Does L-methylfolate have a role in ADHD management?

Olumuyiwa Fatade, MD, MPH, and Stacy Doumas, MD

***Editor's note**: Readers' Forum is a new department for correspondence from readers that is not in response to articles published in* CURRENT PSYCHIATRY. *All submissions to Readers' Forum undergo peer review and are subject to editing for length and style. For more information, contact letters@currentpsychiatry.*

Since the completion of the human genome project, the role of pharmacogenomics in treating mental health disorders has become more prevalent. Recently discovered genetic polymorphisms and mutations in the methylenetetrahydrofolate reductase (MTHFR) gene have led clinicians to seek out new therapeutic approaches to personalize mental health care. MTHFR is a key enzyme of folate metabolism, and changes in its gene can result in reduced enzyme activity, which has been associated with psychiatric illnesses such as schizophrenia, major depressive disorder (MDD), attention-deficit/hyperactivity disorder (ADHD), and autism.[1] Supplementation with L-methylfolate, the active form of folate, has been found to improve clinical and social recovery in patients with psychiatric illnesses such as schizophrenia and MDD.[2] While L-methylfolate is classified as an FDA-approved medicinal food for patients with depression and schizophrenia, its role in ADHD remains controversial.[3] L-methylfolate modulates the synthesis of monoamines such as dopamine and norepinephrine, which are pivotal in reducing inattentiveness and hyperactivity in patients with ADHD.[4,5] As a result, it could play an important role in the management of ADHD in patients with MTHFR deficiency.

Despite its high prevalence in many children, ADHD can persist into adulthood with impairing symptoms that have long-term social and economic impacts. Conventional methods of treating ADHD include stimulant medications such as methylphenidate, which can increase the levels of dopamine and norepinephrine in the brain. Unfortunately, stimulants' cost, adverse effect profile, and high potential for abuse can hinder their use and contribute to treatment resistance.[6] Because L-methylfolate can cross the blood-brain barrier and lacks the adverse effect profile of stimulants, it represents an alternative that could improve the quality of life for ADHD patients, particularly those with MTHFR polymorphisms or mutations.

Conflicting evidence

Several researchers have investigated the role of L-methylfolate as a supplement or alternative to stimulant therapy for patients with ADHD. While some preliminary studies have found some benefit, others have not. Here we describe 2 studies with differing results.

Quilliin[7] (2013). In an open-label study at a children's hospital in Texas, Quillin[7] investigated L-methylfolate for alleviating attention-deficit disorder/ADHD symptoms in 59 patients age 5 to 18. Twenty-seven patients received stimulant therapy. All patients were treated with L-methylfolate, 0.2 mg/kg/d in a chewable tablet form, for 6 weeks. The

continued

Dr. Fatade is a Research Volunteer, Department of Psychiatry, Jersey Shore University Medical Center, Neptune, New Jersey. Dr. Doumas is Chief, Child and Adolescent Psychiatry, Residency Program Director, Vice Chair of Education and Research, Department of Psychiatry, Jersey Shore University Medical Center, Neptune, New Jersey; and Vice Chair, Department of Psychiatry, Hackensack Meridian School of Medicine, Nutley, New Jersey.

Disclosures
The authors report no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

doi: 10.12788/cp.0107

primary endpoint was change on the average Vanderbilt Assessment Scale Total Symptom Score (TSS), which was 30 at baseline. At the study's conclusion, the average TSS score was 22, a 27% reduction. Patients who were taking only L-methylfolate had an average score of 21 at the end of the study, which was a 34% improvement, compared with an average TSS score of 23 in those who were taking stimulants.

Surman et al.[3] (2019). In this 12-week, double-blind, placebo-controlled clinical trial, researchers assessed the efficacy and tolerability of L-methylfolate when added to osmotic-release oral system methylphenidate (OROS-MPH).[3] Surman et al[3] randomized 44 adult patients (age 18 to 55) who met the DSM-5 criteria for ADHD to a placebo group or an active group. The placebo group was treated with placebo plus OROS-MPH, while the active group received L-methylfolate, 15 mg/d, plus OROS-MPH. OROS-MPH was started at 36 mg/d and titrated to optimal response. The primary endpoint was change in score from baseline on the Adult ADHD Investigator Symptom Report scale. Although it was well tolerated, L-methylfolate was not associated with a significant change in measures of ADHD or mental health function.[3] However, researchers noticed that patients who received L-methylfolate needed to receive higher doses of methylphenidate over time. This suggests that supplementation with L-methylfolate could reduce the effectiveness of methylphenidate in adult patients with ADHD.[3]

While more research is needed, the contradictory results of these studies suggests that the relationship between L-methylfolate and ADHD could be impacted by dosing, as well as by differences in adult and childhood ADHD that are not yet fully understood.

An area warranting future research

The growth of pharmacogenomics represents an important opportunity to bridge the gap between our understanding of psychiatric illnesses and new ways to treat them. Using L-methylfolate to treat ADHD might help bridge this gap. For this to occur, psychiatrists need to use evidence-based pharmacogenetic research to inform their decision-making. The differing results in studies evaluating the use of L-methylfolate in adult and pediatric patients pose interesting questions that will require more robust research to answer. Clinicians should be cautious in the use of L-methylfolate and recognize the importance of evaluating every patient with ADHD for MTHFR deficiency. This could help personalize care in ways that may improve the quality of life for patients and their families.

Clinical Point

L-methylfolate might provide benefit to patients with ADHD who have MTHFR polymorphisms or mutations

References

1. Wan L, Li Y, Zhang Z, et al. Methylenetetrahydrofolate reductase and psychiatric diseases. Transl Psychiatry. 2018;8. doi: 10.1038/s41398-018-0276-6
2. Godfrey PSA, Toone BK, Bottiglien T, et al. Enhancement of recovery from psychiatric illness by methylfolate. Lancet. 1990;336(8712):392-395.
3. Surman C, Ceranoglu A, Vaudreuil C, et al. Does L-methylfolate supplement methylphenidate pharmacotherapy in attention-deficit/hyperactivity disorder?: evidence of lack of benefit from a double-blind, placebo-controlled, randomized clinical trial. J Clin Psychopharmacol. 2019;39(1):28-38.
4. Stahl SM. L-methylfolate: a vitamin for your monoamines. J Clin Psychiatry. 2008;69(9):1352-1353.
5. Arnsten AFT. Stimulants: therapeutic actions in ADHD. Neuropsychopharmacology. 2006;31(11):2376-2383.
6. Childress A, Tran C. Current investigational drugs for the treatment of attention-deficit/hyperactivity disorder. Expert Opin Investig Drugs. 2016;25(4):463-474.
7. Quillin R. High dose L-methylfolate as novel therapy in ADHD. Abstract presented at: 2013 American Academy of Pediatrics National Conference and Exhibition; October 28, 2013; Orlando, FL.