It has recently been found (1) that many neuropsychiatric diseases, including bipolar affective disorder (manic-depression), schizophrenia, and seizure disorder, are associated with overactivity of the angiotensin 1-converting enzyme (which is abbreviated as ACE). Although we have no genetic evidence for autism and attention deficit and hyperactivity disorder (ADHD), it is likely that the cognitive and behavioral abnormalities seen in autism and ADHD may be the result of an imbalance of neurotransmitter levels in the brain, especially catecholamine levels, and dopamine in particular (2,3).

Angiotensin II, the product of ACE, is an under-appreciated neurotransmitter. It acts synergistically with catecholamines, promoting dopamine and norepinephrine release and reuptake in the peripheral (and presumably the central) nervous system. Both dopamine and angiotensin II stimulate thirst and the drinking of water, for example. Angiotensin II does this via the type 1 receptor (AT1R) (4).

The practical value of this approach is that ACE inhibitors and angiotensin II type 1 receptor blockers (“ARB’s”) are safe drugs, even for young children. They have been in very widespread clinical use for over two decades. Literally hundreds of millions of people have used them. The only behavioral symptom noted is an elevation in mood in 20% of adult patients, consistent with the association we’ve seen between depression and overactivity of ACE. They can be taken by mouth, and are relatively inexpensive.

This trial therefore would consist of using very safe drugs to try to treat a difficult disease. It is especially useful for children who are not doing well with conventional drugs, e.g. Ritalin for ADHD. The clinical hypothesis is that blockade of angiotensin II action would improve behavior and cognition in children or adults with ADHD.

For the extremely rare child, or the more common adult, with hypertension, a hydrophobic ACE inhibitor would be prescribed. But most children have a low blood pressure. For them, the smallest dose of an ARB already approved for use in children, such as irbesartan (AVAPRO), could be used safely—with even fewer side effects than an ACE inhibitor.

For example, AVAPRO could be used in its lowest dose (a 75 mg pill), or the 75 mg pill could be further divided in half or thirds, in an attempt to avoid lowering the child’s blood pressure at all.

The study would involve treating children with autism or ADHD in an open-label fashion with AVAPRO once a day (at bedtime), and following the children’s behavior for several months (the longer, the better). Practically speaking, 6 months should be enough to see if there’s any difference. AVAPRO would be prescribed by the child’s pediatrician if s/he agreed to participate in the trial.
REFERENCES