

# Folinic Acid (Leucovorin) for Brain Conditions



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**Summary:** Folinic acid (tradename Leucovorin) is a form of folic acid that can be used to treat cerebral folate deficiency. Low folate in the brain means critical brain processes cannot happen. Cerebral folate deficiency can show up in different ways, such as autism spectrum disorder (especially low-functioning autism), hard-to-treat depression, and psychosis. Research suggests folinic acid may help treat at least some of these cases.

## Introduction to Folinic Acid

Folinic acid is a type of folate that has been used for a long time to protect against low folate, such as for people taking cancer treatments (such as methotrexate), or medications such as valproate. Newer evidence shows that it may be helpful for cerebral folate deficiency, a condition that results when there is low folate in the brain.

## Cerebral Folate Deficiency (CFD)

Low folate in the brain can cause different symptoms, which vary depending on the age at which the low folate occurs.

In young children, low brain folate is associated with

- Autism, especially low-functioning autism, where individuals may have trouble with speech or development.
- Neurologic problems such as seizure disorders or troubles with movement.

In children and adolescents

- Psychosis,
- Depression

In adults

- Major depression.

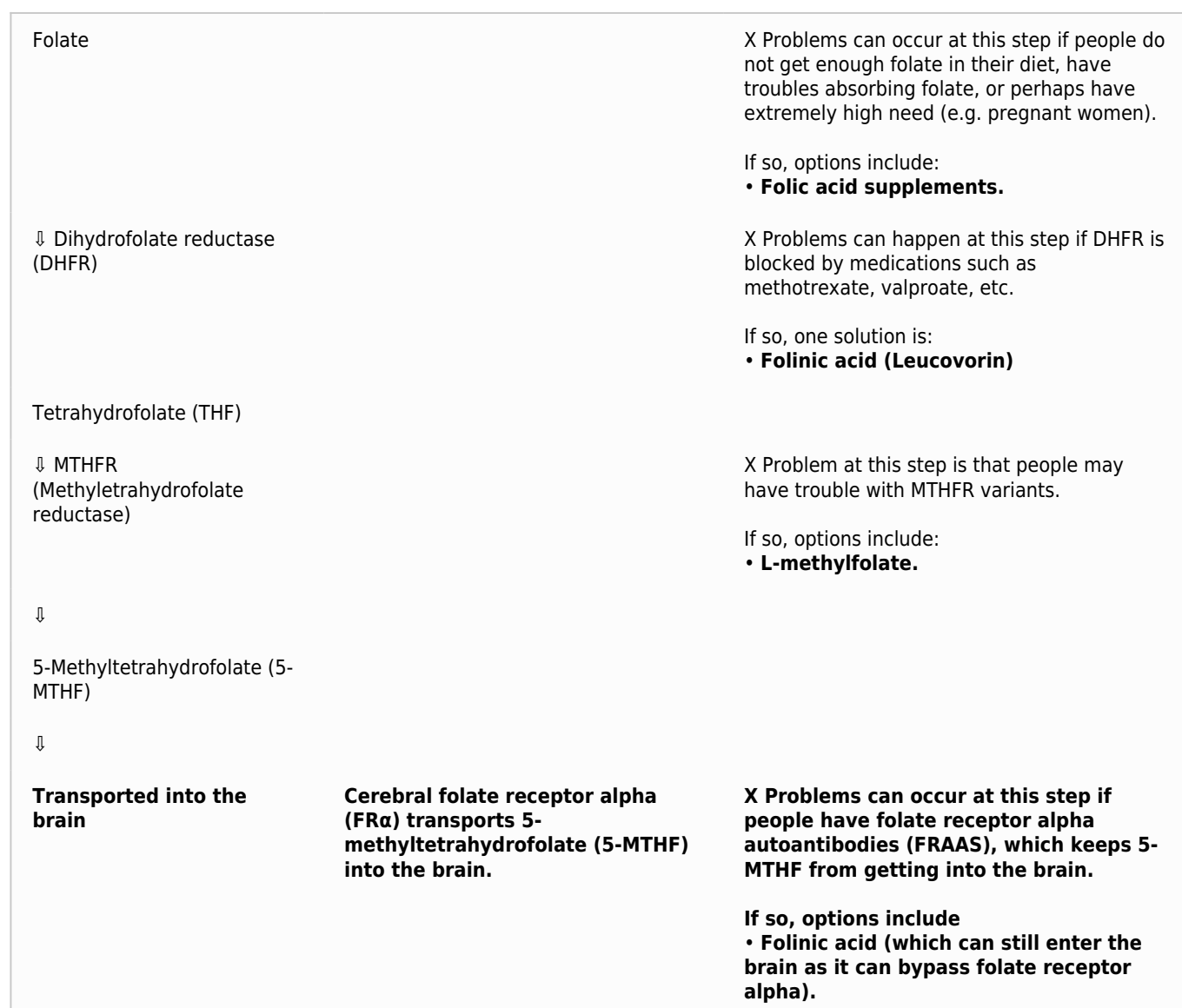
## What Causes Low Folate in the Brain?

There are many causes that can lead to low folate in the brain which include the following:

- Lack of folate in the diet
  - A survey of over 16,000 people aged and up, showed that about 9.5% of the population was NOT getting enough folate in their diet (NHANES 2007-2010)
- Folate receptor antibodies
  - It turns out that in certain populations at least, there appears to be a significant number who have troubles with folate receptor antibodies, which block the normal process of transporting folate into the brain.
  - Folate receptor antibodies have been found in ~ 70% of children with low functioning, early onset autism (Raemakers, 2008).
  - It appears that a diet containing dairy products (i.e. cow's milk, and specifically casein protein) is what triggers certain people to make antibodies to folate receptor alpha ).

## Folinic Acid Bypasses Folate Receptor Alpha Problems

The following diagram shows how folinic acid can bypass problems with folate receptor alpha.



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## What is the Evidence for Folinic Acid?

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There is evidence for the use of folinic acid to treat various conditions.

### Folinic Acid for Treatment-Resistant Depression

Folinic acid appears to help treat depression, particularly treatment-resistant depression (i.e. depression that has not responded to the usual serotonin medications.)

Studies show the following:

- A retrospective chart review revealed that patients who received folinic acid (leucovorin) augmentation at 25 mg daily appeared to have a shorter stay in the hospital (Saxena, 2021).
- In this treatment study of patients who had a poor response to an SSRI, folinic acid (leucovorin) was given at 15-30 mg daily and was felt modestly effective, with response in about 27-31% of patients (Alpert, 2002).

Folinic Acid for Autism Spectrum Disorder (ASD), in particular low functioning, early onset type.

As of Jun 2022, twenty-one studies (including four placebo-controlled and three prospective controlled) have treated individuals with ASD using folinic acid (Rossignol, 2021).

For individuals with ASD and cerebral folate deficiency (CFD), a meta-analysis found improvements with folinic acid in

- Overall ASD symptoms (67%),
- Irritability (58%),
- Ataxia (88%),
- Pyramidal signs (76%),
- Movement disorders (47%),
- Epilepsy (75%).

For individuals with ASD in general, leucovorin improves

- Communication (significant improvement with medium-to-large effect sizes)
- Core ASD symptoms
- Attention (with large effect sizes)
- Stereotypy (i.e. unusual movements) (with large effect sizes).

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## Can We Just Take Folate or Folic Acid?

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It depends. If a person has low brain folate due to folate receptor alpha issues, or folate enzyme issues, then simply eating more foods with folate, or taking folic acid supplements is not enough.

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## How to Find Folinic Acid Treatment?

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Are you in Canada?

- In provinces such as Ontario, physicians can prescribe Folinic acid (Leucovorin).
- Otherwise, folinic acid is also available as a commercially available supplement.

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## Dosage of Folinic Acid (Leucovorin)

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### **Is folinic acid being used to treat ASD?**

Typical dosage of folinic acid (leucovorin) for children aged 6-12

- 0.5-2 mg/kg/day divided twice a day (Frye, 2018)
- Maximum dose 50 mg / day.

Duration of treatment

- 4-months (Frye, 2012).

## Remember Also...

1. **Get enough Vitamin B12**, as folate works together with Vitamin B12. If there is a shortage of Vitamin B12, then folate will not work.

- For most children/youth, eating foods with protein should provide enough B12.
  - Daily Vitamin B12 requirements by age
    - Age 1-3 – 0.9 mcg
    - Age 4-8 -- 1.2 mcg
    - Age 9-13 – 1.8 mcg
    - Age 14+ -- 2.4 mcg
  - However, if the child is having troubles with protein intake (such as being a picky eater), consider:
    - Getting a Vitamin B12 level, and/or
    - Taking a child multivitamin supplement, as most multivits for children will have Vitamin B12 (such as 2 mcg daily).
    - For more information about Vitamin B12  
<https://www.aboutkidshealth.ca...>

## 2. Avoid dairy or cow's milk-containing products for at least 3-6 months

- Studies have shown that cow's milk (i.e. casein) can trigger folate receptor antibodies, hence the theory that reducing or ideally stopping dairy may be helpful for thus with suspected folate issues (Raemakers, 2008).
- Hence
  - Stop using dairy containing products for 6-months.
  - Substitute using soy-, almond-, rice-, coconut or other vegetable based "milk" products.

## Is folinic acid being used to treatment resistant-depression?

Studies have been done in adults with folinic to treat people with depression that has not responded to antidepressants such as SSRIs.

Dosage

- **15-30 mg daily for at least 3-months.**

## Side Effects of Folinic Acid

On one hand, folinic acid seems to be well tolerated by most people. Frye's study found that people taking folinic acid had the same side effects as people taking placebo (i.e. "sugar pill".)

On the other hand, some people may be more vulnerable, and the following side effects have been noted:

- Aggression (9.5%), excitement or
- Excitement or agitation (11.7%),
- Headache (4.9%),
- Insomnia (8.5%), and increased tantrums (6.2%).

## References for Folinic Acid

Alpert J et al. Folinic Acid (Leucovorin) as an Adjunctive Treatment for SSRI-Refractory Depression. *Annals of Clinical Psychiatry*. 2002 Mar (14(1)):33-8.

<http://dx.doi.org/10.3109/10401230209147396>

Bobrowski-Khoury N, Ramaekers VT, Sequeira JM, Quadros EV. Folate Receptor Alpha Autoantibodies in Autism Spectrum Disorders: Diagnosis, Treatment and Prevention. *J Pers Med*. 2021 Jul 24;11(8):710. doi: 10.3390/jpm11080710.

<https://pubmed.ncbi.nlm.nih.gov...>

Frye, R.; Sequeira, J.M.; Quadros, E.V.; James, S.J.; Rossignol, D. Cerebral folate receptor autoantibodies in autism spectrum disorder. *Mol. Psychiatry* 2012, 18, 369–381.

<https://www.nature.com/articles/mp2011175>

Frye RE, Slattery J, Delhey L, Furgerson B, Strickland T, Tippett M, Sailey A, Wynne R, Rose S, Melnyk S, Jill James S, Sequeira JM, Quadros EV. Folinic acid improves verbal communication in children with autism and language impairment: a randomized double-blind placebo-controlled trial. *Mol Psychiatry*. 2018 Feb;23(2):247-256. doi: 10.1038/mp.2016.168. Epub 2016 Oct 18. PMID: 27752075; PMCID: PMC5794882.

<https://pubmed.ncbi.nlm.nih.gov/27752075/>

Kim YI. Folic acid fortification and supplementation—good for some but not so good for others. *Nutr Rev* 2007;65(11):504-511.

<https://doi.org/10.1111/j.1753-4887.2007.tb00275.x>

Ramaekers, V.T.; Sequeira, J.M.; Di Duca, M.; Vrancken, G.; Thomas, A.; Philippe, C.; Peters, M.; Jadot, A.; Quadros, E.V. Improving Outcome in Infantile Autism with Folate Receptor Autoimmunity and Nutritional Derangements: A Self-Controlled Trial. *Autism Res. Treat*. 2019, 2019, 1–12.

<https://www.hindawi.com/journals/aurt/2019/7486431/>

R Prinz-Langenohl, et al. [6S]-5-methyltetrahydrofolate increases plasma folate more effectively than folic acid in women with the homozygous or wild-type 677C→T polymorphism of methylenetetrahydrofolate reductase. *Br J Pharmacol*. 2009 Dec; 158(8): 2014–2021

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2807663/>

Rossignol DA, Frye RE. Cerebral Folate Deficiency, Folate Receptor Alpha Autoantibodies and Leucovorin (Folinic Acid) Treatment in Autism Spectrum Disorders: A Systematic Review and Meta-Analysis. *Journal of Personalized Medicine*. 2021; 11(11):1141. <https://doi.org/10.3390/jpm11111141>

Saxena PP, Kyomen H. Leucovorin as an antidepressant adjunct in elderly inpatients with treatment-resistant depression. *Prim Care Companion CNS Disord*. 2021;23(2):20m02767.

<https://doi.org/10.4088/PCC.20m02767>

Scaglione F, et al. Folate, folic acid and 5-methyltetrahydrofolate are not the same thing. *Xenobiotica*. 2014 May;44(5):480-8

<https://www.ncbi.nlm.nih.gov/pubmed/24494987>

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## Disclaimer

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