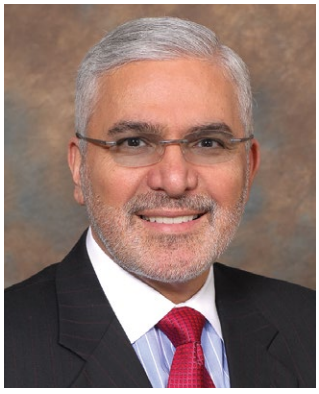

Henry A. Nasrallah, MD
Editor-in-Chief

Are you neuroprotecting your patients? 10 Adjunctive therapies to consider

Recurrent episodes of psychosis, mania, or depression have been shown to be potentially neurodegenerative and associated with neurotoxicity due to neuroinflammation, reactive oxygen and nitrogen species, and apoptosis. This neurodegeneration leads to neural tissue loss and decrease in brain function. Ideally, psychopharmacologic management must not only stabilize clinical symptoms, but also should counteract neurotoxicity of neuropsychiatric illness with neuroprotection.

There are many off-label supplements with strong neuroprotective effects that psychiatrists can use as an adjunct to standard evidence-based pharmacotherapy

Are you 'neuroprotecting' your patients?

Fortunately, many studies have demonstrated that in addition to controlling clinical symptoms, antidepressants, mood stabilizers, and atypical antipsychotics all have neuroprotective effects, including stimulating neurogenesis, preventing apoptosis, and increasing neurotrophins. However, more needs to be done to protect the brain's gray and white matter and to prevent negative neuroplasticity and disconnectivity of brain circuits that often are documented in patients with psychotic and mood disorders.

There are, in fact, many off-label supplements with strong neuroprotective effects that psychiatrists can use as an adjunct to standard evidence-based pharmacotherapy. These agents generally are safe and well tolerated and often are sold over the counter, but are not covered by insurance. However, considering the disability that often is associated with schizophrenia, treatment-resistant depression, or psychotic mania, it is reasonable to consider using these agents, many of which are supported by studies published in peer-reviewed journals. However, because they are widely available and not proprietary and large, expensive registration trials such as the ones conducted by the pharmaceutical industry are not done, none is likely to receive FDA approval. Therefore, it is up to psychiatrists and nurse practitioners to use them judiciously in patients at risk for neurotoxicity.

Here are 10 agents with neuroprotective effects supported by published data that can be considered as add-on to the standard treatments in an effort to mitigate neurotoxicity and protect the brain from the destructive processes that accompany acute episodes of psychosis, mania, and depression.

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Omega-3 fatty acids have been shown in several studies to help reduce psychopathology of psychosis, mania, or depression when used as an adjunctive agent.[1] It appears to be more effective in the early stages of psychiatric disorders than in the chronic phase. It has anti-inflammatory, anti-oxidant, and anti-apoptotic effects; activates cell-signaling pathways; and prevents synaptic loss as well as neuronal and glial death.[2]

***N*-acetylcysteine** (NAC) is a powerful antioxidant that increases glutathione, which is produced in the mitochondria. Schizophrenia is associated with mitochondrial dysfunction with low levels of glutathione, which puts the brain at risk for neurodegeneration caused by high levels of free radicals produced during psychosis. Adding NAC to antipsychotics during acute psychotic episodes—especially the first episode—can significantly reduce the neurotoxic effects of reactive oxygen and nitrogen species, also known as free radicals.[3] In studies of traumatic brain injury in rats, NAC reduced brain edema, neuroinflammation, blood–brain barrier permeability, and apoptosis.[4]

Minocycline. This antibiotic has been studied extensively as an adjunctive treatment in schizophrenia and has proven to have several neuroprotective effects including anti-inflammatory, anti-oxidant, and anti-apoptotic, and reduces glutamate excitotoxicity.[5] Several studies have documented its usefulness in acute psychotic episodes.

Vitamin D. Because of its vital role in neurodevelopment (neuronal differentiation, axonal connectivity), vitamin D deficiency has been associated with several psychiatric disorders including autism, schizophrenia, depression, and Alzheimer's disease.[6] Measure serum levels of vitamin D in patients with psychotic and mood disorders and implement supplementation if it is low—and it often is in these patients.

Nicotine is neuroprotective against glutamate excitotoxicity and it also inhibits apoptosis.[7] However, it should never be administered via cigarettes, which are loaded with hundreds of toxic substances! It can be administered via patches or nicotine gum, which are usually used to help in smoking cessation. Nicotine also also can have a pro-cognitive effect.

Melatonin. Many people associate melatonin with sleep. However, it has multiple neuroprotective effects by being an antioxidant, protecting mitochondrial integrity, and modulating the immune system, as well as attenuating microglial activation, which triggers neuroinflammation and oxidative stress. It also protects against cellular senescence, which is due to inflammation and reactive oxygen species. Furthermore, melatonin is useful in ameliorating the metabolic syndrome, which is associated with neurotoxic effects on brain tissue caused by the pro-inflammatory effects of perinomental fat in obesity.[8] Adjunctive melatonin could be helpful in patients with schizophrenia or depression who suffer from metabolic syndrome.

Erythropoietin is a hormone produced by the kidneys to promote the formation of red blood cells. It is a potent neuroprotective cytokine that promotes neuronal survival via anti-apoptotic effects. It protects against glutamate and nitrous oxide toxicity[9] and haloperidol-induced neuronal death.[10] It is clinically used (since FDA approval in 1989) in severe anemia due to chronic kidney disease or chemotherapy, as well as in inflammatory bowel disease. It does have some "black-box" warnings so its use should be limited.

continued

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Until a cure is found, these little steps could help alleviate our patients' suffering and the risk of neurotoxicity associated with their serious psychiatric disorder

Cox-2 inhibitors. This is a well-known class of anti-inflammatory drugs, which are FDA-approved for pain and inflammation. Studies of adjunctive use of cox-2 inhibitors in acute psychosis show that these drugs accentuate the efficacy of antipsychotic medications.[11] The reason is that acute psychosis is associated with neuro-inflammation, which leads to neurotoxicity.

Lithium. Dosages to treat mania are usually 900 to 1500 mg/d. However, in minute (homeopathic) dosages as low as 1 mg/d, lithium has been shown to prevent progression of amnestic mild cognitive impairment to full dementia.[12] This interesting observation suggests that lithium not only induces neurogenesis and increases gray matter volume,[13] but may be neuroprotective against amyloid neurotoxicity. The effects of very low doses of lithium in depression and schizophrenia have not been studied yet.

Caffeine. Yes, the good old brew people seek all day is neuroprotective and prevents mood and memory dysfunction caused by stress.[14] Caffeine should be avoided in patients with anxiety disorders, but it may be helpful for the brains of patients with mood or psychotic disorders. Caffeine reverses synaptic dysfunction in the circuits of the hippocampus caused by chronic unpredictable stress (quite common among our psychiatric patients).

The above interventions may be helpful for some patients but not others. Practitioners should consider using 1 or more of those adjunctive neuroprotective agents in patients who are at risk for neurodegenerative changes secondary to recurrences of acute and severe psychosis or mood episodes. Although clinicians cannot monitor brain structural integrity, they can assess the rate of symptomatic improvement and degree of functional restoration in their patients.

Until a cure is found, these little steps—taken cautiously and judiciously—could help alleviate our patients' suffering and the risk of neurotoxicity associated with their serious psychiatric disorder.

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