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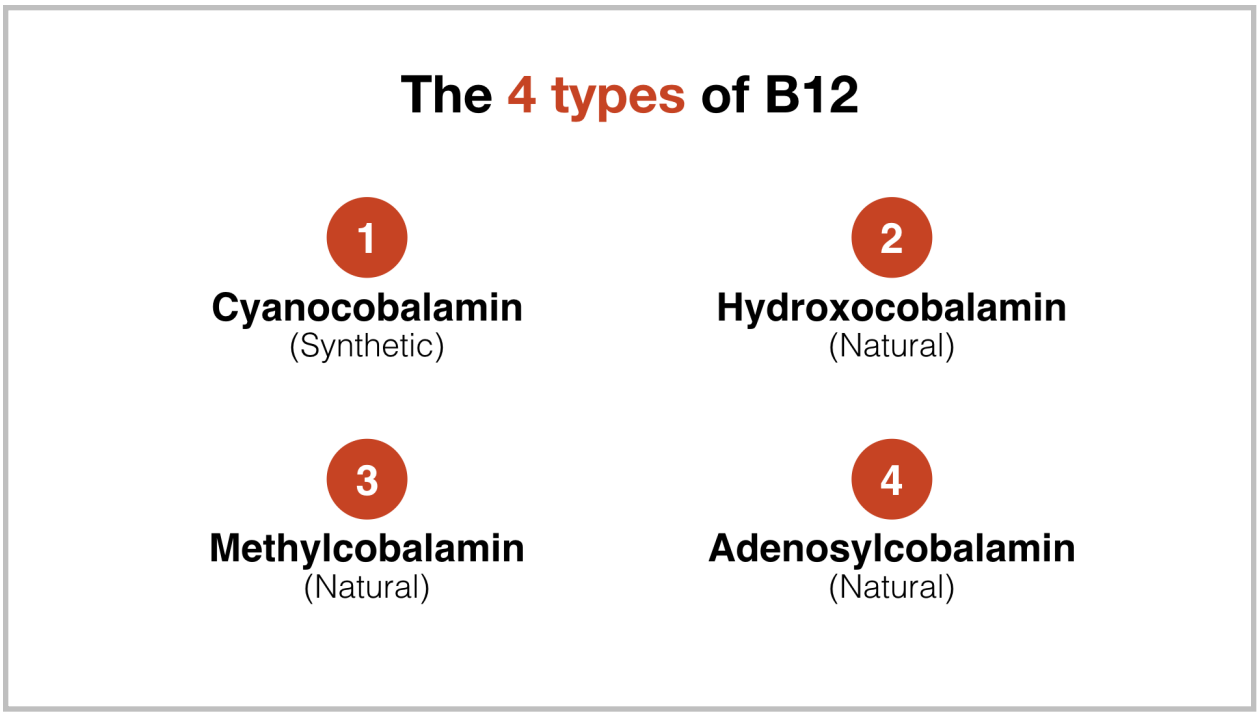
B12 Deficiency - Part Five

Now let's talk about B12 supplementation. The metabolism of B12 is complex and still under investigation, but I'm going to share some clinically relevant parts here. Designs for Health, the supplement company, has a good white paper on B12 that you can read if you're interested in the nitty-gritty details, and I'll put a link to that in the resources section.



There are four types of supplemental B12 available: methylcobalamin, hydroxocobalamin, adenosylcobalamin, and cyanocobalamin. The first three are naturally present in foods. Cyanocobalamin is a synthetic form that can be converted into adenosylcobalamin and methylcobalamin, but its bioavailability is poor compared to the other forms. All forms of B12 are delivered inside cells via lysosomes, where they are reduced to cobalamin, the common core molecule contained in all of them. The resulting cobalamin molecules are converted then into the two active forms of B12, methylcobalamin and adenosylcobalamin, likely in the same amounts regardless of the type of B12 ingested as the initial source.

> Once released from the lysosomes, both MeCbl and OH-Cbl were converted in the same proportions to coenzyme forms, **suggesting equivalent entry** into common cellular pools of cobalamin from which active forms are synthesized. All evidence supported the concept that in human cells the active MeCbl on methionine synthase forms de novo on the enzyme. **Exogenous MeCbl enjoyed no advantage** in binding to methionine synthase, in synthesis of MeCbl, and in supporting cell division. It appeared unlikely that therapeutic MeCbl would have any advantage over OH-Cbl in the treatment of MeCbl deficiency or cobalamin deficiency in general.
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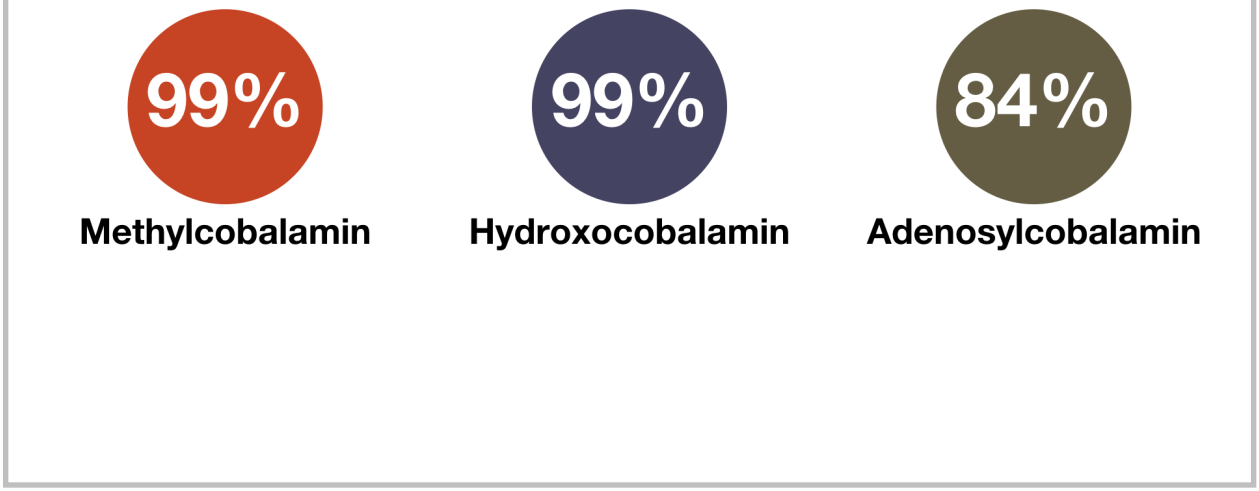
> **Reference:** http://www.ncbi.nlm.nih.gov/pubmed/8487649

A common misconception, and one that I shared until very recently, is that methylcobalamin supplements are somehow more active and have different physiological effects than hydroxocobalamin or adenosylcobalamin. This is based on the incorrect idea that active forms of B12 are absorbed and used without any metabolic conversion in the body. As I mentioned on the last slide, all forms of B12 are taken into the cell where they are converted into methylcobalamin and adenosylcobalamin. This has been confirmed by experiments showing no difference between methylcobalamin and hydroxocobalamin on metabolites of methylation reactions when they are used as supplements. The researchers concluded, once released from the lysosomes, both methylcobalamin and hydroxocobalamin were converted in the same proportions to coenzyme forms, suggesting equivalent entry into common cellular pools of cobalamin, from which active forms are synthesized. All evidence supported the concept that in human cells, the active methylcobalamin on methionine synthase forms de novo on the enzyme. Exogenous methylcobalamin enjoyed no advantage in binding to methionine synthase in synthesis of methylcobalamin and in supporting cell division. It appeared unlikely that therapeutic methylcobalamin would have any advantage over hydroxocobalamin in the treatment of methylcobalamin deficiency or cobalamin deficiency in general.

Studies have also shown that different forms of natural B12 have similar effects on the methylation cycle. The methyl group used in these reactions comes primarily from 5-MTHF and SAM-e, not B12. It is theoretically possible that various forms of B12 have different absorption rates or affinities to blood transport proteins, cellular entry, liver uptake, etc., but there is no solid research on this.



This doesn't mean there is no difference between the forms, though. As mentioned, cyanocobalamin has been shown to be less bioavailable than food-based forms, and it introduces cyanide into the body as a result of its metabolism, so we can cross that off the list. One study showed that adenosylcobalamin is converted into intracellular cobalamin 67 times slower than methylcobalamin. When given in equal amounts, each of the three natural forms of B12 results in percentages of cobalamin shown on this slide. Of the natural forms, methylcobalamin is the cheapest, so if you had to just choose one, that would be it. However, given what we don't yet know about single nucleotide polymorphisms that affect B12 metabolism and the possibility that there may be advantages to one form or another, I think the best approach is probably to use all three natural forms together.

Ensure adequate folate when supplementing with B12

In addition, it's a good idea to ensure adequate folate when supplementing with B12. Methylcobalamin is formed and regenerated with the methyl group provided by 5-methylfolate or SAM-e. Lithium is another nutrient that must be present for adequate B12 metabolism. Back in the 1970s, British researchers found that lithium plays an important role in transporting B12 in the cells, so you can check lithium levels in B12-deficient patients with something such as the Quicksilver

blood metals panel and then supplement with 5 mg of lithium orotate per day, which is a much lower dose of lithium than the one that is used in mental health disorders.

Given all of this, I like Designs for Health Trifolamin. It has all three natural forms of B12 with a combined dose of 3 mg, or 3,000 mcg, plus 400 mcg of Quatrefolic, which is a form of active folate. It is a sublingual form, which means it can be used by patients with pernicious anemia and other absorption issues. It's the only product that I'm aware of currently at the time of this recording that contains all three forms of folate. Some patients are very sensitive, however, to active forms of folate. In these cases, they may not tolerate Trifolamin because it has 400 mcg of active folate. In those cases, the patients can try sublingual methylcobalamin from a company such as Seeking Health or a combination of sublingual methylcobalamin, hydroxocobalamin, and adenosylcobalamin separately.

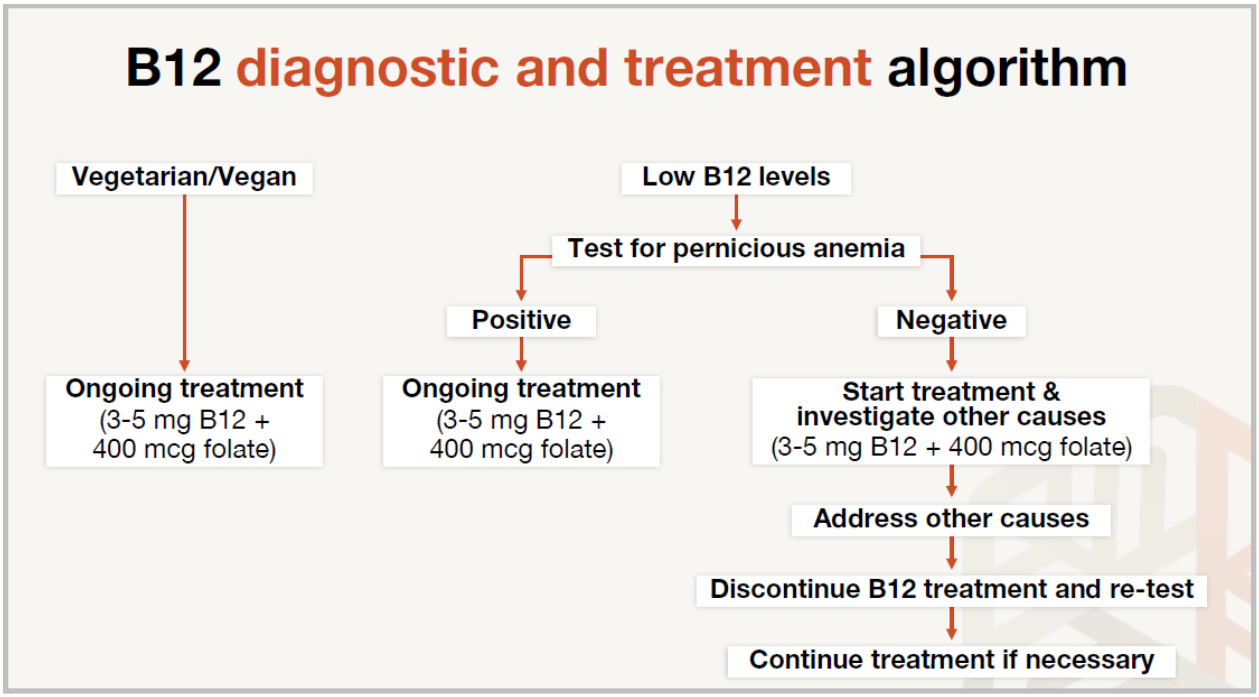
High doses of supplemental B12 can circumvent the deficiency of intrinsic factor and enable B12 absorption through the gastrointestinal border by diffusion. Appropriate therapeutic doses are 3 to 5 mg per day, and remember, there is little to no concern about overdose.

In addition to B12, the patient may also want to supplement with betaine hydrochloric acid to increase absorption, and this is especially warranted if they have low stomach acid. Note, again, that HCl is contraindicated with gastric or duodenal ulcers and patients taking NSAIDs.

Retest after 60 days.
Treatment ranges **from**
2 months to ongoing.

During treatment, observe the symptoms, and then retest serum cobalamin, MMA in the urine or serum, and homocysteine to confirm that the treatment is working. I usually do the first retest after 60 days to make sure it is moving in the right direction. The length of treatment varies considerably depending on the severity of B12 deficiency, how long it has been present, and its cause. This ranges anywhere from two months to two years to ongoing for pernicious anemia. Some patients with longstanding B12 deficiency will need high doses of B12 for an extended period in order to correct damage, and as mentioned, some neurological effects of B12 deficiency are unfortunately irreversible. I would have patients take B12 for at least a year, though, before coming to that conclusion because I've seen some changes happen after a prolonged period of B12 supplementation.

What about B12 injections? Studies have shown that high-dose oral or sublingual therapy is as effective as injections for most patients. That said, if you have a patient who is not responding to oral or sublingual therapy, I think injections are worth a try. They do require a prescription, but the patient can administer them at home. Hydroxocobalamin is the most effective form. Methylcobalamin is very sensitive to light, so it's harder to work with in an injectable form. The typical injected dose is 1 mg, or 1,000 mcg, per day.



Here is a B12 testing or treatment algorithm that you can use. If the patient is vegetarian or vegan, I think they should just, by definition, be supplementing with B12 indefinitely. There are no plant sources of true B12. The risk of B12 deficiency is high. The testing that we have can't detect stage one and stage two B12 deficiency because of the lack of availability of holotranscobalamin, and the effects of B12 deficiency are potentially irreversible. Finally, B12 supplements are nontoxic, so for all of those reasons, I think the benefits of supplementation for vegans and vegetarians outweigh the cost of B12, which is really the only potential downside. If the patient has low B12 levels and he is on an omnivorous diet, you would test for pernicious anemia. If that is positive, he would require ongoing treatment. If it is negative, you could start treating him with B12 supplements to give him some relief while you're investigating underlying causes such as GI malabsorption. You address those other causes, then discontinue the B12 treatment, and retest. If their numbers continue to be low, you continue treatment until you can figure it out.

Okay, that's it for now. Thanks for watching. See you next time.