Targeting the Immune System in Depression: Promising and Primetime

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As the leading cause of disability worldwide, depression affects greater than 350 million people globally.[1] Currently available pharmacological treatments are associated with high rates of treatment-resistance, mood episode relapses, residual symptoms (e.g., cognitive dysfunction), persistent functional impairments, and poor quality of life.[2] As per the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study, approximately one quarter of patients will fail to achieve remission after numerous adequate antidepressant medication trials and combinations are attempted.[2] As such, there continues to be a desperate need to identify novel pharmacological treatments for depression that may improve remission rates and decrease the global burden of depression.

Over the past 60 years, pharmacological treatments for depression have focused on targeting the monoamine system after serendipitously identifying the antidepressant effects of monoamine oxidase inhibitors (MAO-Is).[3] Targeting the monoamine system has yielded great benefits. However, has also been detrimental in shifting the focus of drug development solely on this system, leaving research in other effected systems to be neglected.[4] For example, prior to the discovery of MAO-Is, Julius Wagner-Jauregg suspected that inflammation may be involved in the development of mental illness. As one of the only psychiatrists in history to ever win a Nobel Prize, his research was recognized as important and promising, prior to the discovery of MAO-Is.[5] However, the role of the immune system in depression was largely ignored, as the pursuit for new monoaminergic drugs dominated antidepressant drug development for five decades.[3]

Over the past decade, the role of the immune system in depression has been revisited. Numerous lines of evidence now support a bidirectional interaction between depression and immune dysfunction.[6] Epidemiological evidence has shown a strong association between mood disorders and autoimmune disorders (e.g., rheumatoid arthritis, psoriasis, lupus).[6-10] Furthermore, immune boosting treatments used to treat certain types of cancer and hepatitis C are strongly associated with depression.[11-13] These findings are of particular interest as these medications lead to the resolution of medical illness (e.g., treatment of cancer or hepatitis) but cause patients to develop depression.[11-13] This important finding is helpful to disprove the common misconception that patients with medical illness are only depressed because they are sad about being sick. Certainly, the psycho-social factors of depression are important to consider in the medically ill; however, the important biological role of immune dysfunction should not be discounted. Also of note, induction of an inflammatory state in animal and healthy human models (through injection of pro-inflammatory agents such as vaccines or cytokines) has also been shown to consistently cause significant depressive symptoms, sometimes referred to as "sickness behavior."[14]

In addition to these findings, numerous studies have also shown the strong association between elevated peripheral (i.e., serum) and central (i.e., cerebrospinal fluid) pro-inflammatory cytokines in bipolar and unipolar depression.[15-17] eripherally produced cytokines may traverse the blood-brain barrier and lead to inflammatory changes in the brain. These inflammatory changes have been shown to cause destruction of key neural circuits involved in mood and cognitive function.[18] Numerous pathways have been identified that link immune dysfunction with depression including but not limited to microglial over-activation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, cytokine induced monoamine changes, oxidative stress, and gut-microbiota-brain axis dysfunction, all ultimately leading to destruction of key neural circuits, which subsequently leads to depressive symptoms.[6,19] Notably, immune dysfunction may affect certain domains of depression, such as anhedonia and sleep dysfunction, more significantly.[19,20]

Given the strong evidence to support a causal role of immune dysfunction in depression, the immune system presents as a novel target in the treatment of depression. Over the past decade, numerous proof-of-concept randomized controlled trials (RCTs) have repurposed anti-inflammatory medications to treat bipolar and unipolar depression. Meta-analyses have now demonstrated a medium-to-large effect size of adjunctive anti-inflammatories in the treatment of bipolar and unipolar depression.[21,22] More recent studies have used a stratified ap-

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proach, assessing anti-inflammatory treatments specifically in depressed patients with evidence of immune dysfunction (as determined by inflammatory markers), as evidence and logic have suggested that anti-inflammatory treatments are likely only beneficial for this subset of patients.[23,24] This stratified approach is also a step forward for psychiatry, moving to a more precision-based medical approach (as seen in other specialties, such as when selecting chemotherapy regimens or antibiotics). Of the anti-inflammatories evaluated, N-acetylcysteine (NAC),[25] minocycline[26] and omega-3 polyunsaturated fatty acids[27] show the most promise as adjunctive treatments for depression. These agents also have the benefit of excellent tolerability and safety with minimal adverse effects. As these studies were mostly small proof-of-concept RCTs, further larger studies are still required prior recommending these agents routinely in clinical practice.

Taken together, replicated evidence has demonstrated that immune dysfunction is involved in the etiology and pathophysiology of depression. Numerous mechanisms have been identified that subserve the immune-mood pathway. Targeting these mechanisms presents a novel, biologically-informed, and hypothesis-driven strategy that may advance the treatment of depression and yield improved outcomes beyond what may be achievable through solely targeting the monoamine system. Proof-of-concept studies have already yielded promising results in support of adjunctive anti-inflammatories in the treatment of bipolar and unipolar depression. Future, larger studies using a stratified approach are merited to determine which specific anti-inflammatory agents should be recommended.

Conflicts of Interest

JDR has no conflicts of interest to declare. RSM has received research grant support from Lundbeck, Astra Zeneca, Pfizer, Shire, Otsuka, Bristol Myers Squibb, National Institute of Mental Health, Stanley Medical Research Institute, Canadian Institutes for Health Research, and The Brain and Behavior Research Foundation. RSM has also received speaker/consultant fees from Lundbeck, Pfizer, Astra Zeneca, Elli Lilly, Janssen Ortho, Sunovion, Takeda, Forest, Otsuka, Bristol Myers Squibb, and Shire.

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