Progress in Neuro-Psychopharmacology & Biological Psychiatry 48 (2014) 79–85

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Efficacy of adjunctive celecoxib treatment for patients with major depressive disorder: A meta-analysis

Kyoung-Sae Na [a], Kang Joon Lee [b,*], Ji Sung Lee [c], Young Sung Cho [d], Han-Yong Jung [e]

[a] Department of Psychiatry, Gachon University Gil Medical Center, Incheon, Republic of Korea
[b] Department of Psychiatry, College of Medicine, Inje University Ilsan Paik Hospital, Goyang, Republic of Korea
[c] Biostatistical Consulting Unit, Soonchunhyang University Medical Center, Seoul, Republic of Korea
[d] Department of Psychiatry, Soonchunhyang University Cheonan Hospital, Cheonan, Republic of Korea
[e] Department of Psychiatry, Soonchunhyang University Bucheon Hospital, Bucheon, Republic of Korea

ARTICLE INFO

Article history:
Received 18 June 2013
Received in revised form 5 September 2013
Accepted 11 September 2013
Available online 20 September 2013

Keywords:
Depression
Inflammation
Meta-analysis
NSAID
Randomized controlled trials

ABSTRACT

Background: Numerous studies have reported that inflammation is closely associated with depression, and adjunctive non-steroidal anti-inflammatory drug (NSAID) treatment has been suggested as a novel therapeutic approach for depression.
Methods: We searched electronic databases including Medline, Embase, and the Cochrane Central Register of Controlled Trials. We only included randomized controlled trials comparing adjunctive NSAIDs with placebos for treating depressive episodes.
Results: Of the 654 retrieved entries, we identified four relevant studies with a total of 150 patients (75 NSAID patients and 75 placebo patients) with depressive episodes. All four studies used celecoxib as the NSAID. The patients receiving adjunctive celecoxib had significantly higher mean changes in the Hamilton Rating Scale for Depression scores between baseline and endpoint measurements compared with those receiving placebo (weighted mean difference = 3.26, 95% confidence interval; CI = 1.81 to 4.71). The adjunctive celecoxib group also showed better remission (odds ratio; 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. The all-cause drop-out rate was more favorable for the celecoxib group than for the placebo group (OR = 0.45, 95% CI = 0.18 to 1.13), although the statistical significance was not statistically significant ($p = 0.09$).
Conclusion: Adjunctive treatment with NSAIDs, particularly celecoxib, can be a promising strategy for patients with depressive disorder. Future studies with a larger sample size and longer study duration are needed to confirm the efficacy and tolerability of NSAIDs for depression.

1. Introduction

Major depressive disorder (MDD) is one of the most common psychiatric illnesses (Kessler et al., 2005). According to the World Health Organization (WHO), MDD is expected to be the second leading cause of disease burden by 2030 (Mathers and Loncar, 2006). However, despite the substantial disease burden of MDD, the remission rate with antidepressants is only approximately 60–70% (Rush et al., 2006). The low remission rate requires a more extensive pharmacological approach based on the established etiology for MDD, such as the use of anti-inflammatory medication.

Since Smith (1991) first suggested that macrophage-driven inflammatory activation might play an important role in the pathophysiology of depression (Smith, 1991), numerous studies have suggested that inflammatory activity is associated with depression. Evidence supporting the close relationship between inflammation and depression can be divided into several categories. First, pro-inflammatory cytokines including interleukin-6 (IL-6), interleukin-1beta (IL-1β), and tumor necrosis factor-alpha (TNF-α) are elevated in patients with depression (Dowlati et al., 2010). Second, peripheral inflammatory diseases such as coronary heart disease (Stapelberg et al., 2012) and rheumatoid arthritis (Dickens et al., 2002) have been highly associated with depression. Third, exogenous infusion of pro-inflammatory cytokines such as interferon-alpha (IFN-α)

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; CENTRAL, Cochrane Central Register of Controlled Trials; HRSD, Hamilton Rating Scale for Depression; MDD, Major Depressive Disorder; WHO, World Health Organization; IL-6, interleukin-6; IL-1β, interleukin-1beta; TNF-α, tumor necrosis factor-alpha; IFN-α, interferon-alpha; RCT, randomized controlled trial; DSM-IV, Diagnostic and Statistical Manual for Mental Disorders, fourth edition; DSM-IV-TR, DSM-IV, text revision; MADRS, Montgomery–Asberg Depression Rating Scale; WMD, weighted mean difference; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; LPS, lipopolysaccharide; IDO, indoleamine 2,3-dioxygenase; BDNF, brain-derived neurotrophic factors; STAR*D, Sequenced Treatment Alternatives to Relieve Depression; SSRI, selective serotonin reuptake inhibitor; GENDEP, Genome-Based Therapeutic Drugs for Depression; CNS, central nervous system; hs-CRP, high sensitivity C-reactive protein.

* Corresponding author at: Department of Psychiatry, College of Medicine, Inje University Ilsan Paik Hospital, 2240, Daehwa-dong, Ilsan-dong, Goyang 411-706, Republic of Korea. Tel.: +82 31 910 7260; fax: +82 31 910 7268.
E-mail address: lkj@paik.ac.kr (K.J. Lee).

0278-5846/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pnpbp.2013.09.006

can result in depression (Bonaccorso et al., 2002). Fourth, the severity of depression may be associated with the level of inflammatory markers (Suarez et al., 2003). Finally, antidepressants can exert anti-inflammatory effects in patients with MDD (Hannestad et al., 2011). Evidence supports the possibility that peripheral inflammatory responses manifest themselves in the central nervous system (CNS) in a process known as neuroinflammation. For example, pro-inflammatory cytokines, which have been considered to be principal mediators of inflammatory responses, can cross the blood–brain barrier through several mechanisms (Banks, 2006).

Given the established association between inflammation and depression, adjunctive use of anti-inflammatory drugs could be a novel therapeutic approach. Several clinical trials have been conducted to test the efficacy of anti-inflammatory drugs. Müller et al. first conducted a randomized controlled trial (RCT) to evaluate the efficacy and safety of an adjunctive cyclooxygenase-2 inhibitor, celecoxib, added to antidepressants (Müller et al., 2006). In that study, celecoxib combined with reboxetine had significantly better efficacy than did reboxetine combined with a placebo.

Herein, we report a meta-analysis of RCTs that was designed to evaluate the efficacy and tolerability of adjunctive non-steroidal anti-inflammatory drugs (NSAIDs) combined with antidepressants in patients with MDD.

2. Methods

2.1. Eligibility criteria

All extracted studies were assessed to meet the following criteria: (1) a double-blind, placebo-controlled, randomized trial investigating the efficacy and tolerability of adjunctive NSAIDs combined with antidepressants compared with antidepressants and placebo; (2) a diagnosis of MDD based on the criteria established in the Diagnostic and Statistical Manual for Mental Disorders, fourth edition (DSM-IV) (APA, 1994) or DSM-IV, text revision (DSM-IV-TR) (APA, 2000); and (3) the use of standard instruments to assess depression, such as the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) or the Montgomery–Asberg Depression Rating Scale (MADRS) (Cusin et al., 2011).

2.2. Information sources and search strategy

We searched Embase (1966 to present), Ovid Medline (1946 to present), and the Cochrane Central Register of Controlled Trials (CENTRAL) databases in May 2013. We also manually scrutinized references cited in the systematically searched articles. To optimize sensitivity in searching RCTs, we used the following basic terms: depression, antidepressive agents, non-steroidal anti-inflammatory agents, cyclooxygenase-2 inhibitors, and randomized controlled trial. There were no language restrictions.

2.3. Study selection

After two investigators (KS and KJ) independently reviewed all titles and abstracts identified by electronic and manual searches, the full-text articles of relevant studies were obtained. The two reviewers assessed the full study reports. When there were disagreements, they were resolved through discussion and consensus.

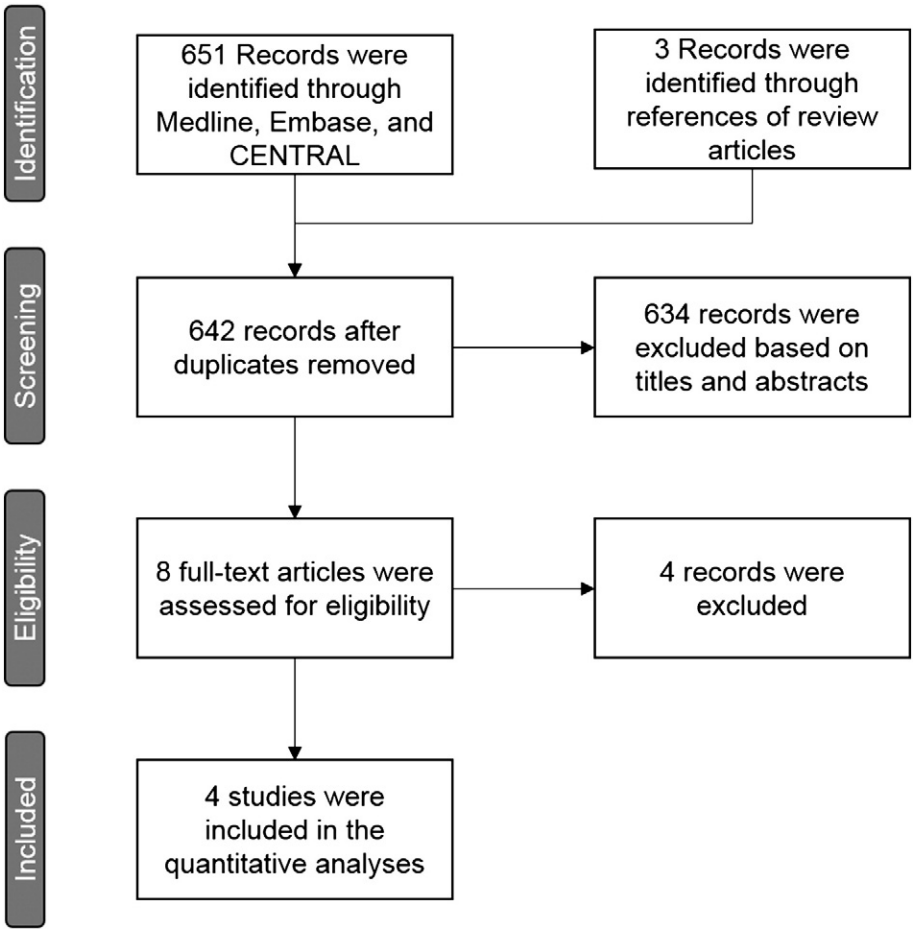

Fig. 1. Flow diagram of the study.