This issue of *Psychiatric Annals*, guest edited by Andrew Farah, MD, summarizes the role of homocysteine and its related chemistry in disease and in psychiatric disorders in particular. Why are we publishing an issue focusing on inflammation and homocysteine metabolism? Have any medications in this area been approved by the US Food and Drug Administration for the treatment of psychiatric disorders? No. So why bother covering these topics?

Well, landmark studies, such as the Sequenced Treatment Alternatives to Relieve Depression study (STAR*D),\(^1\) has forced us to look critically at the proportion of patients with depression who have achieved recovery through alternative therapy. Given the STAR*D longer term relapse rates, a 2014 article published by Hollon et al,\(^2\) suggests that a lack of relapse of major depressive disorder for 6 months would be a better standard treatment outcome than short-term remission. Furthermore, in STAR*D, about 2,500 patients were treated with citalopram, resulting in approximately a 33% remission rate and approximately a 45% relapse rate within 6 months—yielding an overall recovery rate of 18% in step 1 of the study.\(^1\) In treatment step 2, 1 of 6 antidepressant treatments was administered including: cognitive-behavior therapy, serotonin reuptake inhibitor, serotonin-norepinephrine reuptake inhibitor (venlafaxine), bupropion, a weak dopamine reuptake blocker, or a combination of citalopram plus bupropion. As a result, with all three monoamines (serotonin, norepinephrine, and to some extent dopamine) used therapeutically, an additional 25% of the patients remitted with a 55% relapse rate in 6 months for a recovery rate of 11%. For placebo, the recovery rate (not corrected for placebo response) was 36% in total for the first two steps. In antidepressant studies between 1981 and 2000, the placebo response rate at 8 weeks averaged 30%, with a significantly positive correlation between the year of the study and the placebo response ($n = 75$, $P = .45$, $P < .001$)\(^3\) (there was no placebo group in the STAR*D study).

For two treatment steps, monoaminergic antidepressants result in a recovery rate of 36% (failure of two adequate treatments is the most common definition of treatment-resistant depression in the literature). Adding low dosages, in which the average is 35.7 mg/day, of monoamine oxidase inhibitors (MAOIs) in steps 3 and 4 contributed to perhaps another 11% of patients who recovered. What does this mean? We should be looking at sustained response and using recovery—6 months without a relapse—as the standard.

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**Inflammation, Homocysteine, and Systems Biology in Psychiatry**

Jan Fawcett, MD

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Is it probable that depression is not just an illness involving monoamines, but with other causes involving stronger dopamine-acting medications (such as pramipexole and MAOIs at effective dosages), anti-inflammatory medications, medications affecting the homocysteine cycle, and maybe even medications affecting endocannabinoid and other systems we don’t yet know about? It makes you wonder, do major depression or bipolar disorder for that matter, based on a cluster of symptoms lasting for a given period of time, based on The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria, define an illness or are these mixed syndromes really representing many pathophysiologic diseases with different causes—and a range of (presently unknown) treatments? How well do the current diagnoses, based on DSM criteria, predict treatment response? Shouldn’t a valid diagnostic system be a guide to successful treatment? Is the DSM a guide to successful treatment?

In 2011, Loscalzo and Baribasi showed that “contemporary views of human disease are based on simple correlation between simple syndromes and pathological analysis during the 19th century.” In the article, they describe the development of personalized treatment, mainly based on genetic studies and genetically derived approaches to the treatment of cancer.

It may turn out that depression is an illness with a number of causes and treatments. It is of interest that Uher et al. described studies showing that depressed patients with severe inability to initiate behaviors and severe anhedonia (known as hypodopaminergic symptoms) turn out to be highly correlated with treatment resistance. There are few really potent antidopaminergic treatments, with the exception of MAOIs and pramipexole (but are probably ineffective at low doses); the remission rate, on average, is typically 6.9%. A recent case series using higher pramipexole doses has shown much improved response and remission rates.

We don’t know yet if higher medication doses—or addressing inflammation and homocysteine levels for that matter—will result in successful treatment results. However, it does appear that we need new paradigms to generate more effective medications for depression treatment. Maybe monoamine depletion isn’t the only paradigm in a field that could certainly use some improved outcomes—and looking at mechanisms like inflammation and homocysteine cycles could provide the field—and our patients—with a fresh outlook.

REFERENCES