Story of B12

**Cyanocobalamin versus Methylcobalamin**

Typically, there are two major forms of Vitamin B12:

1. **Cyanocobalamin**
2. **Methylcobalamin**

Cyanocobalamin is the most common form of Vitamin B12. This is the form that is usually in multivitamins and B-complexes and is thought to be nearly the best form of Vitamin B12. However, cyanocobalamin is also thought to be the less-than-optimal form of Vitamin B12. This is because cyanocobalamin is a synthetic form of Vitamin B12, which does not occur in normally in nature, as it can’t be synthesized by humans or by other animals. It must first be converted to a usable form of Vitamin B12 which is methylcobalamin, and then into adenosylcobalamin.

It is these latter forms that our body can use.

Some B12 Vitamins contain Cyanide

So, since the body can break down cyanocobalamin, what’s the big deal?

The big deal is in order for the conversion to take place, the cyanide bond must be released.

Of course, cyanide is toxic.

Now if you read about Vitamin B17 (laetrile), you’ll find that cyanide is the basis of banning that particular “vitamin”, despite the fact that we eat cyanide-containing foods everyday such as broccoli and cauliflower.

This synthetic form of Vitamin B12 has had the cyanide essentially added as a by-product of charcoal filtering. The FDA has deemed the cyanide by-product as “insignificant.”

So apparently, according to the FDA, some cyanide is fine for human ingestion. Well, many of you who know me, know that I don’t buy into anything the FDA says; I did a bit of investigating of my own.

Let’s see: Cyanide in foods and in Vitamin B12 are okay, while cyanide in Vitamin B17 is not okay. Why this double standard and is there a difference?

There is a big difference! And it is all about the bonding.

It is well known that cobalamin has a high affinity to cyanide and bonds with it. In fact, a means of counteracting cyanide poisoning is with the use of hydroxocobalamin. However, cobalamin in case of Vitamin B12, cannot bind to the cyanide molecule because it is already bound.
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Though the amounts of cyanide are small, and thought to be “harmless”, when this is added to the already small amounts we are exposed to everyday via road salt, automobile exhausts, and even in table salt (used as a stabilizer), adding more cyanide to already elevated levels can potentially be harmful. This is not the case regarding cyanide-containing foods. Sadly the FDA is banning the wrong substance!

There is an option, to take Vitamin B12 in the form of methylcobalamin, the active form of Vitamin B12, instead.
Methylcobalamin is an active form of cyanocobalamin. It is this form that is necessary for the synthesis of the amino acid, methionine; from homocysteine. Methionine is important for the DNA methylation; essential for normal human development as well as development or inhibition of carcinogenesis (prevention of cancer.)

Interestingly, Proper functioning DNA methylation is being linked with longevity.

Summary points

- Vitamin B12 deficiency is a common but serious condition
- Clinical presentation may not be obvious thus leading to complex issues around diagnosis and treatment
- There is no ideal test to define deficiency and therefore the clinical condition of patients is of the utmost importance
- There is evidence that new techniques such as the measurement of holotranscobalamin and methylmalonic acid levels seem useful in more accurately defining deficiency
- If the clinical features suggest deficiency then it is important to treat patients to avoid neurological impairment even if there may be discordance between the results and clinical features

Vitamin B12 is an essential cofactor that is integral to methylation processes important in reactions related to DNA and cell metabolism, thus a deficiency may lead to disruption of DNA and cell metabolism and thus have serious clinical consequences.1 Intracellular conversion of vitamin B12 to two active coenzymes, adenosylcobalamin in mitochondria and methylcobalamin in the cytoplasm, is necessary for the homeostasis of methylmalonic acid and homocysteine, respectively.2 3 Methylmalonic acid is converted into succinyl-CoA, of which vitamin B12 is a cofactor for the reaction. Homocysteine is biosynthesised from methionine then resynthesised into methionine or converted into amino acid cysteine.

Vitamin B12 (also referred to as cobalamin) deficiency is relatively common, with important and variable clinical consequences. This review presents a concise summary of the most up to date evidence on how to diagnose and manage vitamin B12 deficiency.

Types of B12: Methylcobalamin vs Cyanocobalamin vs Hydroxocobalamin vs Adenosylcobalamin
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Vitamin B12 (cobalamin) is the largest and most complex vitamin out there. It is unique, because it is the only vitamin that contains a metal ion, cobalt (hence its name). The vitamin is a cofactor for two enzymes in mammals like us, one is methionine synthase, the other methylmalonyl-CoA mutase.

The molecule that is attached to the cobalamin is called a donor. The two most common donors in supplements are cyanide (making cyanocobalamin B12, or cyano B12), and methyl (making methylcobalamin B12, or methyl B12). Other forms you might find are hydroxocobalamin and adenosylcobalamin.

All those forms are present to some degree in the foods you eat, but the predominant forms are adenosylcobalamin and hydroxocobalamin. Another vitamin B12 form found in foods is sulphitocobalamin. It won’t be covered here because it’s irrelevant, and no sulphitocobalamin supplement exists.

Anyway, only adenosylcobalamin (AdeCbl) and methylcobalamin (MetCbl) are active within the human body. You’ll find MetCbl mainly in your blood plasma, cytosol cells, and certain body fluids (like cerebral spinal fluid), and AdeCbl in cellular tissues where it is stored in the mitochondria. In fact, the benefits of B12 all boil down to two biochemical reactions:

The conversion of methylmalonyl-coenzyme A to succinylcholine coenzyme A (by methylmalonyl-CoA mutase, with adenosylcobalamin as a cofactor), and the remethylation of homocysteine to methionine (with methylcobalamin being a cofactor for methionine synthase).

But all types of B12 can be converted in the body, so let’s take a look at each to examine which is the best form of B12 to supplement with.
All forms of B12 have that deep pink-red color, both when in powder and in solution.

Cyanocobalamin

(ALSO CN-CBL, OR CYANO B12)

Cyano B12 is a cheap, synthetic, slightly-toxic, inactive form of B12 that is made with a cyanide donor and is used commercially. It is the most stable form, because the cyanide molecule has
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the greatest attraction to the cobalamin and protects it from extreme conditions (like high temperatures). However, it doesn’t absorb well and requires methyl groups to detoxify it.

When cyano B12 does absorb, it converts to hydroxocobalamin (hopefully discarding of the cyanide in the process) and then to methylcobalamin and adenosylcobalamin. When taken orally, absorption of this form is drastically reduced if you have any gastric acid problems.

Personally?

I can never recommend this form to anyone.

Sure, it’s cheap, but it does come with a price. The body must use a methylation reaction to cleave the cyanide out of this form so that it can be converted to a usable, absorbable form. This is a demanding process. Check out this paper (it does come from a questionable site, but I confirmed its content):

*Although the amount of cyanide is considered toxicologically insignificant, humans must remove and detoxify the cyanide molecule, reduce the cobalamin to its usable +1 oxidation state, and then enzymatically convert the cobalamin into one of two metabolically active coenzyme forms. Nutritional inadequacies, enzyme defects, and pathological changes to tissues can all contribute to a reduced ability of the body to accomplish the synthesis of the active forms of vitamin B12 from CN-Cbl (Cyanocobalamin).*

Methylation is one way in which your body detoxifies. But it requires methyl groups, which are often in low supply because of our modern life which is full of toxins. To remove the cyanide out of cyanocobalamin, the body uses a methyl molecule. This is why people with methylation problems (like autistic children) can get worse on CN-Cbl but not on other forms of vitamin B12.

You see, commercial cyanocobalamin only exists because after creating hydroxocobalamin from bacteria, some cobalamins bind to cyanide during the charcoal filtration process. Check out this paper from 1992:

*If the indiscriminate dumping of industrial cyanide waste continues unchecked with the inherent risk of pollution of food and water supplies there may well come a time when more widespread chronic cyanide neurotoxicity occurs in the Western hemisphere from a dietary source in persons with a genetic or acquired error of cyanide or vitamin B12 metabolism.*
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And don’t get me wrong, we all get cyanide into our systems (barbecues, bonfire, second hand smoke, even almonds!), but the body always has to detoxify it. By taking cyano B12, you’re further depriving your body of a natural antidote, an antagonist for toxins.

Because of that detoxification process, cyanocobalamin usage could potentially deplete glutathione (GSH), an important anti-oxidant that helps decrease lipid peroxidation associated with oxidative stress. Once glutathione stores are depleted, high dose cyanocobalamin might theoretically cause cyanide toxicity, especially in renal failure patients.

Also, some people may have clinical or sub-clinical conditions which inhibit them from being able to convert this form of B12 to the active forms, and eventually absorb it. In these cases, you will see your serum B12 levels increased (it counts both active and inactive B12), but you’ll have a functional deficiency of AdeCbl and MetCbl in tissues and other body fluids.

Did you know? Cyanocobalamin can make Leber’s optic atrophy worse, and should never be used in that case.

Besides, it takes more than 48 hours for cyanocobalamin B12 to eventually convert to usable methylcobalamin, and even then only a small amount is converted. And remember, even when it does convert, it requires the interaction (possibly depletion) of glutathione and other agents.

Despite all that, cyanocobalamin B12 is the most commonly prescribed form for vitamin B12 deficiency. Reason? It’s available and it’s cheap. But it’s also the least safe, least effective, and most demanding type of B12.

Not natural to mammals whatsoever.

Why would you try to improve your health with something that, to become absorbable, requires the depletion of other crucial substances in your body?

It makes no sense, especially when the alternatives are so affordable.

Methylcobalamin

(ALSO MECOBALAMIN, MECBL, METCBL, METB12, MEB12, OR METHYL B12)

Methylcobalamin, the kingpin, one of the two active, natural forms of B12. It helps reduce homocysteine concentrations and generates SAMe (S-adenosyl methionine), the most
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important methyl donor in your body, supplying methyl groups for crucial chemical reactions to help maintain your health.

Where methyl B12 shows its greatest utility is with people suffering from degenerative neurological symptoms, where it’s often the only promising treatment. It bypasses several potential issues in the absorption cycle and helps relieve or completely reverse symptoms.

High doses of methylcobalamin have been used to treat multiple sclerosis (improved visual and auditory symptoms, not motor ones), amyotrophic lateral sclerosis, Parkinson’s, and may help regenerate nerves and treat peripheral neuropathies. People with Alzheimer’s noticed an improvement in memory and intellectual function when given this form of B12.

In fact, MetCbl is so effective — in numerous areas — that it is used almost exclusively in Japan to treat B12 deficiency. The science is breathtaking:

It may dramatically improve recovery time for facial nerve function in Bell’s palsy patients. In high doses, it may promote neuronal function, enhance nerve regeneration, and even protect cortical neurons against neurotoxicity.

For diabetic neuropathy patients, it may improve burning sensations, numbness, loss of sensation, muscle cramps, reflexes, vibration sense, lower motor neuron weakness, and sensitivity to pain. The improvement seem to be enhanced by combining methyl B12 with ginkgo biloba extract.

Management of diabetic neuropathy can also be improved by combining methylcobalamin with L-methylfolate and pyridoxal 5′-phosphate.

When hemolytic hyperchromic anemia and impairment of hematopoiesis in the bone marrow were induced in rabbits, a decrease in methylcobalamin in the blood serum was observed during spontaneous recovery. Methyl B12 administration completely normalized some blood and hematopoiesis patterns, improved the ratio between the cobalamin forms, and completely regenerated total B12 content. Adenosylcobalamin, which is the other active form, exhibited a distinctly lower effect on the patterns studied.

What else?

In both in-vitro and in-vivo experiments, methylcobalamin inhibited the proliferation of malignant cancerous cells. It also reduced tumor growth and enhanced survival time of mice with Ehrlich ascites tumor cells.
Methylcobalamin (along with adenosylcobalamin) had also been shown to increase survival time of leukemic mice, whereas cyano B12 was inactive under the same conditions. Experimental evidence suggests it may also enhance the efficacy of methotrexate.

Now, eye function. Chronic administration of methylcobalamin may protect cultured retinal neurons against N-methyl-D-aspartate-receptor-mediated glutamate neurotoxicity. It may also improve deterioration of accommodation following visual work.

As you see, its applications are limitless.

Methylcobalamin even produces improvements in several components of heart rate variability, suggesting a balancing effect on the sympathetic and parasympathetic nervous systems. Under experimental conditions, methyl B12 (adenosyl and hydroxo B12 too actually) also inhibited HIV-1 infection of normal human blood lymphocytes and monocytes.

One study reported a case of a 48 year old woman with motor weakness, dementia, sensory disturbances, and widespread coarse hair. Classic B12 deficiency symptoms. In response to methyl B12 injections (500mcg every other day), her paresthesia resolved, hand grip strengthened, dementia reduced, hair texture normalized, and she was now able to walk on tiptoe.

Let’s talk about male impotence now, shall we.

In one study, methylcobalamin at a dose of 6,000mcg a day for four months improved sperm count by 37.5%. In another one, methyl B12 at doses of 1,500mcg a day for 4-24weeks increased sperm concentrations in 38% of cases, total sperm count in 54% of cases, and sperm motility in 50% of cases.

I see you getting excited over there.

Now, as I said, methyl B12 converts homocysteine to methionine. This is why high levels of homocysteine can be a sign of low methylcobalamin levels. In one study, high homocysteine levels were reduced from 14.7 to 10.2 nmol/ml following methylcobalamin injections. Because of its effect on homocysteine, it has been found useful in treating children with autism and in reducing cognitive decline and cardiovascular outcomes in older patients.

That is not all.
The science on methylcobalamin B12 and sleep disturbances is especially promising. The exact mechanism isn’t completely understood yet, but it seems like this type of B12 could modulate the synthesis of melatonin, a hormone involved in your sleep-wake cycle regulation. It makes sense, because the biosynthetic formation of melatonin requires a methyl group. See this:

*Eight young males were subjected to a single blind cross-over test to see the effects of vitamin B12 (methylcobalamin) on the phase-response of the circadian melatonin rhythm to a single bright light exposure. VB12 (0.5 mg/day) or vehicle was injected intravenously at 12:30 h for 11 days, which was followed by oral administration (2 mg x 3/day) for 7 days. A serial blood sampling was performed under dim light condition (less than 200 lx) and plasma melatonin rhythm was determined before and after a single bright light exposure (2500 lx for 3 h) at 07:00 h. The melatonin rhythm before the light exposure showed a smaller amplitude in the VB12 trial than in the placebo. The light exposure phase-advanced the melatonin rhythm significantly in the VB12 trial, but not in the placebo. These findings indicate that VB12 enhances the light-induced phase-shift in the human circadian rhythm.*

*Another study reported that intravenous (IV) injections of methylcobalamin increased rectal temperature in later hours of the day and improved alertness (assessed with visual analog scale), suggesting “these results may provide evidence of an effect of vitamin B12 on the circadian clock.”*

Want more?

*One study investigated the effects of both methyl and cyano B12 on circadian rhythms, well-being, alertness, and concentration in healthy subjects. Sleep time was significantly reduced in the MeB12 group, reporting improvements in subjective parameters of sleep quality, concentration and refreshed feel. The authors concluded that “only methylcobalamin has a positive psychotropic alerting effect with a distribution of the sleep-wake cycle toward sleep reduction.”*

Here’s another case, this time of a 13 year old boy with adrenoleukodystrophy who had developed a sleep-wake disorder following a complete loss of vision. His sleep-wake cycle had been 25 hours, but normalized after being given methyl B12. MetCbl therapy caused his plasma melatonin and beta-endorphin levels to approximately match those of healthy volunteers, and his peak cortisol time shifted backwards. That is amazing.

There’s more. A 32 year old male patient suffering from recurrent hypersomnia for 12 years was successfully treated with methyl B12. Also see this:
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Two adolescent patients suffering from persistent sleep-wake schedule disorders appear to have responded to treatment with vitamin B12 (methylcobalamin). A 15-year-old girl with delayed sleep phase syndrome (DSPS) and a 17-year-old boy with hypernychthemeral syndrome complained of not being able to attend school despite many trials of medication. The improvement of the sleep-wake rhythm disorders appeared immediately after the administration of high doses (3,000 micrograms/day) of methylcobalamin. Neither patient showed any laboratory or clinical evidence of vitamin B12 deficiency or hypothyroidism (which can cause B12 deficiency). Serum concentrations of vitamin B12 during treatment were in the high range of normal or above normal.

As you see, the science is there. Is your sleep-wake schedule messed up? Can’t you fall asleep before it’s 2 or 3 AM? Then methyl B12 supplementation may help modulate your melatonin secretion, enhance your light sensitivity, and normalize your circadian and sleep-wake rhythm.

What else? Any other benefits to the methylcobalamin form?

In one randomized study of stroke patients, 67 received doses of 1500mcg methyl B12 daily for 2 years, and the remaining 68 remained untreated. After two years, electrophysiologic parameters in sensory nerve in the treated group significantly improved compared to the untreated group.

Speaking of strokes, combined treatment of methylcobalamin and folate was found safe and effective in reducing the risk of hip fractures in elderly patients following stroke. Add clonidine and moxonidine to the mix and you improve baroreflex function in stroke-prone, spontaneously hypertensive rats.

Some Chinese studies found methylcobalamin to be helpful in treating lumbar disc herniation, thalamic pain, glaucoma, cervical spondylosis, and cubital tunnel syndrome. They also found acupoint methylcobalamin injections with acupuncture to be effective in treating intractable facial paralysis.

Now, how does methylcobalamin compare to cyanocobalamin when it comes to absorption and bio-availability? Is it any better?

Because of the effort it takes to reduce it to the active form, cyanocobalamin absorption varies greatly between individuals. Methylcobalamin is significantly better utilized and is around 2.5 times more potent (about 1/3 less is excreted in the urine) than cyanocobalamin. Yes, similar doses are “absorbed”, but once absorbed, MetCbl is accumulated and retained in the body much better.
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In any form, methylcobalamin has higher bioavailability than cyanocobalamin. It is so efficient that even orally it was found effective in pernicious anemia:

A 73-year-old Japanese man with Hashimoto’s disease and diabetes mellitus received regular medical checkups for type 2 diabetes care. Blood tests indicated macrocytic anemia. The laboratory data demonstrated a normal folic acid level with a low vitamin B12 level. An endoscopic examination indicated no signs of gastric or intestinal bleeding. Positive results for anti-intrinsic factor antibodies were strongly suggestive of pernicious anemia. The patient refused cobalamin injections to treat the anemia. However, the oral administration of mecobalamin for the treatment of diabetic neuropathy was simultaneously initiated. Subsequently, the anemia gradually improved. Oral mecobalamin was presumably effective for pernicious anemia management.

Now, I’m not suggesting you treat pernicious anemia with oral MetB12. Vitamin B12 injections should always be used in that case (their absorption and efficiency are far superior, and with PA you can’t take any risks). But it still goes to show you the power of methylcobalamin.

Important: B12 methylcobalamin is stable when dry, even under heat, but it undergoes photolysis (being destroyed by light) when in liquid form. This is why I always recommend wrapping vials of dissolved methylcobalamin for injections in aluminum foil.

Hydroxocobalamin

(ALSO HYDROXYCOBALAMIN, HYDROXY B12, OH-CBL, OR B12A)

Hydroxocobalamin, a predominant form in vitamin B12 rich foods, is an inactive form of vitamin B12, but it has an advantage over cyano B12 in that it doesn’t contain cyanide and bypasses the need for decyanation.

Compared to cyano B12, it has a higher affinity to plasma protein and a longer half life, retaining longer in the blood. This may help reduce injection frequency. Again, it doesn’t contain a toxic donor, so no detoxification reaction is required for it to be absorbed, and the glutathione source is preserved.

Hydroxocobalamin reacts chemically with cyanide (CN), nitric oxide (NO) and nitrous oxide (N2O). In fact, this form of B12 is commonly used as an antidote for cyanide toxicity. Therefore, it can be used safely in tobacco amblyopia cases and in pernicious anemia patients with optic neuropathy.
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Like cyanocobalamin, hydroxy B12 eventually has to be converted in the body to both methylcobalamin and adenosylcobalamin. But it converts much easier. Cyanocobalamin doesn’t react easily to anything else — the cyanide makes it very stable — so expensive energy expenditure is needed for it to convert.

Did you know? Actually, a good amount of methylcobalamin is converted to hydroxocobalamin as soon as it donates its methyl group. Then it has to receive another methyl group if it ever wants to be used as vitamin B12.

So, who is hydroxocobalamin good for? Mainly patients with intrinsic cobalamin metabolic diseases, B12 deficiency cases with tobacco amblyopia, and pernicious anemia patients with optic neuropathy. But be careful:

Suppressing nitric oxide could have adverse affects (elevated blood pressure, digestive disturbances, impotence, susceptibility to infection, even increased risk of cancer), especially during pregnancy where NO helps controlling the feto-lacental circulation. Therefore, anyone who could utilize methyl or adenosyl B12 would be better off with one of them.

Adenosylcobalamin

(ALSO ADECBL, COBAMAMIDE, COBINAMIDE, DIBENCOZIDE, OR ADOB12)

Adenosylcobalamin is the mitochondrial form of B12. It is used by the enzyme methylmalonyl-CoA mutase to convert methylmalonyl-CoA to succinylcholine CoA (used in the synthesis of porphyrin). This is why methylmalonic acid (MMA) levels get high when you’re low on AdeCbl.

Adenosylcobalamin also acts as an intermediate in the degradative pathway for valine, threonine, methionine, thymine, isoleucine, cholesterol and odd-chain fatty acids. Most of our B12 reserves are actually stored in the liver as adenosylcobalamin, and are converted to methylcobalamin whenever needed.

But what about supplementing with adenosylcobalamin?

In one study, carnitine and adenosylcobalamin promoted cerebral mass growth, pyramidal neuron volume, neocortical layer thickness, and fully restored normal structure of the neocortex in an experimental model of anorexia nervosa. In the patients, carnitine and AdeCbl accelerated body weight gain and gastrointestinal function normalization. Latent fatigue disappeared and mental performance sharply increased.
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Speaking of anorexia, another study found that the combined use of carnitine and adenosyl B12 eliminated fluctuations in work rate and normalized the scope and productivity of intellectual work in patients with anorexia nervosa in the stage of cachexia. Latent fatigue wasn’t fully eliminated though.

One Italian study treated 37 persons suffering from viral hepatitis with either adenosylcobalamin or cyanocobalamin. The researchers found that AdeCbl was significantly more efficacious than CN-Cbl in normalizing total bilirubin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and alkaline phosphatase values.

The AdeCbl administered was intramuscular injections at a dose of 1,000mcg per day for the first 12 days, and then orally for the next 12 days. Overall, 13/18 of subjects receiving the adenosylcobalamin had their total bilirubin normalized, 15/18 had their SGOT normalized, 10/18 had their SGPT normalized, and 18/18 (all) had their alkaline phosphatase normalized.

Impressive.

So, is it adenosylcobalamin or methylcobalamin? Which one should you supplement with? Remember, the two inter-convert in the body.

The main benefit methylcobalamin has over adenosylcobalamin is that it comes with a very beneficial methyl group, further enhancing your health in a myriad ways. Also, adenosylcobalamin isn’t available as injections, making it ineffective for pernicious anemia. However, if you can absorb B12 through the stomach, adenosyl B12 tablets can be a great option.

If you’re chronically fatigued and seem to get better only from AdoCbl (and not MetCbl), it is possible that you have some rare condition preventing your body from successfully converting B12 forms into others. In these case, you should supplement with a mixture of MetCbl and AdeCbl.

Verdict: What Is The Best Form of Vitamin B12? Cyanocobalamin vs Methylcobalamin vs Adenosylcobalamin vs Hydroxocobalamin

If you’re confused by all the text and the mass of studies, or if you’re simply a more visual person, this chart should give you a good picture:
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Figure 1. Synthesis of coenzyme forms of B12.
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Credit to George Kelly, 1997.

So, which is the best type of B12?

Let’s summarize things.

**Cyanocobalamin** is an inactive, slightly toxic form of B12. It contains a cyanide molecule, which your body will have to remove through methylation, a reaction that requires precious methyl groups. Glutathione seems to be the substance performing the decyanation.

Only then can the cobalt atom be reduced from an oxidative state of +3 to the biologically active +1, eventually forming methylcobalamin in the cytosol and adenosylcobalamin in the mitochondria. This demanding process can be significantly hampered in a range of conditions.

Cyanocobalamin is especially dangerous to those with liver problems, renal failure, and smokers, because in those people the cyanide can’t be eliminated effectively. It’s also dangerous for pernicious anemia patients or anyone else with high homocysteine levels, because it may deplete the body of glutathione, a substance needed to lower homocysteine.

Recommended to no one.

**Hydroxocobalamin** is also an inactive form of B12, but it is better than cyanocobalamin because it doesn’t contain any cyanide, therefore bypassing the need for decyanation and preserving the glutathione. It also has to be reduced from state +3 to +1 before it can become either MetCbl or AdeCbl.

Recommended to B12 deficiency patients with tobacco amblyopia, cyanide toxicity, and/or early hereditary optic nerve atrophy (Leber’s disease). Nitric oxide levels should always be monitored during administration.

**Adenosylcobalamin** and **methylcobalamin** are the native forms, bypassing several reactions in the absorption cycle. They both retain in the body and increase tissue concentration much better, and often produce clinical results far superior to what cyano or hydroxy B12 can offer.

The use of AdeCbl/MetCbl offers significant benefits and should be considered first line of defense against conditions that may benefit from B12.

Which of them is the superior choice?
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Remember, the two inter-convert. But if you have a rare condition preventing your body from inter-converting them (you’ll know this if you’re chronically fatigued and only AdeCbl — and not MetCbl — seems to benefit your energy levels), you’ll have to use a combination of MetCbl and AdeCbl.

For everyone else, which is more than 99% of people in need of extra B12, methylcobalamin is better. It exhibits distinct neuroprotective effects, improving nerve regeneration while bringing synaptic transmutations and diminished neurotransmitters back to normal levels.

Plus, methylcobalamin donates an extremely valuable methyl group that further enhances your health (and doesn’t steal any, like cyano does). This is especially important for pernicious anemia patients or anyone suffering from high homocysteine levels. This donation of methyl groups may be the reason why methylcobalamin is helpful to so many conditions.

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Vitamin B₁₂ Deficiency

- Easy to diagnose and treat – if you think of it.
- Regardless of cause, takes years to develop.
- Nervous system disease can precede blood changes.
- Subacute combined degeneration of the spinal cord.
- Now that food is heavily supplemented with folic acid, the neurologic presentation of B₁₂ deficiency will be more common and more severe.
- Causes: No food of animal origin
  - Autoimmune stomach disease
  - Blind bowel loop with bacteria
  - Fish tapeworm
  - Crohn’s terminal ileitis

Mental slowing

Mild neuropathy

Loss of proprioception

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Medical intelligence in Sweden. Vitamin B12: oral is as good as parenteral injection

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Abstract

Background: Sweden is the only country in which oral high dose vitamin B12 has gained widespread use in the treatment of deficiency states.

Objective: The aim of the study was to describe prescribing patterns and sales statistics of vitamin B12 tablets and injections in Sweden 1990–2000.

Design, setting, and sources: Official statistics of cobalamin prescriptions and sales were used.

Results: The use of vitamin B12 increased in Sweden 1990–2000, mainly because of an increase in the use of oral high dose vitamin B12 therapy. The experience, in statistical terms a “total investigation”, comprised 1 000 000 patient years for tablets and 750 000 patient years for injections. During 2000, 13% of residents aged 70 and over were treated with vitamin B12, two of three with the tablet preparation. Most patients in Sweden requiring vitamin B12 therapy have transferred from parenteral to oral high dose vitamin B12 since 1964, when the oral preparation was introduced.

Conclusion: The findings suggest that many patients in other post-industrial societies may also be suitable for oral vitamin B12 treatment.

Vitamin B12 deficiency may be treated with oral high dose vitamin B12 as effectively as with injections of vitamin B12.¹ This fact, in practice thought to be “medicine’s best kept secret”,²,³ was confirmed for American conditions 1998.⁴ The efficacy of oral high dose vitamin B12 has also been confirmed by British and French clinicians.⁵,⁶ The only country with widespread experience of oral high dose vitamin B12 in clinical practice is Sweden, where oral preparations have been available in clinical routine from 1964.

The aim of this study is to describe the patterns of vitamin B12 prescriptions and sales in Sweden 1990–2000. It is assumed that such parameters reflect the evaluation of the prescribers, mainly general practitioners (GPs)—a negligible quantity of oral high dose vitamin B12 was sold over the counter without prescription during the period studied (<1%).

METHODS

Background of tradition areas
Story of B12

In Sweden, there is a tension between history (tradition areas) and present organisation of health care (county councils and regions). Present tradition areas approximately correspond to catchment areas of the dominating university hospitals. The present description uses the concept of “tradition area”; differences of medical praxis are thought to be easier to show in such entities than in administrative entities with mingled traditions.

The county councils of Sweden are responsible for the health care of their residents. The organisation traces back to 1862 and was subject to formal legislation in 1928. In the period 1990–2000, there were 21 county councils, organised in six regions for expensive health care and education.

In contrast with the administrative organisation, informal tradition areas had emerged because of the history of the health care of the country. The north east area developed from the university hospitals of Uppsala and Stockholm with younger university hospitals in Umeå, Linköping, and Örebro. The west area developed around the university hospital of Gothenburg. The south Area developed around the university hospitals of Lund and Malmö (fig 1).

Data sources

Sales statistics were analysed from Swedish Pharmaceutical Data (Läkemedelsstatistik AB, Stockholm, Sweden) and Apoteket AB, (Stockholm, Sweden, the Swedish national supplier of drugs) during the period 1990–2000. The sales statistics covers prescriptions carried out in primary care. The B12 prescription in hospital care was negligible (2%). The population figures are from Statistics Sweden (http://www.scb.se).

Calculations and basic assumptions

The calculations of vitamin B12 consumption adhere to the assumptions used by Apoteket AB for their national statistics. Thus, for injections 1 mg of vitamin B12 as hydroxicobalamin (about 80% of the market) or cyanocobalamin was assumed to correspond to 50 defined daily doses (DDD) of parenteral therapy. For tablets (cyanocobalamin), the
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DDD of oral high dose vitamin B12 was assumed to be 1 mg (one tablet, brands Behepan, about 80% of the market, and Betolvex). One patient year is the number of DDDs (tablets) divided by 360.

Statistics
To test the internal consistency within the tradition areas (using comparison between the counties of each area) and the differences between the tradition areas, unbalanced analysis of variance was used. The data analysis was generated using SAS/BASE and SAS/STAT software (version 8, SAS Institute, Cary, NC, USA). This type of analysis of variance was used, as the number of counties varies between the tradition areas.

Facts already known
Oral high dose vitamin B12 provides an efficient therapy for vitamin B12 deficiency.

RESULTS

Oral high dose vitamin B12 in Sweden

Physicians in Sweden have gradually gained confidence in oral vitamin B12 since its introduction to the Swedish market in 1964. It is evident from figure 2 that by 1990 oral vitamin B12 therapy was as common as parenteral vitamin B12 therapy. Since then, the balance between the different forms of therapy has moved towards the tablets. The total experience of oral high dose vitamin B12 in Sweden during the period 1990–2000 corresponds to about one million patient years and for parenteral therapy about 750,000 patient years. The increase of vitamin B12 sales from 1990 to 2000 could not be explained by an increase of elderly people; residents aged 70 or over only increased by 6% during the period.

![Figure 2](image)


Prescription pattern during 2000
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Data for 2000 were calculated from the prescription statistics of Apoteket AB, combined with the population statistics of Statistics Sweden. It is estimated that 13% of the residents aged 70 years and over were treated with vitamin B12, two of three with oral high dose vitamin B12. In the age group below 70, only 1% of the people were treated with vitamin B12, with an equal distribution between tablets and injections.

It is evident from figure 3 that vitamin B12 prescriptions and sales differed in the three tradition areas. The west area had the highest prescription rate of both tablets and injections, the north east area the lowest (p<0.001). In the north east area, 69% of the total vitamin B12 therapy was oral, compared with 58% in the west area and 60% in the south area (p<0.001). Among residents aged 70 years and over, the fraction treated with vitamin B12 was 12% in the north east area, 16% in the west area, and 14% in the south area (p<0.001).

![Figure 3](image)

**Figure 3**

Total prescriptions of vitamin B12 in Sweden in the three tradition areas for residents 70 years and older during 2003. Source: Apoteket AB.

It is obvious from table 1 that the differences seen could not be explained by differences in age and sex between the populations of the three tradition areas. Nor could any internal inconsistency (heterogeneity) in the tradition areas be shown (p=0.75).

<table>
<thead>
<tr>
<th>Table 1</th>
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<tr>
<td>Age and sex distribution in the three tradition areas (female/male, %)</td>
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<tr>
<td><strong>Tradition area</strong></td>
</tr>
<tr>
<td>South</td>
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<tr>
<td>West</td>
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<tr>
<td>North east</td>
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**DISCUSSION**

Oral high dose vitamin B12 is registered for both the short term treatment of vitamin B12 deficiency and for maintenance treatment in Sweden. The experience described (figs 2 and 3) suggests that most patients are suitable
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for tablet regimen, dependent upon patient compliance and physician confidence. The clinical practice of the Swedish physicians studied is based on a high degree of professional knowledge and skill and an intense scientific debate during the past decade.\textsuperscript{8,10,11} The main limitation of this study is its restriction to prescriptions and sales; no figures of patient compliance are available.

It is reasonable to assume that the increase in the use of oral high dose vitamin B12 in Sweden was promoted by the seven crowns reform \textsuperscript{1970.}\textsuperscript{12,13} The reform provided financial neutrality to the choice between tablet and injection for the physician, the patient, and the producer. However, American, British, and Canadian physicians have argued that oral treatment is cheaper for health care and society.\textsuperscript{14,15}

In Sweden, neurologists and psychiatrists are inclined to prefer injections, at least in the initial stages of deficiency treatment. Most patients prefer tablets, a few injections (fig 2). The prominent use of oral high dose vitamin B12 in the north east tradition area of Sweden is thought to reflect the history of the documentation of oral vitamin B12; the team of Ragnar Berlin worked there.\textsuperscript{1}

\textbf{Learning points}

The study provides 1 000 000 patient years of oral high dose vitamin B12 therapy in Sweden during the period 1990–2000, compared with 750 000 patient years of parenteral therapy. The choice between tablets or injectables was approved, monitored, and evaluated by about 10 000 GPs, each with their individual bias.

The main tradition areas formed by history were obvious for those who worked within more than one area.\textsuperscript{1} Despite continuous effort to work towards a consensus, these findings (fig 3) suggest that some differences in prescribing patterns still persist. It is notable that vitamin B12 use was lowest in the north east area, where oral vitamin B12 was most popular. Nevertheless, it should be emphasised that the use of vitamin B12 did not exceed the mapping of preclinical deficiency of vitamin B12 and folate in elderly residents of a post-industrial society;\textsuperscript{16} vitamin B12 deficiency is mainly a feature of aging.\textsuperscript{15}

It is reasonable to assume that the increase in vitamin B12 treatment from 1990 (fig 2) was attributable to the introduction of homocysteine and methylmalonic acid as deficiency markers in Sweden. The new techniques kindled an intense debate,\textsuperscript{8,9,10,11} which improved clinical knowledge and skill.\textsuperscript{15} Findings were compatible with the hypothesis that the laboratory industry was the main sender, supported by pharmaceutical companies with suitable vitamin preparations. The GPs, the predominant prescribers, were main receivers. However, the model is a simplification of a more complex context.\textsuperscript{3}

Recent findings confirmed previous experience that vitamin B12 therapy should be combined with folate therapy as a routine precaution.\textsuperscript{4,10} These vitamins are joined in a series connection in the methionine cycle; lack of substrate (folic acid), blocks the action of coenzyme (vitamin B12), and vice versa.\textsuperscript{4,8,9,10,11,16} The Swedish experience suggests that most patients with deficiency could be managed by oral high dose vitamin B12 therapy.

\textbf{Acknowledgments}

MN as principal investigator and BN as principal scientific adviser had full access to study data and take responsibility for the integrity and accuracy of data analyses. All coauthors also had access to data. All authors contributed to interpretation of findings and drafting of manuscript. MN obtained basic data from official statistics and made the preliminary analyses. MN, JL, and HS obtained the funding.
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Footnotes

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- Competing interests: none declared.
- Ethical approval: not required.

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