

# Vitamin B12/B9 – possible treatment for mental fatigue



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**8 COMMENTS**

## COMMENT

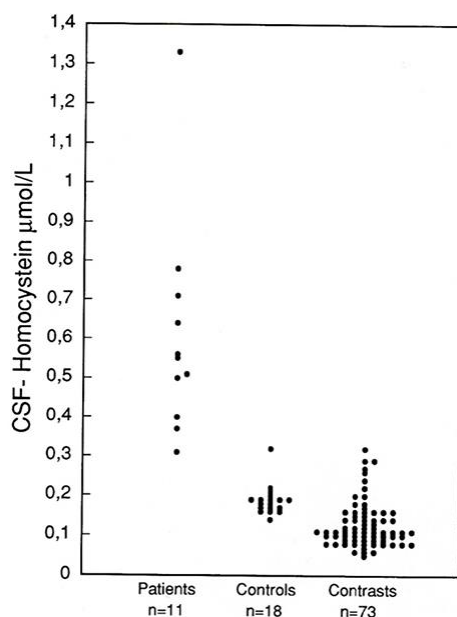


Figure 1. Homocysteine in cerebrospinal fluid in patients who fulfilled criteria for both FM and ME (then called chronic fatigue syndrome), in comparison with a control and a contrast group. Courtesy of Scand J Rheumatol [5]

Already in 1973, a placebo-controlled study showed that patients with unexplained fatigue got significantly better when 5 mg of hydroxocobalamin (vitamin B12) was injected intramuscularly twice a week [1]. Today, they would probably be diagnosed with myalgic encephalomyelitis (ME), but then there were no defined criteria. A similar controlled study in ME has not yet become possible, because the pharmacological expertise employed could not find any currently approved placebo preparation that is red in color and produces red-colored urine.

Vitamin B12, in conjunction with folic acid (vitamin B9), is of fundamental importance in maintaining methylation capacity in various elementary cell processes. As an indirect sign of vitamin B12/B9 insufficiency in ME, hypomethylation has been demonstrated in the majority of certain immune cells [2], as well as in the DNA of genes associated with immune cell regulation [3]. There is a special chemical signature in blood plasma that suggests that ME is a hypometabolic syndrome and should be counteracted by intervention with »B9, B12, glycine, serine and B6« [4]. Interestingly, the three B vitamins, as well as glycine and serine, are related to the metabolism of homocysteine.

ME often occurs together with the intense muscle soreness known as fibromyalgia (FM). In 1997, fluids were examined in a study of patients who met criteria for both FM and ME, then called chronic fatigue syndrome [5]. Homocysteine in cerebrospinal fluid was in all patients higher than the reference range for controls, a clear indication that the central nervous system was exposed to vitamin B12/B9 deficiency. The level of liquors co-varied with the degree of fatigue. Since then, vitamin B12/B9 has been used as a treatment in Mölndal at Sweden's first specialist clinic for patients with ME/FM. For optimal effect, injections are needed in high and frequent dosage [6]. The publication is freely available on the internet and also points out that high doses of vitamin B12/B9 in themselves are completely without serious side effects. But there is an interaction risk to be aware of: vitamins B12 and B9 are potent methyl stimulants, which means that in high doses they interact with many pharmaceuticals that must be demethylated by the liver enzymes CYP 3A4 or 2D6 to have the intended pharmacological effect. This interaction is more common in patients with FM, who often require relief from strong analgesics such as opioids (tramadol, codeine) and duloxetine. SSRIs are also metabolized by demethylation. If the patient is dependent on such drugs, one has to compromise with a lower vitamin B12/B9 dose and unfortunately has a worse effect [6].

Using B12 injections in frequent high dosages has in recent years met almost organized resistance from general practitioners. Many health care centers

refuse continued prescribing because they do not believe in either the treatment or the patient. On the other hand, we have the Patient Safety Act, Chapter 6, Section 1, where it is in principle stipulated that the prescription of medicines must be done according to science and proven experience, and when there is no treatment with a scientifically proven effect, care must be focused on symptom relief, carried out in agreement between patient and doctor, using treatment and drugs that cannot be harmful.

I believe that combining vitamins B12 and B9 constitutes a treatment that does no harm and often provides very good symptom relief. In the right dosage, the response is fairly immediate, and those who appreciate the treatment quickly learn to inject subcutaneously themselves. Research supports that the metabolic disturbances are localized where vitamin B12/B9 is of central importance, and there is some scientific basis for the treatment being effective and without a placebo effect in unexplained severe fatigue. ME/FM is a large patient group, and the diseases cause great suffering with significant disability. It is of the utmost importance that more studies are done in order to come to terms with scientifically based treatment of this public health problem, but one can ask the question whether it is still not reasonable to accept treatment in the meantime based on the proven experience that exists?

Potential ties or relationships: Björn Regland was employed as chief physician at Gottfrieskliniken in Mölndal from 1997–2007 (then chief physician at the neuropsychiatric clinic at Sahlgrenska University Hospital until retirement) and has in recent years been involved in clinical research at Gottfrieskliniken as an unpaid docent and retired physician. This has so far resulted in the publication of [6].

## 8 COMMENTS

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**Very interesting!** 6 år sedan

My teacher in Neurology at Umeå University, Prof. Lisa Welander, examined her patients very carefully in her clinic. The visit often ended with a prescription for B vitamins! I don't know what illness the patient has, but B vitamins sometimes help and never hurt, she used to say  
Leif Bergdahl, Docent, Medgoldkliniken, Juoksengi

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Answer

**Thank´s!**

6 år sedan

Exciting article! What experience do you have with treatment with B12/B9 injections in patients who are diagnosed with Fibromyalgia without therefore meeting the criteria for ME? What are the experiences of the effect of tablet treatment? - Why not tablets?

Regards, Robin  
Robin Verma, ST doctor in General Medicine, Theoretical philosopher, Halsa care center  
Älmhult

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Answer

**Nutrition, exercise, sleep** 6 år sedan

Patients often have bad lifestyle habits and when checking e.g. folate and vitamin D there is often a lab-verifiable deficiency in these. You can often guess these already from a brief cost name. Sugary or carbohydrate-rich foods and being sedentary are other problems. Overweight. Sleep apneas. Believe me they comment on fatigue, forgetfulness etc. A bad spiral that continues for years and results in various health problems and complaints. The elementary concepts of the medical art are ancient, but tragically outclassed in favor of expensive medicines and various technological or therapeutic innovations. They have their place as a complement, but not as a replacement for the commonsense foundation of health. Diet, exercise and sleep are the cornerstones of health. It is only required that the clinics make a habit of cleaning them

Jari Norvanto, Psykiater, Skåne

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Svara

**Redcarrot**

6 år sedan

**As placebo**

Jingcheng Zhao, Med kand, Karolinska Institutet

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Answer

**B vitamins preserve gray brain matter in patients with Alzheimer's disease (AD)**

6 år ago

Supplementation with white B6, B9/folic acid, and B12 for 2 years slowed gray matter decay 7-fold (by 85%) in AD-typical centers as measured by imaging. Pubmed, search: pnas douaud 2013. PNAS is one of America's most respected biomedical journals.

Lars G Burman, Leg.läk, docent, laborator em (SBL, SMI), Hemma

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Answer

**Amalgam damaged better by B-12 injections** 6 år ago

Many amalgam-damaged patients improve considerably with injections of vitamin B12, this was shown by, among other things, a survey of the Dental Association's members' experiences of care published in 2008 ([www.hetprojektet.info](http://www.hetprojektet.info)). I have thought it was because vitamin B-12 is the detoxification and methylation cycle. Maybe it also has other effects on the body. Extreme fatigue is one of several common symptoms in people with amalgam damage, as well as fibromyalgia.

Ann-Marie Lidmark, folkhälsovetare och zoofysiolog, Tandvårdsskadeförbundet Ordförande  
Tandvårdsskadeförbundet

Jäv: Ordförande Tandvårdsskadeförbundet

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Answer

**Interesting and progressive, thanks!** 5 år ago

How does the research approach mutation of the mthfr gene in this context and is there a basis for comparing injections vs supplementation with methylcobalamin and methylfolate orally in the corresponding dosages?

Susanne Andréasson , Leg. Veterinär, Västra Götaland

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Svara

**Thanks for important questions!** 5 år sedan

Gene analysis of MTHFR (MethyleneTetraHydroFolateReductase) has been included in the examination of patients with fatigue problems for 20 years (1). There are two commonly occurring point mutations, C677T and A1298C, which reduce the binding of folate to the enzyme MTHFR, whose activity is thus lower. The activity is related to the saturation of folate around the enzyme, and the activity can therefore be normalized with the addition of vitamin B9 (folic acid).

On the one hand, the presence of these point mutations is not more common in chronic fatigue syndrome than in the healthy population (2). My interpretation is that elevated cerebrospinal fluid homocysteine is primarily an expression of a lack of B12 (cobalamin). On the other hand, B12 treatment must always be paired with B9 supplementation, since cobalamin and folate interact directly in the methylation of homocysteine, whereby methionine is formed and folate is released for DNA synthesis.

The optimal dose of B9 is individual and dependent on the individual's MTHFR genetics. Presence of point mutation generally increases the need for B9, which is accentuated when B12 treatment drives methylfolate turnover. A majority of the population (84%) has such a point mutation from at least one parent. The clinical risk of folate deficiency is most pronounced in homozygosity for 677T (in 11%) or in the combination 677T/1298C (in 20%) (See ref 1, which is freely available online).

The second question concerns injection vs oral supply of methyl-B12, in combination with methyl-B9. As far as I know, no such study exists, but would of course be welcome.

The dose-related response we have described is in itself evidence that patients with ME need a significantly higher dosage than what traditional B12 tablets can provide (1). A special hope could be placed on the special preparation of methyl-B12 that has begun to be marketed abroad for sublingual use, i.e. for rapid dissolution and absorption under the tongue. If sublingual tablets provide such a high blood concentration that enough B12 crosses the blood-brain barrier and provides an equivalent effect compared to injection therapy, then the need for frequent subcutaneous injections would be avoided. But that remains to be seen, and the preparation is not yet available in Sweden.

#### References

1. Regland B, Forsmark S, Halaouate L, et al. Response to vitamin B12 and folic acid in myalgic encephalomyelitis and fibromyalgia. PLoS One. 2015;10(4):e0124648
2. Harmon DL, McMaster D, McCluskey DR, et al. A common genetic variant affecting folate metabolism is not over-represented in chronic fatigue syndrome. Ann Clin Biochem. 1997; 34(Pt4):427-9

Björn Regland, docent leg läk, pensionerad ideell forskare

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Answer