Australian Academy of Health & Medical Sciences

Leucovorin & Autism

An Evidence Brief

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Summary

Leucovorin, the prescription drug form of folinic acid, is a form of folate (vitamin B9) used in several clinical settings including to reduce the toxic effects of certain cancer drugs that interfere with folate metabolism and to treat specific types of anaemia.[1] In September 2025, the United States Food and Drug Administration (US FDA) initiated the approval process for leucovorin for the treatment of cerebral folate deficiency (CFD), a rare neurodevelopmental condition in which folate levels in the brain are low despite normal folate levels in the blood.[2] This announcement was widely framed as an autism breakthrough, leading to confusion about leucovorin's indication and resulting in increased demand for the drug.[3,4] The FDA formally approved leucovorin in March 2026, but limited its use to a specific genetic subtype of the condition – namely CFD caused by a confirmed variant in the gene for folate receptor 1 (this subtype is known as CFD-FOLR1).[5] The approval does not currently apply to other causes of CFD and it does not extend to autism more broadly.[5]

CFD most often begins in infancy or early childhood and may be associated with developmental delay and neurological abnormalities.[6] The FDA approval means that leucovorin can now be prescribed for the CFD-FOLR1, this specific genetic subtype of CFD.

Leucovorin has attracted attention in the context of autism because some children with autism[i] have autoantibodies (parts of the immune system that mistakenly target the body's own tissues) that interfere with folate entry into the brain, which can result in CFD.[6,7] However, the presence of these autoantibodies does not automatically mean a child with autism has CFD; testing of cerebrospinal fluid (CSF, which surrounds the spinal cord and brain), is required to confirm a diagnosis.

Evidence for the effectiveness of leucovorin in the treatment of autism, including in individuals with comorbid CFD, is limited since there have only been a few studies involving a small number of children. Preliminary findings suggest potential benefit in specific biological subgroups; however, the current evidence is insufficient to support routine clinical use of leucovorin for autism or to justify changes to clinical practice. Any change to practice requires substantial evidence from large, robust studies. This is imperative because these investigations demonstrate the efficacy of therapies, identify the patients who stand to benefit from them, determine appropriate dosing, and, importantly, characterise the nature, frequency and severity of potential adverse effects. From the available studies, these questions cannot be answered definitively for the use of leucovorin for autism.

While evidence about leucovorin and autism is limited, there is a strong and robust evidence base for a range of other therapeutic options that can support the learning, participation and wellbeing of people with autism – including social and educational supports, which have been shown to make a meaningful difference.[8–10]

This evidence brief summarises current information on leucovorin, its approved medical uses, and the current evidence in relation to autism and CFD. It summarises the best available evidence at the time of publication. Future studies may refine or update these findings as scientific understanding in this area develops.

[i] *Autism spectrum disorder, or ASD, is the clinical, diagnostic term used by health professionals in diagnostic manuals. "Autism" is the widely used term to describe the same condition. Within this evidence brief, ASD and autism are used interchangeably (see box 2).*

Leucovorin and its uses

Folate, also known as vitamin B9, is an essential nutrient that helps the body make DNA and other genetic material required for cell growth and repair. It also supports the production of red blood cells and healthy brain function. Folate is particularly important during pregnancy because a deficiency can lead to spina bifida, a serious birth defect in which a baby's spinal cord and spine do not form properly.[11]

Folate is naturally present in many foods. Folic acid is the synthetic version used in supplements and fortified products. Once consumed, folic acid must be converted by the body into the active form, folate, to function properly.

The prescription drug form, leucovorin, contains folinic acid – a biologically active form of folate that does not need to be converted by the body. It is approved by the Australian Therapeutic Goods Administration (TGA) for several uses. These include helping to manage side effects of the drug, methotrexate, which is used to treat some cancers and autoimmune conditions, and to make another cancer drug, fluorouracil, more effective. It can also be used to treat accidental methotrexate overdose, clear methotrexate if the body is struggling to eliminate it, correct folate deficiency due to poor absorption, and prevent or treat certain kinds of anaemia related to folate deficiency.

In CFD, folate levels in the brain are lower because the primary route used by folate to enter the brain (folate receptor alpha or FRα) is blocked – see Box 1. This is relevant because the active form of folic acid (folate) depends on FRα to enter the brain, meaning that folic acid supplements cannot adequately compensate when that pathway is blocked.[7,12] Folinic acid, the active form of folate in leucovorin, bypasses this blockage by entering the brain via an alternative transport route, thereby restoring folate levels in the brain.[7] This is why leucovorin, rather than conventional folic acid supplements, is used to treat CFD.

New United States Food and Drug Administration (US FDA) approval of leucovorin

In September 2025, the US FDA initiated the approval process for leucovorin calcium (the formal pharmaceutical product name)[ii] for the treatment of CFD. In March 2026, the FDA formally approved leucovorin as the first treatment for a specific genetic subtype of CFD caused by a confirmed variant in the folate receptor 1 gene (CFD-FOLR1).[5,13]

Key features of cerebral folate deficiency are outlined in Box 1.

[ii] *The terms leucovorin and leucovorin calcium refer to the same drug. This evidence brief uses the term leucovorin throughout.*

Box 1: Understanding Cerebral Folate Deficiency (CFD)

CFD is a neurological condition where folate levels in the brain are low despite normal blood folate levels. It occurs when folate transport across the blood–brain barrier is disrupted. Folate usually enters the brain through a receptor called folate receptor alpha (FR). This transport can be disrupted by genetic causes or by acquired causes such as folate receptor alpha autoantibodies (FRAAs). These causes are explained below.

Causes and prevalence

CFD can result from genetic causes present from birth, such as disorders affecting folate transport or metabolism, or from acquired causes that develop later.[6] The genetic form, most directly relevant to the recent (March 2026) FDA approval, caused by mutations in the FOLR1 gene, is extremely rare, with an estimated prevalence of fewer than one in one million individuals worldwide, with approximately 50 cases identified to date.[13,14] Other genetic causes include deficiencies in enzymes involved in folate metabolism or transport, which can also result in low folate levels in the brain.[6]

Acquired causes develop after birth and are more prevalent than genetic causes.[4] These include FRAAs, mitochondrial disorders, nutritional folate deficiency, and certain medications such as methotrexate and antifolate drugs.[6] CFD is more common as a secondary or comorbid condition, particularly in ASD and other neurological syndromes.[7]

Diagnosis

While FRAA blood testing can support diagnosis and help identify an underlying mechanism, it does not confirm CFD on its own, because the presence of autoantibodies does not necessarily mean folate transport has been sufficiently impaired to cause deficiency in the brain.[6,7] Confirmation requires detecting low folate levels in the cerebrospinal fluid (CSF, which surrounds the spinal cord and brain), usually using a lumbar puncture/spinal tap.[6]

Age of onset

CFD most commonly affects infants and young children. While development is usually normal in the first year of life, early non-specific symptoms such as irritability and sleep problems can appear between 4-6 months of age. By around two years of age, more distinctive features including delayed speech, seizures, movement difficulties, or developmental regression typically become apparent.[15]

Current evidence on leucovorin and autism

Box 2 provides background information on autism to help contextualise the evidence on its overlap with CFD discussed in this evidence brief.

A 2021 review of the existing evidence analysed the results of 21 studies that used leucovorin in ASD, CFD, or children with both conditions.[7] Across these studies, CFD data were analysed for 172 individuals with autism, and autism status was assessed in 79 children with CFD.[7] This kind of review is more useful than single studies as it draws evidence from multiple sources, making it more informative – that said, the number of individuals included (even across 21 studies) is relatively small, reflecting the limited research in this area. The analysis found that CFD was present in about 38% of individuals with ASD, and ASD was seen in 44% of those with CFD, showing significant overlap between the two conditions.[7] The review also reported that folate receptor alpha autoantibodies (FRAAs, a known cause of CFD, see Box 1) were common in a subset of children with autism.[7] Across the reviewed studies, improvements following leucovorin treatment were reported in individuals with ASD who also had CFD or FRAAs. Overall, the review indicates that leucovorin remains a possible treatment for CFD-FOLR1 rather than autism itself, and that the available evidence is insufficient to support routine use in autism. Further large well-designed studies are required to confirm these findings as the evidence to date is drawn from relatively small study populations.[7]

A 2024 randomised controlled trial examined the efficacy of folinic acid (leucovorin) in approximately 80 children aged two to ten years with autism.[18] This study has since been retracted due to errors in reported results, concerns with the statistical analyses performed, and an inability to replicate the findings from the dataset provided.[19]

A 2025 study reported modest improvements in social reciprocity[iii] following folinic acid (leucovorin) treatment among children with autism carrying genetic variants affecting folate metabolism.[20] However, the study did not apply correction for multiple statistical comparisons. The study tested a large number of outcomes across multiple subgroups – the more outcomes you test, the greater the chance of finding a positive result by chance alone. Statistical corrections are usually used to adjust for this increased chance, but these were not applied in this study. The absence of this adjustment increases the risk of false-positive results, limiting the reliability of the findings.[20]

The overall evidence base for leucovorin as a treatment for autism remains limited, with published trials collectively including fewer than 300 children.[21] And in some cases, where positive findings are reported, they are not statistically significant once appropriate statistical corrections have been applied. The evidence is further weakened by insufficient blinding across studies (meaning participants or researchers may have known who was receiving the treatment, which can bias results), gaps in data regarding contraindications (information about who should not receive the treatment) and eligible populations, and safety data that do not meet phase III registration trial standards (the large scale trial data usually needed before a drug is approved for use).[21] The current body of evidence does not meet the standard of substantial evidence that would be required for the US FDA and other regulators to approve leucovorin as a treatment for autism.

[iii] *Social reciprocity refers to a child's ability to engage in back-and-forth social interaction, as measured using a standardised developmental assessment.*

Before any drug can be introduced into the community, large robust studies are required. These studies could reveal whether treatments genuinely work, which individuals are most likely to benefit, what doses and schedules are most effective, and any potential adverse effects, their frequency and severity. The 2021 review noted above reported that side effects across the studies covered in the review were generally mild, but included aggression, excitement or agitation, headache, insomnia and increased tantrums.[7] Leucovorin use should therefore be guided by clear clinical need and not generalised beyond its approved indications.

At the time of this publication, the TGA has approved leucovorin calcium for use in adults and children to reduce toxicity and counteract the effects of medicines that interfere with folate metabolism during cancer treatment and overdose, but not for the treatment of CFD (or ASD) in Australia.[22]

Working with the community

It is crucial that accurate information on what is and is not known about leucovorin and any other potential therapy or other support for individuals with autism is clearly communicated to parents, caregivers and the community. Announcements about the potential of leucovorin as a treatment for autism have caused confusion and concern.[4] If there are drugs that may help with some of the symptoms of autism, they should be explored as quickly and rigorously as possible so that access can be provided if they are effective.

While evidence about leucovorin and autism is limited, there is strong, well-established evidence that having the right social and educational supports makes a big difference for people with autism: inclusive classrooms, workplaces that accommodate their needs, and communities that respect their strengths and needs.[8–10] A 2022 review of 58 systematic reviews of non-pharmacological interventions for autistic children found positive effects across a range of approaches, though no single intervention was effective for all outcomes, highlighting the importance of individualised, evidence-based decision-making.[23]

Support for people with autism should continue to follow evidence-based best practice until the data from clinical trials of leucovorin is more robust.[24]

Box 2: Understanding autism[16]

Autism spectrum disorder (ASD), commonly referred to as autism, is an umbrella diagnostic term for neurodevelopmental conditions characterised by persistent differences in social interaction and communication, alongside restricted or repetitive patterns of behaviour. Autism affects how the brain develops and processes information, shaping how autistic people perceive, understand, and respond to the world around them.

Diagnosis

Autism is diagnosed through clinical assessment based on developmental history and observed behaviour. Diagnosis follows internationally recognised criteria set out in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and the International Classification of Diseases, Eleventh Revision (ICD-11). There is no single biological or laboratory test for autism, and diagnosis is typically made by trained health professionals and involves multidisciplinary assessment.

Causes

Research shows that autism arises from a complex interaction between genetic and environmental factors, most often influencing development before birth. Family history is one of the strongest predictors of autism, and hundreds of genes have been linked to ASD, with genetic contributions varying between individuals. Environmental factors may also play a role, but evidence for most proposed exposures shows weak and inconsistent associations rather than clear causal relationships.

Who is affected

Autism occurs across all populations and presents differently from person to person. It is more commonly diagnosed in males than females and frequently co-occurs with other developmental, learning, or health conditions. Autism characteristics may be recognised in early childhood, although diagnosis can also occur later in childhood or adulthood, for example as social and developmental demands increase.

Prevalence and trends

By 2022, around 1.1% of the Australian population had received an autism diagnosis.[17] Reported prevalence has increased over time, largely due to changes in diagnostic criteria, improved awareness, expanded access to assessment, and system and policy reforms. We explain this trend in more detail in our evidence brief on autism.[16]

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