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Protecting the Brain from Oxidation and Inflammation Caused by First-Generation Antipsychotics

Antioxidants such as melatonin and ginkgo biloba have been shown to provide some benefit in treating TD once it has developed, but the most important role for antioxidants may lie in protecting the brain from the damaging inflammation and oxidation produced by the administration of first-generation neuroleptic medications.

When dopamine receptors are chronically blocked – as is the case when people take first-generation antipsychotics – it increases dopamine turnover which produces hydrogen peroxide, resulting in increased oxidative stress.[i] These free radicals accumulate within the brain's neurons unless detoxified.[ii] In studies with rodents that were administered these typical antipsychotics, the brains of these animals were shown to develop substantial oxidation.[iii] This supports one of the core hypotheses regarding the development of TD, that oxidation plays a major role.

Oxidation may have some impact on the severity of TD, and could explain, in part, why older people are more prone to developing TD. Antioxidant levels gradually diminish with age, leaving neurons more vulnerable to damage.[iv] Postmortem examinations of the brains of people with TD have revealed structural changes including the loss of neurons and gliosis (i.e., change of glial cells in response to damage to the central nervous system) in the basal ganglia after prolonged exposure to typical antipsychotics.[v]

Studies with rodents have shown that taking certain antioxidants along with typical antipsychotic medications not only protects the brain but can actually reduce the incidence of TD. A study published in 2017 examined whether the antioxidant resveratrol helped limit the risk of TD.

Resveratrol is a compound found in the skin of grapes and in several berries. It has the ability to cross the blood-brain barrier and provide protection to the brain. Resveratrol can both reduce inflammation in the brain and protect against damage from free radicals that are produced when typical antipsychotics are taken.

Researchers studied rodents who were injected with a typical antipsychotic for 18 weeks versus another group who also received resveratrol. Seventy percent of those that didn't receive resveratrol developed orofacial TD. However, only 30% of the rodents who also received resveratrol developed orofacial dyskinetic movements.[vi] The rodents in the study were given 20mg/kg of resveratrol, which is equivalent to 1,360mg per day for a 150lb. person. Resveratrol is generally considered safe up to 1,500mg per day for adults. (Safety note: Resveratrol may slow blood clotting and could increase the risk of bleeding in people with bleeding disorders or those taking any blood-thinning medication, such as warfarin. Non-steroidal anti-inflammatory drugs (NSAIDS) like aspirin, ibuprofen and the prescription medication Voltaren® (diclofenac sodium) can also increase bleeding and should be used with caution when taken with resveratrol.)

An additional 2021 study found that resveratrol provides protection against haloperidol-induced mitochondria impairment and abnormal autophagy (the natural breakdown of the cell that removes dysfunctional or unnecessary components).[vii]

Two other antioxidants that have been found to protect the brain from the damaging effects of first-generation neuroleptics are quercetin and grapeseed extract.

Quercetin is a naturally occurring bioflavonoid with powerful neuroprotective properties. When it was co-administered with a typical antipsychotic in rodents, it was found to reduce lipid peroxidation and restore the levels of glutathione, some of the brain's important antioxidant defense mechanisms.[viii] In the study, researchers administered 25-100mg/kg to the rodents. For a 150lb person, 25mg/kg would be equivalent to 1,700 milligrams in supplement form. However, experts recommend that the dose be limited to 1000mg/day. (Note: 100mg/kg for the same person would be equivalent to 6,800mg of quercetin, which is far above the safe daily limit and could damage the kidneys.)

Grapeseed extract is a potent antioxidant that helps protect the brain and the liver while a patient takes first-generation antipsychotics.[ix] Unfortunately, little is known regarding what dosage is safe to take. Grapeseed extract has also been reported anecdotally to reduce TD symptoms. If a patient wishes to try this antioxidant, it should be discussed with their doctor. It is best to start at a low dose with supplements and to only add one into a patient's regimen at a time so they can tell how it is affecting them.

Unfortunately, most psychiatrists don't understand the powerful neuroprotective benefits of these and other antioxidants. If it was standard practice for patients to take one or more of these antioxidants along with first-generation antipsychotics, it's possible that the incidence of drug-induced brain damage and TD could be decreased.

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