

# Can you reduce your patients' chances of developing TD?

## Protecting the Brain from Oxidation and Inflammation Caused by Neuroleptic Medications

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 neuroleptic medications.

When dopamine receptors are blocked – as is the case when people take medications that cause TD – it increases dopamine turnover which produces hydrogen peroxide, resulting in increased oxidative stress.<sup>i</sup> These free radicals accumulate within the brain's neurons unless detoxified.<sup>ii</sup> In studies with rodents that were administered antipsychotics, the brains of these animals were shown to develop substantial oxidation.<sup>iii</sup> It has been found that plasma activity of one of the main enzymes involved in the antioxidant defense mechanism, manganese superoxide dismutase, is elevated in people with TD.<sup>iv</sup> 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.<sup>v</sup> 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 antipsychotics.<sup>vi</sup>

Studies with rodents have shown that taking certain antioxidants along with 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 antipsychotics are taken.

Researchers studied rodents who were injected with an 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 dyskinesic movements.<sup>vii</sup> 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.)

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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).<sup>viii</sup>

Two other antioxidants that have been found to protect the brain from the damaging effects of psychiatric medications are quercetin and grapeseed extract.

Quercetin is a naturally occurring bioflavonoid with powerful neuroprotective properties. When it was co-administered with an 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.<sup>ix</sup> 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 antipsychotics.<sup>x</sup> 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 their medications, it's possible that the incidence of drug-induced brain damage and TD could be decreased by a sizeable percentage.

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<sup>i</sup> Spina MB, Cohen G. Dopamine turnover and glutathione oxidation: implications for Parkinson disease. *Proc Natl Acad Sci U S A*. 1989 Feb;86(4):1398-400.

<sup>ii</sup> Halliwell B, Gutteridge JMC. *Free Radicals in Biology and Medicine*. Oxford (UK): Clarendon Press; 1993.

<sup>iii</sup> Busanello, A., Leal, C.Q., Peroza, L.R. *et al.* Resveratrol Protects Against Vacuous Chewing Movements Induced by Chronic Treatment with Fluphenazine. *Neurochem Res* **42**, 3033–3040 (2017). <https://doi.org/10.1007/s11064-017-2335-4>

<sup>iv</sup> Zhang ZJ, Zhang XB, Hou G, Yao H, Reynolds GP. Interaction between polymorphisms of the dopamine D3 receptor and manganese superoxide dismutase genes in susceptibility to tardive dyskinesia. *Psychiatr Genet*. 2003;13:187–192. doi: 10.1097/00041444-200309000-00010.

<sup>v</sup> Halliwell B, Gutteridge JMC. *Free Radicals in Biology and Medicine*. Oxford (UK): Clarendon Press; 1993.

<sup>vi</sup> Waln, Olga, and Joseph Jankovic. "An update on tardive dyskinesia: from phenomenology to treatment." *Tremor and other hyperkinetic movements (New York, N.Y.)* vol. 3 tre-03-161-4138-1. 12 Jul. 2013

<sup>vii</sup> Busanello, A., *et al.*

<sup>viii</sup> Hu M, Wang R, Chen X, Zheng M, Zheng P, Boz Z, Tang R, Zheng K, Yu Y, Huang XF. Resveratrol prevents haloperidol-induced mitochondria dysfunction through the induction of autophagy in SH-SY5Y cells. *Neurotoxicology*. 2021 Dec;87:231-242. doi: 10.1016/j.neuro.2021.10.007. Epub 2021 Oct 22. PMID: 34688786.

<sup>ix</sup> Naidu PS, Singh A, Kulkarni SK. Quercetin, a bioflavonoid, attenuates haloperidol-induced orofacial dyskinesia. *Neuropharmacology*. 2003 Jun;44(8):1100-6. doi: 10.1016/s0028-3908(03)00101-1. PMID: 12763102.

<sup>x</sup> Sally A. El-Awdan, Gehad A. Abdel Jaleel, Dalia O. Saleh. Alleviation of haloperidol induced oxidative stress in rats: Effects of sucrose vs grape seed extract, *Bulletin of Faculty of Pharmacy, Cairo University*, Volume 53, Issue 1, 2015, Pages 29-35, ISSN 1110-0931, <https://doi.org/10.1016/j.bfopcu.2015.02.004>.