

Recently discovered properties of aspirin may be doubly helpful in bipolar disorders.

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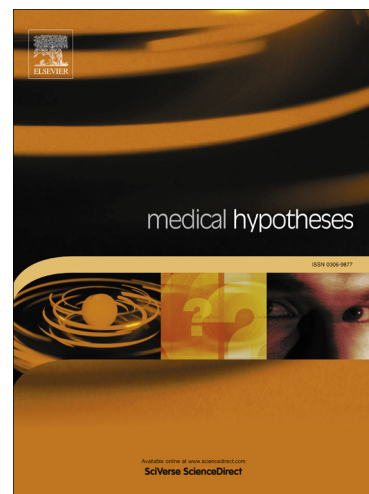
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1 Letter

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3 **Recently discovered properties of aspirin may be doubly helpful in bipolar**
4 **disorders**

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6 Running title : aspirin in bipolar disorders

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49 word count 501

Dear editor,

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3 While aspirin is an ancient folk remedy sold over-the-counter for more than a century
4 and since used in a lot of disorders, new properties of aspirin are still discovered to
5 this day.
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9 Aspirin may be doubly helpful in bipolar disorder. First, bipolar disorder may be the
10 result of a pre-inflammatory multisystemic disorder[1] that affects not only mood
11 regulation but also cardiovascular status. Patients with bipolar disorder may hence be
12 seen as a population at intermediate risk for cardiovascular disease, and aspirin may
13 be helpful in primary prevention in this population. However trials are warranted to
14 confirm the benefit of aspirin in this indication [5].
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21 Second, new properties of aspirin have been recently discovered, especially anti-
22 inflammatory properties, which may be particularly interesting in bipolar disorder that
23 is strongly associated with immunologic and inflammatory dysfunctions [6]. If bipolar
24 disorders may result in some cases in a chronic inflammation of central nervous
25 system (CNS) (due to microglia activation), fixing this inflammation may thus
26 improve mood symptomatology and possibly prevent cognitive decline associated
27 with this disorder. ASA is 50 to 100-fold more potent in inhibiting platelet
28 cyclooxygenase 1 (COX-1) than monocyte cyclooxygenase 2 (COX-2) activity [2].
29 Choi et al [3] proposed in a recent review to reconsider the prevailing hypothesis that,
30 by being the isoform induced in response to inflammatory stimuli, COX-2 is the most
31 appropriate pharmacological target for anti-inflammatory therapy, and suggested that
32 COX-1, owing to its predominant localization in microglia, is the major player in
33 mediating the inflammatory response. It has even been suggested that mood
34 stabilizers and antidepressive agents may improve depressive symptomatology by the
35 inherent anti-inflammatory properties of some of them.
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49 Preliminary data obtained in bipolar disorders suggest beneficial effects on depressive
50 symptoms that are improved using aspirin (acetyl salicylic acid (ASA)) in low doses
51 (in which ASA would inhibit COX-1 but not COX-2)..
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54 In a large pharmaco-epidemiological study, Stolk et al [4] tested in 5145 patients
55 receiving lithium whether non-steroidal anti-inflammatory drugs (NSAIDs) or
56 glucocorticoids would improve bipolar symptoms (based upon the assumption that
57 lithium treatment is relatively specific to individuals with bipolar disorders). The
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main outcome measure was a calculated incidence density of medication events (change in the type or numbers of psychotropic medications prescribed or increase (>30%) in the psychotropic drug dose). Subjects receiving low-dose (≤ 80 mg/day) aspirin were 17% less likely to have a medication event, a finding that remained significant after adjusting for age, sex, chronic disease score and healthcare utilization. Aspirin and lithium may also exert synergistic effects in forming anti-inflammatory brain metabolites [4]. These preliminary observations thus appeared consistent with the hypothesis that COX-1 inhibitors can reduce neuro-inflammatory processes with consequent beneficial improvement of bipolar illness.

It was relatively recently discovered that aspirin administration triggers the biosynthesis of the so-called aspirin-triggered lipoxins (ATLs) (the term "lipoxin" is an acronym for lipoxygenase interaction products). Lipoxins and ATLs are generated from arachidonic acid and are considered to act as 'braking signals' in inflammation, dampening the second-phase inflammatory response via the modulation of microglia [7]. Microglia are considered the "resident macrophages" of the brain and play an essential role in innate immunity, homeostasis, and neurotropic support in the central nervous system. Microglia perform routine maintenance and immune surveillance in their resting state. Once activated, either by injury or an immune stimulus, microglia secrete a variety of pro-inflammatory molecules that may cause neurodegeneration if their up-regulation lasts for an extended period of time [8]. Aspirin also modulates innate and adaptive immune responses : aspirin can suppress the lymphocyte B antibody-mediated humoral immune response, as well as the neutrophil and monocyte/macrophage-mediated innate immune responses (by decreasing inter alia neutrophil cells' extravasation and their adherence to the endothelial lining, a distinctive step in the innate immunity) (for a complete review, see [9]). In addition to its strictly speaking anti-inflammatory and immune properties (that are also neuroprotective), aspirin was found to enhance adenosine production [10], to modulate nitric-oxide synthesis [11] and to inhibit nuclear factor-kappa B (NF- κ B) transcriptional pathway [12], all these mechanisms potentially play a role in its neuroprotective properties.

Basselin et al demonstrated that aspirin extinguishes CNS inflammation at low and high therapeutic doses in rats [13]. In humans, the anti-inflammatory properties of low doses of aspirin have also been demonstrated in a population of subjects with

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metabolic syndrome (that is frequently comorbid with bipolar disorders) : 100-300 mg/d aspirin decreased blood levels of Tumor Necrosis Factor alpha (TNF-alpha), Interleukine 6 (IL-6) and high sensitivity C-reactive protein (hs-CRP), three major inflammatory markers that have been found to be disturbed in patients with bipolar disorders [14] .

Aspirin may be doubly helpful in bipolar disorders, for prevention of cardiovascular events as well as an anti-inflammatory drug that may influence and protect the central nervous system.

Conflicts of interest : All authors declared no conflict of interest in the last 2 years.

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- [1] M. Leboyer, I. Soreca, J. Scott, M. Frye, C. Henry, R. Tamouza, *et al.*, Can bipolar disorder be viewed as a multi-system inflammatory disease?, *J Affect Disord* **141** (2012), pp. 1-10.
- [2] F. Cipollone, P. Patrignani, A. Greco, M.R. Panara, R. Padovano, F. Cuccurullo, *et al.*, Differential suppression of thromboxane biosynthesis by indobufen and aspirin in patients with unstable angina, *Circulation* **96** (1997), pp. 1109-1116.
- [3] S.H. Choi, S. Aid and F. Bosetti, The distinct roles of cyclooxygenase-1 and -2 in neuroinflammation: implications for translational research, *Trends Pharmacol Sci* **30** (2009), pp. 174-181.
- [4] P. Stolk, P.C. Souverein, I. Wilting, H.G. Leufkens, D.F. Klein, S.I. Rapoport, *et al.*, Is aspirin useful in patients on lithium? A pharmacoepidemiological study related to bipolar disorder, *Prostaglandins Leukot Essent Fatty Acids* **82** (2010), pp. 9-14.
- [5] C. Crump, K. Sundquist, M.A. Winkleby and J. Sundquist, Comorbidities and mortality in bipolar disorder: a Swedish national cohort study, *JAMA Psychiatry* **70** (2013), pp. 931-939.

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- [6] K. Munkholm, M. Vinberg and L. Vedel Kessing, Cytokines in bipolar disorder: a systematic review and meta-analysis, *J Affect Disord* **144** (2013), pp. 16-27.
- [7] D.W. Gilroy, The role of aspirin-triggered lipoxins in the mechanism of action of aspirin, *Prostaglandins Leukot Essent Fatty Acids* **73** (2005), pp. 203-210.
- [8] R. Medeiros, M. Kitazawa, G.F. Passos, D. Baglietto-Vargas, D. Cheng, D.H. Cribbs, *et al.*, Aspirin-triggered lipoxin a4 stimulates alternative activation of microglia and reduces Alzheimer disease-like pathology in mice, *Am J Pathol* **182** (2013), pp. 1780-1789.
- [9] M. Hussain, A. Javeed, M. Ashraf, Y. Zhao, M.M. Mukhtar and M.U. Rehman, Aspirin and immune system, *Int Immunopharmacol* **12** (2012), pp. 10-20.
- [10] B.N. Cronstein, M.C. Montesinos and G. Weissmann, Sites of action for future therapy: an adenosine-dependent mechanism by which aspirin retains its antiinflammatory activity in cyclooxygenase-2 and NFkappaB knockout mice, *Osteoarthritis Cartilage* **7** (1999), pp. 361-363.
- [11] D. Taubert, R. Berkels, N. Grosser, H. Schroder, D. Grundemann and E. Schomig, Aspirin induces nitric oxide release from vascular endothelium: a novel mechanism of action, *Br J Pharmacol* **143** (2004), pp. 159-165.
- [12] M. Grilli, M. Pizzi, M. Memo and P. Spano, Neuroprotection by aspirin and sodium salicylate through blockade of NF-kappaB activation, *Science* **274** (1996), pp. 1383-1385.
- [13] M. Basselin, E. Ramadan, M. Chen and S.I. Rapoport, Anti-inflammatory effects of chronic aspirin on brain arachidonic acid metabolites, *Neurochem Res* **36** (2011), pp. 139-145.
- [14] X.R. Gao, C.M. Adhikari, L.Y. Peng, X.G. Guo, Y.S. Zhai, X.Y. He, *et al.*, Efficacy of different doses of aspirin in decreasing blood levels of inflammatory markers in patients with cardiovascular metabolic syndrome, *J Pharm Pharmacol* **61** (2009), pp. 1505-1510.

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