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Research Article

Safety Signals And Adverse Drug Reactions Associated With Folic Acid: A Pharmacovigilance-Oriented Systematic Review

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ABSTRACT

Folic acid is the chemical form of folate, vitamin B9. It is used as a dietary supplement and as part of certain medicines. In fact, it is a very important micronutrient that can be hardly overstated in its role in treatment of folate deficiency, megaloblastic anemia, and neural tube defects during pregnancy. Besides treatment applications, folic acid is also given together with antifolate drugs like methotrexate, to lessen the harmful effects of these drug. However, it has been shown in various studies that it may have some side effects and risks known to some extent but has not been fearing people from using it yet. We have aimed in this review to gather all adverse drug reactions, safety signals from pharmacovigilance databases, and major drug interactions to portray the overall safety profile of folic acid more thoroughly. Reports through spontaneous systems like worldwide pharmacovigilance databases are very useful in providing information about the rare or unexpected adverse events which might not be revealed in clinical trials. Reported side effects include digestive upset, skin problems, allergic reactions, and a concern that vitamin B12 deficiency might be hidden and this can result in brain damage if not diagnosed. Also, it has been seen that some drugs such as anticonvulsants and antifolates when taken together with folic acid may affect the treatment results and need a very close watch. New tools in drug safety monitoring including data science and actual data from medical database evidence from healthcare databases have helped in getting more drug safety signals. Drug safety monitoring at present should include better documentation of drug side effects and further studies of long-term safety outcomes. Without any doubt, pharmacovigilance is a very important element to be able to safely and sensibly use folic acid in clinical and public health contexts.

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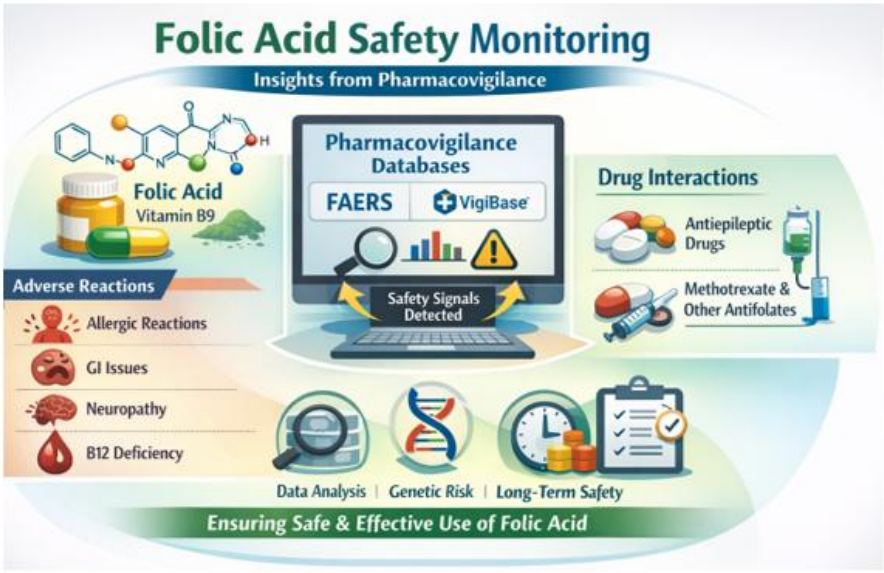


Figure 1. Folic acid safety monitoring

INTRODUCTION

Folic acid, known chemically as pteroylmonoglutamic acid, refers to the synthetic, very stable version of folate, which is one of the B9 vitamins. In its natural state, folate is a water-soluble vitamin serving as a cofactor in a number of crucial biochemical pathways within the human body. It enables nucleic acid synthesis, DNA repair methylation as well as several other types of amino acid metabolism. Folate coenzymes biologically mediate one-carbon units in the biosynthesis of purines and thymidylate. These reactions are indispensable for the normal growth, replication, and differentiation of cells. Due to the enormous significance of these physiological functions, folic acid intake has been recognized as an efficient therapeutic avenue to complement dietary intake in the treatment and prevention of folate deficiency and subsequent hematological disorders. [1]

Clinically, folic acid is most often used in the treatment of megaloblastic anemia caused by folate deficiency. Besides that, it is highly recommended to be taken by women during pregnancy as proper uptake of folate is necessary not only for fetal development but also for the prevention of neural tube defects in babies. Additionally, folic acid is a common accompaniment to antifolate drugs, such as methotrexate, which is aimed at lessening side effects and decreasing drug-induced toxicity. In addition to its use in treatment, several countries have taken the move of making their staple food products undergo folic acid fortification so as to reduce the incidence of birth defects associated with folate deficiency. Consequently, through both medicinal supplementation and food fortification measures, a large percentage of the worlds population is exposed to folic acid from multiple sources. [2]

Table 1. Major Therapeutic Uses of Folic Acid

Indication	Purpose
Megaloblastic anemia	Correction of folate deficiency
Pregnancy	Prevention of neural tube defects
Methotrexate therapy	Reduction of drug toxicity

Hyperhomocysteinemia	Lowering homocysteine levels

Besides its well-recognized benefits and extensive application, some latest findings indicate that folic acid supplementation might come along with certain adverse drug reactions (ADRs) and safety issues. [3] In fact, even though folic acid is generally well-tolerated by most people, there are reports of clinical literature describing rare cases of hypersensitivity reactions, skin problems, digestive issues, and even neurological complications. An additional major issue is the ability of folic acid to mask the symptoms of vitamin B12 deficiency which if not detected, results in permanent neurological damage. Also, excessive intake of folic acid has been linked to potential drug interactions with a range of medications including antiepileptic drugs, chemotherapeutic agents, and immunosuppressive therapies. [4]

Pharmacovigilance is indeed a significant aspect of ensuring drug safety, especially in tracking the effect of drugs and nutritional supplements upon their approval for use in the population. Quite a few adverse drug reactions (ADRs) are not detected in the preclinical tests and clinical trials mainly because these studies usually involve a limited number of participants and are conducted under very strict regulations. As a result, very rare or long-term side effects may only be observed after a medicine is quite widely used by the public. So, post-marketing surveillance programs are very important in discovering such drug safety issues. Besides, big pharmacovigilance databases like the FDA Adverse Event Reporting System (FAERS) and the World Health Organization global safety database VigiBase gather spontaneous reports of suspected adverse reactions from healthcare professionals, researchers, and patients. Such databases are great tools for finding potential safety signals and seeing the therapeutic agents safety profiles in real-world conditions. [5]

The present pharmacovigilance-oriented systematic review intends to thoroughly analyze the scientific literature on the adverse drug reactions and safety signals associated with folic acid. It primarily focuses on the documented ADRs, possible biological mechanisms underlying these reactions, known drug interactions, and safety signals detected through pharmacovigilance reporting systems. This review combines evidence from previous studies and safety databases to present a comprehensive picture of the safety profile of folic acid. In addition, the study aims to emphasize clinically significant considerations that could help healthcare professionals enhance patient safety and reinforce drug monitoring procedures. [6]

PHARMACOLOGICAL AND BIOCHEMICAL PROFILE OF FOLIC ACID

Folic acid belongs to the B-complex vitamin group consisting of water-soluble vitamins. It serves as a precursor to tetrahydrofolate which is the biologically active form of folate in the human body. The metabolite is involved in numerous essential metabolic pathways which contribute to the maintenance of normal cellular function. One of its major roles is the synthesis of nucleic acids along with the involvement in the metabolism of amino acids and regulation of the cell's growth and division. As a result of its major role in these biochemical activities, folic acid is very significant for the tissues that continually undergo rapid cell changes such as bone marrow, gastrointestinal mucosa, and developing fetal tissues. [7]

Chemical Identity and Molecular Characteristics

Folic acid, which is chemically known as pteroyl-L-glutamic acid, is the oxidized and synthetic form of vitamin B9 that is mostly found in pharmaceutical and dietary supplement products. The folic acid molecule consists of three main components: a pteridine ring, para-aminobenzoic acid (PABA), and a glutamic acid unit. Biologically, these three structural components combine to make the folate structure which is responsible for its biological activities. [8] The molecular formula of folic acid is CHNO and the molecular weight is 441. 40 g/mol. When completely purified, folic acid usually has the form of a yellow to orange crystalline powder. It is scarcely soluble in water and practically insoluble in most organic solvents. The compound is fairly stable under normal storage conditions but can slowly break down when exposed to light, high temperature, or very acidic environments. [9]

Structural Features

The molecular architecture of folic acid is characterized by three essential components that collectively form the folate molecule:

1. **Pteridine ring system**
2. **Para-aminobenzoic acid (PABA)**
3. **Glutamic acid residue**

These structural units are arranged by means of specific chemical linkages, which not only connect them but also stabilize the overall molecular structure. The special configuration of these elements enables folic acid to be enzymatically reduced inside the body transforming into biologically active coenzyme forms such as tetrahydrofolate. These reduced forms carry out one-carbon transfer reactions that are essential for various metabolic activities, e. g. DNA synthesis and cell division. [10]

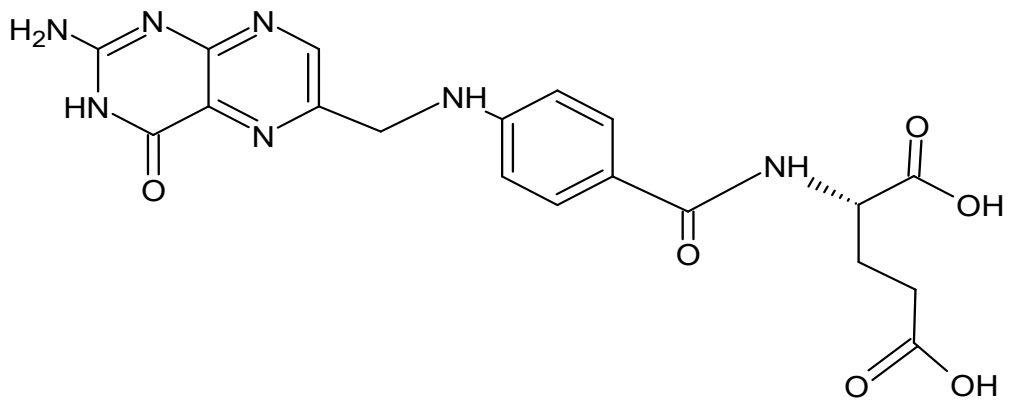


Figure 2. 2D Structure

Absorption and Metabolic Conversion

Folic acid is mainly absorbed in the upper part of small intestine, mostly in duodenum and jejunum, after being taken orally. The absorption mechanism is through the carrier-mediated transport systems located on the intestinal epithelial cells. The role of these transporters is to aid folic acid movement from the intestinal lumen into the bloodstream. [11]

Folic acid is mainly directed to the liver, which is the key organ in the metabolism of folate, after its absorption. In the liver, folic acid is first converted into dihydrofolate (DHF) and then tetrahydrofolate (THF) by enzymatic reactions.

The enzyme dihydrofolate reductase is responsible for these reactions. Tetrahydrofolate and its derivatives are indispensable coenzymes that take part in various metabolic reactions in the body. [12]

Role in One-Carbon Metabolism

One of the major biochemical roles of active folate is involvement in one-carbon metabolism - a series of pathways which are essential for the functioning of many biochemical reactions. The folate coenzymes act as carriers of one-carbon units in these pathways, which are then used for the synthesis of purine and pyrimidine nucleotides. [13]

Since folic acid participates in one-carbon transfer reactions, it plays a role in the support of the following important physiological functions:

- DNA synthesis and repair
- RNA formation
- Cellular proliferation and tissue growth
- Amino acid metabolism

Growing cells rapidly require these metabolic processes, which is why folate is very crucial in bone marrow, gastrointestinal mucosa, and fetal tissues as these tissues normally have very high rates of cell division. [14]

Role in Hematopoiesis

Folic acid has a very significant role in the formation and development of red blood cells in the bone marrow. Without a sufficient supply of folate, the necessary DNA production that happens during erythropoiesis cannot function properly. [15]

When there isn't enough folate, the production of DNA is interrupted which causes the red blood cells to develop abnormally. The outcome is the creation of very large and not fully-developed red blood cells, also called megaloblasts. The above described is the cause of megaloblastic anemia, which is the decrease in red blood cell and usually presents symptoms such as tiredness, lack of strength, and a lower capability of the blood to carry oxygen. [16]

Role in Homocysteine Metabolism

besides its role in hematopoiesis, vitamin B9 is also very important in the metabolic pathways of the amino acid homocysteine. Metabolism of homocysteine involves folate derivatives in the remethylation route to methionine. At the same time, this process requires the presence of vitamin B12. It is useful to maintain homocysteine level normal for healthy heart and brain. High homocysteine level has been associated with higher risk of certain diseases, including: [17,18]

- Cardiovascular diseases
- Stroke
- Neurodegenerative disorders
- Cognitive impairment

Adequate intake of folic acid therefore supports the regulation of homocysteine metabolism and may contribute to reducing these associated health risks.

Therapeutic Applications

Folic acid is commonly prescribed by doctors to prevent and treat diseases that are caused by lack of folate. The major trafficking role of folic acid in human health is in preventing ectopic neural systems. It has demonstrated that the regular use of folic acid during the first trimester of pregnancy can significantly reduce the risk of CNS malformations. The other major use of folic acid is the therapy of megaloblastic anemia resulting from folate deficiency. [19]

The administration of folic acid leads to the resumption of the natural production of

erythrocytes and the improvement of blood parameters in patients with folic acid deficiency. Besides that, folic acid is occasionally given as part of the treatment procedure to patients taking methotrexate, which drug action is to block folate metabolism. The addition of folic acid contributes to lessening the negative effects of methotrexate, especially the irritation of the stomach and the hematological side effects. Due to its wide range of roles in the body and the healing properties, the addition of folic acid to a diet is one of the most common vitamin supplementation programs in the present time. [20]

METHODOLOGY OF THE SYSTEMATIC REVIEW

This systematic review was a pharmacovigilance perspective to review the frequency of adverse drug reactions and the identification of potential safety signals of folic acid. Different major electronic databases such as PubMed Scopus Web of Science, ScienceDirect, and Google Scholar were searched for a comprehensive survey of the scientific literature. The search was done using the combination of important keywords such as folic acid, folate, adverse drug reactions, drug safety, pharmacovigilance, hypersensitivity, and drug interactions. Only English language publications describing safety concerns, adverse reactions, or pharmacovigilance data of folic acid were deemed suitable for the study. [21]

Clinical trials, observational studies, pharmacovigilance reports, case reports and review articles addressing safety aspects of folic acid were included. Studies not reporting adverse effects or reporting only nutrition outcomes without safety aspects were excluded from the review. The data was systematically extracted from selected articles, including type of adverse reactions reported, patient characteristics, clinical outcomes and drug interactions. Critical analysis and synthesis of the collected data were performed to offer a broad summary of safety profile and adverse event patterns in relation to folic acid use. [22]

ADVERSE DRUG REACTIONS ASSOCIATED WITH FOLIC ACID

Folic acid is typically regarded as a safe and vital nutrient; however, several adverse drug reactions (ADRs) have been recorded through clinical studies and pharmacovigilance reports. Frequently, the reported reactions are minor and reversible, but very occasionally, more severe adverse effects can happen. Whether or not these reactions occur, depends on a number of things, such as the dose given, the length of time that the therapy lasts, the age of the patient, other health conditions of the patient, and the use of other medications. Being informed about these possible side effects is a key element to make sure that folic acid is used safely and correctly in medical settings.[23]

Gastrointestinal Adverse Effects

Folates are a critical nutrient that is involved in several biologic processes. Besides that, they are also very sensitive and can easily be disturbed by various drugs. A grid of drug-folate interactions was made based on published papers, whereby 20 drug groups were found to be associated with folate depletion. Disturbances of the gastrointestinal tract are one of the most frequently cited consequences of folic acid supplementation.[24] Nausea, abdominal pain or discomfort bloating excessive gas formation, and even in some cases, loss of appetite is some of the symptoms that a person undergoing folic acid therapy can go through. These symptoms are usually not severe and in fact, folic acid in high doses or long-term exposure is what really causes these side effects. The precisely biological

mechanism behind the development of such gastrointestinal disorders resulting from folic acid is still not known. Nevertheless, it has been proposed that folic acid may briefly affect intestinal metabolic processes or lead to slight irritation of the gastric mucosa. Usually, these symptoms are transient and disappear either when the dosage is lowered or when the supplement is stopped. Moreover, co-administration of folic acid with food and proper dose adjustment can alleviate these gastrointestinal problems.[25]

Dermatological Reactions

Also, some patients undergoing treatment with folic acid have reported skin-related adverse effects. These include symptoms such as skin rash, erythema (redness of the skin), pruritus (itching), and urticaria/hives. Such allergic responses to folic acid or possibly to the excipients of its pharmaceutical preparation are very rare. [26] Occasionally, these skin-related adverse effects associated with folic acid supplementation will occur shortly after the folic acid is taken. In the majority of instances, the side effects are minimal and will resolve once the supplementation is stopped. Nevertheless, if the symptoms are persistent or worsen, it is recommended that the affected person gets a medical review and ceases using the medication. [27]

Hypersensitivity Reactions

Hypersensitivity reactions are a very uncommon but medically significant unwanted effect of folic acid. These reactions are believed to be caused by immune-mediated mechanisms that trigger an excessive reaction towards the substance. The hypersensitivity symptoms described are bronchospasm angioedema extensive urticaria, and very rarely anaphylactic reactions. These reactions are believed to involve immunoglobulin E (IgE)-mediated pathways, leading to the release of histamine and other inflammatory substances from immune cells such as mast cells and basophils. [28]

Individuals who have hypersensitivity reactions may show signs of breathing problems, swelling of the face or throat, severe itching, or extensive skin rashes. Emergency medical treatment is necessary in such cases as without proper therapy, severe allergic reactions can be fatal. [29]

Masking of Vitamin B_{12} Deficiency

One of the major clinical worries about supplementing with large doses of folic acid is that it can mask the symptoms of vitamin B12 deficiency. Both folate and vitamin B12 are essential for the normal production of red blood cells and the synthesis of DNA. A lack of vitamin B12 leads to megaloblastic anemia, which is marked by the presence of enlarged and immature red blood cells. [30]

If high doses of folic acid are given, the problems with blood cells caused by the lack of vitamin B12 may get better. Nevertheless, even if the anemia seems to be fixed, the vitamin B12 deficiency-related nerve damage may secretly get worse. Eventually, this situation without warning can cause very serious nervous system problems, such as damage to peripheral nerves, loss of memory and other mental abilities, and degeneration of the spinal cord. [31]

The problem is especially grave for the elderly, those suffering from gastrointestinal malabsorption disorders, and anyone who lacks sufficient vitamin B12 in the diet. As a result, it is advisable to check one's vitamin B12 level before starting a therapy with large doses of folic acid.

Neurological and Long-Term Safety Concerns

Whilst folic acid is vital for maintaining normal neurological function, there is a possibility that taking too much or for a very long time could lead to adverse effects. It has been proposed that very high-dose vitamin supplementation may affect certain metabolic and neurological pathways. A few studies have shown that increased folic acid levels might change methylation reactions or disrupt normal folate metabolism. Besides that, there has been talking about the fact that a very high folic acid intake might be a factor in the development of some types of cancer in individuals who are, to some extent, genetically predisposed to it. [33]

Nevertheless, the literature is inconsistent, and more well-designed studies are needed to be able to draw accurate conclusions on the matter. Therefore, pharmacovigilance systems and post-marketing surveillance programs should be continuously employed so that any emerging safety concerns related to the use of folic acid can be detected and properly assessed.[33]

Table 2. Common Adverse Drug Reactions of Folic Acid

System Affected	Adverse Reaction
Gastrointestinal	Nausea, abdominal discomfort
Dermatological	Rash, itching
Immune System	Hypersensitivity reactions
Neurological	Masking of vitamin B12 deficiency

SAFETY SIGNALS FROM PHARMACOVIGILANCE DATABASES

Pharmacovigilance databases are essential in finding and through follow-up monitoring identifying the possible adverse drug reactions to medicines and dietary supplements which will become evident after they are approved for clinical use. On one hand, preclinical experiments and clinical trials offer very important preliminary safety data but on the other hand, these studies are carried out on limited numbers of participants in controlled environments. More specifically, the uncommon, late onset, or population-specific side effects may only be noticed once the product is broadly used in the everyday medical practice settings. Therefore, pharmacovigilance systems are the key component for post-marketing surveillance as well as for the quick identification of newly arising safety issues. [34]

Spontaneous reporting systems collect data on suspected adverse reactions from healthcare professionals, patients, and pharmaceutical companies. These reports are entered into large safety databases that help researchers and regulatory authorities to identify adverse event patterns and investigate potential associations between drugs and reactions. The ongoing monitoring and signal detection analyses carried out within these systems have a major role in the enhancement of drug safety and the improvement of patient care. [35]

Global Pharmacovigilance Databases

Several international pharmacovigilance platforms are commonly used for drug safety monitoring and detection of adverse drug reactions. One of the biggest ones is the FDA Adverse Event Reporting System (FAERS), a database run by the U. S. Food and Drug Administration. This system gathers voluntary reports of adverse events linked to drugs

available on the market in the United States. Data from FAERS offer insight into the real-world safety of drugs and assist in identifying the emergence of adverse reactions that may not be drug development clinical trials. [36]

Yet another significant international pharmacovigilance database is VigiBase, maintained by the World Health Organization (WHO) through the Uppsala Monitoring Centre in Sweden. VigiBase contains hundreds of thousands of Individual Case Safety Reports, which are submitted by national pharmacovigilance centers of more than one hundred countries. This huge database allows for large-scale assessment of adverse drug reactions and encourages worldwide cooperation in drug safety monitoring. [37]

Besides these global systems, there are also a number of regional and national pharmacovigilance programs. As an illustration, EudraVigilance functions in the European Union to gather and study reports of suspected adverse reactions linked to medicinal products. In fact, these pharmacovigilance systems, taken together, constitute an international network focused on drug safety monitoring and the timely identification of potential risks related to therapeutic agents. [38]

Methods for Signal Detection in Pharmacovigilance

Detection of signals plays a central role in pharmacovigilance and it mainly refers to discovering a previously unknown or poorly documented association between a drug and an adverse event. They are mostly identified through the analysis of large collections of spontaneous adverse event reports using statistical and epidemiological methods. Disproportionality analysis is one of the approaches which is most often used for signal detection and consists of finding out whether an adverse event is reported more often for a specific drug than for other drugs in the same database. [39]

For this purpose, several statistical measures are used including the Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), and Bayesian statistical methods such as the Bayesian Confidence Propagation Neural Network (BCPNN). These methods help drug safety scientists detect unexpected reporting patterns that may point to a safety concern. After a signal has been flagged a drug safety professional will need to further explore the signal to understand if the drug indeed induces the adverse event. Such a study can be based on clinical review of case reports, epidemiological research, mechanistic studies, and regulatory assessment. Hence, signal detection is the first and a very significant step that leads to the investigation of possible drug safety problems.[40]

While folic acid was generally perceived as a safe and necessary nutrient, pharmacovigilance investigations have uncovered some safety issues with its administration. These issues mainly concern adverse effects on the immune system, digestive system, nervous system, and blood-related processes. Although such incidents are quite rare, their discovery serves as a reminder of the importance of ongoing surveillance of folic acid intake. Of the various safety concerns raised, hypersensitivity reactions top the list. Reports in the pharmacovigilance system have detailed allergy symptoms, including skin rashes itching hives, and on very rare occasions, severe allergic reactions like bronchospasm and anaphylaxis. It is thought that these reactions may be immune responses mediated by folic acid itself or other ingredients in the preparation.

Reported Safety Signals Associated with Folic Acid

Folic acid
has traditionally been considered a very safe and vital nutrient. However, several safety signals have been linked to its use, especially those related to immune system, gastrointestinal, nervous system, and hematological adverse reactions, that were revealed by pharmacovigilance analyses. These incidents are very rare but they emphasize how monitoring of folic acid supplementation must be a regular activity. Hypersensitivity reactions are among the adverse effects that have been raised as safety issues most frequently. Pharmacovigilance data include allergic reactions like skin rashes itching urticaria, and in exceptional cases, severe allergic reactions such as bronchospasm and anaphylaxis. It is thought that these reactions are the result of immune-mediated responses brought about either directly by folic acid or by other ingredients contained in the folic acid preparations.[41]

Gastrointestinal disturbances are also among the most commonly reported adverse effects associated with folic acid supplementation. Patients may have symptoms such as nausea, abdominal pain, bloating, and other complaints related to the digestive system. While these effects are usually mild and go away on their own, they might cause a person to feel uncomfortable and, at times, even reduce their willingness to continue with the treatment. Furthermore, a significant safety issue drawn from pharmacovigilance data is the potential for high doses of folic acid to mask a vitamin B deficiency. These high doses can fix the blood-related symptoms of a vitamin B deficiency, which might result in the vitamin B deficiency being overlooked. Due to this, nerve problems like peripheral neuropathy or issues with cognition could progress without being noticed. This concern is quite significant for older patients, who are at a higher risk of having a vitamin B deficiency.[42]

Besides that, pharmacovigilance reports through the analysis of large databases have indicated the possibility of drug interaction signals with folic acid. When combined with certain drugs such as antiepileptic drugs or antifolate chemotherapeutic agents, folic acid may affect drug metabolism or change the drug's efficacy. It is these kinds of interactions which alter the drug response and which would need very careful clinical monitoring. Therefore, with respect to safety issues, these signaling of risks underscore the necessity of continuous pharmacovigilance monitoring of folic acid use. The ongoing review of adverse event reports from extensive safety databases allows not only healthcare professionals but also regulatory authorities to have comprehensive knowledge of the safety features of folic acid and, if the need arises, to carry out relevant risk management measures. [43]

Table 3. Safety Signals Identified in Pharmacovigilance Reports

Safety Signal	Clinical Concern
Hypersensitivity reactions	Allergic reactions such as rash, urticaria, and rare anaphylaxis
Neuropathy risk	Masking of vitamin B_{12} deficiency leading to neurological complications
Gastrointestinal effects	Nausea, abdominal discomfort, and digestive disturbances
Drug interaction signals	Altered therapeutic response with certain medications

DRUG INTERACTIONS INVOLVING FOLIC ACID

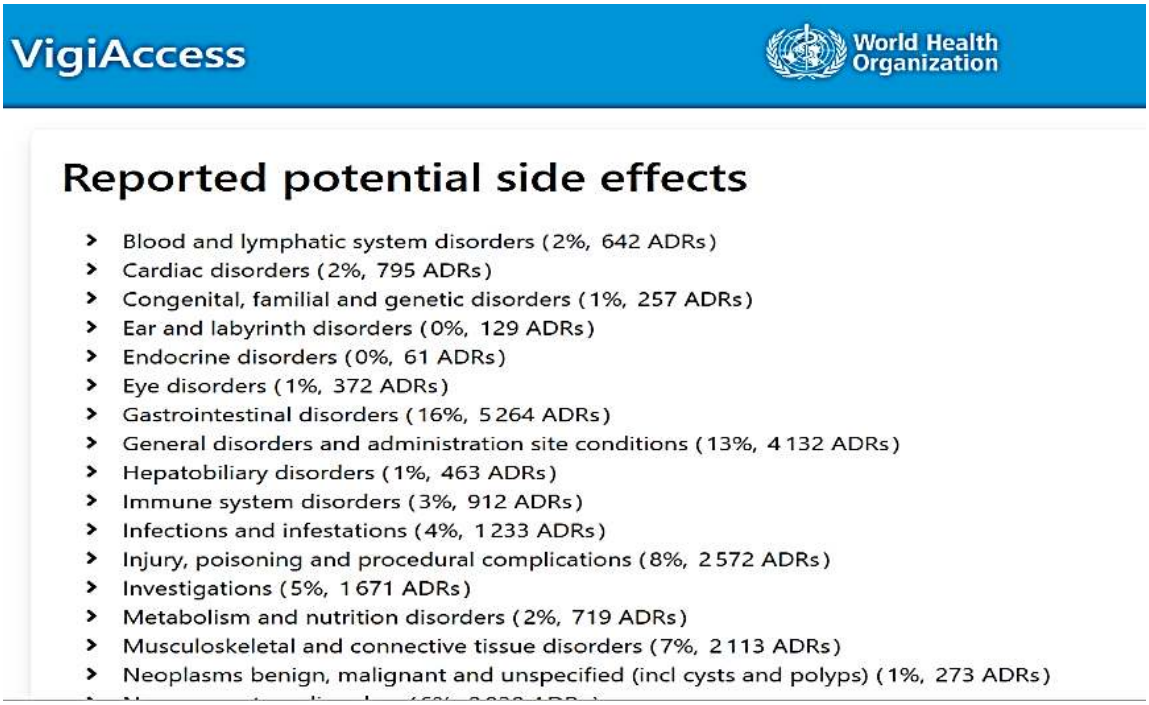
Folic acid can interact with a number of drugs, potentially changing the safety and effectiveness of the drugs used together. One of the most widely

known interaction scenarios points to methotrexate, a type of antifolate drug that is employed in cancer and autoimmune diseases therapies. [44] Methotrexate mechanism of action consists in blocking the activity of the enzyme dihydrofolate reductase, which disrupt folate metabolism and subsequently DNA synthesis. Introducing folic acid in the regimen is one of the measures taken to alleviate the negative effects of methotrexate such as gastrointestinal toxicity and bone marrow suppression. Nevertheless, very high doses of folic acid might compromise the efficacy of methotrexate, which is why it is very important to be properly dosed and timed with respect to administration. [45]

Cases of folic acid interacting with antiepileptic drugs have been reported to some extent. Drugs like phenytoin, carbamazepine, and phenobarbital are known to decrease the level of folate in the body and this may result in folate deficiency if the therapy is pursued for a long time. In contrast, taking folic acid might lower the plasma levels of the antiepileptic drugs raising the risk of seizures. Medicines such as trimethoprim and sulfonamides - commonly known as antibiotics - can also cause folate-related issues, as they are known to disrupt folate metabolism. Such interactions can lead to changes in the pharmacological effects of both the antibiotic and folic acid. [46]

Table 4. Important Drug Interactions

Drug	Effect of Interaction
Methotrexate	Reduces toxicity but may affect efficacy
Phenytoin	Decreases anticonvulsant levels
Carbamazepine	Alters folate metabolism
Trimethoprim	Interferes with folate pathway



- Nervous system disorders (6%, 2030 ADRs)
- Pregnancy, puerperium and perinatal conditions (2%, 525 ADRs)
- Product issues (0%, 134 ADRs)
- Psychiatric disorders (3%, 1008 ADRs)
- Renal and urinary disorders (1%, 381 ADRs)
- Reproductive system and breast disorders (1%, 177 ADRs)
- Respiratory, thoracic and mediastinal disorders (4%, 1149 ADRs)
- Skin and subcutaneous tissue disorders (13%, 4275 ADRs)
- Social circumstances (1%, 169 ADRs)
- Surgical and medical procedures (1%, 287 ADRs)
- Vascular disorders (2%, 628 ADRs)

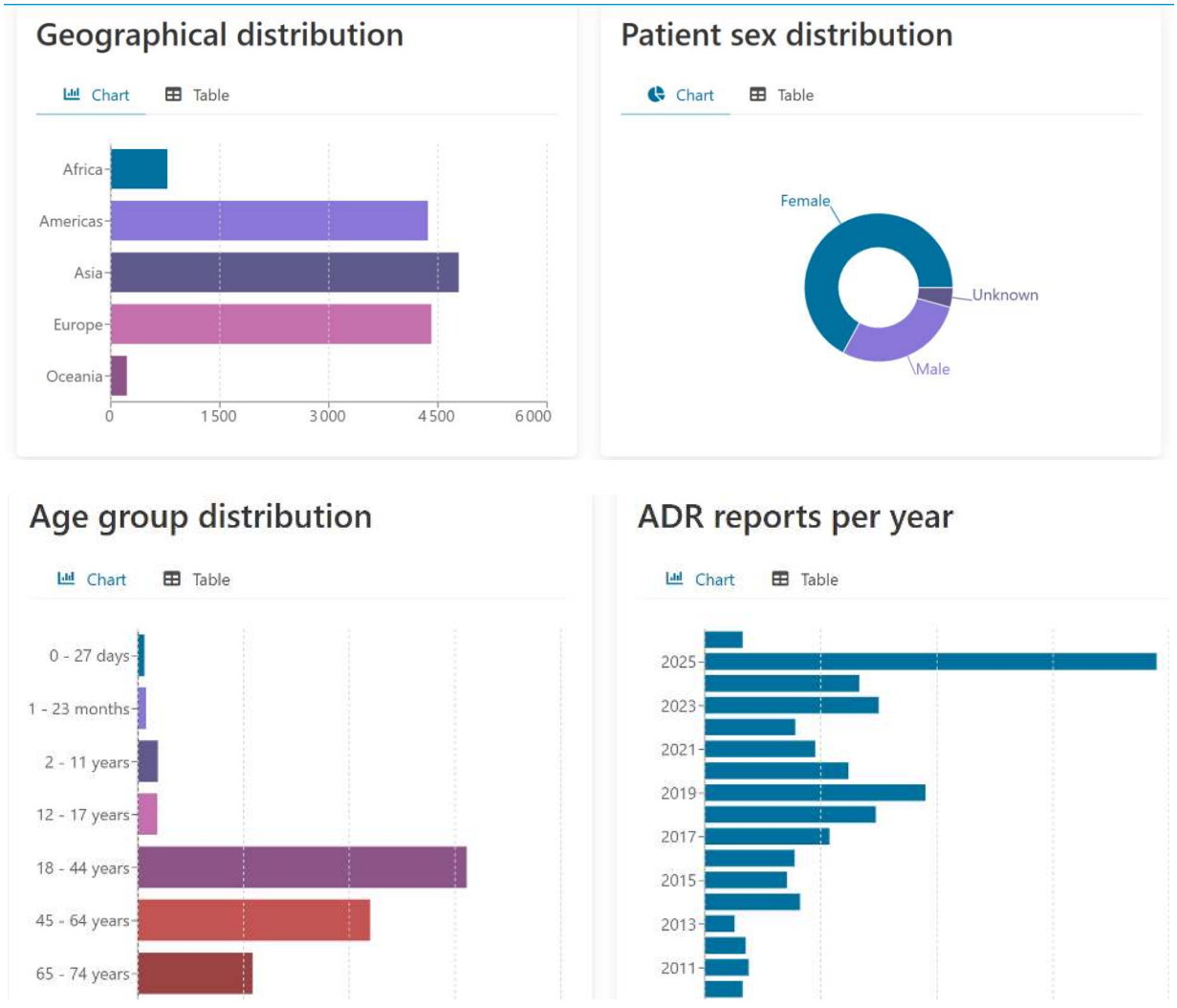


Figure 3. VigiAccess Database Information

CLINICAL IMPLICATIONS AND RISK MANAGEMENT

Understandings of the side effects of folic acid on people have really changed the way doctors and specialists work. When making plans to give folic acid, especially if it's at large amounts, healthcare workers should look kindly at a patient's disease records and overall health condition including diet. [47]

Doing checks for vitamin B shortage are good to do in some groups of people, mainly old ones and those suffering from problems absorbing food. Catching vitamin B shortage early and dealing with it properly may help to avoid the brain-related problems which could be hidden if folic acid is given. People getting folic acid with other types of drugs should be kept on watch for their body functions and any negative side effects. Also, those systems which take in reports about drug side effects should be employed in recording cases where adverse reactions are suspected; in turn, these reports will help in worldwide safety monitoring and drug surveillance. [48]

Table 5. Risk Factors for Adverse Effects

Risk Factor	Possible Outcome
High-dose supplementation	Increased ADR risk
Vitamin B_{12} deficiency	Neurological damage
Polypharmacy	Drug interactions
Elderly patients	Higher susceptibility

FUTURE PERSPECTIVES IN PHARMACOVIGILANCE

Advances in pharmacovigilance techniques have significantly enhanced our ability to identify, assess, and manage drug safety signals. Modern pharmacovigilance systems are making use of sophisticated analytical methods like big data analysis, machine learning, and artificial intelligence to process large safety datasets obtained from multiple sources. Using these technologies, it is possible to quickly detect potential adverse drug reactions and facilitate the early identification of safety problems. In addition, the use of real-world data from electronic health records, patient registries, and healthcare databases provides valuable information about the safety and effectiveness of drugs and supplements in different patient groups over time. The target of future pharmacovigilance studies on folic acid should be the evaluation of long-term side effects, especially in those who obtain a high level of dietary folate through the national food fortification program and supplementation. [49]

Even though folic acid is considered safe in standard doses, prolonged high-dose exposure might alter metabolic pathways, thus a continuous safety monitoring to unveil any unexpected issues would be prudent. Besides, pharmacogenomic studies may unravel genetic and metabolic variations affecting folate metabolism thus potentially, an individual's chance of experiencing side effects or different responses to treatment.[50]

In fact, another major direction for research in this field is the use of extensive pharmacovigilance databases and worldwide collaborative networks to improve the identification of safety signals and the assessment of risks. By enhancing global pharmacovigilance systems and motivating the spontaneous reporting of adverse drug reactions, it is possible to collect richer drug safety data. Therefore, partnership between healthcare workers, drug regulators, scientists, and drug

companies will be vital for the thorough surveillance of folic acid safety. These joint initiatives could lead to the formulation of scientifically substantiated guidelines and help in ensuring safe and proper use of folic acid both in clinical settings and public health interventions. [51]

CONCLUSION

Folic acid, a vital water-soluble B-complex vitamin, is among the most widely used vitamins in clinical medicine for the prevention and treatment of folate deficiency, megaloblastic anemia, and neural tube defects. Besides these, it is also used to reduce the toxicity of some antifolate drugs. Although it has been considered generally safe and well-tolerated, pathogenetic data and clinical cases have indicated that side effects may sometimes occur, such as gastrointestinal disturbances, skin reactions, hypersensitivity responses, and vitamin B12 deficiency masking. Detecting these kinds of safety signals through pharmacovigilance databases underlines the necessity for ongoing monitoring and systematic evaluation of adverse events related to the use of folic acid. Improving pharmacovigilance systems, encouraging spontaneous reporting of adverse events, and carrying out additional studies on the long-term safety and genetic variability of folate metabolism will shed more light on the overall benefit-risk profile of folic acid. In essence, prudent clinical application along with an efficient pharmacovigilance system will go a long way in safe and rational use of folic acid in therapies as well as in the prevention of healthcare.

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CONFLICT OF INTEREST:

Authors have no conflict of interest.

REFERENCES

1. Bailey LB, Gregory JF. (1999). Folate metabolism and requirements. J Nutr., 129(4):779-82.
2. Crider KS, Bailey LB, Berry RJ. (2011). Folic acid food fortification—its history, effect, concerns, and future directions. Nutrients., 3(3):370-84.
3. Smith AD, Refsum H. (2012). Do we need to reconsider the desirable blood level of vitamin B12 J Intern Med.271(2):179-82.
4. Reynolds EH. (2002). Benefits and risks of folic acid to the nervous system. J Neurol Neurosurg Psychiatry. 72(5):567-71.
5. World Health Organization. (2002). The importance of pharmacovigilance: safety monitoring of medicinal products. Geneva: WHO Press.
6. Edwards IR, Aronson JK. (2000). Adverse drug reactions: definitions, diagnosis, and management. Lancet. 356(9237):1255-59.
7. Scott JM, Weir DG. (1994). Folate/vitamin B12 interrelationships. Essays Biochem. 28:63-72.
8. O'Neil MJ. (2013). The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. 15th ed. Cambridge.: Royal Society of Chemistry
9. Sweetman SC. Martindale: (2009). The Complete Drug Reference. 36th ed. London: Pharmaceutical Press.
10. Stover PJ. (2004). Physiology of folate and vitamin B12 in health and disease. Nutr Rev. 62(6): S3-12.
11. Said HM. (2011) Intestinal absorption of water-soluble vitamins in health and disease. Biochem J. ,437(3):357-72.

12. Shane B. Folate chemistry and metabolism. In: Bailey LB, editor. Folate in Health and Disease. 2nd ed. Boca Raton: CRC Press; (2010). p.1-24.
13. Tibbetts AS, Appling DR. (2010). Compartmentalization of mammalian folate-mediated one-carbon metabolism. Annu Rev Nutr. 30:57-81.
14. Lucock M. (2000). Folic acid: nutritional biochemistry, molecular biology, and role in disease processes. Mol Genet Metab.71(1-2):121-38.
15. Hoffbrand AV, Moss PAH. (2016). Essential Haematology. 7th ed. Oxford: Wiley-Blackwell.
16. O'Leary F, Samman S. (2010). Vitamin B12 in health and disease. Nutrients. 2(3):299-316.
17. Selhub J. (1999). Homocysteine metabolism. Annu Rev Nutr.19:217-46.
18. Clarke R, Smith AD, Jobst KA, Refsum H, Sutton L, Ueland PM. (1998). Folate, vitamin B12, and serum homocysteine levels in confirmed Alzheimer disease. Arch Neurol. 55(11):1449-55.
19. Czeizel AE, Dudás I. (1992). Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med. 327(26):1832-35.
20. Ortiz Z, Shea B, Suarez-Almazor ME, Moher D, Wells GA, Tugwell P. (2000). Folic acid and folinic acid for reducing side effects in patients receiving methotrexate. Cochrane Database Syst Rev. (2):CD000951.
21. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses. BMJ. 339: b2700.
22. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. (2019) Cochrane Handbook for Systematic Reviews of Interventions. 2nd ed. Chichester: John Wiley & Sons.
23. Bailey LB. (2012). Folate in health and disease. 2nd ed. Boca Raton: CRC Press.
24. Institute of Medicine. (1998). Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12. Washington DC: National Academy Press.
25. Lucock M. (2000). Folic acid: nutritional biochemistry, molecular biology, and role in disease processes. Mol Genet Metab.71(1-2):121-38.
26. Reynolds EH. (2001). Adverse effects of folic acid supplementation. Lancet. 358(9290):1501-02.
27. Hoffbrand AV, Moss PAH. (2016). Essential Haematology. 7th ed. Oxford: Wiley-Blackwell.
28. Green TJ, Skeaff CM, McMahon JA, Williams SM. (2013). Reported adverse reactions to folic acid supplementation. Nutrients. 5(11):4702-16.
29. Wallerstedt SM, Brunlöf G, Sundström A, Eriksson AL. (2009). Reporting of suspected adverse reactions associated with folic acid. Pharmacoepidemiol Drug Saf. 18(6):478-84.
30. O'Leary F, Samman S. (2010). Vitamin B12 in health and disease. Nutrients. 2(3):299-316.
31. Reynolds EH. (2014). The neurology of folic acid deficiency. Handb Clin Neurol. 120:927-43.
32. Smith AD, Kim YI, Refsum H. (2008). Is folic acid good for everyone. Am J Clin Nutr. 87(3):517-33.
33. Kim YI. (2006). Folate and cancer: a tale of Dr Jekyll and Mr Hyde. Am J Clin Nutr. 84(6):1361-62.
34. Edwards IR, Aronson JK. (2000). Adverse drug reactions: definitions, diagnosis, and management. Lancet. 356(9237):1255-59.
35. World Health Organization. Safety monitoring of medicinal products: guidelines for setting up and running a pharmacovigilance centre. Geneva: WHO Press; (2000).

36. U.S. Food and Drug Administration. FDA Adverse Event Reporting System (FAERS): Latest quarterly data files. Silver Spring: FDA; (2023).
37. Lindquist M. VigiBase, (2008). the WHO global database of individual case safety reports. Ther Innov Regul Sci. 42(5):409-19.
38. European Medicines Agency. (2022). EudraVigilance: European database of suspected adverse drug reaction reports. London: EMA.
39. Bate A, Evans SJ. (2009). Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf. 18(6):427-36.
40. Hauben M, Aronson JK. (2007). Gold standards in pharmacovigilance: the use of disproportionality analysis. Drug Saf. 30(8):645-58.
41. Green TJ, Skeaff CM, McMahon JA, Williams SM. (2013). Adverse reactions associated with folic acid supplementation: review of the literature. Nutrients. 5(11):4702–4714.
42. Reynolds EH. (2002). Folic acid, ageing, depression, and dementia. BMJ. 324(7352):1512–1515.
43. Hauben M, Aronson JK. (2009). Pharmacovigilance and signal detection: principles and practice. Drug Saf. 32(2):99–109.
44. Ortiz Z, Shea B, Suarez-Almazor ME, Moher D, Wells GA, Tugwell P. (2000). Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. Cochrane Database Syst Rev. (2):CD000951.
45. Morgan SL, Baggott JE, Vaughn WH, Austin JS, Veitch TA, Lee JY, et al. (1994). Supplementation with folic acid during methotrexate therapy for rheumatoid arthritis. Ann Intern Med. 121(11):833–841.
46. Perucca E. (2006). Clinically relevant drug interactions with antiepileptic drugs. Br J Clin Pharmacol. 61(3):246–255.
47. Bailey LB. (1990). Folate status assessment. J Nutr. 120(11):1508–1511.
48. World Health Organization. Pharmacovigilance: ensuring the safe use of medicines. Geneva: WHO Press; (2004).
49. Harpaz R, DuMouchel W, Shah NH, Madigan D, Ryan P, Friedman C. (2012). Novel data-mining methodologies for adverse drug event discovery and analysis. Clin Pharmacol Ther. 91(6):1010–1021.
50. Bailey LB, Stover PJ, McNulty H, Fenech MF, Gregory JF, Mills JL, et al. (2015). Biomarkers of nutrition for development—folate review. J Nutr. 145(7):1636S–1680S.
51. Lindquist M. (2008). VigiBase and global pharmacovigilance: international collaboration for drug safety monitoring. Ther Innov Regul Sci. 42(5):409–419.

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