



# The Purinergic System as a Target for the Development of Treatments for Bipolar Disorder

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## Abstract

The neurobiological and neurochemical mechanisms underlying the pathophysiology of bipolar disorder are complex and not yet fully understood. From circadian disruption to neuroinflammation, many pathways and signaling molecules are important contributors to bipolar disorder development, some specific to a disease subtype or a cycling episode. Pharmacological agents for bipolar disorder have shown only partial efficacy, including mood stabilizers and antipsychotics. The purinergic hypothesis for bipolar disorder emerges in this scenario as a promising target for further research and drug development, given its role in neurotransmission and neuroinflammation that results in behavioral and mood regulation. Here, we review the basic concepts of purinergic signaling in the central nervous system and its contribution to bipolar disorder pathophysiology. Allopurinol and novel P2X7 receptor antagonists are promising candidates for treating bipolar disorder. We further explore currently available pharmacotherapies and the emerging new purinergic targets for drug development in bipolar disorder.

## 1 Introduction

Bipolar disorder (BD) is a major neuropsychiatric condition with complex and multicomponent pathophysiology, involving changes in a wide range of neurocircuitries and signaling pathways [1]. Patients with BD experience different symptoms within the disease spectrum, cycling from severe depression to substantial euphoria, known as mania. It has been well established that genetic and epigenetic factors, metabolic and biochemical pathways, structural and functional brain alterations, and social and environmental triggers may contribute to the disorder's onset, development, and progression [2]. Many molecular hypotheses have emerged to explain its vast neurobiological spectrum,

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## Key Points

The new generation of P2X7 receptor antagonists represents a potential breakthrough in treatments for bipolar disorder.

There is a promising antimanic effect of allopurinol but additional well-designed research on the topic is required.

Modulation of the P2X4, A<sub>1</sub>, A<sub>2A</sub>, and P2Y1 receptors are possible new targets encouraged to be further explored for drug development in bipolar disorder.

including changes in neurotransmission systems such as the  $\gamma$ -aminobutyric acid (GABA)ergic, glutamatergic, and dopaminergic systems [3–6].

BD affects about 39.5 million people worldwide [7]. It is a severe, chronic, and debilitating disease in which patients exhibit an overall impairment in autonomy and cognitive and psychosocial functioning [8]. The many facets of BD and such a broad umbrella of symptoms and phenotypes often lead to misdiagnosis, resulting in delayed initiation of appropriate treatments [9, 10]. Current therapeutic approaches rely mainly on managing and preventing manic and depressive episodes with mood stabilizers, adjunctive antipsychotics, and/or antidepressants; however, long-term treatment is still challenging and with limited effectiveness

[11]. Hence, it is of great relevance for BD management that new pharmacotherapies are developed, aiming to stabilize mood, restrain disease progression, protect against neurodegeneration, minimize dangerous behavior and suicide attempts, attenuate side effects, increase life expectancy, and improve overall quality of life.

From the neurobiological perspective, the purinergic system has gained considerable attention given that adenosine and adenosine 5'-triphosphate (ATP) are signaling molecules that modulate neurotransmission and neuroinflammation pathways linked to behavioral and mood regulation mechanisms relevant for BD [12]. Therefore, in this review we explore the role of purinergic signaling in BD pathophysiology and provide an overview of current and potential new purinergic targets for drug development.

## 2 Purinergic System in the CNS

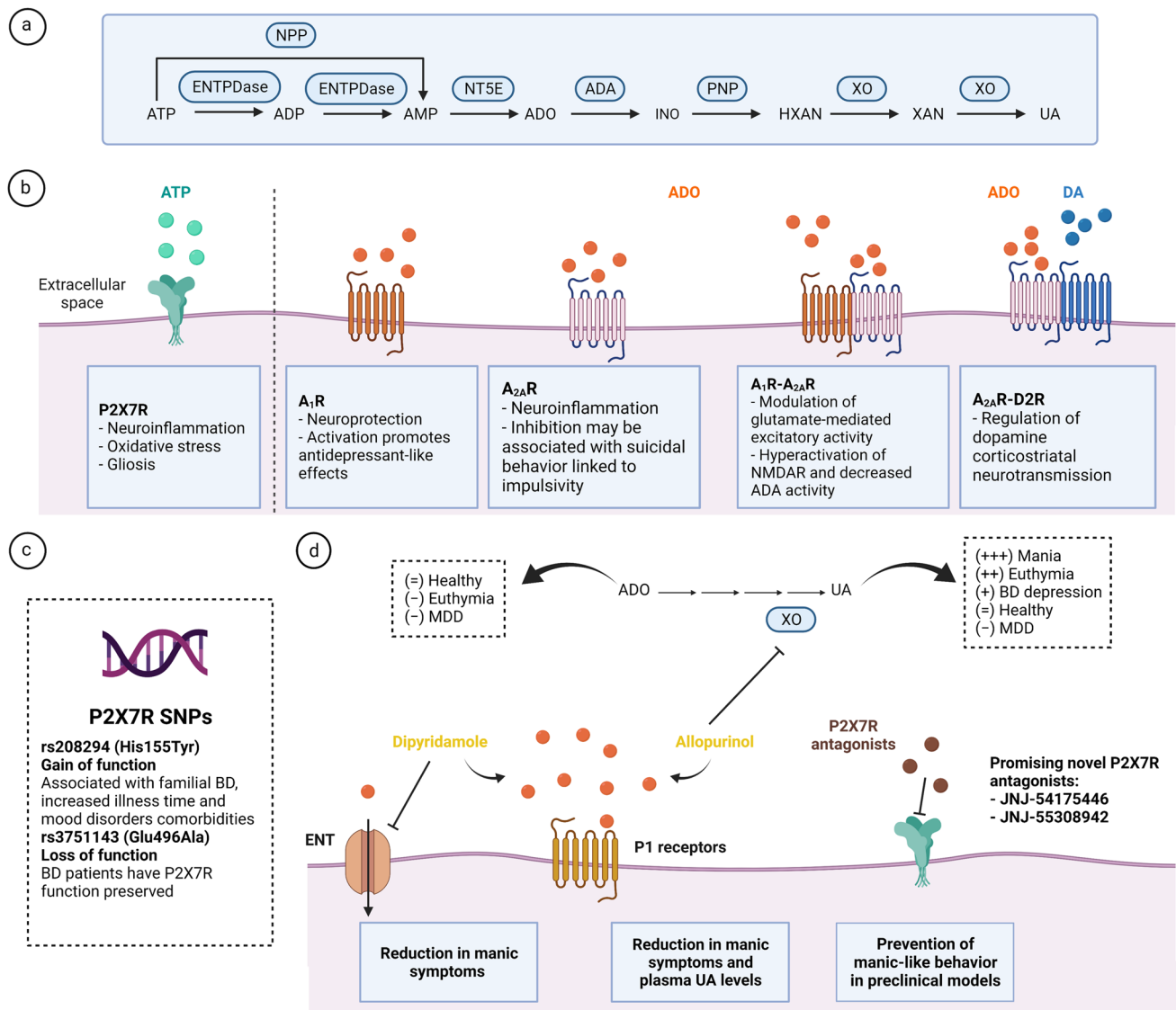
ATP is a nucleotide stored intracellularly, and its signaling is vital for the energy production of all cellular processes. ATP reaches the extracellular space by different mechanisms, including: (1)  $\text{Ca}^{2+}$ -dependent exocytosis [13]; (2) connexin hemichannels and pannexin channels, according to its concentration gradient; (3) cell membrane damage from injured cells [14]; and (4) P2X7 receptor (P2X7R)-induced transmembrane pore after sustained activation. The latter mechanism, however, is still debated [15, 16]. In the central nervous system (CNS), ATP can be physiologically released from neurons [17], astrocytes [18], and microglial cells [19] by exocytosis. In addition, ATP is classified as a neurotransmitter and can also be co-released with acetylcholine, noradrenaline, GABA, dopamine, and glutamate [20, 21].

Extracellular ATP acts on purinergic receptors P2X (P2XR) and P2Y (P2YR), inducing several intracellular signaling cascades. P2X(1-7)R are ionotropic receptors that elicit  $\text{Ca}^{2+}$  and  $\text{Na}^{+}$  influx, and  $\text{K}^{+}$  efflux under activation [22]. P2XR can occur as homomeric or heteromeric assemblies and consist of three subunits [22]. P2Y(1, 2, 4, 6, 11, 12, 13 or 14)R are metabotropic G-protein-coupled receptors sensitive to ATP, adenosine 5'-diphosphate (ADP), uridine 5'-tri- or diphosphate (UTP or UDP, respectively), or UDP-glucose, which will either activate or inhibit adenylyl cyclase, or activate phospholipase C [23]. These receptors are present in neurons, astrocytes, microglial cells, and oligodendrocytes [23]. In the brain, the majority of P2XR and P2YR are expressed in the hippocampus where they can regulate glutamate release [24]. The P2Y1R activation induces dopamine release in the rat striatum [25], the medial prefrontal cortex, and the nucleus accumbens [26]. The P2X7R activation also facilitates glutamate, GABA, and nitric oxide release [27–30], and negatively modulates serotonin levels [31]. It also regulates *N*-methyl-D-aspartate

receptor (NMDAR) expression and basal levels of brain-derived neurotrophic factor in the hippocampus.

ATP is hydrolyzed into ADP, adenosine 5'-monophosphate (AMP), and adenosine by ectoenzymes that precisely control extracellular purine concentration. These cell surface enzymes are part of the family named ectonucleotidases, which mainly comprises the ecto-nucleoside triphosphate diphosphohydrolases (ENTPDases), pyrophosphohydrolases/phosphodiesterases (NPP), and ecto-5'-nucleotidase. ENTPD1, 2, and 3 (also known as CD39, CD39L2, and CD39L3, respectively) hydrolyze ATP and ADP into AMP [32]. NPPs hydrolyze ATP directly into AMP, generating pyrophosphate [33]. The final ectonucleotidase in the chain, ecto-5'-nucleotidase (also known as CD73), hydrolyzes AMP into adenosine [33]. Adenosine is inactivated by adenosine deaminase (ADA), generating inosine, which is further metabolized into hypoxanthine, xanthine, and uric acid (UA) (Fig. 1a). Inosine can modulate inflammation, neuroprotection, pain, and cognition [34], while UA is associated with sleep, locomotion, cognition, impulsivity, and mood [35–37]. Remarkably, this fine-tuning regulation by ectonucleotidases is strictly necessary as both ATP and adenosine can act as neuromodulators and frequently have counteracting effects.

Adenosine, in its turn, exerts multiple brain functions through the adenosine/P1 receptors, which are classified as  $\text{A}_1\text{R}$ ,  $\text{A}_{2\text{A}}\text{R}$ ,  $\text{A}_{2\text{B}}\text{R}$ , and  $\text{A}_3\text{R}$ . Adenosine receptors are metabotropic G-protein-coupled receptors that mainly activate or inhibit adenylyl cyclase [38]. The  $\text{A}_1\text{R}$  is the most abundant P1 receptor expressed in the CNS [38]. Adenosine is well known for exerting neuroprotective properties in the CNS, mediated by  $\text{A}_1\text{R}$  activation and  $\text{A}_{2\text{A}}\text{R}$  inhibition [39]. The  $\text{A}_{2\text{A}}\text{R}$  also mediates several essential functions in brain homeostasis, such as neurotransmitter release.  $\text{A}_{2\text{A}}\text{R}$  is mainly expressed in dopaminergic areas, such as the striatum, nucleus accumbens, and olfactory tuberculum [38]. In the striatopallidal GABAergic neurons in the striatum,  $\text{A}_{2\text{A}}\text{R}$  interacts with the dopamine D2 receptor (D2R), forming a heterodimer that results in decreased D2R affinity to dopamine when  $\text{A}_{2\text{A}}\text{R}$  is activated [40] (Fig. 1b). Moreover, it is well accepted that adenosine can modulate spontaneous locomotor activity through striatal  $\text{A}_{2\text{A}}\text{R}$  that interacts with D2R and dopamine D1 receptor (D1R) of the mesolimbic dopamine circuits [41–43]. In addition,  $\text{A}_{2\text{A}}\text{R}$  interact with metabotropic glutamate 5 receptor in the striatum [44, 45] and hippocampus [46].  $\text{A}_{2\text{A}}\text{R}$  stimulation also facilitates glutamate release [39] and GABA release [47] from the hippocampus [48], whereas  $\text{A}_1\text{R}$  counteracts  $\text{A}_{2\text{A}}\text{R}$  effects by inhibiting glutamatergic neurotransmission [49, 50]. As adenosine receptors interact and modulate glutamate and dopamine receptor activity, pathological adenosinergic signaling has become a



**Fig. 1** Purinergic signaling in bipolar disorder (BD). **a** Overview of physiological purine metabolism. Adenosine 5'-triphosphate (ATP) is hydrolyzed by ectonucleoside triphosphatase diphosphohydrolases (ENTPDases) or ecto-nucleoside pyrophosphohydrolases/phosphodiesterases (NPPs) into adenosine 5'-monophosphate (AMP), which is hydrolyzed into adenosine (ADO) by ecto-5'-nucleotidase. Adenosine deaminase (ADA) converts adenosine into inosine (INO), further metabolized into hypoxanthine (HXAN), xanthine (XAN), and uric acid (UA). **b** Proposed mechanisms in purinergic dysfunction contributing to BD pathophysiology. It is described that P2X7 receptor (P2X7R) activation drives neuroinflammation, oxidative stress, and gliosis in preclinical studies. Few reports scrutinized the direct role of P1 receptors in BD; however, it is known that A<sub>1</sub> receptor (A<sub>1</sub>R) is primarily neuroprotective and its activation promotes an antidepressant-like effect, whereas A<sub>2A</sub> receptor (A<sub>2A</sub>R) is mainly proinflammatory and its inhibition may promote impulsivity, which can be associated with suicidal behavior. A<sub>1</sub>R-A<sub>2A</sub>R heteromeric interaction modulates glutamate activity and induces hyperactivation of *N*-methyl-D-aspartate receptor (NMDAR), which is exacerbated in BD pathology. Additionally, heteromeric formation between adenosine A<sub>2A</sub> and dopamine D2 receptors (A<sub>2A</sub>R-D2R) in basal ganglia regulates corticostriatal dopamine neurotransmission,

which is hyperactive in patients with BD. **c** P2X7R single nucleotide polymorphisms (SNPs) associated with BD. The SNP rs208294 promotes gain of function of the P2X7R, and is associated with familial BD, increased illness time, and comorbidities with other mood disorders. The SNP rs3751143 promotes loss of function of P2X7R, and patients with BD possess the allele that preserves P2X7R function. **d** Proposed purinergic-based treatments for BD. Allopurinol is a promising therapeutic strategy; it can decrease UA levels and increase ADO availability, both dysregulated in patients with BD. Dipyridamole also acts on rising ADO levels and consequently modulates P1 receptors, showing beneficial effects in patients with BD. P2X7R antagonism has been proven effective in preclinical studies, and there are promising novel P2X7R antagonists able to cross the blood-brain barrier that could be explored in clinical trials. – indicates lower levels compared to healthy controls, = indicates equal levels compared to healthy controls, + indicates a subtle increase in levels compared to healthy controls, ++ indicates a moderate increase in levels compared to healthy controls, +++ indicates a high increase in levels compared to healthy controls, DA dopamine, ENT equilibrative nucleoside transporter, MDD major depressive disorder, NT5E ecto-5'-nucleotidase, PNP purine nucleoside phosphorylase, XO xanthine oxidase. Figure created with BioRender.com

relevant hypothesis for psychiatric disorders [51–53], especially BD and schizophrenia [54–56].

Both ATP and adenosine are immunomodulators that act during brain inflammatory processes in opposite directions [57]. ATP acts as a damage-associated molecular pattern (DAMP) when released by injured or stressed cells, triggering proinflammatory cascades [58, 59], whereas adenosine acts as an immunosuppressant [60]. As a DAMP, ATP activates nuclear factor- $\kappa$ B signaling and consequently upregulates proinflammatory cytokines and NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome [61]. P2X7R activation is an essential step in the NLRP3 cascade. It activates caspase-1 and converts pro-interleukin-1 $\beta$  and pro-interleukin-18 into their mature forms, increasing their release [61, 62]. The microglial P2X7R is the major known modulator of inflammation among P2 receptors. Its activation by millimolar ATP concentration elicits proinflammatory and immunostimulatory effects, promoting the production and release of proinflammatory cytokines, including interleukin-1 $\beta$ , interleukin-6, and tumor necrosis factor [57, 63]. This effect activates microglial cells and induces the release of additional ATP to the extracellular space. As a feedback loop, exacerbated ATP levels in the extracellular space will establish an excitotoxic microenvironment [64]. Consequently, primarily via P2X7R activation, the purinergic system has been strongly associated with neurodegenerative processes and neuropsychiatric disorders with a neuroinflammatory and excitotoxic component, including BD [51, 65].

### 3 Pathophysiology and Treatment Strategies for BD

#### 3.1 ATPergic Signaling and Genetic Predisposition to BD

The P2X7R has emerged as a promising target to study the genetic predisposition in BD as its gene is highly polymorphic [66]. Genome-wide association studies have identified the region 12q23-q24 as a locus with genes influencing susceptibility to BD [67–69]. Furthermore, P2X7R and P2X4R genes are located on chromosome 12 in close proximity, at 12q24.31 and 12q24.32, respectively [66, 70]. Similar functions that trigger proinflammatory cascades [71] and evidence for a P2X4-P2X7 heteromeric formation were found [72, 73], although this association is still questioned [74, 75].

A massive effort has been directed to understand the role of P2X7R single nucleotide polymorphisms (SNPs) in BD. However, the current evidence for the involvement of the majority of the studied targets is controversial, including

the P2X7R SNP rs2230912 [76–83] and rs1718119 [84]. A study conducted with British individuals did not detect any association between nine promising P2X7R SNPs (rs591874, rs208293, rs1186055, rs208298, rs503720, rs1718133, rs1718119, rs2230912, and rs1621388) and BD susceptibility [80]. P2X7R SNPs that have not been refuted yet are the rs208294 and the rs3751143. The rs208294 coding for His155Tyr promoted the gain of function of the P2X7R. It was associated with familial major depressive disorder (MDD) and BD, including increased illness time and comorbid anxiety, alcoholism, psychotic symptoms, and suicide attempts [78]. On the contrary, the rs3751143 coding for Glu496Ala promoted the loss of function of the P2X7R. The decreased 1513C allele frequency and the tendency of increased 1513 AA/AC genotype were found in patients with BD, suggesting that P2X7R functionality is preserved in these patients compared to healthy individuals [85] (Fig. 1c). Linkage disequilibrium, functional effects, and haplotype block structure (regions with high linkage disequilibrium) might explain these controversial findings within the genome [86]. Some authors have described haplotype blocks in the P2X7R gene [66, 87], which might partially explain the failure of previous association studies. Nevertheless, preclinical studies strongly support the beneficial effect of the P2X7R inhibition, which will be discussed in the upcoming sections.

To our knowledge, no studies have found an association between functional SNPs in the P2X4R gene and BD susceptibility [76]. Furthermore, no preclinical or clinical study directly evaluated the modulation of P2X4R in BD. Nonetheless, growing preclinical evidence indicates the role of P2X4R in modulating dopamine transmission. Mice deficient in the P2X4R gene presented with increased striatal tyrosine hydroxylase, dopamine transporter, and D1R and D2R expression. Remarkably, both deletion and activation of the P2X4R induced impairment in prepulse inhibition, whereas selective D1R and D2R antagonists reverted this deficit [88, 89].

Moreover, P2X4R knockout mice also exhibit alterations in the subunit expression of glutamate receptors, such as NMDAR and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, and GABA<sub>A</sub> receptors in several brain regions [90, 91]. Behaviorally, other reports corroborate that P2X4R knockout mice present deficits in sensorimotor gating and social behavior, including increased ethanol intake [90, 91]; however, no anxiety-like behavior or altered locomotor activity were found [90]. In addition, a recent study showed that increased P2X4R density in the knock-in mice hippocampus induced synaptic deficits, anxiolytic-like behaviors, and impaired spatial memory processing [92]. Corroborating these findings, ivermectin, a potent P2X4R positive allosteric modulator, induced anxiolytic-like and depressive-like behaviors in mice [93]. These data support the hypothesis that P2X4R may modulate

dopaminergic, glutamatergic, and GABAergic neurotransmission, suggesting its participation in reward mechanisms and ethanol abuse with particular relevance to BD pathogenesis and progression.

### 3.2 The Purinergic Hypothesis for BD: A Look Into Hyperuricemia

Whilst the purinergic hypothesis for BD has been mostly explored in the past two decades after being revisited by Machado-Vieira et al. [94], the link between components of the purinergic system and mood fluctuation was described more than a century ago [95]. The first insights date from 1846 owing to the accidental discovery of lithium salts as mood stabilizers for patients with gout and hyperuricemia, which are conditions known by the increased levels of peripheral UA [95]. Elevated amounts of UA were then firstly reported in 1968 by Anumonye et al. in the urine, but not in the blood, of patients with BD, including those receiving lithium treatment [96].

Current knowledge indicates that blood levels of UA in patients with BD, during mania, depression, or remission, are higher than in healthy controls [97] (Fig. 1d). While higher levels of peripheral UA are associated with manic and hypomanic episodes, lower levels are observed during depressive episodes [98–101]. Still, a decrease in UA levels during mania indicates lower severity of the episode; however, such a correlation was not observed during a depressive episode, as measured by the Young Mania Rating Scale and Hamilton Depression Rating Scale, respectively [97]. Of note, patients with MDD have shown the lowest levels of UA when compared to patients with BD or healthy subjects. These findings indicate an emerging role of UA as a biomarker for BD [102], potentially able to distinguish BD and MDD [103–106]. However, notwithstanding the current evidence, the UA-based discrimination between BD phases or between BD and MDD was only partially supported when further analyzed using a meta-analytical approach [107].

UA levels are also enhanced in metabolic syndrome, a prevalent (approximately 37%) comorbidity in patients with BD, especially in those receiving antipsychotic treatment [108–110]. Still, the effect of BD on hyperuricemia seems mostly direct, being only partially mediated by metabolic abnormalities [111]. From the pharmacotherapy perspective, psychotropic and antipsychotic drugs commonly considered in the psychiatric clinic for BD management might have different effects on serum UA levels. For example, it has been shown that lithium [96], carbamazepine [112], phenytoin [112], aripiprazole [113], a combination of zotepine and mood stabilizers (lithium or sodium valproate) [114], and a combination of quetiapine and sodium valproate [115] are likely to reduce peripheral UA levels. In contrast, sodium valproate monotherapy [112], phenobarbital [112],

haloperidol [116], and risperidone [117] may increase UA levels.

### 3.3 Adenosinergic Dysfunction and Its Impact on Other Neurotransmission Systems

Increased UA levels might reflect an abnormal purine turnover with a consequent reduction in adenosine levels [36]. Peripheral adenosine levels were found reduced in patients with BD during the euthymic phase, with lower levels linked to higher functional impairment [118]. The authors suggested that, at low levels, adenosine would not exert its neuroprotective role, possibly impacting immune response and neuroinflammation [118].

The purinergic system, mainly via adenosine, can also regulate circadian rhythms, modulating the physiological response to light [53, 119]. It has been recently proposed that downstream signaling of  $A_1R$  and  $A_{2A}R$  antagonism controls clock genes *PER1* and *PER2* activity both in vitro and in vivo via  $Ca^{2+}$ -extracellular-regulated kinase-AP-1 pathway [119]. Although the causal mechanisms involved in the connection between circadian rhythm disruption and mood disorders are yet to be reasoned [120], sleep cycle impairment is highly prominent in most patients with BD, being clinically associated with disease onset and development [121–126]. Thus, further understanding on the role of adenosinergic signaling in the context of mood control can be an attractive approach with potential therapeutic implications for BD.

Most evidence of adenosine receptor dysregulation in mood disorders comes from MDD [53, 127]. Their role in BD can be hypothesized from the therapeutic effect of carbamazepine, the first anti-seizure drug used for BD back in the 1970s. Carbamazepine is currently considered a second-line mood stabilizer with limited applicability for treating acute mania and mixed episodes or for maintenance and preventive therapy [128–131]. Its mechanism of action includes the antagonism of  $A_1R$ , which results in long-term mRNA upregulation and an increased number of  $A_1R$  receptors. This was shown to directly potentiate phospholipase C activity in primary astrocytes isolated from low-rich adenosinergic regions of the rat brain [132]. Of note,  $A_1R$  activation has proven to exert antidepressant-like effects in preclinical studies, potentially linked to glutamatergic modulation [53, 133].

As mentioned above, adenosine-mediated neuroprotection is mainly attributed to  $A_1R$  activation and  $A_{2A}R$  blockade [39]. The evidence of the  $A_1R$ - $A_{2A}R$  heterodimer formation on striatal glutamatergic terminals [134] raises attention to the regulatory effect of different concentrations of adenosine over glutamate-mediated excitatory activity, which is enhanced in patients with BD [135] (Fig. 1b). A dopaminergic signaling imbalance has also been extensively discussed

as a major contributor to mood alterations, especially in BD [136]. The capability of adenosine receptors to form heterodimers with dopamine receptors becomes especially relevant in this context, as  $A_{2A}R$ - $D_2R$  heterodimers in the basal ganglia regulate corticostriatal dopamine neurotransmission, found hyperactive in patients with BD [137, 138] (Fig. 1b). Adenosine-dopamine might also interact to modulate glutamatergic neurons in the hippocampus [53], although there is no evidence pointing to such a mechanism specifically in BD. The most promising hypothesis by which adenosinergic-dopaminergic interactions might control mood suggests the balance between excitatory (glutamate) and inhibitory (GABA) neurotransmission along with heteromeric formation, as recently reviewed [127]. Further research is still necessary to determine any mechanistic causality and clinical relevance and applicability of targeting adenosinergic-dopaminergic heteromers as a therapeutic approach for BD.

Finally, one of the clinical features of BD that has received less attention from the molecular perspective is the substantially increased suicide risk among patients. It is expected that 30–50% of patients with BD will attempt suicide once in their lifetime, and 15–20% will commit suicide [139]. Although there is a lack of evidence directly linking purinergic signaling to suicidal behavior, some hypotheses have been recently proposed. A reduction in adenosinergic signaling through the inhibition of  $A_{2A}R$  is thought to play a role in suicidal behavior by promoting impulsivity, a common trait in patients with BD [140]. Interestingly, UA levels have also been positively correlated with impulsive traits during a manic episode [100]. An expanded hypothesis has also proposed a role for neuroinflammation and glutamate-derived excitotoxicity mediated by P2X7R activation and  $A_1R$ - $A_{2A}R$  heterodimer response to accumulated adenosine resulting from hyperactivation of the NMDAR and decreased activity of the enzyme ADA [141].

## 4 Current Therapeutic Strategies for BD Targeting the Purinergic Signaling

### 4.1 Lithium, The Gold Standard Mood Stabilizer

Lithium is still the first-line therapy for BD, even with its mechanism of action remaining only partially understood [142, 143]. A systematic review and meta-analysis, including seven clinical trials reports on the efficacy and effectiveness of lithium, revealed that it remains the most efficient long-term treatment option for preventing overall mood switches, especially for managing manic episodes [144]. Purinergic signaling has been suggested as one of the systems mediating the biological effects of lithium, either as a neuroprotective or a nephrotoxic drug [145–148]. It was previously shown that lithium increases ATP and AMP

hydrolysis, and is neuroprotective against ATP-induced cellular death by acting on P2X7R in rat hippocampal slices [149]. More recently, an *in vitro* study conducted in murine neuronal and microglial cell lines corroborated the neuroprotective action of lithium against ATP-induced cell death and revealed a neuronal rather than a microglial response for this effect [145]. Molecular studies using a multinuclear, multi-dimensional, solid-state, nuclear magnetic resonance approach have shown that lithium binds to ATP [150, 151], suggesting a direct mode of action via a lithium-ATP complex in which its consequences should be further explored *in vitro* and *in vivo*.

### 4.2 The P2X7R Antagonism

P2X7R antagonism has been shown as a promising BD therapeutic candidate in preclinical models of mania. In addition to the translational limitations of modeling bipolar disorder in animals, amphetamine-induced hyperactive locomotion is still the most accepted and widely used model to mimic manic-like behavior, helping with the investigation of the molecular basis of mania. Both the pharmacological blockade and the genetic deletion of the P2X7R were demonstrated to be effective in preventing the hyperlocomotion induced by amphetamine [152–155]. Still, it was demonstrated that this receptor plays a role in the sustained neuroinflammation observed in a preclinical model of mania [152], and the observed behavioral effects on amphetamine-induced hyperlocomotion might be via dopaminergic and astrogliosis modulation [153] (Fig. 1d).

Despite the preclinical potential herein described, to our knowledge, there is no clinical trial currently investigating antagonists of P2X7R in patients with BD. The slow progression in this field might be due to the inherent challenges to developing brain penetrant P2X7R antagonists [155–158]. A few compounds have been identified, including JNJ-54175446 [159] and JNJ-55308942 [160], as well as P2X7R positron emission tomography-computed tomography-identified ligands, which can potentially accelerate the transition into clinical drug development for neuropsychiatric disorders [161]. The first investigational P2X7R antagonists have completed phase I trials. In a randomized single-ascending dose study in 77 healthy human subjects, JNJ-54175446 in doses from 0.5 to 600 mg showed a safe and successful dose-dependent response, attenuating the P2X7R-mediated interleukin-1 $\beta$  release from isolated peripheral blood cells (indicating P2X7R antagonism) [162]. The compound demonstrated a robust brain target engagement by using positron emission tomography imaging for P2X7R [163]. In addition, by using an oral dexamphetamine challenge model in 64 healthy male individuals in a randomized, double-blind, placebo-controlled, multiple ascending dose trial for the P2X7R antagonist JNJ-54175446, it was demonstrated that

this compound was well tolerated and effective in suppressing ex vivo lipopolysaccharide-induced release of cytokines (an indicator of P2X7R antagonism). A proof-of-concept study also showed increased locomotion and mood-elevating effects of 50–450 mg JNJ-54175446 administration over a baseline oral dexamphetamine (20 mg) challenge paradigm in a randomized, double-blinded, placebo-controlled, multiple ascending dose, crossover trial in 64 healthy male subjects [164]. The potential mood-modulating outcome observed can be considered of great relevance in the context of BD, although no specific trial addressing these patients has been proposed yet. Additionally, future trials should seek stronger external validity, enlarging the sample size, and minimizing stratification per age, sex, or other unjustified exclusion criteria.

Taken together, these studies reveal an interesting potential for clinical antagonism of P2X7R, which has been explored in different CNS disorders, such as amyotrophic lateral sclerosis [165] and MDD. A randomized, placebo-controlled, double-blind trial is currently recruiting patients with MDD to primarily evaluate the effect of 50 mg/day JNJ-54175446 on depressive symptoms scores after 8 weeks of treatment compared to baseline (ClinicalTrials.gov Identifier: NCT04116606).

However, to our knowledge, no ongoing clinical trials are being conducted with any of the novel compounds for BD. At this stage, we can only speculate on the reasons: one possibility is related to pharmaceutical interests, given that MDD is still the most disabling psychiatric disease causing substantial social and economic impact; other than that it might also rely on the fact that the current evidence supporting the role of P2X7R in mood disorders is much more robust towards MDD. This should be taken as an encouragement for further investigation and validation of emerging hypotheses addressing BD through a purinergic perspective.

### 4.3 The Adenosine and UA Balance

Notably, drugs that increase adenosine levels, such as dipyridamole and allopurinol, have been investigated as adjuvant purinergic modulators for the treatment of BD [54, 166]. Dipyridamole is an antiplatelet and antithrombotic drug with a complex mechanism of action, including the inhibition of cellular adenosine reuptake [167, 168]. Allopurinol, in its turn, is an urate-lowering drug primarily acting in decreasing purine degradation through the inhibition of xanthine oxidase, thus treating hyperuricemia (high UA levels) [169]. Allopurinol has been used in different clinical contexts that include: (1) the management of patients with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, UA lithiasis, and/or nephropathy) [170]; (2) the management of patients with leukemia, lymphoma, and malignancies who are experiencing elevations

of serum and urinary UA levels due to the cancer therapy [171]; and (3) the management of patients with recurrent calcium oxalate kidney and urinary calculi whose daily UA excretion exceeds 800 mg/day in male patients and 750 mg/day in female patients [172, 173]. Although no direct evidence has confirmed a causal correlation, an allopurinol-driven UA reduction is thought to result in increased adenosine levels [54].

The first case report exploring the therapeutic potential of allopurinol in BD found an improvement in manic symptoms and a decrease in peripheral UA levels in two treatment-resistant patients with mania associated with hyperuricemia [174]. A double-blind, randomized, placebo-controlled trial including 41 patients with BD with moderate-to-severe mania evaluated the effect of allopurinol (300 mg/day), lithium, and haloperidol compared to placebo for 8 weeks, observing an improvement of manic symptoms induced by allopurinol [175]. Similarly, a double-blind, randomized, placebo-controlled study investigated the use of a higher dose of allopurinol (600 mg/day,  $n = 60$ ) and dipyridamole (200 mg/day,  $n = 60$ ) compared to placebo ( $n = 60$ ) in addition to lithium for 4 weeks. This study demonstrated that allopurinol not only improves manic symptoms in comparison to dipyridamole and placebo, but also correlates with decreased plasma UA levels [176]. Likewise, 50 in-patients with acute mania received allopurinol (600 mg/day) or placebo in addition to sodium valproate (15–20 mg/kg) for 4 weeks in a randomized, placebo-controlled, double-blind trial, resulting in a similar antimanic action of allopurinol that was correlated with UA levels [177] (Fig. 1d).

In contrast, a nation-wide population-based longitudinal study in Denmark used a regression analysis to investigate new drug candidates for BD but no association between allopurinol and a positive outcome was found [178]. Additionally, a small double-blind, randomized, placebo-controlled trial pilot on 27 patients with BD investigated the addition of allopurinol or placebo to the BD standard treatments [179]. The study did not find any effect of allopurinol on manic symptoms but revealed a greater therapeutic response in patients restricted to caffeine [179]. These findings suggest that caffeine intake should be both better monitored and specifically addressed in future studies involving adenosinergic compounds for mood [179]. In addition, a large multi-center placebo-controlled trial performed with 180 patients with BD in acute manic episodes over 6 weeks with allopurinol (300 mg/day) or placebo added to the standard BD treatment also showed no antimanic effect of allopurinol [180]. However, it is essential to note that these two studies share a few limitations, including the heterogeneity of the concurrent treatment that patients were submitted to, which makes isolating the effect of allopurinol challenging. Furthermore, it should

be considered that Fan et al. had a very small sample size [179] and Weiser et al. used the lowest dose of allopurinol [180], which might have limited the efficacy of the drug.

Nevertheless, a systematic review and meta-analysis have combined all the randomized controlled trials that used allopurinol and dipyridamole as adjuvant therapies in BD. This study promisingly revealed an overall significant reduction in manic symptoms in participants receiving the purinergic modulators compared with placebo [54] (Fig. 1d). Subsequently, further systematic reviews and meta-analyses of randomized controlled trials focusing on allopurinol administration revealed a small-to-moderate effect size along with existent but limited beneficial effects of allopurinol as an add-on treatment for BD [181, 182]. It must be critically observed that the efficacy might be related to the primary antimanic medication regimen, with lithium showing the most promising combination [182]. Finally, a recent meta-review and critical appraisal of the existing meta-analyses of randomized placebo-controlled trials have classified the current evidence as of low quality, confirming a higher efficacy of allopurinol over placebo on attenuating manic symptoms [183]. Considering the limited evidence so far, the potential benefit of allopurinol as an adjunctive treatment for mania requires further investigation.

## 5 Limitations and Future Perspectives

The literature here discussed pointing to the role of purinergic signaling in BD pathophysiology and highlighting new potential therapeutic targets for drug development still relies mostly on basic and preclinical research. While *in vitro* studies bring to light cellular and molecular mechanisms involved in specific pathophysiological pathways linked to BD, their overall health impact and clinical relevance in the psychiatric clinic must be taken as minimal. Similarly, animal models are extremely limited in capturing the complexity of human diseases, particularly psychiatric disorders. Current animal models of mania fail on mimicking hypomanic and cycling states, and are mostly based on hyperlocomotion behavior, whereas manic behavior in humans is much more complex and involves several psychosocial, cognitive, and emotional facets. In addition, the difficulty of assertively assessing the neurobiological traits that distinguish bipolar depression from unipolar depression in preclinical models also limits the applicability and efficacy of potential drugs designed to target general aspects of a depressive episode in BD.

With these limitations in mind, the new generation of P2X7R antagonists configures the most promising new phase of accelerated discoveries to either monotherapies or adjunctive therapies for BD and related disorders that affect the CNS. The use of allopurinol as an

add-on therapy for BD, while promising and relatively well explored, still has many roadblocks associated with study design, heterogeneity of primary BD medication, as well as the doses and length of administration, limiting consistent conclusions from being drawn. Future research should focus on additional well-designed translational approaches, with more robust and clinically-oriented pre-clinical studies followed by randomized multi-center clinical trials with larger sample sizes. Special attention should be directed towards identifying biomarkers for BD to be used both as diagnostic tools and disease-specific targets for drug development. Notably, new methods to manage suicidal behavior, neuroinflammation, and neurotransmission imbalance, especially dopaminergic dysfunction, are of great relevance for BD.

## 6 Conclusions

Although limited clinical data are currently available, extensive basic and preclinical research points to the purinergic system as an important modulator of mood in the context of BD. Here, we highlighted a few promising purinergic targets and compounds to be further explored, including the modulation of P2X4R, A<sub>1</sub>R, A<sub>2A</sub>R, and P2Y1R. We encourage future research aiming to clarify the applicability, safety, and efficacy of current and new purinergic-targeting candidates such as allopurinol, adenosinergic compounds, and the novel P2X7R antagonists as therapeutic approaches for BD.

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