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A critical review of the efficacy of non-steroidal anti-inflammatory drugs in depression

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) require further investigation given mixed results regarding efficacy. We critically and systematically reviewed the literature to determine whether selective COX-2 and non-selective COX inhibitor NSAIDs as adjuncts or monotherapy affect depressive symptoms. Electronic databases including Embase, PsycINFO, Ovid Medline, ScienceDirect, Google Scholar and the Cochrane Central Register of Controlled Trials database were searched up to September 2013. We utilised randomised controlled trials (RCTs), cohort studies and an open label study examining the efficacy of NSAIDs as adjuncts or monotherapy on depressive symptoms in subjects without major comorbidities. There were a total of 6 studies exploring the efficacy of selective COX-2 inhibitor NSAIDs on depressive symptoms with a total of 2706 subjects from 6 RCTs. 4 of the RCTs showed a significant effect of NSAIDs; 2 demonstrated no effect. There were a total of 5 studies exploring the efficacy of non-selective COX inhibitor NSAIDs on depressive symptoms with a total of 7978 subjects. There was 1 RCT, 3 cohort studies and 1 open label pilot study. The RCT failed to show a significant result. 1 of the retrospective cohort studies showed a positive result, with the other 2 showing no effect. The pilot study showed a positive result for NSAIDs. These studies demonstrated significant methodological heterogeneity (i.e. age range, sex, presence of antidepressant use, method of depression measure, severity of depressive symptoms, duration and study design (RCT vs. cohort)). The efficacy of NSAIDs on depressive symptoms appears negligible, however firm conclusions are difficult given the inconsistent findings and substantial methodological heterogeneity. Further high quality research is needed to explore NSAID efficacy in clinical and biological subtypes of depression, as monotherapy and adjunct with various antidepressants, and across various ages.

1. Introduction

The Global Burden of Disease 2010 Study suggests that unipolar depression currently ranks 11th for disability adjusted life years, a 37% increase since 1990 (Murray et al., 2012). Hence, increased effort is required to find novel therapeutic agents for the treatment of depression (Licinio, 2011) given this high and rising burden of depression (Holtzheimer et al., 2008, Murray et al., 2012). Additionally, more than 50% of patients on antidepressants will not achieve remission following initial treatment (Trivedi et al., 2006), and nearly one-third will not achieve remission even following several treatment steps (Rush et al., 2006a,b).

Inflammatory processes are suggested to play an important part in the development of depression and it is believed that inflammation may be a promising target in the treatment and prevention of depression (Baune et al., 2012, Dantzer et al., 2008, Eyre and Baune, 2012, Maes, 1999, Miller et al., 2009). A meta-analysis by Dowlati et al. (2010) concludes that a pro-inflammatory state is associated with clinical depression. This study pooled 24 cross-sectional studies involving unstimulated measurements of serum cytokines in patients meeting Diagnostic and Statistical Manual (DSM) criteria for major depression and found significantly higher concentrations of tumour necrosis factor (TNF)-α and interleukin (IL)-6 in depressed compared with control subjects. From a neurobiological perspective, the pro-inflammatory state found in depression, mediated via elevations in TNF-α, IL-6, interferon (IFN)-γ and IL-1β, is found to impair hippocampal (HC) neuroplasticity (e.g. neurogenesis, synaptic plasticity, long-term potentiation (LTP)), induce glucocorticoid insensitivity of the hypothalamo-pituitary-adrenal (HPA) axis, increase oxidative stress in the HC, and reduce serotonin levels and create neurotoxic serotonergic metabolites

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; COX, cyclooxygenase; RCT, randomised controlled trial; DSM, Diagnostic and Statistical Manual; TNF, tumour necrosis factor; IL, interleukin; IFN, interferon; HC, hippocampus; LTP, long-term potentiation; HPA, hypothalamo-pituitary-adrenal; 3-HK, 3-hydroxykynurenine; QA, quinolinic acid; SSRI, selective serotonin reuptake inhibitor; OR, odds ratio; WMD, weighted mean difference; CI, confidence interval; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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(i.e. 3-hydroxykynurenine (3-HK) and quinolinic acid (QA)) (Dantzer et al., 2008, Eyre and Baune, 2012, Leonard and Maes, 2012, Miller et al., 2009, Moylan et al., 2012).

Given this clinical and mechanistic relationship between inflammation and depression, both selective cyclooxygenase (COX)-2 and non-selective COX inhibitor non-steroidal anti-inflammatory drugs (NSAIDs) have been investigated as possible adjuncts in the treatment of depression, with mixed results (Akhondzadeh et al., 2009, Almeida et al., 2010, Almeida et al., 2012, Fields et al., 2011, Fond et al., 2013, Gallagher et al., 2012, Muller, 2013, Muller et al., 2006, Musil et al., 2011, Nery et al., 2008, Pasco et al., 2010, Shelton, 2012, Uher et al., 2012, Warner-Schmidt et al., 2011). Studying the efficacy of these compounds is important given that they are widely prescribed and have been associated with reduced efficacy of antidepressants (Shelton, 2012). These drug compounds have been examined with a number of study designs, such as retrospective cohort studies (Almeida et al., 2010, Almeida et al., 2012, Fields et al., 2011, Gallagher et al., 2012, Pasco et al., 2010), randomized-controlled trials (RCTs) (Fields et al., 2011, Muller et al., 2006, Musil et al., 2011, Nery et al., 2008) and nested case–control studies (Pasco et al., 2010). Some studies have found positive antidepressant effects (Akhondzadeh et al., 2009, Muller et al., 2006, Nery et al., 2008, Pasco et al., 2010), others have found no effect (Almeida et al., 2010, Fields et al., 2011, Uher et al., 2012) and yet others have found detrimental effects suggesting that NSAIDs may reduce the antidepressant effect of selective serotonin reuptake inhibitors (SSRIs) (Gallagher et al., 2012, Warner-Schmidt et al., 2011). These mixed results may be due to various reasons such as differing anti-depressant utilization and doses, the use of varying selective COX-2 and/or non-selective COX inhibitor NSAIDs, study design, age of study population, as well as study populations with varying degrees of depressive symptomatology and presence of general medication conditions. Common selective COX-2 and non-selective COX inhibitor NSAIDs are outlined within Table 1.

The differing efficacy of selective COX-2 vs. non-selective COX inhibitor NSAIDs raises questions about their pharmacological actions. It appears that the understanding of the physiological and pathophysiological effects of COX-1 and 2 is limited. For example, COX-1 is predominantly pro-inflammatory and detrimental to the brain (Aid and Bosetti, 2011), whereas COX-2 can exert both beneficial and detrimental effects on the brain (see for review (Berk et al., 2013)). A meta-analysis of RCTs suggests that celecoxib, a selective COX-2 inhibitor NSAID, has a therapeutic effect when used adjunctively with other antidepressants (Na et al., 2013), however, mechanistic evidence suggests that selective COX-2 inhibitor NSAIDs may actually increase neuroinflammation, Th1 immune responses and increase glial cell activation (Aid and Bosetti, 2011, Aid et al., 2008, Maes, 2012).

An early study by Muller et al. (2006) utilised a prospective (6 weeks), randomized, double-blind, add-on methodology to examine the therapeutic effect of 400 mg of celecoxib in addition to reboxetine on 40 patients suffering from an acute depressive episode. The celecoxib plus reboxetine group showed significantly greater improvement compared to the reboxetine-alone group (testing time × group: Greenhouse–Geisser-corrected $F = 3.220$; df 2.434; $p = 0.035$). A recent study by Gallagher et al. (2012) investigated the effects of NSAIDs (various classes) on depression in a population-based treatment cohort of 1528 outpatients with depression in a New England health care system. NSAID exposure was associated with a greater likelihood of depression classified as treatment resistant compared with depression responsive to SSRIs (odds ratio (OR) = 1.55, 95% CI = 1.21–2.00). This association was apparent in the NSAID-only group but not in those using other agents with NSAID-like mechanisms (i.e. selective COX-2 inhibitor NSAIDs and salicylates). Associations with the outcome were no longer significant in fully adjusted models. A recent meta-analysis by Na et al. (2013) has investigated the efficacy of adjunctive celecoxib treatment for patients with major depressive disorders. This analysis included only 4 double-blind, placebo-controlled, randomised trials investigating the efficacy and tolerability of adjunctive COX-2 inhibitors combined with antidepressants, compared with antidepressants and placebo. This analysis examined four studies with 150 patients in total. The patients receiving adjunctive celecoxib had significantly higher mean changes in the Hamilton Rating Scale for Depression scores between baseline and endpoint compared with those receiving placebo (weighted mean difference (WMD) = 3.26, 95% confidence interval; CI = 1.81 to 4.71). The group receiving adjunctive celecoxib also showed better remission (OR; OR = 6.58, 95% CI = 2.55 to 17.00) and response rates (OR = 6.49, 95% CI = 2.89 to 14.55) than the placebo group. Whilst this meta-analysis is useful, it is highly selective, has a small number of pooled participants (n = 150) and includes studies that capture only a short time frame in the treatment process. The studies all had reported low risk of bias, with the exception of Akhondzadeh et al (2009) whose allocation concealment method was unclear. It is unclear if the study by Hashemian et al. (2011) is peer-reviewed as it is a conference presentation abstract in a journal supplement. The Na et al. meta-analysis did not include studies examining non-selective NSAIDs.

Taken together, it remains to be critically and systematically investigated whether all NSAIDs have clinical effects on depressive symptoms, or if only selective COX-2 or non-selective COX inhibitor NSAIDs exert such effects, or no effects. In this critical systematic review, we have included a variety of studies that use selective COX-2 and non-selective COX inhibitor NSAIDs, as either monotherapy or adjuncts, and estimate their combined, as well as their individual clinical effects on depression. The purpose of a broader study inclusion is to highlight the methodological heterogeneity of the field, to suggest caution in drawing conclusions with respect to efficacy, to explore biological explanations and recommend future research strategies.

Table 1
Common selective and non-selective COX inhibitors.
References for table: (Solomon, 2014a,b).

Selective COX-2 inhibitors	Non-selective COX inhibitors
Celecoxib	Aspirin
Valdecoxib	Indomethacin
Parecoxib	Diclofenac
Lumiracoxib	Ketoralac
Etoricoxib	Ibuprofen
Rofecoxib	Naproxen
	Mefenamic acid
	Meloxicam

2. Methods and materials

2.1. Data sources

The literature search for this systematic review was carried out according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines as they apply to systematic reviews (Liberati et al., 2009). We searched Embase, PsycINFO, Ovid Medline, ScienceDirect, Google Scholar and the Cochrane Central Register of Controlled Trials database up to September 2013. We also manually scrutinized references cited in the systematically searched articles. To optimise sensitivity in searching clinical studies, we used the following basic terms: unipolar and bipolar depression, antidepressant, non-steroidal anti-inflammatory agent, clinical trial, observation study.

2.2. Study selection

Studies in the English language were selected for data extraction and analysis based on the following inclusion criteria: (a) RCTs and/or prospective cohort studies examining the efficacy of NSAIDs; (b) including adult participants (aged ≥ 16); and (c) examining for depressive symptoms by self- or clinician-reported scales, or by clinical interview. We