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Living Friendly Summaries of the Body of Evidence using Epistemonikos (Frisbee)
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Is augmentation with folate effective for major depressive disorder?

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Abstract

INTRODUCTION
Antidepressant treatment does not lead to a satisfactory response in a significant proportion of patients with depression. It has been postulated that co-administration of pharmacologically standardized nutrients (nutraceuticals), such as folate, would potentiate the effect of antidepressants.

METHODS
To answer this question we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

RESULTS AND CONCLUSIONS
We identified four systematic reviews including nine studies overall, of which eight were randomized trials. We concluded augmentation with folate for the treatment of major depressive disorder probably results in little or no difference in depressive symptoms. It would be interesting to evaluate the effects of specific presentation forms of folate or in population with objective folate deficit.

Problem

After the introduction of antidepressants in the 1950s, the number of pharmacological treatments for major depressive disorder has increased, but the efficacy of these has remained largely unchanged. Approximately 50% of patients who initiate antidepressant treatment show little or no response after a first trial. Moreover, after several therapeutic approaches, non-remission rates are still around 30% [1],[3]. Adding a drug of a different pharmacological class to the current antidepressant treatment has showed an enhancing effect. Most of the evidence is focused in lithium and atypical antipsychotics. New approaches, such as co-administration of nutraceuticals, in particular folate, as both folic acid and its active presentation (methylfolate), could provide a novel and safer alternative for the treatment of depression [1],[2],[3].

Folate deficiency is a common finding in psychiatric patients and low folate levels have been associated with a worse response to pharmacological treatment. In addition, an association between folate and serotonin metabolism has been observed in patients with congenital defects of the metabolism of the former and in patients with neuropsychiatric disorders. This association could be explained by the role that folate plays in the methylation of homocysteine, necessary for its conversion into s-adenosyl methionine, which has been shown to influence the metabolism of serotonin. Another hypothesis is folate is involved in the methylation reactions of tetrahydrobiopterin, an essential cofactor for the hydroxylation enzymes involved in the synthesis of serotonin [1],[4]. However, the clinical impact of the use of folate as an augmentation strategy in depressive disorders is still controversial.

Methods

To answer the question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages

- The addition of folate as augmentation in the treatment of major depressive disorder probably results in little or no difference in depressive symptoms at the end of treatment.

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About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found four systematic reviews [1],[2],[3],[4], which included nine primary studies overall [5],[6],[7],[8],[9],[10],[11],[12],[13], of which eight were randomized trials [6],[7],[8],[9],[10],[11],[12],[13]. This table and the summary in general are based on the latter, since the observational study did not increase the certainty of the existing evidence or provide relevant additional information.
What types of patients were included*	Six trials [6],8],[9],[10],[12] included patients diagnosed with major depressive disorder according to DSM III or IV criteria, and two trials included patients with the same diagnosis according to ICD-10 [7],[13]. Of the eight trials selected, only one [9] exclusively included patients with low folate levels. On the contrary, two trials [6],[7] only included patients without baseline folate or B12 deficiency, and one trial [8] excluded patients with altered laboratory tests (including megaloblastic anemia). The rest of the trials [10],[12],[13] did not report this data.
What types of interventions were included*	All of the trials used selective serotonin reuptake inhibitors (SSRIs) as antidepressant, except two trials that did not report which antidepressant was used [7],[9]. Methylfolate was used as supplementation in three trials [9],[10] and folic acid in five trials [6],[7],[8],[12],[13]. Six trials compared against placebo [7],[8],[9],[10],[12], one trial compared against antidepressant monotherapy [6] and another trial compared different ranges of folate doses [13].
What types of outcomes were measured	The trials measured multiple outcomes, which were grouped by the systematic reviews identified as follows: • Improvement of depressive symptoms: Meassured with Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (BDI), Montgomery-Asberg Depression Rating Scale (MADRS) • Dropout rate • Hospital admission • Adverse effects • Mortality. The average follow-up of the trials was eight weeks with a range from 6 to 26 weeks.

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

Summary of Findings

The information on the effects of folate augmentation for depression is based in four randomized trials [7],[8],[9],[12] that included 591 patients.

Four trials [7],[8],[9],[12] measured the outcome depressive symptoms at the end of the trial (591 patients), one trial [8] reported hospital admission (127 patients) and only one trial [8] reported the rate of adverse effects (127 patients).

The summary of findings is as follows:

- The addition of folate as augmentation in the treatment of major depressive disorder probably results in little or no difference in depressive symptoms at the end of treatment. The certainty of the evidence is moderate.
- The addition of folate as augmentation in the treatment of major depressive disorder probably results in little or no difference in adverse effects. The certainty of the evidence is moderate.

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Augmentation with folate for the treatment of major depressive disorder				
Patients	Major depressive disorder			
Intervention	Folate augmentation			
Comparison	Placebo			
Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITH folate	**WITHOUT folate**		
	Difference: patients per 1000			
Depressive symptoms**	SMD***: 0.26 points lower (Margin of error: 0.6 points less to 0.08 points more)			⊕⊕⊕◯[1] Moderate
Adverse effects	615 per 1000	468 per 1000	RR 0.76 (0.55 to 1.05)	⊕⊕⊕◯[1] Moderate
	Difference: 147 patients less (Margin of error: 277 less to 31 more)			
Hospital admission	One trial [8] reported one admission to the hospital in the placebo group.			--

Margin of error: 95% confidence interval (CI).
RR: Risk ratio.
SMD: Standardized mean difference.
GRADE: Evidence grades of the GRADE Working Group (see later).

*The risk **WITHOUT folate** is based on the risk in the control group of the trials. The risk **WITH folate** (and its margin of error) is calculated from relative effect (and its margin of error).

**Depressive symptoms: evaluated with the Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI); expressed in standardized mean difference.
***The standardized mean difference is used when the outcome has been measured at different scales and is difficult to interpret clinically. A general rule is that values less than 0.2 are of little clinical relevance, values of 0.5 of moderate relevance and 0.8 of very important clinical relevance.

[1] The certainty of the evidence was downgraded in one level due to serious risk of bias in the trials.

Following the link to access the interactive version of this table (Interactive Summary of Findings – iSoF)

About the certainty of the evidence (GRADE)*
⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.
⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate
⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.
⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.
*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- The conclusions of this summary are applicable to adult patients diagnosed with major depressive disorder.
- The objective of this article was to include any type of folate (folic acid or methylfolate) in any population (with or without folate deficiency). It would be interesting to explore the effects of folate augmentation in population with objective deficit, its role associated with other B-complex nutraceuticals and the specific effects of methylfolate.

About the outcomes included in this summary

- The outcomes selected are those considered critical for decision-making by the authors of this summary. In general, they coincide with those reported by the identified reviews.
- Although only one trial [8] presented data about adverse effects suitable to estimate an effect measure, the other seven trials [6],[7],[9],[10],[12],[13] were in agreement with the first, reporting folate was generally well tolerated, with gastrointestinal symptoms (constipation, abdominal discomfort and diarrhea) being the most commonly reported.
- Only one trial reported hospitalization rate with a single event in the placebo group.

Balance between benefits and risks, and certainty of the evidence

- Folate would be an intervention probably ineffective, but without adverse effects in comparison to placebo.
- One systematic review [3] emphasizes there might be adverse effects when used in high doses, prolonged periods of time or in combination with certain medications. Possible carcinogenic, neurological and haematological effects are highlighted.
- Folic acid has also been implicated in the acceleration of age-related cognitive deterioration and reduction of the effect of certain antifolate drugs such as immunosuppressants [3].
- It should be taken into account that in the context of a deficit of B12, the addition of folate can have harmful consequences at a neurological and hematological level [2].

Resource considerations

- Folate is generally a low-cost intervention, so this factor should not play an important role in decision-making.

What would patients and their doctors think about this intervention

- The use of nutraceuticals in psychiatry corresponds to a relatively emerging field. Over the past two decades and fostered by both experimental and epidemiological studies [2], the influence of nutritional factors has experienced increasing attention by the scientific community.
- On the other hand, the interest for alternative treatments versus traditional medicine has grown in the general population, and studies have suggested higher willingness-to-pay for them and higher placebo effect properties [14],[15],[16]. Therefore, it is relevant for mental health professionals to be aware of the best available evidence in this area.
- Regarding folate, most patients and physicians should lean against the intervention based on the information presented in this summary.

Differences between this summary and other sources

- In two systematic reviews [1],[4], concluded the available evidence suggested folate could have a potential role as an augmentation treatment, but it was not clear if this applied to both people with normal and low levels of folate. In addition, they remarked the eventual appearance of one or two relatively small trials with neutral or negative results could have a substantial impact on the estimate.
- In the most current systematic reviews [2],[3], which include more studies and more recent, the authors conclude there is a non-significant difference between folic acid and placebo. In relation to methylfolate in particular, they estimate there is too little evidence to reach firm conclusions yet. They mention it could be tentatively recommended, but they also note that although trials had a sound methodology, there might be bias towards positive results since they are funded by industry.

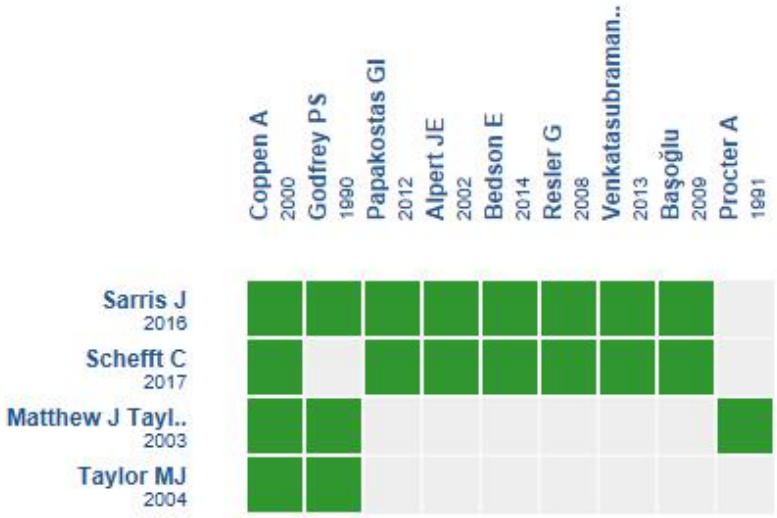
- Regarding the main clinical guidelines, both the 2010 American Psychiatric Association's (APA) Practice Guideline for the Treatment of Patients with Major Depressive Disorder [17] and the 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder of the Canadian Network for Mood and Anxiety Treatments (CANMAT) [18] agree on the recommendation for the use of folate. On one hand, the APA considers there is modest evidence to recommend the addition of folate, but it is a low-risk intervention with general health benefits. On the other hand, CANMAT recommends folate augmentation as a third-line alternative for mild to moderate major depressive disorder. It should be noted that the guideline Depression in adults: recognition and management guide of the National Institute for Health and Care Excellence (NICE) [19] does not mention folate or other nutraceuticals as alternatives for enhancement, indicating the possibilities of using lithium, antipsychotics such as quetiapine or other antidepressants such as mirtazapine

Could this evidence change in the future?

- The likelihood that the information provided in this summary changes with future evidence is low, since the investigation provides a good indication of the likely effect.
- More evidence is needed to assess if there are benefits in populations with folate deficiency, or with the use of methylfolate.
- We identified at least one ongoing systematic review [20] in PROSPERO and at least five ongoing trials [21],[22],[23],[24],[25] in the International Clinical Trials Registry Platform of the World Health Organization, which could provide relevant information in the future.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version**: Folate for depressive disorders

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

Potential conflicts of interest

The authors do not have relevant interests to declare.

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