## Dextromethorphan/Quinidine For Neuropsychiatric Manifestations of Wilson's Disease

**To the Editor:** Wilson's disease is an autosomal recessive disorder in which copper accumulates in the brain and liver of affected individuals, resulting in a wide range of symptoms. Most individuals with Wilson's disease have neurologic sequelae such as dystonia, parkinsonism, and extrapyramidal symptoms. Patients also experience psychiatric manifestations, such as irritability, impulsivity, personality changes, and depression. Neurologic damage that occurs prior to treatment is often permanent.[1] We describe a case in which dextromethorphan/quinidine was utilized to treat mood lability in an individual with Wilson's disease intolerant of other agents.

***Case report.*** Ms A, a 34-year-old woman with a 14-year history of Wilson's disease, was treated for neuropsychiatric manifestations of the disorder in a clinic for individuals with neurologic deficits or traumatic brain injuries. Her symptoms consisted of mood lability, depression, impulsivity, dystonia, and parkinsonian features such as hypophonia, hypomimia, bradykinesia, impaired fine motor coordination, and an ataxic gait. She had no family history of Wilson's disease, but there was a family history of Parkinson's disease. She was first diagnosed with Wilson's disease at age 20, and her initial chelation therapy resulted in a paradoxical worsening of her neurologic symptoms, most likely resulting in further neurologic damage. Since being stabilized, Ms A has been maintained on zinc acetate to prevent further copper accumulation. Prior treatments included lithium, haloperidol, chlorpromazine, and olanzapine. No therapeutic effect was observed with these treatments but rather a worsening of extrapyramidal symptoms and no change in mood lability and impulsivity. Notably, use of first-generation neuroleptics has been cautioned against in Wilson's disease.[2] Ms A had also been started on quetiapine, which has been shown to have a lower risk of causing Parkinsonian symptoms. However, despite a sustained treatment dose of 400 mg for 4 months, quetiapine was discontinued due to lack of efficacy and the emergence of akathisia.

Dextromethorphan/quinidine was started and titrated to 20/10 mg twice a day. There was a marked improvement clinically in mood lability and impulsivity, with a Clinical Global Impressions—Improvement scale (CGI-I) score of 2 indicating response and no worsening of her extrapyramidal symptoms.

Dextromethorphan/quinidine is approved by the US Food and Drug Administration for the treatment of pseudobulbar affect, a condition consisting of uncontrolled laughing or crying and mood lability. Dextromethorphan/quinidine was initially studied in hopes of slowing amyotrophic lateral sclerosis progression. While ineffective in this regard, dextromethorphan/quinidine was found to reduce episodes of emotional lability, resulting in approval for pseudobulbar affect.[3]

Dextromethorphan is a sigma-1 receptor agonist and noncompetitive *N*-methyl-D-aspartate receptor antagonist. Sigma-1 receptors are distributed throughout the brain with a dense localization in the limbic system, suggesting a role in stress and mood regulation.[3] Additionally, agonism of these receptors inhibits glutamate neurotransmission in the cerebellum and brainstem.[4] If abused, dextromethorphan, the chief ingredient in over-the-counter medications such as Coricidin and Robitussin DM, can induce stimulation, euphoria, and dissociative states. However, the threshold for euphoria and stimulation is 100–200 mg and for dissociative states is 200–400 mg, making it unlikely that dextromethorphan/quinidine would be abused.[5] Quinidine functions to increase plasma levels of dextromethorphan by competitively inhibiting cytochrome P450 2D6, which metabolizes dextromethorphan. Dextromethorphan/quinidine is, in this sense, analogous to carbidopa/levodopa, a treatment for Parkinson's disease, in that quinidine serves to prevent the breakdown of dextromethorphan like carbidopa serves to prevent the peripheral conversion of levodopa into dopamine.

Excess glutamate can result in neuron excitotoxicity and cell death and may be a factor in traumatic brain injuries and chronic neurologic disorders.[6] Dextromethorphan/quinidine may lower available glutamate and so reduce emotional lability and impulsivity. A previous case report[4] demonstrated that dextromethorphan/quinidine was effective in treating aggression and agitation associated with a cerebellar injury. The positive response in our case with abolition of mood lability suggests that this compound may have some mood stabilization properties. This case report appears to be the first to show benefit with dextromethorphan/quinidine in treating mood lability and stabilizing mood in Wilson's disease.

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