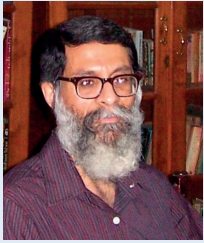




Antidepressant Augmentation With Anti-Inflammatory Agents

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Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

Antidepressant augmentation strategies are commonly employed to treat depressed patients who do not respond to antidepressant monotherapy. Neuroinflammatory mechanisms have been implicated in depression, and nonsteroidal anti-inflammatory drugs (NSAIDs) have been found effective in animal models of depression both in monotherapy and when used to augment antidepressant drugs. However, results with NSAIDs have been mixed in human observational studies, with both better and worse depression outcomes reported. Four small (pooled N = 160) randomized controlled trials suggest that celecoxib (200–400 mg/d) augmentation of antidepressant medication improves 4–6 week outcomes in major depressive disorder. There are no data, however, to support the use of celecoxib or other NSAIDs in antidepressant-resistant depression. There are also concerns about adverse events associated with NSAID treatment, and about pharmacodynamic drug interactions between these drugs and serotonin reuptake inhibitors. A reasonable conclusion for the present is that NSAID augmentation of antidepressants is, at best, a tentative approach in nonrefractory major depression.

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Clinical Problem

Ms L, a 38-year-old woman, has been diagnosed with an episode of major depression. She experienced her first episode of depression 5 years earlier and remitted with sertraline (150 mg/d). Sertraline was tapered and withdrawn after 18–20 months of uneventful maintenance therapy. She remained well, without medication, for about 3 years. She developed her second episode of depression about 5 months ago. The present episode has not responded to adequate trials of sertraline and venlafaxine (225 mg/d; her current medication). She is reluctant to augment venlafaxine with an atypical antipsychotic drug because of the risk of weight gain. Given that some studies have found antidepressant benefits with nonsteroidal anti-inflammatory drug (NSAID) augmentation, might the addition of an NSAID to her current antidepressant be a viable treatment strategy for her?

Introduction

A large body of evidence suggests that depression is associated with inflammatory changes in the brain and in the periphery and that immune activation, prostaglandin synthesis, and proinflammatory cytokine production may be involved in the mechanisms of depression through direct effects on monoamine levels, dysregulation of the hypothalamic-pituitary-adrenal axis, abnormal microglial cell activation, impaired neuroplasticity, and structural and functional brain changes.^{1–4} If this is true, then anti-inflammatory drugs may improve depression outcomes by attenuating the neuroinflammatory changes⁵ or by other mechanisms, such as increased norepinephrine and serotonin levels.⁶ Data from animal models show that NSAIDs in monotherapy^{7,8} and in combination with conventional antidepressants⁵ indeed attenuate indices of inflammation and depression. What do the clinical data show?

Clinical Benefits With Anti-Inflammatory Drugs in Depression

Diverse strands of evidence indicate possible clinically relevant antidepressant benefits with NSAIDs. For example, data extracted from five 6-week randomized controlled trials (RCTs) of NSAIDs in 1,497 patients with osteoarthritis showed that ibuprofen (2,400 mg/d), naproxen (1,000 mg/d), and celecoxib (200 mg/d) were each associated with significantly lower depression ratings than placebo; the greatest benefits were recorded with celecoxib.⁹ It is not clear, however, to what extent the better depression outcomes were due to better pain control. In this context, the large (N = 2,528) Alzheimer's Disease Anti-inflammatory Prevention Trial, conducted in cognitively normal elderly subjects, found that neither celecoxib (400 mg/d) nor naproxen (440 mg/d) influenced depression scores, even in the subgroup of subjects who were depressed at baseline.¹⁰ It therefore appears that NSAIDs in monotherapy do not improve depression when pain is not the indication for their prescription.

In a small (N = 24), uncontrolled, open-label study in depressed patients who had not responded to at least 4 weeks of selective serotonin reuptake inhibitor (SSRI) treatment, Mendlewicz et al¹¹ obtained response and remission rates of 52% and 43%, respectively, after 4 weeks of SSRI

Table 1. Important Findings From a Meta-Analysis of Celecoxib Trials in Antidepressant-Treated Major Depressive Illness¹²

1. Relative to placebo augmentation, celecoxib augmentation of antidepressant treatment was associated with a significant 3.3-point (95% CI, 1.2–5.3) advantage on the HDRS at week 4 and a significant 3.4-point (95% CI, 1.9–4.9) advantage at week 6.
2. The response rate was higher with celecoxib than with placebo (OR = 6.6; 95% CI, 2.5–17.0). The remission rate was also higher with celecoxib than with placebo (OR = 6.6; 95% CI, 2.7–15.9). However, pooled response and remission rates were not provided.
3. The odds of response and remission were attenuated after adjustment for possible publication bias; however, the findings (ORs of 3.7 and 4.5, respectively) remained statistically significant in favor of celecoxib. The HDRS advantage (3.0 at week 4) also remained significant after adjustment for publication bias.
4. To the extent that adverse effects were reported and compared between groups, celecoxib appeared to be well tolerated and no different from placebo.

Abbreviation: HDRS = Hamilton Depression Rating Scale.

augmentation with aspirin (160 mg/d). Marked improvement in the responder subgroup was apparent as early as within a week of initiation of the aspirin augmentation.

The best evidence available on the subject is for celecoxib. This evidence is examined in the next section.

Celecoxib RCTs: A Meta-Analysis

Faridhosseini et al¹² described a meta-analysis of the use of celecoxib as an antidepressant augmentation agent. These authors searched electronic databases, reference lists, and other sources and identified 5 placebo-controlled RCTs of celecoxib for the treatment of unipolar (4 RCTs) or bipolar (1 RCT) depression in adults. Only data from the 4 unipolar depression RCTs^{13–16} were included in the meta-analysis; one¹⁵ of these 4 RCTs had not been published as a full paper. Three studies were conducted in Iran,^{14–16} and 1, in Germany.¹³ The antidepressant that was augmented was sertraline (50–200 mg/d) in 2 RCTs, fluoxetine (40 mg/d) in 1, and reboxetine (4–10 mg/d) in the last. The dose of celecoxib was 200 mg/d in 1 RCT and 400 mg/d in the rest.

The sample size was 40 in each RCT; the pooled sample size was 160. The mean ages of the patients in the RCTs were 35–45 years, where information on this variable was available. Heterogeneity in the different analyses was low. Only 2 of the 4 RCTs were judged to be at low risk of bias.

Important findings from the meta-analysis¹² are summarized in Table 1. Essentially, the meta-analysis showed that 4–6 weeks of treatment with celecoxib (200–400 mg/d) was associated with significantly greater reduction in depression ratings and with significantly greater response as well as remission rates in depressed patients receiving antidepressant medication. Adverse effects did not differ between celecoxib and placebo groups, but the RCTs were underpowered for these outcomes. Very similar results were obtained in another meta-analysis on the subject.¹⁷

Can the results of the meta-analysis¹² encourage antidepressant augmentation with celecoxib or other NSAIDs in major depressive illness? No, for several reasons. Faridhosseini et al¹² did not include the mostly negative

- Neuroinflammatory mechanisms have been described in depression, and some animal studies and some observational data in humans suggest that nonsteroidal anti-inflammatory drugs (NSAIDs) may improve depression outcomes.
- Four small randomized controlled trials found that celecoxib (200–400 mg/d) improved response and remission rates after 4–6 weeks of treatment in nonrefractory patients with major depressive disorder.
- There are no data to support the use of NSAID augmentation in antidepressant-refractory patients. Additionally, concerns about NSAID adverse effects and pharmacodynamic drug interactions further limit their clinical potential in depression.

RCT of Nery et al¹⁸ in their meta-analysis because this RCT was conducted in bipolar patients (N = 28) experiencing a depressed (n = 24) or mixed (n = 4) episode. Nery et al¹⁸ had randomized patients to 6 weeks of treatment with celecoxib (400 mg/d) or placebo. They found that celecoxib was superior to placebo only at the end of 1 week, and only in patients who completed the whole trial. Two patients dropped out due to celecoxib-induced rash. The findings of this study¹⁸ are a small counterweight to the results of the meta-analysis.¹²

There are other and more important reasons why NSAID augmentation cannot as yet be recommended to depressed patients. Three^{14–16} of the 4 meta-analyzed RCTs came from a geographically localized region, and 1¹⁵ was not peer-reviewed. The pooled sample (N = 160) in the meta-analysis was too small for confident clinical recommendations to be possible. Importantly, none of the 4 RCTs in the meta-analysis selected patients for prior antidepressant refractoriness; therefore, anecdotal data¹⁹ notwithstanding, the findings of the meta-analysis cannot be generalized to antidepressant-refractory patients. At best, the results of the meta-analysis suggest that celecoxib augmentation may improve short-term response in antidepressant-treated depressed patients.

Several other imponderables also need to be resolved. For example, are benefits with celecoxib limited to patients in whom peripheral markers of inflammation are demonstrably elevated? Or are there other predictors of response to celecoxib? How long should a celecoxib trial last, and for how long should the patient continue to take celecoxib after successful treatment? Finally, given that celecoxib has been associated with adverse medical outcomes (as discussed in a later section), what is the long-term safety profile of celecoxib in depressed patients?

NSAIDs and Possible Worsening of Depression Outcomes

Laboratory data exist to suggest that cyclooxygenase-2 (COX-2) inhibitors may increase lipid peroxidation, decrease the levels of important antioxidants, damage mitochondria,

and otherwise aggravate the cellular pathophysiology of depression.²⁰ Drugs such as ibuprofen may antagonize the action of SSRI antidepressants on neuroinflammatory mechanisms.²¹ In this connection, some data seem to suggest that NSAIDs may worsen depression outcomes and predispose to antidepressant resistance.²² For example, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, use of NSAIDs or analgesics was associated with significantly decreased chances of response to citalopram; use of vitamins, in contrast, had no effect on citalopram outcomes.²¹ Other observational studies also noted worse antidepressant outcomes in NSAID-treated patients, but the findings attenuated or were no longer significant after adjusting for confounding.^{23,24} Furthermore, non-NSAID (opiate) analgesics were also associated with poorer antidepressant outcomes, and NSAIDs were associated with poorer cognitive-behavioral therapy outcomes as well²³; these findings indicate that the most likely explanation for the data is that the burden of medical illness (for which NSAIDs are prescribed) is what probably attenuates antidepressant responsiveness.²²

NSAIDs and Medical Risks

NSAIDs are known to increase the risk of gastrointestinal bleeding, and this risk is heightened with concurrent treatment with SSRI and other antidepressants that inhibit the reuptake of serotonin.^{25,26} Next, depression is associated with an increased risk of ischemic heart disease events,²⁷ and NSAIDs may further increase this risk. For example, a meta-analysis of 25 studies showed that most of the commonly used NSAIDs were associated with a dose-dependent increase in the risk of myocardial infarction²⁸; some NSAIDs may additionally increase the risk of stroke.²⁹ COX-2 inhibition by NSAIDs may also worsen high blood pressure and exacerbate stable congestive heart failure.³⁰ These and other adverse effects of NSAIDs must be weighed before considering NSAID augmentation of antidepressants in depression.

Summing up

Limited data exist to suggest that celecoxib (200–400 mg/d) improves short-term treatment outcomes in antidepressant-treated major depressive disorder. However, an advantage with NSAID augmentation in antidepressant-refractory patients remains to be demonstrated. Furthermore, NSAID augmentation of antidepressants is associated with medical

risks. NSAID augmentation may therefore be an uncertain and experimental option for the patient described at the beginning of this article.

Parting Notes

NSAIDs have been studied in psychiatry in contexts ranging from the prevention of amnesic deficits associated with electroconvulsive therapy^{31–33} to the treatment of Alzheimer's disease.³⁴ Readers who are interested in the subject may wish to consult 2 recent reviews^{35,36} that examined the use of anti-inflammatory treatments in psychiatric disorders. The possible use of NSAIDs in schizophrenia was examined in an earlier article in this column.³⁷

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