The Promise and Limitations of Anti-Inflammatory Agents for the Treatment of Major Depressive Disorder

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Abstract This review provides a critical perspective on recent meta-analyses suggesting that several anti-inflammatory modalities, including nonsteroidal anti-inflammatory drugs (NSAIDs), omega-3 fatty acids, and cytokine antagonist, possess generalizable antidepressant properties. By examining confounds and limitations in the available literature it is suggested that current data suggest that only a sub-group of individuals with major depressive disorder (MDD) have evidence of increased inflammatory biomarkers and it is in these individuals that anti-inflammatory agents show promise for reducing depressive symptoms. The treatment implications of this cautionary perspective are discussed.

Keywords Antidepressants • Cytokine antagonists • Cytokines • Inflammation • Major depressive disorder • Nonsteroidal anti-inflammatory drugs • Omega-3 fatty acids

Contents

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1 Introduction

What do hula hoops, the dexamethasone suppression test, country western dancing, lobotomies, cabbage patch kids, and gabapentin for the treatment of mania have in common? They are all fads, phenomena that swept through their respective cultures with the intensity of a forest fire, only to fade as quickly and almost as completely as they had come. And while cultural fads generally come and go without inflicting much long-term damage, we have been less lucky in the field of mental health research.

For us, fads have caused mischief for at least two reasons. First, the hope for a "magic bullet" that would provide clarity to our diagnostic quandaries and power to our treatments has caused us to prematurely implement interventions that were either ineffective or damaging. Second, the overly enthusiastic embrace of complex scientific findings has led us, time and again, to prematurely abandon these same findings when they failed to deliver on our unrealistic expectations of them.

Thus, rather than filling me with satisfaction, as one who has long researched links between inflammation and brain function, I fear our current romance with the notion that major depression is an inflammatory condition to be treated with anti-inflammatories. I fear it because I suspect that valuable scientific insights associating the immune system with major depression (MDD) will be down-graded and dismissed when they fail to deliver the type of definitive treatments that we so desperately need. And I fear it because available data suggest that – when taken as a whole – patients with depression may be as likely to be hurt as helped by a well-meaning blanket application of anti-inflammatory modalities to assuage these individuals' symptoms.

In this paper I provide a critical review of the notion that MDD is an inflammatory condition and that anti-inflammatory agents hold potential as "all-purpose" antidepressants. This perspective is at odds with recent meta-analyses suggesting that MDD is associated with increased inflammation and that – taken as a whole – anti-inflammatory agents produce antidepressant effects. I will attempt to show that while true, these conclusions mask the fact that positive findings result from heterogeneity within the respective datasets. Said more simply, I suggest that inflammation likely contributes to the development and maintenance of depression in only some individuals and that it is these individuals who may well benefit from pharmacologic interventions that inhibit inflammatory activity. Disturbingly, I will provide some evidence that anti-inflammatory strategies may actually harm some patients with MDD.

2 Is Depression an Inflammatory Condition and Does It Matter?

By way of a thought experiment, suppose a middle-aged patient complaining of severe depression comes to your office for treatment. Believing that MDD is an inflammatory condition, you measure plasma concentrations of inflammatory cytokines and the acute phase reactant c-reactive protein (CRP). For extra measure, you perform a lumber puncture in your office to measure cerebrospinal fluid concentrations of the same inflammatory markers. A few days later the patient returns, and you hold the lab results in your hands. No evidence of increased inflammation in either the central nervous system (CNS) or periphery. The patient is weeping, can't sleep, doesn't want to eat, is exhausted, and says he can think of nothing but killing himself. Would you decide that because the patient's inflammatory measures are normal he cannot be depressed?

In fact this situation is far from hypothetical. While numerous studies indicate that inflammatory biomarkers (especially interleukin [IL]-6, IL-1-beta and tumor necrosis factor [TNF]) are elevated in groups of depressed individuals compared to groups of non-depressed individuals [1–5], many severely depressed patients have low levels of inflammation. Indeed, in study after study the values for any given inflammatory marker overlap between groups of depressed and non-depressed individuals, regardless of how much higher the marker's mean value may be in the depressed group. This means that a large proportion of the depressed group in any given study has values similar to the non-depressed group, and always in the "normal" range for the marker in question [6–11], when such a norm has been established [12]. Given this, in what way can MDD be conceived of as an inflammatory condition, and why would we expect an anti-inflammatory treatment to benefit patients without evidence of increased inflammation?

In fact, there is a sense in which MDD could be an inflammatory condition even in those individuals demonstrating low levels of inflammatory biomarkers, just as we recognize depression as linked to the functioning of norepinephrine and serotonin, even though a majority of depressed patients do not show measurable abnormalities in these neurotransmitters [13]. As with monoamine neurotransmitters, inflammatory pathways do not exist in functional isolation from other physiological systems in the body that have been implicated in the pathogenesis of MDD, but rather have been shown repeatedly to interact these systems in ways known to promote depression [14–17]. As a result of response differences in these systems people appear to vary widely in their sensitivity to the behavioral effects of inflammatory signaling. For example, women have appeared to be more likely than men to develop depressive symptoms in response to a dose of lipopolysaccharide (LPS) [18], and a variety of pre-treatment behavioral and biological factors have been shown to increase the risk of depression in response to chronic inflammatory stimulation induced by therapy with interferon (IFN)-alpha [19–23]. Thus, some individuals' overall physiology might protect them from developing depression in response to all but the highest levels of inflammatory stimulation; whereas

the physiology of others might make them prone to developing depressive symptoms in response to even low levels of inflammatory stimulation.

These considerations suggest that MDD might be an inflammatory condition as a result of at least two semi-independent processes. First, inflammation might directly contribute to MDD in the sub-group of patients with chronically elevated inflammation. Second, inflammation might contribute indirectly to the development/maintenance of MDD in a larger group of depressed individuals with normal levels of inflammation, but who demonstrate increased sensitivity to the depressogenic effects of inflammatory signaling.

This scenario lends itself to two strong predictions. First, modalities that reduce inflammatory cytokine activity should produce an antidepressant effect that is observable in patients with both elevated and normal levels of inflammatory biomarkers. And second, because a wide range of systems may contribute to the downstream antidepressant effects of anti-inflammatory agents, one would not expect to see a clear association between baseline inflammatory levels and subsequent antidepressant response.

Alas for those of us who would like to view inflammation as a process central to the pathogenesis of MDD writ large, available data do not support either prediction. As I discuss below, several lines of evidence suggest that anti-inflammatory agents only show an antidepressant signal in patients with elevated peripheral inflammatory biomarkers prior to treatment, and in the largest study of a cytokine antagonist conducted to date in medically healthy individuals with MDD, a strong correlation was observed between baseline inflammatory biomarkers and subsequent antidepressant response [24]. Moreover, cytokine antagonism actually appears to produce an adverse effect by blocking placebo responses in patients with lower levels of inflammation, a finding in direct contradiction to the idea that MDD might be a condition of generalized hypersensitivity to inflammatory signaling [24, 25].

I revisit this issue toward the end of the article when considering why various anti-inflammatory agents may fail as antidepressants. Now let us turn to an examination of the evidence for and against the proposition that specific anti-inflammatory modalities hold promise as antidepressants.

3 Do Anti-Inflammatory Agents Work as Antidepressants and If So When?

A number of meta-analyses have been conducted to assess the impact on depressive symptoms of agents with anti-inflammatory effects. In the current review I focus on three of these, because they are the most recent. Kohler et al. combined data from 14 trials (6,262 participants) that examined nonsteroidal anti-inflammatory drugs (NSAIDs) or cytokine antagonists in both primary MDD and for depressive symptoms in patients with medical conditions for which anti-inflammatories are primary treatment modalities [26]. They report that across these agents and conditions anti-

inflammatories reduced depressive symptoms (SMD −0.034; 95% CI −0.57 to −0.11). Rosenblat et al. combined data from 8 randomized trials (312 participants) that examined NSAIDs, omega-3 fatty acids, n-acetylcysteine, or pioglitazone as adjuncts in the treatment of depressive or mixed states in patients with bipolar disorder [27]. The overall effect size of anti-inflammatory agents on reducing depressive symptoms was −0.40 (95% CI −0.65 to −0.14). Finally, Mocking et al. followed up on several previous meta-analyses finding null effects of omega-3 fatty acids, by conducting a meta-analysis limited to patients with rigorously diagnosed MDD and reported that omega-3 fatty acids (and especially eicosapentaenoic acid [EPA]) reduced depressive symptoms with a pooled effect size of −0.398 (95% CI −0.682 to −0.114) [28].

Taken at face value these pooled effect sizes seem to suggest a level of promise for the antidepressant efficacy of inflammatory blockade that a closer examination of the data does not support. I say this because of the presence – singly and in combination – of at least three serious confounds in the extant literature. These confounds include: (1) off target (i.e., non-immune) effects of the agents; (2) the possibility that depression improved secondary to improvements in the primary immune-based disease state; and (3) irregularities/limitations in the design of the studies that disproportionately drive positive meta-analytic findings. As we shall see all three confounds are relevant to studies of NSAIDs; omega-3 fatty acids are subject to confound 1 and studies of cytokine antagonists are bedeviled by confound 2.

Prior to examining these confounds a more general point is worth highlighting, which we might call the "apples and oranges problem." There is a tendency to see inflammation as a unitary, monolithic process, but nothing could be further from the truth. Because of this, combining findings from NSAIDs and cytokine antagonists under a single anti-inflammatory rubric may hide as much as it reveals. Although both classes of agents have anti-inflammatory effects, they act at very different points in the inflammatory cascade. Cytokine antagonists specifically target cytokines, such as TNF-alpha and interleukin (IL)-12 and 23, that 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 they have also more recently 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 [29].

4 Off Target Effects

Because inflammatory processes are driven to a large extent by the actions of cytokines, what most of us mean when we describe MDD as an inflammatory condition is that cytokines are elevated in the disorder, and – more boldly – that elevated cytokines may be a cause of the condition. If so, then the purest test of the inflammatory hypothesis of depression would be to show that blocking proinflammatory cytokine activity treats MDD. It is for this reason that the antagonists of IL-1-beta, TNF, and IL-6 offer the most straightforward method for testing whether anti-inflammatory agents work as antidepressants. These large biologic agents have remarkable specificity of action. They block their respective cytokine targets without having other appreciable biological activities that might promote or hinder their potential antidepressant properties.

The same cannot be said for the other anti-inflammatory agents that have been tested as antidepressants and that have contributed to the effect size estimates of recent meta-analyses. Consider NSAIDs. In addition to the complication mentioned above (i.e., that they may actually have proinflammatory properties in the context of chronic inflammation), these agents have a number of depression-relevant actions not directly connected with their immune effects.

For example, celecoxib, the agent most often studied for its antidepressant properties, enhances the translocation of the glucocorticoid receptor from cytoplasm to nucleus, inhibits NA+ and K+ channels in neurons, and increases cadherin 11, an adhesion molecule that plays an important role in synaptic plasticity and that produces antidepressant- and anti-anxiety-like effects in animal models [30]. On the other hand, NSAIDs also block the CNS actions of p11. In animal models, SSRIs acutely activate cytokines in the CNS, which is necessary for p11 induction [31]. Induction of p11, in turn, is required for these agents to produce an antidepressant-like effect. Taken together, these findings suggest that NSAIDs have off target effects that might explain why they would work as antidepressants, as well as off target effects that might explain why they might not work as antidepressants.

Omega-3 fatty acids have multiple biological effects that likely contribute to their anti-inflammatory capacity, including suppression of arachidonic acid content/activity and inhibition of nuclear factor kappa-beta, as well as stimulation of g-protein receptor 120 and peroxisome proliferator-activated receptor (PPAR)-gamma [32, 33]. But like NSAIDs, omega-3 fatty acids have a number of off target effects that might contribute to an antidepressant effect. In addition to wide ranging effects on membrane stability and function, both EPA and DHA have been shown to promote neurogenesis independently of effects on inflammation, which – in animal models at least – appears to be an important prerequisite for inducing antidepressant-like effects [34].

5 Antidepressant Effects Secondary to Improvement of the Underlying Medical Disease

A second potential confound in meta-analyses of the antidepressant effect of anti-inflammatory agents derives from the fact that many of the included studies examined populations with medical diseases that are likely to benefit directly from anti-inflammatory therapies. For example, three of the four cytokine antagonist studies included in the Kohler et al. meta-analysis examined patients with psoriasis, and five of the ten NSAID studies (including all that evaluated NSAIDs as monotherapy for depression) examined patients with active and symptomatic osteoarthritis (OA) [26].

The obvious challenge posed by the inclusion of these studies is that anti-inflammatories may have antidepressant properties in these illnesses primarily because they reduce primary disease symptoms that are contributing to the depression in the first place. Indeed, both psoriasis and osteoarthritis are associated with high levels of 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 Kohler et al. meta-analysis that examined patients with psoriasis or osteoarthritis. In the five included studies that compared ibuprofen, naproxen, celecoxib with placebo in patients with osteoarthritis improvement in OA symptoms was strongly associated with improvements in depressive symptoms. [35] A similar picture emerges from studies examining the impact of cytokine antagonists on depressive symptoms in patients with psoriasis. While a large study that compared the TNF antagonist etanercept with placebo found that improvements in depression did not correlate with improvements in psoriasis symptoms (although improvements in fatigue did correlate with improvements in psoriasis) [36], two subsequent studies found medium to large effect–size correlations between improvements in depression and psoriasis in response to treatment with the TNF antagonist adalimumab ($r = 0.50$, $p < 0.0001$) and the IL-12/IL-23 antagonist ustekinumab ($r = 0.32$, $p < 0.0001$) [37, 38].

6 Limitations in Study Design and Irregularities in the Presentation of Findings

We have highlighted the fact that studies examining the antidepressant effects of anti-inflammatories in patients with psoriasis or OA suffer from confounds. These studies in medically ill patients suffer from another limitation, which is that they did not specifically enroll participants with clinically significant levels of depression. In the Tyring et al. study of etanercept in psoriasis only 15% of 618 participants entered the study with depressive symptoms of severity sufficient to qualify for

entry into most antidepressant trials [36]. Similar low levels of depressive symptom severity also characterized the Langley et al. study of ustekinumab in 1,230 patients with psoriasis (11% with moderate or greater severity depressive symptoms) [38]. In the final cytokine antagonist study in psoriasis approximately 33% of participants qualified for having depression based on a Zung score $\geq$50 [37]. In the 5 trials comparing celecoxib, naproxen, ibuprofen, and placebo in patients with OA, baseline scores were even lower (average score of 3 on the 9-item Patient Health Questionnaire, with moderate depression starting at a score of 15) [35].

The same issue plagues the largest study of healthy individuals included in the Kohler et al. meta-analysis ($N = 2233$) [39]. This trial examined the effects of celecoxib vs. naproxen vs. placebo on depressive symptoms cognitively normal adults over the age of 70. Despite the large sample size, however, only 1/5 of the study subjects had "significant depression" defined by cut-off score of >5 on the Geriatric Depression Scale. No effect of NSAID treatment was seen on depression scores in the population as a whole, or in participants who entered the trial with elevated depressive symptom scores.

These low levels of depressive symptoms have the potential to introduce a "floor effect" that might well obscure efficacy had these studies been conducted in participants with clinically relevant depression. Convergent support for this possibility comes from the literature examining omega-3 fatty acids. A recent meta-analysis that only included participants with rigorously defined MDD found a larger effect size for omega-3s than did earlier meta-analyses that included participants with lesser degrees of depression did not [28]. And in a negative meta-analysis conducted by Bloch and Hannestad, increasing baseline depressive symptom severity was associated with a larger effect size difference between omega 3s and placebo [40].

A recent meta-analysis of anti-inflammatory agents in patients with bipolar disorder included two studies of NSAIDs. One study examined their efficacy as augmenting agents in patients currently in a depressed or mixed state and found no effect [41]. The other study examined the addition of aspirin to euthymic patients with bipolar disorder and – not surprisingly given the patients' baseline status – found no effect [42]. On the other hand, the Kohler et al. meta-analysis found evidence for an anti-inflammatory effect of NSAIDs based on the inclusion of four trials that examined the impact of augmenting standard antidepressants with the selective cyclooxygenase (COX) 2 inhibitor celecoxib in medically healthy individuals with diagnosed major depression.

But, as with the literature more generally, issues with these studies suggest caution in our interpretation of their findings. Muller et al. conducted a well-designed and described study that has received significant attention since its publication in 2006 [43]. In this study 40 individuals with DSM-IV diagnosed major depression were randomized on a 1-to-1 basis to 6 weeks of reboxetine plus celecoxib or 6 weeks of reboxetine plus placebo. Although drop-out rates were very high (i.e., 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 as $d = 0.58$).

Given the small sample size and high drop-out rate, results from the Muller et al. study should certainly be considered suggestive and intriguing rather than definitive. Deeper difficulties plague the remaining three studies of celecoxib augmentation of SSRIs. Two of these studies were conducted by the same research group, based at the Tehran University of Medical Sciences [44, 45], and a third small trial was published by another group in Iran (Moshiri et al.) [26]. Both studies from the Tehran University of Medicine group show strikingly large effect size advantages for celecoxib vs. placebo augmentation (calculated by us as $d = 1.09$ for Akhondzadeh et al. and reported as $d = 0.95$ for Abbasi et al.).

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 concerns in the west need to enroll at least 100 participants per randomized arm, consistent with the fact that effect sizes for antidepressant trials are typically a third of those observed in the two Iranian-based trials of celecoxib augmentation. So how did the two celecoxib augmentation studies achieve such large effect sizes and concomitant statistical significance with such small populations and modest between-group differences in mean symptom change?

The answer lies in the fact that the Iranian study samples showed little variation in outcomes (i.e., the standard deviations for change scores in both study arms are very small). A similar pattern of small variations in outcome and very large effect sizes has been reported by this group for a number of non-traditional interventions in psychiatric conditions (i.e., effect size of 1.76 for crocus sativus [saffron] as an antidepressant) [46], strongly suggesting that the relevant subject populations are qualitatively different from those recruited in other cultural milieus. Although the third study of adjunctive celecoxib reports more modest statistical differences between active treatment and placebo as a result of using more rigorous non-parametric statistics appropriate to the small sample size, the absolute differences in change score between celecoxib and placebo were similar to those observed in the Tehran University studies. Taken together, these considerations suggest that caution may be in order regarding any expectation that NSAID augmentation will show similarly large effects in other sociocultural settings.

7 What Can We Learn from Cytokine Antagonism in Medically Healthy Adults with MDD?

It is an interesting paradox that in a field filled with studies there is, to my knowledge, only one randomized, double-blind, placebo-controlled study in the world's literature to date that utilizes an anti-inflammatory agent with no "off-

target" effects (infliximab) in patients with rigorously defined major depression [24]. Because we conducted the study I am especially aware of its limitations and weaknesses. Nevertheless, because it is the only study of its type, I suggest that it provides the most direct insights currently available into the question of whether anti-inflammatory activity, per se (and cytokine blockade in particular), 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) vs. three infusions of salt water 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 (i.e., pre-treatment) and at study weeks 1, 2, 3, 4, 6, 8, 10, and 12. Enrolled subjects were either off antidepressants or on a stable antidepressant regimen for at least 4 weeks prior to study entry without appreciable clinical response. Subjects who entered on an antidepressant regimen were required to maintain this regimen throughout the study period. Ninety percent of the randomized sample completed the 12-week study.

The results from the study were unequivocal. The groups were as close to each other in outcome as could be expected by chance (i.e., $p = 0.92$), and – in fact – placebo outperformed infliximab on a numeric basis. These findings do not auger well for the hypothesis that cytokine blockade holds promise as an "all purpose" antidepressant modality, with the caveat that placebo rates were strikingly high (i.e., around 50%) which might have obscured real – but small – antidepressant effects of the infliximab.

Interestingly, however, the similar responses to placebo and infliximab hid a complexity that I believe provides an important key to understanding not just the antidepressant potential of anti-inflammatory agents, but the relationship between inflammation and MDD more generally. We entered the study predicting that increased measures of peripheral inflammation prior to the receipt of a study intervention would be associated with an improved response to infliximab, but not placebo. This hypothesis turned out to be truer than we would have guessed based on what we understood about the association between inflammation and depression at the time we designed the study. As expected, a linear relationship was observed between increasing plasma concentrations of high-sensitivity c-reactive protein (hs-CRP) and antidepressant response to infliximab and TNF. What we didn't expect was that this relationship would show a true dose–response pattern, meaning that depressed participants 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, but that is what we found.

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 (MDD) symptoms of depressed mood and anhedonia, and from other symptoms often considered "emotional" as opposed to "somatic," including suicidal ideation and psychic anxiety.

8 Facing the Etiologic and Treatment Implications of the U-Shaped Curve

Results from our infliximab study await replication. Pending this, it is striking that an exactly similar pattern of findings was observed in a study that examined EPA vs. docosahexaenoic acid (DHA) vs. placebo as monotherapy in MDD [25]. Neither of the omega-3 fatty acids showed any evidence of superiority over placebo in the group as a whole. But EPA showed a large effect size advantage over both placebo and DHA in participants with increases in any of a number of inflammatory biomarkers at baseline. Conversely, depressed participants with low levels of inflammatory markers actually did worse on omega-3s than on placebo, exactly as we observed with infliximab.

These findings present us with a conundrum. We know from studies with both acute inflammatory stimulators (i.e., LPS) and chronic stimulators (i.e., IFN-alpha) that individuals vary in their sensitivity to inflammation. For any given "dose" of inflammatory exposure some individuals get far more depressed than others. This suggests that even low levels of inflammation should be depressogenic in vulnerable individuals, and that because of this they might well benefit from an anti-inflammatory intervention. But, as we've seen, treatment studies do not support this, and in fact suggest the opposite: that blocking inflammatory signaling in depressed individuals with low levels of inflammation is actually counter-productive.

In beginning to resolve this paradox two points are important to consider. First, studies of the behavioral effects of acute cytokine stimulation are universally conducted in participants without clinical depression. Second, the doses of IFN-alpha used in treatment studies are so high that all individuals are being exposed to levels of inflammatory stimulation that far exceed anything relevant for individuals with MDD and low levels of inflammation. It may be that such high chronic cytokine exposure distorts relationships between the immune system and brain/neuroendocrine pathways that pertain at lower levels of inflammatory signaling.

That the relationship between inflammation and depression might be complex (i.e., non-linear or "u-shaped") has been suggested by studies in the literature that

have not gotten the attention they deserve. For example, significant evidence from animal studies that at lower concentrations inflammatory cytokines in the CNS play a pivotal role in learning and memory and other processes in the brain that maintain neuronal integrity including synaptic plasticity [47]. 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 [48]. But paradoxically, once mice had been exposed to the CUS, anti-inflammatory interventions worsened their depressive and anxiety-like behavior, whereas treatment with several inflammatory stimulators (including LPS) actually reversed the already-existent depressive-like behavior, and did so in concert with stimulation of hippocampal microglial proliferation.

Is it possible that acute inflammatory stimulation may produce depression in humans who are not depressed, but have antidepressant properties in patients – who like the mice already exposed to the chronic stressor – have endured long-term activation of stress pathways in the brain and body? Although this sounds far-fetched, at least one study in humans suggests this idea may have some merit. In a small open trial conducted in the 1990s, Bauer et al. administered LPS to seven melancholically depressed adults and monitored sleep using polysomnography for two nights prior to, and two nights following the LPS administration [49]. LPS increased plasma concentrations of TNF-alpha and IL-6, suppressed REM sleep, and produced a significant reduction in depressive symptoms the following 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 2 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 inflammatory cytokines play important roles in healthy brain functioning when not chronically elevated.

9 Conclusions

Although much work remains to be done, data collected to date suggests that the role of inflammatory cytokines 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 sub-group of depressed individuals most likely to benefit from anti-inflammatory treatment strategies. But the converging lines of evidence suggesting that cytokines may have positive effects at lower concentrations or as acute stimuli in the context of severe depression/chronic stress highlight the need for restraint in our desire to apply a “cookie-cutter”

approach to the use of anti-inflammatories in the treatment of depression more generally.

Finally, for all the reasons I've discussed, anti-inflammatory agents are unlikely to be antidepressants as the term is typically conceived. But in this regard they may be no different than other agents currently approved for the treatment of MDD. 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, John Crystal's group at Yale has shown that approximately 75% of patients who receive antidepressants obtain significant short-term clinical benefit [50]. However, 25% of patients actually do much worse on antidepressants than on placebo. This result, and others like it [51], strongly resembles our findings with infliximab in treatment-resistant depression and the findings of Rapaport et al. with omega-3 fatty acids. The only difference may be that in the case of anti-inflammatory interventions, we have biomarkers that make who does and doesn't respond seem a little less mysterious than is the case with classical antidepressants.

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