequately treated in a subset of patients. The endocannabinoid system (ECS) is known to exert neuromodulatory effects on other neurotransmitter systems critical in governing emotions. Several studies ranging from clinical to molecular, as well as anecdotal evidence, have placed a spotlight on the potential role of the ECS in the pathophysiology of BD. In this perspective, we present advantages and disadvantages of cannabis use in the management of illness course of BD and provide mechanistic insights into how this system might contribute to the pathophysiology of BD. *Results* We highlight the putative role of selective cannabinoid receptor 2 (CB_2) agonists in BD and briefly discuss findings which provide a rationale for targeting the ECS to assuage the symptoms of BD. Further, data encourage basic and clinical studies to determine how cannabis and cannabinoids (CBs) can affect mood and to investigate emerging CB-based options as probable treatment approaches. *Conclusion* The probable role of the ECS has been almost neglected in BD; however, from data available which suggest a role of ECS in mood control, it is justified to support conducting comprehensive studies to determine whether ECS manipulation could positively affect BD. Based on the limited available data, we suggest that activation of CB_2 may stabilise mood in this disorder.

Summations

- Bipolar disorder (BD) may be a disorder of the entire body and not just the brain.
- Cannabis can affect age of onset of BD, severity, and the number of affective episodes. Both arachidonic acid (AA) and inflammatory mediators can play a part in the pathophysiology of BD.
- A proposed new treatment strategy of selective activation of cannabinoid receptor 2 (CB_2) and antagonism of ***cannabinoid receptor 1 (CB_1)*** may alleviate the symptoms of BD and should be rigorously explored.

Perspectives

1. The role of endocannabinoid system (ECS) in mood control and BD is suggested based on scant available data; however, data from these studies warrant more comprehensive studies, which are essential to empirically test whether ECS is involved in mood and to determine the mechanisms of action for ECS in regulation of affect. Although there is a surge in research on CB_s, the possible role of the ECS in neuropsychiatric disorders, especially BD, has almost been neglected. Thus, there is an unmet need for conducting more clinical investigations of agents which affect the ECS in bipolar patients in order to pursue other treatment strategies than those currently available to normalise mood.
2. The lipophilic nature of the CB ligands, as well as their long biological half-life, confers the ability to cross the blood–brain barrier easily. Further, their high therapeutic index reduces the risk of overdose in BD patients which is highly relevant in the management of the BD population.
3. Selective activation of CB_2 could provide mood stabilisation by suppressing AA turn over, which is a mechanism common to various types of currently available mood stabilisers.

Introduction

Bipolar disorder (BD) is a debilitating lifelong neuropsychiatric disorder that is characterised by unstable high and low episodes of moods which swing between the extremes of (hypo)mania and depression. Extremes in the mood state tend to alternate in a cycle and are usually punctuated by periods of remission (Oswald *et al.*, 2007; Fagiolini *et al.*, 2013; Arjmand *et al.*, 2017). BD takes a heavy toll and influences most aspects of the life of those who suffer from this disease with negative effects on their personal relationships, their social interactions, their performance in the workplace, and their ability to pursue educational goals (Leclerc *et al.*, 2013).

Lithium is a commonly used approach in the pharmacological toolbox for the management of BD, which remains popular some 70 years after its introduction. Along with this gold standard treatment approach, other mood stabilisers including sodium valproate, carbamazepine, lamotrigine, and atypical antipsychotics, such as quetiapine and olanzapine, have been broadly used to alleviate the symptoms of both (hypo)mania and depression (Ashton *et al.*, 2005; Shorter, 2009; Rapoport, 2014; Sportiche *et al.*, 2016). Despite possessing a wide range of compounds with diverse mechanisms of action with which to ameliorate the acute affective symptoms and preclude episodic relapse, BD is sometimes inadequately treated (Ashton *et al.*, 2005).

Both serotonergic (Burokas *et al.*, 2014) and dopaminergic transmissions play a prominent role in the pathophysiology of neuropsychiatric disorders, and the fact that these systems are modulated by the endocannabinoid system (ECS) suggests examination of this system to potentially facilitate developing a new target to better control mental illnesses including BD (Van Der Stelt & Di Marzo, 2003; Arjmand *et al.*, 2017; Ashok *et al.*, 2017).

The ECS is comprised of cannabinoid (CB) receptors, endogenous lipid ligands, as well as enzymes which are in charge of both endocannabinoid synthesis and degradation that together play a neuromodulatory role in the central nervous system (CNS) (Arjmand *et al.*, 2015; Lu & Mackie, 2016). CB receptors are in a class of G protein-coupled receptors and are divided into two main subtypes, CB receptor types 1 and 2 (CB_1 and CB_2, respectively) (Arjmand *et al.*, 2015; Lu & Mackie, 2016). CB_1 receptors are ubiquitous in the CNS and are located pre- and postsynaptically on neurons, whereas CB_2 receptors were originally thought to occur only in the periphery and to be located on monocytes, macrophages, B cells, and T cells, where they played a role in immune system functions (Arjmand *et al.*, 2015; Lu & Mackie, 2016). However, recent evidence indicates that CB_2 receptors are present in the brain, albeit to a lesser extent than the CB_1 receptors (Atwood & Mackie, 2010). These receptors have been detected in microglia and therefore play a role in the brain's immune system, and there are reports showing that in pathological conditions their presence is enhanced (Viscomi *et al.*, 2009; Lu & Mackie, 2016).

The ECS and signaling pathways to which the system is coupled have emerged to be of key importance in the regulation of processes underlying executive function, including emotion, reward, learning, and memory (Vinod & Hungund, 2006; Roche & Finn, 2010; Haghani *et al.*, 2012; Wei & Piomelli, 2015; Abbassian *et al.*, 2016). The ubiquitous neural presence of CB receptors, particularly CB_1 receptors, means they are present in brain areas which are involved in mood disorders such as the hippocampus, cerebellum, basal ganglia, and cortex. The localisation of the ECS system, when coupled with the well-known psychoactive properties of *Cannabis sativa*, has encouraged a dramatic peak of research to truly understand the role this intricate system plays in mental illnesses (Vinod & Hungund, 2005, 2006; Carvalho & Van Bockstaele, 2012; Esteban & García-Sevilla, 2012; Hillard *et al.*, 2012).

Aims of the study

The aim of this current mini review is to provide evidence that dysfunction of the ECS could play a role in the course of BD and via examination of a range of studies including clinical work and molecular investigations to challenge the idea of whether this system represents an avenue to pursue the development of another mechanistic treatment option for BD.

From clinical observations into the cells and genes

The use of the plant *C. sativa* dates back to several millennia, and from this use, it is known to possess several actions including inducing analgesia and euphoria, as well as serving as an anticonvulsant and inducing hallucinations (Walker & Huang, 2002; Zuardi, 2006; Atakan, 2012; Jones *et al.*, 2012; Pearce *et al.*, 2014; Arjmand *et al.*, 2015). Many active ingredients have been extracted from *C. sativa* among which Δ^9-tetrahydrocannabinol (Δ^9-THC), cannabidiol (CBD), cannabigerol, cannabichromene, and cannabinol have drawn the greatest degree of attention as it is believed that these are the main components which confer exploitable pharmacological actions (Atakan, 2012; Andre *et al.*, 2016). Prevalence of cannabis use/abuse has been reported in numerous studies to be high in patients with BD, and some of these reports have suggested that cannabis use may increase the risk of developing BD (Cassidy *et al.*, 2001; Van Laar *et al.*, 2007; Tijssen *et al.*, 2010; Agrawal *et al.*, 2011). In longitudinal studies, weekly to almost daily use of cannabis was associated with increased incidence of BD, whereas in adjusted models, only increased risk of (hypo)mania was noted (Feingold *et al.*, 2015).

Age at onset

Cannabis has been suggested to reduce the age of onset of BD with psychotic features. In a study of 90 BD patients, not only was a high rate of cannabis use among these patients noted but also use of cannabis was associated with a decrease in the age of onset of BD symptoms which was more pronounced than the decrease in the age of onset of schizophrenia (De Hert *et al.*, 2011). These findings have led to the suggestion that there is a partly shared, pre-existing genetic liability for BD and schizophrenia; this liability could involve interactions with the ECS during neurodevelopment and, further, this liability could be unmasked upon cannabis exposure (De Hert *et al.*, 2011).

Although the aforementioned study was limited to BD patients with psychotic features, Lagerberg *et al.* (2014) conducted a large, representative clinical sample comprised of patients presenting with BD type 1 (BD-I), BD type 2 (BD-II), or BD not otherwise specified which concluded that a lower age of onset of BD is associated with cannabis use and does not rely on polydrug use and that BD occurrence is independent of the presence of either depressive or (hypo)manic mood or a history of psychosis (Lagerberg *et al.*, 2014). Further, the results of this study indicate that cannabis use may influence all subtypes of BD and that its use decreases age of onset of BD in a dose-dependent manner with a greater effect on depressive episodes (Lagerberg *et al.*, 2014). When taken together, the findings from both of the studies with large groups of BD patients showed that cannabis' impact on BD is not gender specific

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which has also been previously reported (Öngür *et al.*, 2009; De Hert *et al.*, 2011; Lagerberg *et al.*, 2014).

In agreement with these findings, in another comprehensive study, cannabis use among BD patients (BD-I and BD-II) was associated with a significantly earlier age of onset of BD irrespective of the first manifestation of the disease, including whether the first episode was a state of depression or (hypo)manic (Lev-Ran *et al.*, 2013). Likewise, it has been noted that cannabis use can dramatically affect the age of onset of both the first manic or depressive episodes about 5.6 and 5.9 years earlier, respectively, in diagnosed BD patients (Leite *et al.*, 2015).

Onset of (hypo)manic or depressive episodes

Cannabis is likely to produce a range of psychological effects. There are many case studies reporting that cannabis use may induce the onset of clinical or subclinical symptoms of (hypo)mania (Henquet *et al.*, 2006; Baethge *et al.*, 2008; Merikangas *et al.*, 2008; Tijssen *et al.*, 2010; Feingold *et al.*, 2015; Mariangela Corbo, 2015).

Recent findings of Tyler *et al.* (2015) posited that cannabis use can be correlated with an increase in mania, positive affect, and depressive symptoms but not negative affect and reported that greater levels of positive effect were associated with an increase in the odds of cannabis use. Consistent with this study, when compared with individuals without co-occurring cannabis use, a significantly greater number of both (hypo)manic and depressive episodes with higher illness severity was seen in BD patients taking cannabis (Lev-Ran *et al.*, 2013).

Many other studies, largely case studies, have also highlighted that there is an association between co-occurrence of cannabis use with exacerbation and even emergence of mania symptoms (Bertolín-Guillén *et al.*, 2008; Khan & Akella, 2009). In a systematic and meta-analysis review, Gibbs *et al.* (2014) reported nearly a threefold increase in the advent of new manic episodes prior to the onset of disorder in cannabis users and a worsening of mania symptoms in cannabis users with pre-existing diagnosed BD.

Treatment outcome

Cannabis has been shown to contribute towards a reduction in treatment compliance among large samples of acutely manic BD patients who received anticonvulsants, antipsychotics, and/or lithium in a longitudinal study over the course of 1 year (van Rossum *et al.*, 2009). Furthermore, cannabis users exhibited a more severe course of illness when compared with that of non-users (van Rossum *et al.*, 2009). Two other studies also support these findings and suggested that cannabis users are likely to experience longer periods of mania than non-users and are non-compliant in utilisation of their medication during not only the acute phase but also maintenance, and hence, alternative therapeutic approaches might be required for this patient population (Baethge *et al.*, 2005; Gonzalez-Pinto *et al.*, 2010). Finally, poorer treatment outcomes and a higher frequency of developing rapid cycling and mixed episodes were reported in BD patients who presented with the comorbidity of cannabis use (Strakowski *et al.*, 2007; Agrawal *et al.*, 2011; Bally *et al.*, 2014).

Self-medication

There are several anecdotal reports and semi-structured, qualitative interviews which suggest that cannabis use acts as an antimanic and antidepressant that can alleviate the associated symptoms of both mania and depression, as well as reduce the side effects of lithium in BD patients, which implies that some use of cannabis in BD patients could reflect self-medication (Gruber *et al.*, 1996; Grinspoon & Bakalar, 1998; Healey *et al.*, 2009). These findings are in accordance with the suggestion of Ashton *et al.* (2005) that both Δ^9-THC and CBD have proved to be of great value in the management of anxiety, depression, and psychotic-like behaviours. Despite these observations, a human trial on two manic BD-I patients concluded that administration of oral CBD, even at tolerable high doses, did not show promising results for controlling manic episodes of BD (Zuardi *et al.*, 2010; Micale *et al.*, 2013).

A functional magnetic resonance imaging study

Hyperactivities of the right amygdala, left nucleus accumbens, and bilateral thalamus have been reported in non-cannabis using, adolescent bipolar individuals, whereas this over-activation is reduced in BD patients who are comorbid cannabis consumers. These interesting findings raised the question of whether cannabis use alters the functionality of brain areas involved in emotional processing and reward in BD subjects or whether differences are due to the presence of unique endophenotypes (Bitter *et al.*, 2014).

Into the genes

Relying on twin and family studies, it is evident that genetic factors contribute to the pathophysiology of BD (Kato, 2007), and there are a large amount of studies being conducted to unravel the genetically-determined molecular signatures associated with BD, as well as to elucidate the mechanisms underlying varying responses to different treatment approaches (Rybakowski, 2013; Hou *et al.*, 2016). In this regard, some studies examining BD have focused scrutiny on the role of genes encoding for players within the ECS. A recent study carried out on Turkish bipolar patients with the purpose of investigating CB receptor 1 gene (*CNR1)* single nucleotide polymorphisms (SNPs) reported that among three examined SNPs (rs6454674 T/G, rs806368 T/C, and rs1049353 A/G), only rs6454674 differed significantly in BD patients in comparison with healthy controls (Alpak *et al.*, 2014). This study also demonstrated that a significantly greater number of episodes of mania were associated with heterozygote rs6454674 polymorphisms, rather than homozygote ones, a relationship which was not observed for other clinical parameters including age at onset, duration of illness, and total number of BD episodes (Alpak *et al.*, 2014).

Genetic associations between BD, pharmacological management of BD, and the CB_2 have also been examined. In an Italian cohort, the presence of the CB_2 gene (*CNR2*) polymorphism, rs41311993 (524C/A), was significantly associated with BD, without any significant association in the SNPs of rs2229572 (1073C/T) or rs2501432 (315A/G) noted (Minocci *et al.*, 2011). This study unfortunately did not include pharmacogenetic evaluation. Although the sample sizes were small and therefore need to be corroborated in larger patient groups, when taken together, these reports are suggestive of a role for both CB receptors in BD and leave the door open to considerations that different genetic polymorphisms could confer varying responses to different treatment strategies. Countering this suggestion, Pisanu *et al.* (2013) have reported that there are no significant associations with polymorphisms in BD patients which could substantiate the involvement

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of SNPs of *CNR1*. Further, in the same study, SNPs of fatty acid amide hydrolase (FAAH) or *N*-acyl phosphatidyl ethanolamine phospholipase D, which are two of the major enzymes responsible for endogenous CB inactivation and biosynthesis, respectively, were also not found to be associated with BD. Additionally, none of the SNPs of players in the ECS which were examined showed an association with responses to treatment with lithium (Pisanu *et al.*, 2013). Along the same lines, Monteleone *et al.* (2010) failed to show that the *CNR1* SNP, rs1049353 (1359 G/A), was associated with BD in a caucasian population; however, a trend was noted when the association of the FAAH SNP, rs324420, was examined. Further, no differences in the expression of the *CNR1* and *CNR2* genes were seen postmortem in the prefrontal cortex of BD patients compared with aged-matched controls (Choi *et al.*, 2012). Moreover, immunohistochemistry analyses of postmortem brain tissue of bipolar patients revealed no significant changes in the density of CB_1 receptors in the anterior cingulate cortex. However, a marked decrease in numerical density of CB_1-immunoreactive glial cells following administration of first-generation antipsychotic drugs was seen (Koethe *et al.*, 2007; Leweke & Koethe, 2008).

Into the cells: inflammation, the arachidonic acid pathway, endocannabinoids, and BD

As investigations of the pathophysiology underlying BD have increased, an idea has emerged that BD might represent an inflammatory disorder, which could lead to the consideration that BD is a disorder not only of the brain but also of the body (Leboyer *et al.*, 2012). A potential role for inflammation in the etiology of BD is based partly on the findings that pro-inflammatory cytokines, such as interleukin-1 (IL-1), IL-2, IL-4, IL-6, and tumour necrosis factor-alpha (TNF-α), are present at elevated levels when mania is dominant in BD patients, and IL-6 is explicitly increased during the depression phase. Elevated levels of all of these pro-inflammatory cytokines, with the exception of IL-4 return back to normal levels when bipolar individuals become euthymic (O'Brien *et al.*, 2006; Kim *et al.*, 2007; Ortiz-Domínguez *et al.*, 2007; Brietzke *et al.*, 2009a,b; Hamdani *et al.*, 2012).

Differences in the levels of some of the ILs appear to vary at different stages of BD. In the early stages of BD, IL-10 is elevated, whereas TNF-α and IL-6 are at high levels at both early and late phases of BD (Berk *et al.*, 2011; Leboyer *et al.*, 2012). Moreover, treatment with mood stabilisers has been shown to return the higher levels of pro-inflammatory cytokines back to their baseline levels (Boufidou *et al.*, 2004; Hamdani *et al.*, 2012). Presence of heightened levels of C-reactive protein has been associated with both the manic and depressive states, as well as with the severity of manic symptoms (Wadee *et al.*, 2002; Dickerson *et al.*, 2007; Huang & Lin, 2007; Cunha *et al.*, 2008; De Berardis *et al.*, 2008). Interestingly, BD and players in inflammation processes may be associated at the molecular level as they share genetic polymorphisms and gene expression (Goldstein *et al.*, 2009).

Another connection between BD and inflammation is a link detected between BD and activation of microglia, a phenomenon that can amplify both pro- and anti-inflammatory cytokines (Ekdahl, 2012; Weitz & Town, 2012; Stertz *et al.*, 2013). CB_2 receptors that are found in the periphery are mostly located within the immune system, which suggests that CB_2 receptors and the ECS play a role in regulating immune cell functions (Arjmand *et al.*, 2015; Turcotte *et al.*, 2016). Consistent with this, studies on CB_2 receptor knockout mice, in which the *CNR2* gene has been inactivated, have confirmed the crucial role for CB_2 receptor as an immunomodulator and extended the notion that CB_2-selective agonists may well improve inflammation and act as immunosuppressive (Ashton & Glass, 2007; Turcotte *et al.*, 2016). Additionally, Ehrhart *et al.* (2005) have provided mechanistic insights regarding how a CB_2-selective agonist attenuates release of microglial, pro-inflammatory cytokines and suppresses microglial activation, which is interesting in light of the heightened microglial activation seen in BD. CB_2 agonists have been shown to abrogate the activity of the immune system by affecting several pathways (Malfitano *et al.*, 2014). Stimulation of CB_2 receptor, which is coupled to Gi protein, dampens the activity of adenylyl cyclase resulting in diminished cyclic adenosine monophosphate (cAMP) and in a subsequent reduction in the activity of protein kinase A that is responsible for phosphorylation of cAMP response element binding protein (CREB) (Malfitano *et al.*, 2014). CREB is a transcription factor in charge of modulating both proliferation and differentiation of the immune system's components (Malfitano *et al.*, 2014). In addition, activation of CB_2 receptor can affect several cell survival pathways, such as MAPK, ERK, STAT1, and JAK (Ehrhart *et al.*, 2005; Malfitano *et al.*, 2014). CB_2 agonists have demonstrated a capability to hamper interferon gamma, a key element in processes leading to suppression of expression of CD40, microglial TNF-α, production of nitric oxide, and STAT1/JAK phosphorylation with a net result of immune system inhibition (Ehrhart *et al.*, 2005).

While actions at the CB_2 seem to inhibit inflammatory processes, stimulation of the CB_1 has been shown to lead to activation of inflammatory mediators. The endogenous CB_s, anandamide, and 2-arachidonoylglycerol are substrates for cyclooxygenase-2 (COX-2) and via oxygenation are converted to prostaglandin glyceryl esters, prostaglandin ethanolamides and arachidonic acid (AA)-derived prostaglandin E_2 (PGE_2), which results in a reduction in the amount of endocannabinoids (Yang *et al.*, 2008; Turcotte *et al.*, 2015). Δ^8-THC, a more chemically stable isoform of Δ^9-THC, as well as Δ^9-THC, and a potent CB_1 agonist, HU-210, were found to augment the amount of PGE_2 through actions at the CB_1 receptors, which could be antagonised by COX-2 inhibitors (Yamaguchi *et al.*, 2001; Kim *et al.*, 2011). The effects of CB_1 on AA production are interesting in light of findings from postmortem investigations of the brains of patients with BD, which revealed an up-regulation of the AA cascade (Kim *et al.*, 2011).

Mood stabilisers such as lithium, carbamazepine, and lamotrigine have been shown to downgrade AA turnover and thus diminish PGE_2 concentration specifically by lowering the expression of COX-2, whereas valproate tends to affect both COX-1 and COX-2 (Sublette *et al.*, 2004; Rapoport, 2014). Although two rather old studies are indicative that use of some non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin and tolmetin may exacerbate the associated symptoms of mania, this could be due to their non-selective inhibitory action on both COX-1 and COX-2. However, there is also a case report that COX-2 selective NSAIDs induced hypomania despite maintenance of treatment with mood-enhancing drugs, and symptoms remitted following 3 days of discontinuation of the NSAID (Sotsky & Tossell, 1984; Bishop *et al.*, 1987; Mahajan *et al.*, 2012).

When taken together, it is plausible that enhancing endocannabinoid level by utilising selective COX-2 inhibitors or endocannabinoid hydrolysis inhibitors in combination with CB_1-selective antagonists and CB_2-selective agonists represents a new strategy to not only manage BD in treatment-resistant patients but also vigorously dissect the exact underlying molecular pathways and

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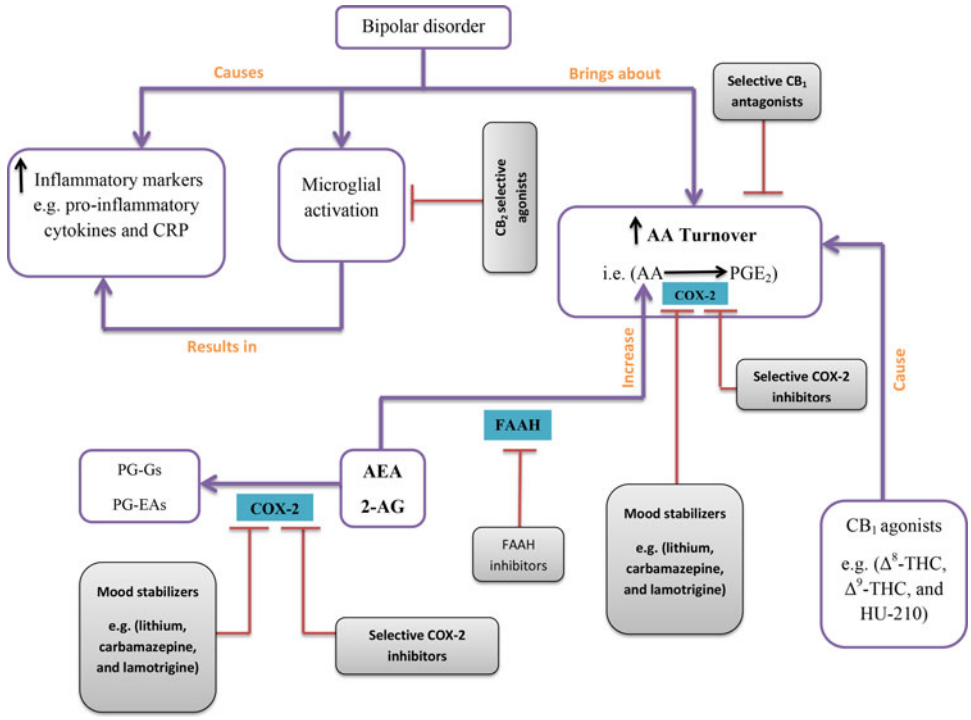

Fig. 1. Bipolar disorder (BD) is associated with some changes in the arachidonic acid (AA) cascade and inflammatory markers. This concept map presents a simplified schematic of changes in the AA cascade and inflammatory markers in the course of BD as well as providing a concise proposal on how to modulate these alterations. In BD, increased AA turnover and increased level of both pro-inflammatory cytokines and C-reactive protein (CRP) have been detected. Activation of microglial cells itself can induce an increase in the concentration of inflammatory markers which can be inhibited by use of cannabinoid receptor type 2 (CB_2)-selective agonists (red lines are indicative of inhibitory mode of action). In another pathway, cyclooxygenase-2 (COX-2) oxygenates AA to classic prostaglandin E_2 (PGE_2), whereas anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are converted to new PGs called prostaglandin glyceryl esters (PG-Gs) and prostaglandin ethanolamides (PG-EAs). Preventing AA metabolism and enhancing the amount of endocannabinoids might also lead to the assuagement of BD symptoms, a strategy which can be achieved by using CB_1-selective antagonists, mood stabilisers, and selective COX-2 inhibitors.

potentially reveal further improved therapeutic opportunities to better manage BD (Fig. 1).

Rimonabant: a controversial scenario?

It has been well proven that rimonabant, an inverse agonist of CB_1 receptors, can induce depression and anxiety, whereas the opposite anxiolytic and antidepressant effects of drugs that boost CB_1 receptor activity have been established (Moreira & Crippa, 2009; Kruk-Slomka *et al.*, 2015). Moreover, acute pretreatment with a CB_1 antagonist, AM251, has been demonstrated to abolish the antidepressive effects of desipramine (Hill & Gorzalka, 2005). Such observations were followed by genetic studies on CB knockout mice that exhibited a depression-like phenotype which resembled that triggered in mice who underwent mild chronic stresses (Beyer *et al.*, 2010). The behavioural profile of the knockout mice supported the suggestion that CB_1-deficient mice can be used as an animal model for depression (Valverde & Torrens, 2012). There are also studies of rimonabant that are indicative of either no effect on depression or anxiety or an antidepressant-like effect which makes the evaluation of the role played by this drug in depression difficult (Gobbi *et al.*, 2005; Griebel *et al.*, 2005; Adamczyk *et al.*, 2008; Steiner *et al.*, 2008). However, we have suggested that CB_1 antagonists may modulate mood by suppressing AA turnover and that they might act as a mood stabiliser. It should be noted that a preferable mood stabiliser should reduce mood swings and maintain euthymia, as well as prevent episodic relapse of the illness (Malhi *et al.*, 2018). It has been previously demonstrated that mood stabilisers are capable of targeting brain's AA signaling and can stabilise mood by downregulation of AA cascade (Chang *et al.*, 2001; Rao & Rapoport, 2009). Here, we suggest a mood stabilising mode of action for CB_1 antagonists and not an antidepressant effect. Moreover, rimonabant is an inverse agonist, and development of a putative neutral antagonist may diminish the depression-like effect of such agents (Giraldo, 2010; Ward & Raffa, 2011). However, at this time, this remains a speculation, and the potential for CB_1 antagonists to stabilise mood needs to be rigorously examined.

Conclusion

Although data from the studies are somewhat inconsistent and no direct measurement of the plasma levels of endocannabinoids and their associated enzymes has yet been reported in BD, it is apparent that the ECS is involved in control of mood. Different routes of administration, rather small sample sizes, a large variety of active ingredients of cannabis, and different doses may affect the results of clinical studies and make the final conclusion obscure and controversial. The first evidence of this role sources from clinical observations, which are largely anecdotal, that triggered experimental studies which have shown that BD and endocannabinoids may share a link (Table 1). Cannabis has been shown to affect the age of onset of BD, severity, and the number of affective episodes. It has also been demonstrated that both AA and inflammatory pathways can play a part in the pathophysiology of BD, and a link from the ECS to inflammatory pathways has been strongly established. After consideration of these studies, the majority of which have been molecular, we proposed that COX-2 inhibitors, endocannabinoid hydrolysis inhibitors, CB_1-selective antagonists, and CB_2-selective agonists may lead to remarkable advances pertaining to pharmacotherapy of BD based on modulation of the ECS, and this

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Table 1. Endocannabinoids and BD; the story so far

Highlights
• Cannabis use may increase the incidence of BD.
• Cannabis use is significantly associated with a lower age of onset of BD irrespective of mood episodes.
• Cannabis can trigger a significantly greater number of both (hypo)manic and depressive episodes with higher illness severity.
• Cannabis use results in poorer treatment outcome and less treatment compliance.
• Cannabis use was beneficial in mitigation of both (hypo)mania and depression in almost every BD patient self-medicated with cannabis.
• There are noticeable differences in the functional activity of the amygdala, thalamus, and nucleus accumbens of BD patients with co-occurring cannabis use when compared with the activity in non-comorbid patients.
• Some single nucleotide polymorphisms in both *CNR1* and *CNR2* genes of bipolar patients were detected; however, very few studies show differential expression of such genes in BD subjects.
• Enhanced levels of pro-inflammatory cytokines and C-reactive protein level and increased microglial activation as well as shared genetic architecture with inflammation were seen in BD.
• Treatment normalises the elevated level of inflammatory markers.
• CB_2-selective agonists could improve inflammation and act as an immunosuppressor.
• Mood stabilisers have been shown to downgrade AA turnover and thus diminish PGE2 concentration specifically by lowering the expression of COX-2.
• Mood stabilisers are thought to exert their influence in part by targeting the AA cascade.
• The approach of augmenting endocannabinoid levels by utilising selective COX-2 inhibitors or endocannabinoid hydrolysis inhibitors in combination with CB_1-selective antagonists and CB_2-selective agonists may start a new era of research geared towards development of novel treatment approaches for BD.

BD, bipolar disorder; *CNR1*, cannabinoid receptor 1; *CNR2*, cannabinoid receptor 2; AA, arachidonic acid; PGE_2, prostaglandin E_2; COX-2, cyclooxygenase-2.

approach offers a brand-new treatment strategy to broaden the arsenal available to pharmacologically mange BD. Since increased turnover of AA is evident in BD and disparate classes of currently available mood stabilisers share the mechanism of diminishing AA turnover, activation of CB_2 receptors might offer BD patients' stabilisation of mood with the same final outcome. The lipophilic nature of the CB ligands, as well as their long biological half-life, bequeaths them the advantage of crossing the blood–brain barrier easily and could possibly reduce the risk of overdose (Stratton *et al.*, 2013) in BD patients, some of whom are predisposed to suicidal ideation and attempts. Given the failure of control of BD in a subset of patients with the medications currently available, when taken together with the studies examining a role of endocannabinoids in control of mood, examination is warranted of whether selective activation and inhibition of endocannabinoid receptors can serve as a suitable treatment approach for BD.

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Author contributions. SA has conceived and designed the concept and road map of the study, searched the literature, and drafted the manuscript. She also designed the concept map and box. MB has searched the literature, categorised the searched papers, and helped design the study and box. KAK has critically reviewed the manuscript for its content, originality, usage of English language, and accuracy of the interpreted data. SM and AS have reviewed the manuscript for the intellectual content and approved the final version for submission. MS has critically reviewed the manuscript, designed the study, and helped in manuscript preparation. He is the archival author and attests to the integrity of the original data and the analysis reported in this manuscript. All authors have made substantive contribution and attest to approving the final manuscript.

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