CME

Anti-Inflammatory Agents as Antidepressants: Truth or Dare

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ABSTRACT

Mounting data suggest that there is a reliable association between inflammatory markers and depression. This association has led to the speculation that anti-inflammatory drugs may have antidepressant activities. Although an increasing number of studies have addressed this issue, there are several considerations that have confounded attempts to interpret the extant literature in this area. These include: (1) the use of anti-inflammatory drugs with potential antidepressant effects unrelated to inflammation, (2) the evaluation of antidepressant effects of anti-inflammatory drugs in patient populations whose underlying inflammatory disorder may directly benefit from anti-inflammatory treatment (unrelated to mood), (3) potential cultural biases of available studies, and (4) a nonlinear relationship between inflammation and depression that may contribute to a differential response in anti-inflammatory-treated versus placebo-treated patients depending on inflammatory status. Taken together, these data indicate that anti-inflammatory agents do not likely exhibit generalized antidepressant effects and may only be effective in subgroups of patients with increased inflammation. Moreover, the data raise the larger question of whether any antidepressant agent is truly an antidepressant, or whether all medications are only antidepressants for select populations of patients with more biologically discreet disease states we have yet to identify or name. **[*Psychiatr Ann.* 2015;45(5):255-261.]**

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Are anti-inflammatory agents antidepressants? Probably not. Do anti-inflammatory agents have antidepressant properties in some patients? Probably yes. Confusing? Read on.

THE META-ANALYSIS

In asserting that anti-inflammatory agents are probably not antidepressants, we fly in the face of a recently published, high-profile, meta-analysis.[1] Based on combined data from 14 trials (6,262 participants), Kohler et al.[1] concluded that anti-inflammatories decrease depressive symptoms, thereby supporting "a proof-of-concept concerning the use of anti-inflammatory treatment in depression." Because this meta-analysis is the largest assemblage of relevant data currently, it is likely to receive a good deal of attention, and to be taken as evidence in support of the notion that anti-inflammatory agents are antidepressants. Hence, we feel that a close examination of the studies included in this meta-analysis is an excellent place to start our exploration of the antidepressant potential of anti-inflammatories.

In fairness, Kohler et al.[1] are careful to highlight many of the weaknesses in the studies included in their analysis and offer a far more nuanced series of conclusions than will likely be considered in secondary reports of their findings. Interestingly, one complication they do not highlight is the fact that outcomes were combined from two very different classes of medications: nonsteroidal anti-inflammatory agents (NSAIDs) and cytokine inhibitors/antagonists. Although both classes of agents have anti-inflammatory effects, they act at different points in the inflammatory cascade. Cytokine antagonists specifically target cytokines, such as tumor necrosis factor (TNF)-alpha and interleukin (IL)-12 and 23, which play primary roles in launching inflammation, whereas NSAIDs target downstream enzymes that modulate the production of arachidonic acid-derived molecules such as prostaglandins. Importantly, although prostaglandins have multiple proinflammatory properties, more recently they have been shown to play active roles in resolving inflammation. Some evidence suggests that this may explain why NSAIDs worsen outcomes in some chronic inflammatory states, such as cardiovascular disease, and why several lines of evidence suggest that they may also worsen depression, at least in some circumstances.[2] In addition to these concerns, NSAIDs and other "anti-inflammatory agents," such as minocycline, have off-target biological effects that could conceivably contribute to any observed antidepressant activity. For example, the NSAID celecoxib inhibits NA+ and K+ channels in neurons, enhances glucocorticoid receptor translocation from cytoplasm to nucleus,[3] and increases synaptic plasticity through the induction of the adhesion molecule cadherin 11.[4]

Both psoriasis and osteoarthritis are associated with high levels depression.

A second complication in the meta-analytic data derives from the fact that many of the included studies examine populations with diseases that are likely to benefit directly from anti-inflammatory therapies. For example, 3 of the 4 cytokine antagonist studies examined patients with psoriasis, and 5 of the 10 NSAID studies (including all that evaluated NSAIDs as monotherapy for depression) examined patients with active and symptomatic osteoarthritis.

The inclusion of these people poses two challenges. The most obvious is that anti-inflammatories may have antidepressant properties in these illnesses mostly because they reduce primary disease symptoms that are causing the depression in the first place. Indeed, both psoriasis and osteoarthritis are associated with high levels depression, raising the possibility that the effective treatment of these disease states might reduce depression in and of itself. If so, then the antidepressant effects of anti-inflammatories should be associated with their ability to improve underlying disease-state symptoms. In fact, this was the case for both the cytokine antagonist and NSAID studies included in the meta-analysis that examined patients with psoriasis or osteoarthritis. A second related challenge also relates to these underlying disease states. Both psoriasis and osteoarthritis are inflammatory conditions, and a substantial database in animals and humans demonstrates that increased peripheral inflammatory activity promotes the development of depressive symptoms, as well as physiological changes with which these symptoms have been associated.[5]

Although the degree to which increased peripheral inflammation contributes to depression in either psoriasis or osteoarthritis is unknown, it is quite conceivable that anti-inflammatory agents might be more likely to have antidepressant properties in these patients than in patients who are depressed in general, precisely because these agents reduce patterns of disease-related inflammatory activity that are driving depression in these conditions. Although, to our knowledge, this possibility has never been directly examined, we note that an association between increased pretreatment peripheral inflammation and antidepressant responses in patients with major depressive disorder who are medically healthy has been observed[6] as is discussed below in more detail.

In aggregate, the complications examined so far suggest that we might more profitably examine what type of antidepressant signal emerges from studies conducted in medically-healthy people with depression. By far the largest sample of healthy people included in the Kohler et al.[1] meta-analysis (n = 2,233) comes from a study of cognitively normal adults older than age 70 years. This trial[7] examined the effects of celecoxib versus naproxen versus placebo on depressive symptoms, as assessed by the Geriatric Depression Scale (GDS). Despite the large sample size, however, only one-fifth of the study participants had "significant depression" defined by the cut-off score of >5 on the GDS. No effect of NSAID treatment was seen on depression scores, either in the population as a whole, or in participants who entered the trial with elevated depressive symptom scores.

The apparent bright spot in the meta-analysis comes from the four trials[8-11] that examined the impact of augmenting standard antidepressants with the selective cyclooxygenase-2 inhibitor celecoxib in patients with diagnosed major depression who are medically healthy. Presently, these are the only randomized, placebo-controlled studies[8-11] reported in the world literature. In particular, a well-designed study by Muller et al.[11] has received significant attention since its 2006 publication. In this study, 40 people who met the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (*DSM-IV*)[12] criteria for major depression were randomized on a 1-to-1 basis with 6 weeks of reboxetine plus celecoxib or 6 weeks of reboxetine plus placebo. Although drop-out rates were high (ie, 10 in the celecoxib group and 9 in the placebo group) at the end of the trial, a last-observation-carried-forward methodology found a significantly larger improvement in depressive symptoms in the group randomized to adjunctive celecoxib than to adjunctive placebo (effect size calculated by us as d = .58).

Given the small sample size and high drop-out rate, results from the Muller et al.[11] study should be considered suggestive and intriguing, rather than definitive. Deeper difficulties plague the remaining three studies on celecoxib augmentation of selective serotonin reuptake inhibitors (SSRIs). Two of these studies[8,10] were conducted by the same research group, based at the Tehran University of Medical Sciences, and a third recently published small trial[9] was also conducted in Iran. Both studies show strikingly large effect size advantages for celecoxib versus placebo augmentation (calculated by us as d = 1.09 for Akhondzadeh et al.[8] and reported as d = 0.95 for Abbasi et al.[10]).

Intriguingly, the absolute difference in change scores between randomized groups in these studies was quite modest—approximately 3 points on the 17-item Hamilton Depression Rating Scale. To show statistical significance for this type of difference (which is typically what antidepressants deliver), pharmaceutical companies in the West require at least 100 participants per randomized arm, consistent with the fact that effect sizes for antidepressant trials are typically one-third of those observed in the two Iranian-based trials.

So how did the two celecoxib augmentation studies[8,10] achieve such large effect sizes and concomitant statistical significance with such small populations and modest between-group differences in mean symptom change? The resolution to this mystery is that the Iranian study samples showed remarkably little variation in outcomes (ie, the standard deviations for change scores in both study arms are small). A similar pattern of small variations in outcome and large effect sizes has been reported by this group for a number of nontraditional interventions in psychiatric conditions (ie, effect size of 1.76 for *Crocus sativus* [saffron] as an antidepressant), strongly suggesting that the relevant subject populations are qualitatively different from those recruited in other cultural milieus. Although the third study[9] of adjunctive celecoxib reports more modest statistical differences between active treatment and placebo as a result of using more rigorous nonparametric statistics appropriate to the small sample size, the absolute differences in change score between celecoxib and placebo were similar to those observed. Taken together, these considerations suggest that caution may be warranted regarding any expectation that NSAID augmentation will show similarly large effects in other sociocultural settings.

LESSONS FROM CYTOKINE ANTAGONISM IN MAJOR DEPRESSION

Thus far, our discussion has covered all randomized trials of anti-inflammatory agents available in the world's literature, except one. This final study[6] also has its strengths and weaknesses. Nonetheless, we have reserved it for a special discussion for two reasons. First, because we conducted it and we are intimately acquainted with its design, implementation, and outcomes. Second, and more importantly, it is the only randomized, double-blind, placebo-controlled study in the world's literature to date that uses an anti-inflammatory agent with no "off-target" effects in patients with rigorously defined major depression. As such, we suggest that it provides the most direct insights currently available into the question of whether anti-inflammatory activity, per se, will emerge as an "all-purpose" antidepressant mechanism.

This study randomized 60 medically healthy adults with treatment-resistant major depression (defined as a score ≥2 using the Massachusetts General Hospital Staging method) to either three infusions of the TNF-alpha antagonist infliximab (5 mg/kg) versus three infusions of the saltwater placebo. Infusions were delivered at baseline, study week 2, and study week 6, and clinician- and self-report–based assessments of depressive symptoms and related constructs were obtained at baseline (ie, pretreatment) and at study weeks 1, 2, 3, 4, 6, 8, 10, and 12. Enrolled subjects had either discontinued antidepressants use or were taking a stable antidepressant regimen for at least 4 weeks prior to study entry without appreciable clinical response. Those who entered with an antidepressant regimen were required to maintain this regimen throughout the study period. Ninety percent of the randomized sample completed the 12-week study.

With the caveat that placebo response rates were remarkably high (50%), the results from the study were unequivocal. The groups were as close to each other in outcome as could be expected by chance (ie, $P = .92$), and, in fact, placebo outperformed infliximab on a numeric basis.

In a typical antidepressant trial, the story would have ended here. But we entered the study with a second hypothesis: that increased measures of peripheral inflammation prior to receipt of the study intervention would be associated with an improved response to infliximab, but not placebo. This hypothesis turned out to be truer than expected based on what we initially understood about the association between inflammation and depression. As expected, a linear relationship was observed between increasing plasma concentrations of high-sensitivity C-reactive protein (hs-CRP) and antidepressant response to infliximab. What we didn't expect was that this relationship would show a true dose-response pattern, meaning that participants who were depressed with low levels of baseline peripheral inflammation did worse on infliximab than placebo. Because we expected a null relationship between placebo administration, inflammation, and antidepressant responses, we also did not predict that increasing peripheral inflammation would be associated with reduced placebo responses. Taken together, these findings produced the pattern of results illustrated in **Figure 1**.

Anti-inflammatory agents may well have both antidepressant and prodepressant effects.

As **Figure 1** shows, the "sweet spot" for infliximab effectiveness was an hs-CRP plasma concentration of 5 mg/L. Participants with inflammatory activity above this level did better with infliximab than placebo, with a medium effect size of 0.41, which is in line with the efficacy of antidepressants against placebo in most studies. On the other hand, participants with hs-CRP below 5 mg/L did better on placebo than infliximab (effect size 0.82). Importantly, in participants with hs-CRP levels about 5 mg/L, the response to infliximab was not the result of only impacting "sickness symptoms" such as fatigue, but resulted from a reduction in the core major depressive disorder symptoms of depressed mood and anhedonia, and from other symptoms often considered "emotional" as opposed to "somatic," including suicidal ideation and psychic anxiety.

EVIDENCE FOR A NONLINEAR RELATIONSHIP BETWEEN INFLAMMATORY ACTIVITY AND DEPRESSION

The most straightforward interpretation of the infliximab study is that a "u-shaped" curve exists between peripheral inflammatory activity and depression. Because of this, anti-inflammatory agents may well have both antidepressant and prodepressant effects, depending on the inflammatory status of any person with depression. Inflammatory pathways likely contribute significantly to the development and/or maintenance of depressive symptoms in people with higher levels of inflammation, given that blocking inflammatory activity can induce an antidepressant effect. This finding is consistent with the known depressogenic effects of anything that promotes chronic inflammatory activity. On the other hand, in people with serious clinical depression, but low levels of background inflammation, inflammatory activity appears to provide some type of benefit rather than harm; further blocking of this activity antagonizes the antidepressant effects of placebo. However, here a subtle distinction must be made: infliximab did not, on average, worsen depressive symptoms in people with low-levels of baseline inflammation, it only improved these symptoms less effectively than the placebo. So perhaps, the strictest interpretation of this finding is that the placebo response is dependent on some minimal level of inflammatory activity, while being antagonized by higher levels of inflammation? This is an important open question that can be easily addressed by any depression study using a placebo arm and measured pretreatment levels of inflammation.

The complex relationship between inflammation and depression (ie, nonlinear) has been suggested by studies that have not been widely disseminated. For example, Yirmiya and Goshen[13] have marshalled significant evidence from animal studies indicating that at lower concentrations inflammatory cytokines in the central nervous system (CNS) play a pivotal role in learning and memory and other processes in the brain that maintain neuronal integrity including synaptic plastic-

ity (see article by Franklin and colleagues for further discussion of the role of cytokines in neuroplasticity, this issue). In addition to the importance of the amount of inflammation present at any given time, it may well be that inflammatory activity has different effects on depression depending on its timing relative to initiating environmental causes. For example, blocking CNS microglial activation at the onset of a chronic unpredictable stressor (CUS) abrogated the later development of depressive-like symptoms in a rodent model, consistent with the likely role of inflammation as a transducer of environmental stress into behavioral pathology.[14] But paradoxically, once mice had been exposed to the CUS, treatment with several inflammatory stimulators (including lipopolysaccharide [LPS]) actually reversed the already-existent depressive-like behavior, and did so in concert with stimulation of hippocampal microglial proliferation.

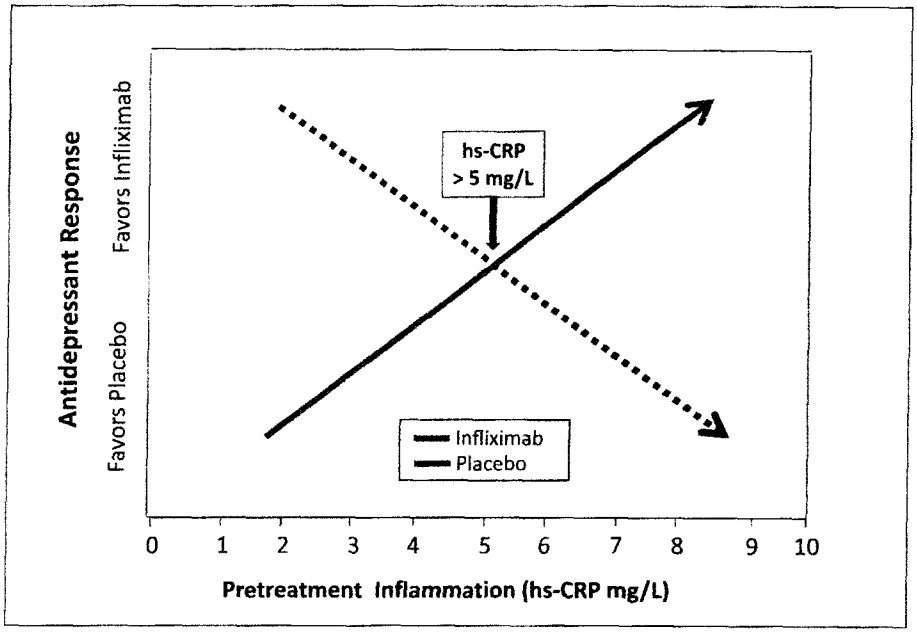

Figure 1. The relationship between pretreatment levels of inflammation and antidepressant responses to a cytokine antagonist. Patients with treatment-resistant major depression (TRD) showed opposite patterns of response to the tumor necrosis factor (TNF)-alpha antagonist infliximab or to placebo based on levels of pretreatment levels of peripheral inflammation, indexed by plasma concentrations of C-reactive protein (CRP). Patients with TRD and higher levels of peripheral inflammation responded preferentially to infliximab versus placebo, whereas an opposite pattern was observed in TRD patients with lower levels of inflammation. hs-CRP, high-sensitivity C-reactive protein.

The idea that inflammatory stimulators might actually demonstrate antidepressant properties sounds farfetched, but it has at least one human study in its favor. In a small open trial conducted in the 1990s, Bauer et al.[15] administered LPS to seven adults with depression and monitored sleep using polysomnography for 2 nights prior to and 2 nights following the LPS administration. LPS increased plasma concentrations of TNF-alpha and IL-6, suppressed rapid eye movement (REM) sleep and produced a significant reduction in depressive symptoms the next day. The more IL-6 increased in response to LPS, the more depressive symptoms decreased the following day. Upon recovery sleep the next night, 5 of the 7 subjects relapsed, but two continued to show improved depression scores. The limitations of this type of small, open trial are obvious, but the results are nonetheless intriguing, and when coupled with animal data showing that NSAIDs impair the ability of SSRIs to activate the protein p11 in cortex, and by doing this, block the antidepressant-like behavioral effects of these agents,[16] point to under-appreciated complexities in the relationship between inflammation and mood.

CONCLUSIONS AND TWO OPEN QUESTIONS

It is not our intention to valorize inflammatory cytokines, but rather to highlight that their role as pathogenic agents in major depression is likely limited to a subset of patients with evidence of inflammatory hyperactivity. Fortunately, increasing data suggest that easily obtainable measures of inflammation, such as hs-CRP, hold promise as markers for the subgroup of people with depression most likely benefit from anti-inflammatory treatment strategies. However, the converging lines of evidence that point to positive effects of cytokines at lower concentrations highlight the need for restraint in the "cookie-cutter" approach of using anti-inflammatories for depression treatment.

Two open questions warrant special attention in closing. Almost all human data linking inflammation to depression has been based on measures of peripheral inflammation. Are these peripheral measures merely proxies for inflammatory activity in the CNS, or might it be that peripheral inflammation is itself depressogenic? The answer to this question is consequential, because it will determine whether future anti-inflammatory antidepressants will need to penetrate the CNS to be effective, as opposed to being effective merely by lowering inflammation in the periphery.

Increasing evidence favors this latter possibility. Although we did not measure cerebrospinal fluid levels

of infliximab in our study, other researchers have shown that—even in autoimmune conditions in which the blood-brain barrier is leaky—infliximab is too large to enter the CNS to any appreciable degree.[17] If this is the case, then infliximab may have worked in depressed subjects with hs-CRP levels above 5 mg/L not by targeting the brain directly, but rather by reducing peripheral inflammatory activity. The corollary assumption would be that in participants who responded to infliximab, peripheral inflammatory activity was signaling the brain to adopt activity patterns that produce depression. With the resolution of this peripheral inflammatory signal, the brain reverted to functional states that produced more normal moods. Recent animal studies support *this possibility.* Hsiao et al.[18] showed that bone marrow transplant reversed a number of "autistic-like" behaviors in rodents exposed to *in utero* inflammation, and more recently treatment of mice with an antibody against IL-6 too large to enter the CNS produced a stress resilient phenotype characterized by antidepressant properties.[19] Similar results have been reported for infliximab that blocked the development of depression and anxiety-like behavior in laboratory animals exposed to chronic mild stress.

Finally, for the reasons marshaled thus far, we suggest that anti-inflammatory agents are unlikely to be antidepressants as the term is typically conceived. But this begs a deeper question and that is whether any medications are truly "pure" antidepressants. Recent mathematical modeling suggests that behind the modest differences in mean change scores typically observed between antidepressants and placebo hides a more complex truth. Based on a large subject sample, a group at Yale University[20] has shown that approximately 75% of patients who receive antidepressants obtain significant short-term clinical benefit. However, 25% of patients actually do much worse when taking antidepressants over placebo. This result, and others approve,[21] strongly resemble our findings with infliximab in treatment-resistant depression. The only difference may be that in the case of infliximab we have a biomarker that makes which people do respond or don't respond seem a little less mysterious than is the case with classical antidepressants.

Similar results have been reported for infliximab that blocked the development of depression.

So maybe after all, anti-inflammatory agents aren't so different than other antidepressants?

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