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# Aspirin for recurrence prevention in bipolar disorder—Promising, yet clinically understudied?

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## 1 | BACKGROUND

Current available maintenance pharmacotherapy for bipolar disorder (BD) leaves ample room for improvement. Up to 50% of patients with BD do not respond adequately to available treatments and still suffer from manic and/or depressive episodes. Although a number of pharmaceutical companies have invested in novel medications, none of the recently developed compounds has shown efficacy for recurrence prevention.

Given that BD is associated with dysregulations of the immune system, there is increasing interest in the therapeutic potential of immune-modulating medications. Although aspirin (acetylsalicylic acid) has been investigated to treat depressive symptoms,<sup>1</sup> low-dose (typically  $\leq 150$  mg/day) aspirin may be a particularly promising candidate for recurrence prevention: it is well tolerated, even with long-term use, well absorbed, passes the blood-brain barrier, and likely exerts anti-inflammatory effects in both the brain and the periphery.

In this perspective article, we will give an overview of the neuropharmacodynamics of (low-dose) aspirin, reflect on the published clinical studies and argue that aspirin is a promising, yet understudied option for recurrence prevention.

## 2 | PATHOPHYSIOLOGICAL MECHANISMS

Aspirin can exert its effect on the neuroimmune system in BD via two pathways: modification of the cyclooxygenase enzymes (COX

enzymes) and by stimulation of myelination. Aspirin is unique among the NSAIDs in that it covalently modifies COX-1 and COX-2 where it has differential effects.<sup>2</sup> Aspirin treatment of COX-1 irreversibly inhibits the cyclooxygenase activity of the enzyme and subsequently the production of prostaglandin G<sub>2</sub> (PGG<sub>2</sub>), blocking the conversion of arachidonic acid (AA) to prostaglandins and thromboxane A<sub>2</sub>. In the brain, COX-1 is predominantly expressed by microglia, known to be activated in BD. Preclinical evidence suggests that inhibition of COX-1 is neuroprotective after intracerebroventricular administration of lipopolysaccharide (LPS).<sup>2</sup> In contrast to full inhibition of COX-2 by selective COX-2 inhibitors, which is thought to have detrimental effects by increasing leukocyte recruitment into the brain and exacerbating tissue damage,<sup>2</sup> aspirin acetylation of COX-2 results in a shift in reaction specificity, converting enzyme activity from a cyclooxygenase to a lipoxigenase. Lipoxigenase activity results in the generation of anti-inflammatory mediators such as lipoxin A<sub>4</sub> and 15-epi-lipoxin A<sub>4</sub>, as well as docosahexaenoic acid (DHA) to 17-(R)-OH-DHA. The increase of these anti-inflammatory lipoxigenase metabolites is dose dependent, being increased in low-dose aspirin treated humans in a randomized trial by Chiang et al. Interestingly, aspirin shares these effects with lithium synergistically, which was found to reduce rat brain COX-2 activity and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) concentration, while increasing brain concentrations of DHA-derived anti-inflammatory metabolites.

Lithium and low-dose aspirin in BD may have an additional synergistic mode of action, involving the myelination of white matter

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tracts.<sup>3</sup> Results from anatomical magnetic resonance imaging (MRI) and more recent whole-brain diffusion tensor imaging (DTI) studies suggest widespread white matter abnormalities in BD, associated with mood episodes and cognitive functioning. A DTI study that we performed demonstrated myelination aberrations in lithium-using patients with BD compared to non-lithium-using patients in large white matter fibers, comparable to observations made in another DTI study by Benedetti et al. Based on these observations, it has been suggested that lithium may have a counteracting effect on white matter microstructural disturbances, possibly being one of its therapeutic mechanisms, via a known inhibition of glycogen synthase kinase 3 beta (GSK-3 $\beta$ ). Interestingly, low-dose aspirin was also found to have a stimulating effect on myelin-forming oligodendrocytes in mice,<sup>3</sup> potentially enhancing the effect of lithium via this route. In oncological research, aspirin is known to have an inhibitory effect on GSK-3 $\beta$  as well.

### 3 | CLINICALLY UNDERSTUDIED

Aspirin has been investigated in only three published clinical studies on treatment of mood and medication side effects in BD.

Savitz et al. tested the efficacy of aspirin and minocycline as augmentation therapy for bipolar depression.<sup>1</sup> Ninety-nine depressed outpatients with BD were enrolled in a 6 week, double-blind, placebo-controlled trial, and randomized to one of four groups with equal allocation probability: active minocycline (100 mg b.i.d.) + active aspirin (81 mg b.i.d.) (M + A); active minocycline + placebo aspirin (M + P); placebo-minocycline + active aspirin (P + A); and placebo-minocycline + placebo aspirin (P + P). When all four arms were included in the analysis, there was a main effect of aspirin on depressive symptoms that was driven by both the M + A and the P + A groups ( $p$ (two-tailed) = 0.019, odds ratio = 3.7, number needed to treat = 4.0).

Stolk et al performed a pharmacoepidemiological study related to BD<sup>4</sup> in which medication histories on subjects who had been prescribed lithium were collected using health care registry data. After stratification of drug classes that inhibit phospholipase A2 (PLA2) and/or COX enzymes, and duration of use, incidence density (ID) of medication events (dose increase or substance change) was compared as a proxy for clinical worsening. Low-dose aspirin produced a statistically significant duration-independent reduction in the relative risk of clinical deterioration in subjects on lithium (ID ratio 0.82), whereas other NSAIDs and glucocorticoids did not.

Saroukhani et al assessed the effect of 240 mg aspirin on lithium-related sexual dysfunction in 32 men with stable bipolar affective disorder in a 6 week randomized, double-blind, placebo-controlled study.<sup>5</sup> At the end of the study, patients in the aspirin group showed significantly greater improvement in total sexual function (63.9% improvement from baseline) and erectile function domain (85.4% improvement from baseline) scores than the placebo group (14.4% and 19.7% improvement, respectively). The mood symptoms remained stable over the course of the study.

There were no severe adverse events related to aspirin in any of these studies. Of particular importance in BD, low-dose aspirin does not increase serum lithium, contrary to other NSAIDs.

## 4 | DISCUSSION

The study by Savitz et al points toward an ameliorating effect of aspirin on depressive symptoms in BD. Since the pathophysiological action of immune modulators primarily focuses on improving the stability of the underlying dysregulated immune and glial cells, they may be even more effective in preventing recurrences.

It is interesting that this hypothetical recurrence-preventing mode of action of low-dose aspirin is supported by the pharmacoepidemiological study by Stolk et al. In this study, low-dose aspirin was found to have a statistically significant duration-independent reduction in the relative risk of clinical deterioration, when compared to subjects not using aspirin.<sup>4</sup> Indeed, studies that investigated cytokines, gene-expression, T-cell populations, and CRP across mood states, including those from our group, have shown the immune system to be more severely dysregulated during mood episodes. Nevertheless, clinical trials to improve mood stability and reduce the recurrence rate by administration of aspirin to stabilize the immune system in (a more immune dysregulated subgroup of) patients with BD have never been performed. In conclusion, the high burden of illness in combination with the limited available treatment options make the clinical investigation of a recurrence-preventing mode of action of low-dose aspirin in BD an important endeavor. Since aspirin's patent has passed historically long ago, it is unlikely pharmaceutical companies will investigate this possible new indication. However, when proven to be efficacious in patients with BD, this would be of great clinical relevance since aspirin is well tolerated, has other beneficial health effects, is affordable, and therefore would have a strong favorable cost/benefit ratio, emphasizing the importance of public funding for such trials.

### AUTHOR CONTRIBUTION

All authors contributed in the concept and design of the study and authors have seen and approved the final version of this manuscript.

### CONFLICTS OF INTEREST

None of authors have any financial and personal relationships with other people or organizations to report that could inappropriately influence (bias) this work.

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