“AFTERGLOW” FROM DRINKING:

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(/u/quijonido + Chadwick are the same person.) —>

~> quijonido (reddit):

“I’m a medical student who has spent years trying to figure out the exact mechanism behind this. I I started a thread a few years ago at Longecity (http://www.longecity.org/forum/topic/64835-chronic-dopamine-deficiency-consistently-disappearing-during-alcohol-hangovers/page-1) about this phenomenon - my username there is Chadwick.

These days I’m basically free from initial symptoms (mainly lack of sociability) thanks to a tetrahydrobiopterin supplement I’m taking.

EDIT: **5-MTHF (methylfolate) has helped me a lot in the last couple of years but nowadays I use tetrahydrobiopterin instead.**

My theory is that variations in the MTHFR and DHFR enzymes reduce folate metabolism which in turn leads to high peroxynitrite, as methylfolate is a peroxynitrite scavenger. The high peroxynitrite then leads to low tetrahydrobiopterin which is a cofactor for monoamine (dopamine, norepinephrine, serotonin) synthesis.

Acetaldehyde, a waste product of alcohol, blocks the enzyme methionine synthase during hangovers and raises the levels of available methylfolate, which can be used for peroxynitrite scavenging. This leads to higher tetrahydrobiopterin.

Alcohol consumption also leads to higher NADH which in turn increases tetrahydrobiopterin formation.

(*in response to /u/FLSverker’s reply, ‘Shouldn’t supplementing 5-MTHF and NADH be an effective substitute for supplementing tetrahydrobiopterin? It seems like the latter is hard to come by in the United States without a prescription.’*):

It can be, but methylfolate/MTHF will also increase methylation, and increased methylation can lead to increased breakdown of catecholamines through the COMT enzyme. The effects are not necessarily equal.

I’ve used 23andme. I’m compound heterozygous for MTHFR, so I’m heterozygous for both the A1298C and the C677T. I have the fast versions of both MAOA and COMT and I’m heterozygous for DRD2 Taq1a. I’m also homozygous for a variation in the DHFR gene (RS1650697) that seems common among people with chronic fatigue syndrome —> (http://forums.phoenixrising.me/index.php?threads/snps-for-dihydrofolate-reductase-dhfr.19563/), presumably because it lowers levels of active folate.

In other words: both my dopamine and folate levels should be lower than average.

~> Chadwick (longecity.org):

“**My current theory of the whole hangover/euphoria connection is this**: Alcohol increases the body’s levels of NADH. This increases the recycling of BH4, a major cofactor in dopamine (and serotonin+norepinephrine) synthesis. **The people who feel this effect are people who have insufficient BH4 production, which can be caused by either mutations in the genes coding for the enyzmes involved in BH4 synthesis (uncommon) or a lack of folate in its bioavailable form, 5-MTHF (more common). A lack of 5-MTHF can be caused by a lack of folate (due to poor diet, malabsorption etc) or a low 5-MTHF synthesis due to mutations in the gene coding for the enzyme MTHFR, which is fairly common. 30% have one defect copy of the gene, and 10% have two defect copies.**

I used NADH for a few days with great results. Clear thinking, great mood, sociability, motivation and drive. I don't use it anymore, however, since I don't need it.

After coming up with the theory that low dopamine that goes away during hangovers could be caused by MTHFR mutations **I bought some 5-MTHF (methylated folate) from iherb.com. Within a day from the first 4 mg dose the low dopamine symptoms I've had my whole life (I'm 22 now) was completely gone. An absolutely mind-blowing feeling. It has been 5 days now, and I'm still feeling great. It will take a few more weeks for my 23andme.com genotyping results will come, so I don't know if I actually have an MTHFR mutation, but that would make so much sense.**

It’s difficult of course to quantify well-being, but **I’d say the quality of my life have improved by 25-30% over the last week. I don’t feel euphoric in any way, I just feel… great. Like the best possible version of myself.**

So, I got my 23andme results back. There are a few interesting things relating to dopamine that I've found so far. **I'm homozygous Val/Val for the Val158Met in COMT, which means I'm breaking down dopamine, norepinephrine and epinephrine fast. I'm heterozygous for the Taq1A form of DRD2/ANKK1, which means my D2 dopamine receptors are less sensitive to dopamine. I'm also heterozygous for two mutations in the MTHFR enzyme: 1298 and 677. This means I'm producing less MTHF than the average person.**

(*in response to ‘Guardian4981’s reply, ‘I took my first 500mcg dose of 5-MTHFR last night. Within a half hour I started feeling anxiety, so I went for a jog, the anxiety wore off. One interesting effect is my senses seemed to be heightened, when I listened to music I felt like there was subtle sounds I heard in the music I never had before, making it a more enjoyable experience. I also did feel a lift in mood. I have read on here that if you have been deficient in something for a while when you first take it you may feel some unpleasant feelings at first which could be the initial anxiety. So I am going to start slow using this every other day and see how it goes.’*):

Personally I had an amazing time on 4 mg MTHF per day, without side effects, but that only lasted a week. After that anxiety and brain fog set in. After doing some googling I found this site —> (http://mthfr.net/methylfolate-side-effects/2012/03/01/) which describes my experience quite well. It seems as if some people does not experience any side effects, some get side effects after a week and some never have

any trouble. This can be explained by the fact that MTHF has a methyl group, and therefore increases methylation which in turn can cause anxiety and brain fog.

For me this resolved after lowering my dose to 800 micrograms x2 per day, and adding 250 mg time-release niacin (vitamin B3). Niacin is broken down by methylation, and can therefore decrease excessive methylation. Sadly, the amazing results I felt the first week wore off, but I'm still doing better than I did before.

(*in response to 'zaratoo's reply, 'This thread made me register, which I usually don't do (having no will to be social ;)) But this time I just couldn't watch silently. I don't really know why, but I started to dig into dopamine quite recently, while I've been researching (self-edu I mean) biochemistry and neurophysiology for 10+ years now. Too sporadically I see now… As for motivation, I'd fit my situation well in Chadwick's description. Thanks for formulating that man, I've never been motivated enough to start do it myself. Though I always saw that problem had it's place… And well, I have some social anxiety, but it's totally gone, when I need to communicate e.g. officials/bosses (municipal, military, in university etc no matter) for some important (often not for me personally) reason. Actually when I learned the name of Asperger, I said it's about me! Light form obviously, no one except me would notice my stress and inabilities.. As for ethanol and hangovers… I often think and say to people that I even drink to get hangover. They laugh thinking it's a joke or just look 0_o this way. Sorry for being too wordy about myself, I'm just really excite to meet people like myself)) Also hangover and dopamine. No one mentioned (or I missed) the marvelous sex drive in this state. Physical and mental. And to mention the mentality on the whole it's kinda psychedelic state. Without junkie tail of this term. Wisdom is good suitable word. You think wider and deeper at the same time). And I enjoyed being drunken too. But most people would say it's like Jekyll and Hyde)) Nothing delirious though, just two really different personalities - from the side view'*):

I've noticed the increased sex drive too, and I love it. It's uncommon for me to have morning wood, but I often do when I'm hungover. I've also been experiencing the same thing you are describing about having no social anxiety when talking to officials, like job interviews or whatever.

However - after lowering my dose of MTHF to 800 mcg per day and adding 1500 mcg of folic acid I've gotten back the effects I got from MTHF the first week. I'm feeling great now - all the lack of social interest is gone and I'm out there interacting with lots of energy and a great mood. **After digging deeper into my 23andme results I've come to find I have an uncommon homozygous mutation in DHFR, another enzyme involved in the metabolism of folate. I think this had caused a 'hidden' deficiency, i.e. blood panels look normal but in reality you have a higher than normal need for folate due to slower conversion to its active forms.**

I'm personally feeling cured now, after 22 years, which is absolutely amazing.

It would be interesting to see how you reacted to supplementing higher doses of folic acid (or MTHF if possible) together with iron, which is also important for dopamine production. :)

(*in response to 'Psionic's reply, 'My first dose of 1mg (1000mcg) MTHF ended with severe anxiety and hindered thinking. I don't know what genetics mutations I can have but the hangover effects is remarkable in me. So the route should be to lower the dose of MTHF and add some niacin? Chadwick, whats the reason you take MTHF and folic acid at the same time?'*):

The reasoning behind MTHF+folic acid is that they both raise the body's total MTHF levels. Taking a combination is more effective than only taking folic acid, and has less side effects than taking only MTHF.

I'm sorry to hear MTHF produces these effects for you. You could try lowering the dose and combining niacin, or you could try taking only folic acid (4 mr per day or so, which would be my preferred route).

'tritium': 'I also experienced this. I heard that 'hindered thinking' is a common detox symptom when starting this regimen as it is kick starting your methylation cycle. Folic acid should be avoided if you have the genetic mutation which reduces the ability to convert it (60% of the world's population have this mutation) as it blocks methylfolate from being absorbed. Instead, B-12 should be brought to normal levels first before starting methylfolate. Here's a good site with more information: —> (http://forums.phoenixrising.me/index.php?threads/active-b12-protocol-basics.10138/) '

(*in response to 'Galaxyshock's reply, 'There's a 4 to 5-fold increase in glutamate release during hangovers, of course you are going to feel fucking different.'*):

True. Yet the shift in glutamate release is far from the only thing that happens during a hangover. For me personally, the mood boost was not replicable by using glutaminergics (Sarcosine), only dopaminergics (e.g. NADH).

((*in response to 'manny's reply, 'Check out a post I put out last year, sounds very similar to my own experience: (http://www.mindandmuscle.net/forum/43182-alcohol-next-day-euphoria-excitement-motivation) 1. So Chardwick are you still feeling the effects or have you built up tolerance? 2. Also what supplements are you taking, and which ones did you drop? Are you taking MTHF + folic acid + niacin? 3. Are you still taking them sublingually, or swallowing them? 4. Is 5-MTHF and MTHF the same thing? 5. Is there any point taking NADH, or do you think going the MTHF route is all that's needed?'*):

I'm still taking methylfolate (MTHF), and I doing great on it. Really great. I had dopaminergic problems for the first 22 years of my life, but the last six months or so that I've been using this I feel like a different, and much better, person. The social and mental inhibition I've felt before is totally gone now, which of course feels amazing.

After some experimenting I've found out a simple regimen that works for me, and I also believe I've figured out why my previous problems disappeared during hangovers. It's somewhat complicated, but I'll try to explain. :)

The alcohol that we consume is broken down to acetaldehyde, a toxic substance that is responsible for some of the negative effects of a hangover. Acetaldehyde interacts with several enzymes and processes in the body, and one of these is methionine synthesis, an enzyme in the metbolism of (methyl)folate

and B12 that is needed to make methyl groups. It binds this enzyme and blocks it temporarily, reducing the usage of folate and B12 for this purpose. When the folate in our bodies can't be used for this purpose, it is instead used to create BH4, a cofactor in the synthesis of dopamine, norepinephrine and serotonin.

This, I believe, is my personal problem - that I don't have enough conversion of inactive forms of folate (such as folic acid or folate from food) to the active form (methylfolate) and therefore not enough to support both the methylation and the BH4 pathways. Lack of methylation can gives rise to a number of problems, such as acne, low immune function, lack of mental and physical energy, and lowered detoxification of heavy metals. Lack of BH4 on the other hand can decrease the production of neurotransmitters. By supplementing methylfolate I can normalize the activity of both of these biological pathways.

I feel a distinct effect from taking methylfolate within an hour, and it lasts for six hours after that. Since I want to have this effect 24/7 I'm taking small doses (200 mcg) every six hours, so four times a day.

The problem that can arise is that too much methylfolate can deplete the body of the active form of B12, methylcobalamin. When B12 gets low inside the cells the usage of methylfolate for it's two purposes are blocked, and somehow it starts going from the cells to the plasma. So basically we get high folate levels in plasma but we're unable to use it, so we get a functional deficiency. Taking more methylfolate without B12 will just make the functional folate deficiency worse. This phenomenon is known as methyl trap, folate trap or methylfolate trap. It will take a week or so to develop low intracelullar B12 levels when we take high doses of methylfolate, and this is why people (including me) will feel great for a week when starting taking this supplement, but then crash.

This can be avoided by taking B12 with the folate, and there are two main ways to approach this. The first way is to take methylcobalamin - usually sublingually and in doses of >1 mg. This will kickstart methylation and give you all the benefits this might bring, but it won't leave much folate for the synthesis of BH4, and therefore it won't help our dopamine problems. The other way to solve the B12/methyl trap issue is to take sublingual hydroxocobalamin, which is an inactive for that converts to methylcobalamin at a steady but low rate. This will prevent methyl trapping as well as preventing all the folate from going down the methylation route.

So, the MTHFR/dopamine regimen I use myself is this:

~ 200 mcg of oral methylfolate, every six hours

~ 1 mg of hydroxocobalamin once a day

According to my 23andme results I personally have incredibly bad genetics for dopamine - the Val/Val version of COMT, the highly active version of MAO, one Taq1 mutation in the D2 receptor and so on - **but it doesn't seem to affect me that much when I've normalised my folate metabolism. I think this might be true for other people as well - that low dopamine levels are mainly caused by a decrease in synthesis, not an increase in breakdown. :)**

1. Yes, and **there is no buildup in tolerance.**

2. **Hydroxocobalamin and methylfolate (MTHF), nothing else. I don't need niacin when taking hydroxocobalamin as this doesn't cause overmethylation. Methylcobalamin can overdrive the methylation cycle, so if you choose that route niacin may be useful since it can decrease methylation in the case of overmethylation.**

3. **Hydroxocobalamin sublingually, methylfolate orally (just swallowing).**

4. Yep. **Methylfolate = MTHF = 5-MTHF**.

5. **No, I don't think NADH is needed.**

(*in response to 'Oner's reply, 'great info, i'll be starting TMG, 5-MTHF, and Methyl B12 today. Chadwick, I don't quite understand your reasoning of the methyl trap. Wouldn't raising the dosage of methylfolate allow it to synthesize BH4 and also methylate other necessary things? I don't see why including Methyl B12 would prevent success when taken together with the 5-MTHF. I read here: (*http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1574248/*) that 5-MTHF has an oral bioavailability 7x higher than folic acid. Though I can't find much info out their on whether or not to take 5-MTHF sublingually. What made you decide to take it orally?'*):

The methyl trap phenomenon is somewhat of a paradox - by taking more methylfolate we lower B12 even more, and more methylfolate is expelled from the cells. Taking more methylfolate without B12 therefore lowers intracellular folate levels while raising extracellular levels. BH4 synthesis takes place inside the cells where folate now is low, and is therefore impaired. I honestly don't fully understand the mechanisms behind this, but it seems to be fairly well documented.

The reason I'm sceptical towards methyl B12 is that it makes us use our folate for production of methionine and in extension methyl groups rather than BH4. Instead of using some folate for methylation (which is regulated by access to methylfolate AND methyl B12) and some for BH4 production there would be a shift towards more methylation and less BH4. Since BH4 is needed to make neurotransmittes and methylation is needed to break down catecholamines, this would lead to lower levels of dopamine.

I take methylfolate orally as it seems to be working very well for me. I've seen various numbers regarding it's bioavailability and it seems like there is no consensus yet —> (http://jn.nutrition.org/content/131/4/1376S.full), but since it's working as intended I don't see any reason for myself to take it sublingually instead. :)

Edit: Oh, and I'm not sure if TMG is needed, since methylfolate and methyl B12 will increase methylation by a fair amount anyway.

(*in response to 'Oner's reply, 'I'm still a bit confused, off to do more research lol, I'm actually using TMG, 5-MTHF, and Methyl B12 in order to stimulate SAMe production. B12 and B9 are cofactors there, so I'm not sure how that fits into the methylation and BH4 cycles. Isn't methionine used to produce SAMe?'*):

Yeah, B12 and folate (B9) are used to create methionine, which in turn is used to make SAMe (S-adenosylmethionine). SAMe increases methylation by donating its methyl group to other substances. (link to picture of cycle:

http://www.katepowe.com/wp-content/uploads/2014/02/MTHFR-TetraFolateMethyl-Cycle-700x414.jpg)

Edit: Above pic should say '5-MTHF'. MTHFR is the enzyme used to produce 5-MTHF/methylfolate.

Edit 2: regarding the site I linked to earlier —> (http://mthfr.net/methylfolate-side-effects/2012/03/01/), **the side effects listed there (increased inflammation, acne, rashes etc) seems to actually be symptoms of methyl trapping - in other words symptoms of LOW folate due to a functional deficiency.**

(*in response to 'Oner's reply, 'So why would it be undesirable for folate to be channeled towards methionine production? It seems that at any route 5-MTHF will have some beneficial energy and mood properites. Also you seem to suggest that B12 is kind of a rate limiting step for BH4 production, meaning that however much B12 is taken, the same amount will be used of B9 for methylation process not neurotransmitter ones. Do you have evidence of this? It seems to make sene since they methylate well together, but I just want to confirm it.'*):

I believe it's important to have a healthy level of methylation going on. **The reason methyl B12 can be a problem is that taking large amounts of it can overdrive the methylation cycle, thereby leading to overmethylation and decreased BH4.** Normally the body will regulate methyl B12 production on its own, keeping it at a steady and low pace, which allows normal levels of methylation.

There are some cases where very high elvels of methylation may be beneficial, such as for people with neuropathy (http://www.ncbi.nlm.nih.gov/pubmed/8021696).

I don't believe B12 is a rate-limiting step for BH4 production or recycling, but some B12 is needed to prevent a methyl trap. B12 is, however, used by methionine synthase, which is the rate-limiting step in the methylation cycle. **The statement that methyl B12 decreases BH4 production by re-routing folate usage towards methylation was made by Rich van Konynenburg, an authority in the treatment of chronic fatigue syndrome with methyl B12. It seems to be true in my experience, and somewhat logical. :)**

(*in response to 'normalizing's reply, 'If I order the gene test from 23andMe, how do they really tell you and explain in detail to you whats wrong and right with you? I have never done this gene test, I have no clue how to read it! And you are smart enough to have figured it out by yourself without them telling you I assume? I have to take this test but if they cannot help me with information, I'll waste money on something I don't even really understand at all. But I assume you can read those tests and help me out? I dunno if you self taught yourself all that biochemistry and knowledge on genetic problems, but you know what you are talking about so I put trust in you. Perhaps you even have a job related to this? Anyway any help much appreciated!! :)*'):

It took me two years of medical school as well as a lot of thinking and reading on my own to figure out what my own problem really was. And now that I've done that and learned how to treat it, I can tell you that it was so, so worth it. I changed my life for the

better, and I would be glad if I could help other people with similar problems to do the same.

I'm curious about how you see your problem subjectively - is it lack of motivation, depression, fatigue, or how would you describe them?

23andme will tell you some basic information about disease risks, but **if you want to find out about your genes relating to neurotransmission I'm afraid you'll have to download the raw data and analyze it yourself. The easiest way to do this is to use Promethease (https://promethease.com/ondemandlicense) which is an easy analytic tool, GeneticGenie Methylation Analysis (https://geneticgenie.org/methylation-analysis/), which will give some info about genes relating to methylation, and SNPedia (http://www.snpedia.com/index.php/SNPedia) which is a wiki-site that explains various genes. The easiest ways to see your polymorphisms (gene variations) is to download your raw data from 23andme and upload it to Promethease, and then download the files you get from them. In the 'report_ui2.html' file you can then search for certain SNPs (point mutations), that have names like Rs123456 and so on below. For the genes with many important SNPs you can just search for the gene name in Promethease and it will tell you if it finds something unusual.**

These are the genes and SNPs I believe are the most important to look at when it comes to dopamine:

MTHFR - A gene involved in producing the active form of folate, which is needed to make several neurotransmitters.

RS1801133 aka C677T. C is good to have, T is bad.

RS1801131 aka A1298C. A is good, T is bad.

DHFR - Another gene involved in folate metabolism AND BH4 recycling. Not quite as important but still relevant. It's not known which SNPs are important here. Personally I'm homozygous RS1650697 which is somewhat uncommon. C is good to have here, and T is bad.

GCH1 - Involved directly in BH4 synthesis. Many SNPs that are important, see —> (http://www.snpedia.com/index.php/GCH1).

PCBD1 - Involved in BH4 synthesis. Many SNPs, see —> (http://www.snpedia.com/index.php/PCBD1).

PTS - Involved in BH4 synthesis. Many SNPs, see —> (http://www.snpedia.com/index.php/PTS).

QDPR (aka DHPR) - Involved in BH4 synthesis. This enzyme uses NADH, which I believe is the reason that NADH can raise BH4. Many SNPs, see —> (http://www.snpedia.com/index.php/QDPR).

SPR - Involved in BH4 synthesis. Many SNPs, see —> (http://www.snpedia.com/index.php/SPR).

TH (tyrosine hydroxylase) - Converts tyrosine to L-DOPA, which is then used to make dopamine. TH is an iron-containing enzyme, which is the reason that iron deficiency can lead to lower dopamine levels. Many important SNPs, see —> (http://www.snpedia.com/index.php/TH)

DDC (aka AADC, dopa decarboxylase) - Turns L-DOPA into dopamine, and 5-HTP into serotonin. Several important SNPs, see —> (http://www.snpedia.com/index.php/DDC).

COMT - Breaks down dopamine and other neurotransmitters.

RS4680 aka the warrior/worrier SNP. The Met version (A) will give you lower COMT activity and therefore more dopamine. This will lead to higher pleasure response and higher extraversion, but also lower threshold for stress. The Val version (G) will give you higher COMT activity and therefore less dopamine. This will lead to lower pleasure response, lower extraversion but also higher threshold for stress. Val will make you calm and collected while Met will make you motivated and outgoing.

MAO - Breaks down dopamine and several other neurotransmitters.

RS6323 - G will lead to higher enzyme activity and lower dopamine, and T to lower activity and higher dopamine.

DAT (aka SLC6A3, dopamine transporter) - Removes dopamine from the synapse so it can't bind its receptors. RS27072 is involved in alcohol withdrawal as well as ADHD. C increases risk for ADHD and alcohol withdrawal, T lowers it.

DRD1 (dopamine receptor D1) - Involved in neuronal development and varous behavioral responses. Several semi-important SNPs, see —> (http://www.snpedia.com/index.php/DRD1).

DRD2 (dopamine receptor D2) - Involved in social functioning, extraversion and social status. Low D2 binding correlate with social phobia —> (http://www.researchgate.net/publication/246729161_Low_Dopamine_D2_Receptor_Binding_Potential_in_Social_Phobia).

RS1800497 aka Taq1a polymorphism. C is good to have, T is bad.

DRD3 (dopamine receptor D3) - Low activation is involved in cognitive problems and depression. See —> (http://www.snpedia.com/index.php/DRD3).

DRD4 (dopamine receptor D4) - Links to lots of psychiatric conditions, including ADHD.

RS1800955 is linked to personality. T is the normal variant, and C increases novelty seeking.

DRD5 (dopamine receptor D5) - (http://en.wikipedia.org/wiki/DRD5) - Not sure if it's involved in anything unique.

If your main focus is how low dopamine connects to social phobia or lack of social drive/motivation, I believe that MTHFR, DHFR, MAO, COMT and DRD2 are the most important. And yeah - personally have bad versions of them all. ;)

If you wanna do more reading I suggest this article —> (http://jn.nutrition.org/content/137/6/1568S.full). Also if you want pictures explaining the reactions connecting folate metabolism with BH4 and dopamine, you can check this out —> (http://www.altmedrev.com/publications/13/3/216.pdf).

Methylation in itself can impact dopamine and other catecholamines. So BH4 isn't the only connection between folate and neurotransmitters.

I've experimented a lot with B vitamins over the past few months, and increasing or decreasing methylation has several noticeable effects on me:

Low methylation: Low mood, fatigue, increase in salivation, increase in perspiration, increased acne, poor wound healing, flaky skin around fingernails (this is my earliest warning sign that methylation is low), skin histamine reactions and low tolerance to high histamine foods (such as tuna).

High methylation: Increase in mood, high-energy, low-normal salivation, low-normal perspiration, smooth skin, fast wound healing, low histamine.

You can always try methyl B12 to see if it helps you. 500 is a good starting dose, but it has to be taken sublingually. This will increase methylation, but it might also decrease BH4.

I'd use methylfolate with it even if you don't have any MTHFR mutations. This is because methylfolate will regenerate methyl B12 from its inactive form after it's been used for methylation. Also, using folic acid instead of methylfolate can actually lower methylation by using methyl groups to form methylfolate out of the non-methylated folic acid.

(*in response to 'chris106's reply, 'First of all, I agree with many others that this is an amazing thread. :) I will get myself tested with 23&me as soon as possible, since I suspect a MTHFR mutation might be the root of my problems. Anyways, I have a question, Chadwick: Is this product a legit form of MTHF?: 'Doctor's Best Best Fully Active Folate Featuring Quatrefolic'. t seems odd to me that it is so much cheaper than any other MTHF product I can find, and it's the only one that uses this 'quatrefolic' branding.The ingredients-description makes it seem as though it could be a lower form of Folate masked as MHTF...? Also, I can only seem to find few sources of hydroxocobalamin - the only one that seems affordable comes as nasal spray: (http://www.ebay.de/itm/B12-Nasal-spray-500mcg-Hydroxocobalamin-per-spray-Yuliv-/321184858805?pt=UK_Health_Beauty_Vitamins_Supplements&hash=item4ac81c02b5*) *Do you have any other/cheaper sources you would be willing to share?'*):

The folate you linked to is legit - I have that one as well at home but I currently don't use it since it has 400 mcg of folate in capsules, that are difficult to split to get the 200 mcg I want. Quatrefolic is another form of methylfolate and I'm not exactly sure of the (tiny) difference between it and Metafolin that I use, but both work well for me and many others. **This is the one I personally use:** (http://www.iherb.com/Solgar-Folate-As-Metafolin-800-mcg-100-Tablets/13961#p=1&oos=1&disc=0&lc=en-US&w=metafolin&rc=40&sr=null&ic=3) For hydroxycobalamin I use this one: (http://www.iherb.com/Advanced-Orthomolecular-Research-AOR-Classic-Series-Hydroxy-B12-60-Lozenges/52244#p=1&oos=1&disc=0&lc=en-US&w=hydroxy%20b12&rc=4&sr=null&ic=1) It doesn't seem to matter if I skip a day or two every now and then when it comes to the B12, and it might even be possible to just take it every other day. It's somewhat more expensive than the folate, so if that works it could be a way to keep expenses down. :)

Edit: also, www.iherb.com is a good site to buy supplements, regardless of where you live. I pay $8 for 4-day shipping to Sweden.

(*in response to 'Lufega's reply, 'Funny thing about mb12. Every time i take it, it makes me very sleepy and groogy. I was expecting an abundancy of energy. I read something about increasing conversion of serotonin to melatonin or it could be that its increasing methylation or decresing bh4. All in all, im not feeling a boost in motivation but it does help with focus some. I can try to take it at night but im afraid i'll get a wired, sleepy effect.'*):

I personally know of one possible reason for this, but there are probably several other explanations as well:

People with a very high heavy metal burden, mainly mercury, can have a paradoxical reaction to methyl B12. The reason for this is that methyl B12 reacts directly with elemental mercury in the body and forms methylmercury, a MUCH more toxic substance than elemental mercury. When this methylation takes place the mercury is also mobilized from intracellular storage to the blood and from there distributed in the body, including passing the blood-brain barrier.

Ironically, mercury, and especially methyl mercury since it's so much more toxic, acts as a strong inhibitor of methionine synthase, the same ezyme that methyl B12 is used by. The end result is that methyl B12 in mercury toxic people DECREASES methylation and gives symptoms of undermethylation, like fatigue and brain fog. Somewhat of a paradoxical reaction.

So, the theory is that having a high heavy metal load (due to industrial exposure, amalgam fillings etc) could possibly be a reason for methylation problems in people who have a genetic predisposition for it, such as unfortunate polymorphisms in the genes relating to methylation (MTHFR, DHFR, MTRR, MTR and so on). These people will be undermethylated but will react poorly to methylation supplements.

Do you currently have any amalgam fillings, or have you had any in the past?

But as I said - there might be other more likely explanations

'Vision': 'Methylfolate (800-3200ug), Uridine (2x250mg) and St. John's Wort (3-5x 300mg, 0.2-0.4% Hypericins, 2-4% Hyperforins) seems to emulate this hangover effect for me. ~5 days on this stack, will report if effects diminish.'

'Lufega': '500 mcg MB12 wasn't doing anything for me so I increased it to 5,000 mcg sublingual. At this dose, I'm having a surge of motivation and it's allowed me to get a whole lot done today. I'll repeat this dose for the upcoming week to see if the effects are permanent. Once that is done, I'll titrate down using 1,000 mcg to see if I can duplicate that effect with a smaller dosage.'

(*in response to 'Chadwick's post 'So, I got my 23andme results back. There are a few interesting things relating to dopamine that I've found so far. I'm homozygous Val/Val for the Val158Met in COMT, which means I'm breaking down dopamine, norepinephrine and epinephrine fast. I'm heterozygous for the Taq1A form of DRD2/ANKK1, which means my D2 dopamine receptors are less sensitive to dopamine. I'm also heterozygous for two mutations in the MTHFR enzyme: 1298 and 677. This means I'm producing less MTHF than the average person. Personally I had an amazing time on 4 mg MTHF per day, without side effects, but that only lasted a week. After that*

anxiety and brain fog set in. After doing some Googling I found this site —> (http://mthfr.net/methylfolate-side-effects/2012/03/01/) which describes my experience quite well. It seems as if some people do not experience any side effects, some get side effects after a week and some never have any trouble. This can be explained by the fact that MTHF has a methyl group, and therefore increases methylation which in turn can cause anxiety and brain fog. For me this resolved after lowering my dose to 800 micrograms x2 per day, and adding 250 mg time-release niacin (vitamin B3). Niacin is broken down by methylation, and can therefore decrease excessive methylation. :) Sadly, the amazing results I felt the first week wore off, but I'm still doing better than I did before.'):

Area-1255: 'That's interesting, overmethylation tends to produce ahedonia by causing both low histamine and high serotonin (bad combination for nerves as well). In regards to your DRD2/ANKK1 - that is an unfortunate predicament - does it involve only the D2 short allele or the long strand as well? I haven't looked much into that particular gene, but if you have less sensitivity to dopamine at the D2S - you would have more dopamine due to less autoreceptor activity - so I am going to assume based on your symptoms that can't be the case - and that D2L is most certainly cross-interacting with that gene.

In addition, please remember there is a range of complex interactions when speaking about NMDA, for example, low NMDA activity is associated with elevated Zinc status, low serum histamine levels and possibly elevated magnesium as well - in addition to having significantly LESS reuptake of dopamine (leading to more dopamine activity) - ironically people still get ahedonia - but because of different reasons. Some commonly tied to overmethylation - and here is why.

When you are overmethylated, as said, serotonin continues to elevate - so no matter how much your raise dopamine, it is always going to be blunted to an extent --> or placed into the wrong area's, by the wrong receptors. In addition, overmethylation leads to LOW HISTAMINE - which leads to less dopamine being produced. Reason?

Same reason clenbuterol and albuterol BOOST dopamine synthesis - the activation of adenylyl cyclase which leads to TYROSINE HYDROXYLASE activation - which leads to MORE dopamine being produced from Tyrosine - and increased sensitivity (more of a stimulant effect) from protein containing foods. Especially nuts and other foods that contain high amounts of tyrosine.

What this means is overmethylation may cause increased dopamine in the synapse, but that is short-cirtcuited and irrelevant because the enzymes necessary for production of dopamine are Decreased dramatically.

Forskolin and Beta-Agonist usage is a good way to determine if this is your problem. if you respond well or get euphoria off of albuterol, clenbuterol, forskolin or similar cAMP boosting chemicals, then you are most likely OVERMETHYLATED.

If you are undermethylated, you would have the opposite effect, with increased rates of dopamine production, but less utilization and increased uptake.

High Histamine is associated with low serum norepinephrine, dopamine and serotonin… {Undermethylation}

Read my article for more information —> (http://area1255.blogspot.com/2014/08/how-to-tell-if-you-are-low-histamine-or.html?showComment=1408892625677)

Also… one of the symptoms shared by both low NMDA-activity and low histamine - <u>is feeling like people can read your thoughts and a state of constant racing mind.</u>

(http://area1255.blogspot.com/2014/06/signs-and-symptoms-of-low-nmda-receptor.html)
'

(*in response to 'Furniture's reply, 'theres a few anecdotes and a little bit of evidence suggesting that glutathione binds to active b12 and depletes it from the body. You can read about people talking about it here: (http://forums.phoenixrising.me/index.php?threads/b-12-the-hidden-story.142/page-2) This may be a problem for anyone on here taking glutathione, glutathione precursors, and/or glutathione promoting substances. These may be interfering with your methylation and B12 use. I have been successfully boosting glutathione with l-cysteine, l-glutamine, glycine, vitamin c, sustained release alpha lipoic acid, and more. I found that sublingual methyl B12 in a dose of 4mg and oral 5-MTHF gave me that sudden energy. I felt motivated and alive. It came on within 20 mins of the B12. I also have lost my social drive and energy which I think is related to dopamine and this brought it all back. I was 100%. But then I took my morning mix of supps and the effect of B12 was gone. I think the glutathione boosting substances took the B12 right out of me from active use preventing methylation. I'm looking into using B2 and NAD+ to prevent this. beware people*'):

I actually tried protandim, a supplement said to increase glutathione synthesis, a few weeks back, and ended up with extreme fatigue. The fatigue felt exactly the same as when I tried high doses of niacin a year ago, which also decreases methylation.

(*in response to 'Lufega's reply, 'You should have seen some benefit from methylB12 but you said you felt better on hydrxyB12. Any ideas why? I'm homozygote for MTRR A664A rs1802059 AG +/+ and hetero for a few others and I wonder if I should include hydroxy of dibencozide in addition to methyl. Thanks.'*):

<u>It seems like methylation isn't a big problem for me, but low BH4 synthesis is.</u> <u>Methyl B12 can reduce BH4 synthesis further, which is the opposite of what I want. Hydoxocoblamain doesn't affect it at all.</u> The reason I take B12 at all is that I want to avoid 'methyl trapping', which is when methyl folate uses up all the B12 in the cells. The low intracellular B12 will then cause the cells to expel folate.

(*in response to 'Kingsley's reply, 'Very interesting thread. Any updates on your progress, Chadwick? Is your regimen still effective? I relate to many of the symptoms that you described in your original posts and have experimented with methyl donors. I am homozygous for the MTHFR C667T mutation, so by all rights I should benefit greatly from methyl folate and related supplements. In the beginning I had some success, but now methyl folate, methyl b12, and SAM-E all put me into an absolute brainless stupor*

following a brief rush of energy. Each one will do this to me on its own even in the absence of the others. It's funny--all the overmethylation symptoms you read about online relate to overstimulation. You rarely hear about methyl donors causing brain-dead zombie syndrome. I'd kill for some overstimulation! Anyway, due to my genetics it seems that methyl donors really should have a place in my regimen if I can just figure out how to benefit from them. You seem to have found a good balance. How's it going for you? Anyone else having success with methyl donors? Has anyone else experienced insane brain fog on them?'):

My regimen is still going strong, as effective as it was a year ago :) I too get brain fog from most methyl donors (methyl-B12, TMG, SAMe), plus fatigue and a total lack of interest in social situations. This is believe has to do with that I am homozygous for the Val158Met variation of the COMT (Catechol-O-methyl transferase) gene. This variation makes the COMT enzyme more active, and as it uses methyl groups for breaking down dopamine, norepinephrine and epinephrine, an excess of free methyl groups results in too low levels of these neurotransmitters. People with the Val158Met variation of COMT have a tendency towards getting fatigued/brain fogged from methyl donors, while people without the Val158Met variation get stimulated.

This is why I use hydroxy-B12 instead of methyl-B12 - the combination of methylfolate and hydroxy-B12 increases my BH4 and dopamine without changing my methylation very much. This works great for me. The only side effect I have is that my hemoglobin is somewhat high from constantly having high plasma levels of folate and B12, but it's not giving me any real symptoms.

^ I mean the Val variation of the 158 position of the COMT gene (i.e. Val158Met -/-).

(*in response to 'Kingsley's reply, 'Thanks for the quick reply! I am actually met/met for the val158met variation (against all odds), and I still get crazy fatigue and brain fog from methyl donors, though maybe it takes longer for this overload to occur since my COMT enzyme is less active. I've been resetting methylation with niacin/niacinamide the past few days (assuming that's not a myth) and will try adding a low dose of methyl folate back in, along with some non-methyl b12. Any problem with cyanocobalamin in your opinion? Recently I decided to give iron supplements a shot on the off chance I was deficient. I haven't been tested for iron levels and know it's not advisable to mess around with unnecessarily, but I was a bit desperate and figured I'd only continue if I noticed a benefit. Oh man, what a difference in terms of cognition and energy. I believe you said in an earlier post that you noticed a similar benefit from iron. Anyway, between the iron and cutting way back on my methyl donors, I believe I am seeing a light at the end of the tunnel. I won't bore you with a list of my symptoms right now but suffice to say they are very similar to the ones you reported in your previous posts, though with perhaps more of a cognitive deficit. Intriguing progress in the last few days though. We'll see if it continues, but your posts have given me a lot of hope, and I thank you for that!'*):

The problem with cyano-B12 is that it can only be absorbed in the gut, which reduces the absorption rate to 1%. Hydroxo and methyl-B12 can be absorbed

sublingually which gives it an absorption rate of approximately 20%. It is, in other words, difficult to get enough cyano-B12 into your body without injecting it intravenously.

Iron can make a large difference for your well-being, but beware - if the effects are immediate (within an hour or two) it may have to do with the effects of free radicals (breaking down the instable enzyme methionine synthase, rerouting methylfolate towards BH4 production and thereby increasing dopamine) rather than increasing iron stores in the body.

I'm curious though - have you noticed any observable signs or other symptoms in addition to your cognitive symptoms, like skin changes, infections, itching or such? It would be interesting to see a summary of all the symptoms you are experiencing :)

'Kingsley': 'As to my symptoms, I have a diagnosis of ADHD-PI, though the emerging concept of Sluggish Cognitive Tempo (SCT) is probably more applicable. It is nothing recent--I've had lifelong issues with attention, focus, working memory, mental fatigue, sluggish processing, malaise, amotivation, asociality, etc. It runs in my family, too, so seems as genuine a case of ADHD-PI/SCT as you could find.

I am now interested in the idea that I may have had life-long low or borderline low iron, maybe a genetic predisposition to such, though I'm not going to assume anything. In some ways it would make sense: I've always had extra pale skin, fatigue easily, out of breath easily, etc. I remember distinctly having a lot less stamina than my friends as a child. In more recent years I have also noticed a tendency to bruise, and there are times when physical activity causes me to feel dizzy or generally unwell. These things seem in line with some of the iron deficiency symptoms I've read about. And, there are at least a couple of studies showing a strong association between ADHD and low iron status.

When I began iron supplementation, the effects were quite rapid. I feel more energetic, less fatigued, though time will tell on that. Also, my coloring appears affected. My hands for example seem to have a deeper and more reddish hue than normal.

I'm skeptical, and am prepared to be disappointed. It wouldn't be the first time. However, it is an interesting turn of events, worth exploring.

Your comment about the potential effect of free radicals is interesting. What are the signs that this would be the case? Is it at least feasible that my life-long issues could be related, at least in part, to iron status?'

Interesting. Is there something that can reduce or remove your symptoms temporarily, like supplements or exercise? Have you tried any medication, like Ritalin?

Iron deficiency can cause ADD/SCT-like symptoms, and it can make existing ADD/ADHD/SCT worse. If you want to be sure if iron or other deficiencies plays a part in your symptoms, get a doctor to do some blood tests on you (including at least hemoglobin, iron, ferritin, B12, folate, TSH, calcium).

The noticeable effects from treating an iron deficiency comes over days or weeks, while the energizing effects from free radicals can (in my experience)

come in an hour or so, lasting a few hours before crashing down into fatigue again. I read about this last summer but can unfortunately not remember the source.

EDIT: It is feasible that your symptoms are iron-related, but it is important to remember that life-long symptoms are usually not products of a nutritional deficiency. It's more likely caused by genetics. This said, as mentioned above, an existing condition can become worse if your iron levels are low.

'Kingsley': '**I'm paraphrasing, but Chadwick's situation is essentially a success story about treating issues with mood, energy, and social drive with supplements targeting the methylation cycle, i.e. methylfolate and hydroxocobalamin, with remarkably long-term success. I think that one of Chadwick's key insights is the importance of not overdoing the methyl donors. That is, he takes low dose methylfolate and zero methyl b12, after having observed that too much of either causes their benefits to diminish.**

This runs directly counter to so much of what you read on the internet about methylation support, which often recommends fanatic levels of methylfolate and methyl B12. There are forums where people suffering from various health and cognitive issues are convinced that huge doses of methyl folate and methyl b12 are the solution to their problems, yet you hardly ever hear of anyone having long-term success. It is often the same story: exciting results in the beginning that are eventually lost. And somehow they always think the solution is MOAR METHYLFOLATE/METHYL B12.

This was exactly the case for me, but like Chadwick, **I am now getting much more consistent results by vastly reducing my methyl donor intake. Despite having the homozygous C677T mutation greatly reducing my ability to metabolize folate into methylfolate, I find that significant doses of methylfolate just end up putting me into a stupor and making me feel worse. The best approach for me so far has been high-dose non-methyl b12 (cyano or hydroxo), low dose methylfolate or moderate folic acid, along with a balance of the other b vitamins and other vitamins and minerals.**

Chadwick's position is, I believe, that the problem with high dose methyl donors is that they route folate away from BH4 production at the expense of dopamine production and/or they overdrive the COMT enzyme, causing the breakdown of too much dopamine. Another possibility, which I suspect is the case for me and which I think Chadwick talks about, is that too much methylfolate ends up using up the available b12 causing the so-called 'methyl trap,' paradoxically causing folate to be expelled from cells and mimicking a deficiency or at very least losing the benefits. My understanding is that b12 from most supplements is only absorbed in very small amounts, compared to folate which is much better absorbed, so it would not be surprising if b12 supplementation simply can't keep up with the methylfolate supplements for some people. It's a bit confusing because methyl donors are apparently involved both in production and breakdown of neurotransmitters.

In summary, I don't have much to add except to suggest that, if you do try a methyl donor supplement, keep in mind that less is more and don't over-supplement. And please let us know your results.'

(*in response to 'Apprentice_Bob's reply, 'Would one of the posters who has found success through playing with methyl donors and B vitamins post explicitly the supplements they have turned to? I was doing really well using a B-Complex and fish oil, better than my whole use history of exotic and promising nootropics, and then went on a bender for three days. Since then, I've had brain fog. I've switched over to an Activated B complex, by Swanson, and I cannot say that I feel at the level that I felt I was at before the bender. I'm also curious to see whether those who have experienced the hangropic effect also have positive nootropic experience with Phenibut.'*):

'Kingsley': 'My take on this is constantly evolving, but I am in a very good spot right now in terms of managing my cognitive complaints. Currently I am doing well taking one or two 800 mcg Solgar methylfolate tablets per day, along with a lot of b-12 as 2mg cyanocobalamin and 2mg methyl-b12.

In previous posts I speculated on the need to keep methylfolate/methylb12 doses low, and described how too much of either makes me feel stupid and sick. This appears to mirror Chadwick's experience. It never made much logical sense to me since, in my case, I am homozygous for the C677T MTHFR mutation which indicates a critical need for methylfolate and/or methyl-b12.

I had read a lot of speculation and anecdotal accounts on other forums that methyl donors can increase the need for potassium, a shortage of which can cause issues with fatigue, mood, etc. After having a bit of success with adding a few potassium tabs and a banana here and there, I decided to go all out. After all, the daily recommended dose of potassium for adults is about 3.5 grams, and many of us fall woefully short of this. So, I began purchasing V-8 Low Sodium, which contains 900 mg of potassium per serving, and drinking probably 3-5 servings per day with some 99mg potassium tabs thrown into the mix. BINGO. I no longer have ANY mal-effects from methylfolate or methyl-b12, no matter how much I take. Not to mention I am feeling healthier all around and I'm pretty sure my blood pressure has come down. Bottom line: if you are among those who react negatively to methyl donors, try upping your potassium intake significantly.

I have had another breakthrough as well by adding calcium supplements. In another post on this or another thread, I commented that I was having great success from magnesium. I was actually taking calcium/magnesium pills and just assumed the effect was from the magnesium. However, after switching to just straight magnesium for a while I found that the benefit was subsiding. I just recently added calcium back in and the cognitive gains are staggering. This makes some sense considering that I speculate that my issues are related to the glutamate-receptors and calcium-signaling, though why such a dramatic effect I am not sure. Don't know if I was deficient or what was going on.

For the first time in a long time I feel like a fully functioning human being, and am praying that these gains hold. My current regimen looks like:

Methylfolate: 1 or 2 800 mcg Solgar tablets per day. I often break tablets in twos or fours and spread my dosage throughout the day.

Cyanocobalamin: 2mg per day spread out. For some reason I seem to benefit from cyanocobalamin no matter how much methyl-b12 I take. I suspect that you need

some non-methyl B12 (either cyano or hydroxo) for the methylfolate to really do its job, since methyl-b12 already has its methyl group and doesn't need methylfolate)

Methyl-b12: 2 1mg Jarrow sublingual tabs per day.

Potassium: Hard to get enough through diet, and potassium pills are limited by law to 99mg since potassium can be dangerous to some subset of the population with certain conditions. So, I chug V-8 Low Sodium like there's no tomorrow (900mg potassium per serving).

Calcium: 1 gram+ throughout the day. Should be balanced with magnesium at 2:1 ratio.

NAC: Jarrow 500mg 2-3 times per day.

Sarcosine: about 4 grams per day. (I have noticed acute benefits from it though not sure if such benefit is consistent. May try going without it).

Tyrosine & 5-HTP: I take as needed for a boost to mood and cognition. I try to maintain a 10 to 1 balance as is typically recommended: Some days I take non, some days up to 3000mg tyrosine/300mg 5-HTP. Less needed with my recent gains from methyls, potassium and calcium.

Other key vitamins/minerals: All other B-Vitamins, Magnesium, Iodine, etc. A good multivitamin will do.

So, that is where I am at right now, subject to further tweaking. Would be curious to hear if anyone else makes any consistent gains.'

(*in response to '.Moose's reply, 'Kingsley, do you notice the effects of a single dose? I've tried a couple of methyl donors and comprehensive methyl factor and see no effects - negative or positive - at all. Being only hetero C677T, I'm sure I don't need too much. I don't understand why others do so well on it, even though I share the original symptoms Chadwick listed as well as the reaction to alcohol.'*):

'Kingsley': 'I do notice acute effects from single doses of methylfolate and methyl-b12, even cyano-b12. However, the acute effects are becoming less and less aparent over time while the overall benefits remain. Your experience is probably the most common. I suspect that you have to have some level of deficiency to feel a strong acute effect from a vitamin or mineral. Though the methyls are particularly strong for vitamin supplements and many seem to feel them.

Same with calcium--strong acute effects at first but less so over time. I am almost certain I had a least a border-line calcium deficiency. I have had almost no dairy in my diet for a while, and was experiencing some muscle spasms in my hands and calves that resolved upon adding calcium, along with the strong cognitive benefit I described in a previous post, which, knock-on-wood, appears to be holding.

Again, if your levels of b-vitamins or calcium are already solid, I wouldn't expect any kind of acute reaction, and I have no doubt that my experience is idiosynchratic. The idea of feeling each dose of calcium as if it's a nootropic seems so silly, and yet it's what I have experienced. The next step for me is to figure out why I seem to be prone to vitamin and mineral deficiencies. I suspect poor absorption potentially due to digestive issues/inflammation.'

I've been away for the last seven weeks so I haven't replied to any posts in this thread or PMs, sorry for this. **Regarding potassium I agree that it might be a problem for people using high doses of *methyl B12* in combination with methylfolate. People doing this should pay attention to symptoms such as cramps or muscle spasms. This should not be a problem if you use hydroxocobalamin.** The methylation experts over at http://forums.phoenixrising.me/ know much more about this.

The reason why American potassium supplements are limited to 99 mg is that too much potassium in the same place in the GI tract can cause local damage to the mucosa. This is avoided by taking several small pills (<100 mg) instead of a single larger one.

_____ I thought I should give you an update as I've progressed somewhat more in all of this. Methylfolate and hydroxocobalamin has helped me a lot over the years but somehow I've still felt that I've only been able to get rid of my symtoms by 85% or so, and I've been longing to get to 100%. The protocol I've described before (200 mcg methylfolate 3 times a day and only small amounts of hydroxocobalamin) helps with dopamine is seems but it also increases methylation, which breaks down dopamine. The net effect is noticeable and good but not really perfect.

Two and a half weeks ago I stopped using both of these supplements and switched to pure BH4/tetrahydrobiopterin/sapropterin (three words for the same thing) instead. BH4 is what the methylfolate protocol aims to increase and getting that without the methylation should in theory be even more effective for increasing dopamine.

I use 0,5 mg of BH4 twice a day, which is a much much lower dose than what is used in Kuvan which the pharmaceutical version of the substance. Kuvan is used for treating some versions of the disease phenylketonuria and the doses used then are not really applicable for me. 0,5 mg has a pronounced effect which sets in about 30 minutes after oral consumption and it lasts for about 8 hours, hence the two doses a day. Higher doses than that can give me headaches.

BH4 is a whole new game for me and so far I can say it's easily the best supplement I've ever used. All the symptoms I described in the first post of this thread are 100% gone now. I could use very big words to describe it but I think you get the point.

There are a few ways to get BH4. It's sold as a supplement called Pteridin-4 from Ecological Formulas, which I use, but it seems like it's out of stock often and for long periods. It can also be purchased from several suppliers in China at Alibaba. If you try that, then the form of BH4 you want is 6R-5,6,7,8-tetrahydro-L-biopterin (cas no 69056-38-8)."

~> atlas_benched (reddit):

“Alcohol Afterglow Theory: NMDA, BH4, Methylation, ON/ONOO-cycle

Update (5/31/2018): <u>Boosting Nitric oxide through supplementation has proved extremely beneficial for myself and has been beneficial for others as well. For anyone whos struggling with this issue I highly recommending starting there, as it could allow many of the other solutions found in this post, and even more so in the comments, to be beneficial whereas before they might have not worked or have been counterproductive.</u> I suggest buying the NO test strips since it wasn't until I tested as having optimal NO on the strips that I received a constant, sustained benefit. Frequent smaller doses of NO boosting supplements may be better than larger, more infrequent doses, as I often felt worse after taking my NO boosting stack. Improvement was not linear, the majority of benefit was received upon reaching optimal levels and until that time did not feel like it was going to work. Just to be clear this is most likely not a complete or final solution for the overwhelming majority of people, but it could be a crucial part for many. BH4 is most likely a superior or possibly a far superior solution to NO boosting supplements but has not been tested to the extent that NO/BH4 boosting supplements have.

A simpler, more concise post with more recent information will be made in the future. That post will most likely include information and anecdotal experiences of supplemental BH4, suggestions how to test if you experience afterglows, a more concise presentation of theories and suggestions on supplementation.

<u>Sarcosine + NAC has not worked for everyone (who gets afterglows), with some reports of it having very negative effects.</u> I personally have not given the solution a fair shot, but I did experience some temporary benefits from high dosing which lasted about 24hrs and then dissipated in the span of about 20 minutes. Despite this, I don’t think sarcosine + NAC is the complete solution for me, and I do not think it is the complete solution for many others either.

Here’s my theory. I think that the people who experience afterglows but do not benefit much from sarcosine are most likely experiencing one of these problems confounding problems which prevent it from working or from working completely.

———

<u>Theory summary:</u>

<u>My theory is that our subjective problems primarily are a result of NMDA hypofunction.</u> This could be an independent problem, or, as I assume is the case for many of us, it could be caused by or compounded by the more important core problem of low BH4 or a new possibility I have come up with is low levels of folate in the brain, which probably has many similarities to low BH4. Something else that I am considering, at least in my case, is that overmethylation could also be a secondary problem. An additional possibility is that too many MAO’s is also a problem.

NOTE: Low levels of folate in the brain is a new possibility, so I don't refer to it in most of this post, but just assume that when I say 'low BH4' there is a possibility I am referring to low brain levels of folate as well. I haven't looked into it much yet but I there's a link to an article talking about it that links to a study at the end.

I think they all need to be treated as separate problems. I also think that either low BH4/folate or overmethylation could prevent solving the NMDA issue, so they should be solved first before attempting to fix NMDA. The reason for this is that low BH4 causes hypofunction of DA, NE, SE and glutamate. It is possible that either low BH4/folate or overmethylation are just compounding things and it is most likely the too many MAO's would just compound things but not prevent progress in other areas.

Alcohol, specifically red wine, fixes all these problems.

- Increased NMDA activation
- Glutamate rebound
- Increased BH4
- Decreased methylation and increased histamine (under normal circumstances)
- Uses up MAO's so there is less of them

So, to get the benefits of alcohol on a daily basis, we must recreate whichever of the above mechanisms are helping a given individual, since it is possible that not fixing all of them could prevent the other mechanisms from working.

I don't think that every person has every problem, and there could be problems that other people have that I or others do not. Hopefully from this people can see which problems they have and if we get some discussion going maybe we can find similar problems that others are having which are not listed here.

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Suspected root causes of symptoms which are cured during hangover afterglows (in order of mostly likely to be a problem):

- Hypofunctioning of the NMDA receptor/Glutamate system
- Brain Inflammation
- Low BH4: possibly causing above problems, in the case of inflammation a vicious cycle.
- Overmethylation (histamine deficiency)
- Too many MAO's

Low BH4 and inflammation are a vicious cycle (**dysfunctional ON/ONOO-cycle**). **Low BH4 also causes hypofunction of NMDA and glutamate. However, I think that even if you solve BH4 it will not fix hypofunctioning of the**

NMDA receptor completely, and therefore it will have to be treated as a separate problem as well. Besides those things I believe each problem is independent of others, which part of the reason why it is so difficult to fix and why sarcosine + NAC may not work for everyone.

That being said, there may be other problems that alcohol fixes, that I don't have but that others do. Look into these suggestions first, and if these don't explain your symptoms/experiences then investigate other avenues. I suggest seeing what is going on during a hangover and then taking something that does that same thing to see if it helps. At the same time don't forget there could be synergy, so you may have to activate two or more different pathways at the same time to get the results you are looking for. It's complicated.

———

Resulting effects of root causes:

A lot of this is speculative or based of my experience. Some of the stuff that has scientific backing will be in the support section below, this is just to try to help people identify where their problems are stemming from. I'm sure there is a lot missing, but I'm just trying to present the most important things and the stuff that stands out the most.

1) Hypofunctioning of NMDA/Glutamate system:

- Negative & cognitive symptoms of schizophrenia
- Feelings of not having access to parts of your brain
- Holes in memory, especially working and short-term memory
- Inability to learn
- Depersonalization
- Problems with language, especially written language
- Problems with executive function
- Socially withdrawn
- Poverty of speech and thought
- Apathy/Anhedonia
- Insomnia
- Fatigue
- Low testosterone
- ADHD
- Possibly tremors and shaking, related to glycine

2) Low BH4/Brain Folate/Brain inflammation (probably separate effects but I'm including them together):

- Difficulty waking and feeling like you were in NREM sleep stages
- Chronic fatigue and lethargy
- Lack of motivation
- Brain fog, mental fatigue
- Hypofunction of neuro transmitters and glutamate system

- Low BH4 causes low dopamine, norepinephrine, serotonin.
- BH4 both directly and indirectly modulates the glutamate system
- Mitochondrial dysfunction (lowered energy charge, ATP)
- Hypofunctioning of NMDA
- Inflammation causes low BH4
- Hypofunction of NOS/NO
- Peroxynitrite elevation: from brain inflammation, causes low BH4
- Problems with executive function
- Tremors/rapid shaking
- High blood pressure, especially during exercise
- ADHD

3) Overmethylation

- Histapenia (low histamine)
- Too much empathy
- Negative reaction to methyl donors
- Anxiety
- Paranoia
- Depression
- Insomnia
- Hyperactivity

4) Too many MAO's

- Low dopamine, norepinephrine and serotonin
- Major depression disorder

Related Theories and Notes:

- I believe that the daily state of afterglowers is less severe but otherwise extremely similar or identical to the negative state that some people can induce by using dissociative multiple times in a short time span.

Experiments/Things to Try:

The only thing that matters is real world results. Almost all of the conclusions I came to have been a result of real world experience and only after I found the studies to back it up. I think it is much more efficient this way, since every time you think you got something related to neurochemistry figured out it turns out it's the opposite.

To test for alcohol afterglows:

- Drink a decent amount of vodka, see how you feel the next day
- Drink a decent amount of red wine, see how you feel the next day
- Some people get afterglows from one but not the other and it goes both ways. I seem to only get afterglows from red wine while others feel awful after drinking red wine but get great afterglows after drinking vodka or some other alcohol. I

think that these two cover it, but there could be differences in other kinds of alcohol as well. If you get afterglows from red wine but not vodka, then you might want to look into overmethylation and MAO's.

To test for DXM afterglows:

- Try taking DXM before bed, see how you feel the next day
- It doesn't have to be a full tripping dose, I have gotten subtle afterglows from 30mgs, but higher doses work best
- Don't do this more than once, I believe that people who get afterglows are strongly susceptible to getting long term, negative effects from frequent dissociative use

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Possible Solutions:

1) NMDA:

- Sarcosine + NAC
- This should be a long term fix
- Tianeptine
- Might be a long term fix
- Racetams
- Short term fix unless fixing BH4 allows it to be a long term fix

2) BH4:

- Supplements and Increased Nitric Oxide production (I doubt this will be adequate)
- Supplement BH4
- Selegiline
- A round about way, increases Nitric oxide and dopamine

3) Overmethylation:

- Niacin

4) Too many MAO's:

- Micro dosing Syrian Rue (risky, can't be combined with many things)

Support for NMDA/Glutamate:

Studies:

NMDA receptors role in Schizophrenia: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5518924/

- "This review describes the structure-function relationship of the NMDAR channel and how the glycine modulatory site (GMS) acts as an important regulator of its activity. In addition, this review highlights the genetic, pharmacologic, and biochemical evidence supporting the hypothesis that NMDAR hypofunction contributes to the pathophysiology of schizophrenia."

- "It has been long known that the dissociative anesthetics and NMDAR antagonists, PCP and ketamine, produce the full range of schizophrenia symptoms and cognitive deficits in healthy subjects (Javitt & Zukin, 1991; Krystal et al., 1994), while ketamine exacerbates symptoms in stabilized schizophrenia patients (Lahti, Weiler, Tamara Michaelidis, Parwani, & Tamminga, 2001)."

- Summary: NMDA plays a role in schizophrenia and NMDA antagonists replicate the symptoms of schizophrenia in healthy subjects and exacerbates them in healthy individuals.

Sarcosine heals NMDA Damage from Schizophrenia: https://www.ncbi.nlm.nih.gov/pubmed/26306650

- "This is the first study showing that a pharmacological intervention in schizophrenia, particularly augmentation of the antypsychotic treatment with sarcosine, may reverse the pathological increase in glutamatergic transmission in the hippocampus. The results confirm involvement of glutamatergic system in the pathogenesis of schizophrenia and demonstrate beneficial effects of GlyT-1 inhibitor on the metabolism in the hippocampus and symptoms of schizophrenia."

- Summary: Sarcosine heals damage done to the NMDA receptor as a result of schizophrenia.

I'm pretty sure NMDA messes with DAT in a bad way. If anyone could suggest a study I'm having trouble finding one right now.

Experiences:

- Several people who experience afterglows have benefited from supplementing sarcosine and NAC.

- I have experienced an afterglow from a DXM trip that was a cleaner, possibly better afterglow than that experienced from red wine. Similarly, I experienced the opposite, negative effects from tripping on DXM 3 times in a row, which had long lasting negative effects on my cognition and mental state. I had a less intense but otherwise identical experience from high dose NAC and beer. I think our normal state is a less extreme version of what some people, such as myself, can experience from frequent, high dose DXM use. I have spoken with others who have experienced the same thing. After comparing my symptoms with the symptoms of those who are

experiencing long lasting negative effects from dissociative use I find that they are extremely similar.

- Small amount of red wine + Sarcosine had a dramatic effect and I thought I was fixed but it burned out on me less than 2 days. Had a bit of a stimmy feel to it.
- Large doses of Piracetam and Aniracetam before bed drastically improved my cognition (and apathy, motivation, self-confidence, depression, depersonalization, etc.…) the next day and the morning of the day after that as well, and then burned out on me like the sarcosine. While it lasted it felt more complete and natural than the sarcosine did.
- Tianeptine, Longvida Curcumin, Biotredin, magnesium and Galantamine I have all responded well to and all have effects on NMDA.

Support for Low BH4, Dysfunctional ON/ONOO-cycle:

BH4 and Schizophrenia: https://www.karger.com/Article/Pdf/89002

- "BH4, Neurotransmitter and NMDA: “Tetrahydrobiopterin (BH4) is a vital cofactor maintaining availability of the amine neurotransmitters [dopamine (DA), noradrenaline (NA), and serotonin (5-HT)], regulating the synthesis of nitric oxide (NO) by nitric oxide synthase (NOS), and stimulating and modulating the glutamatergic system (directly and indirectly).”

- “A deficiency of BH4 could lead to hypofunction of the systems of DA, NA, 5-HT, NOS/NO, and glutamate, all of which have been independently implicated in schizophrenia psychopathology. Further, evidence has been accumulating which implicates the critical interdependence of these neurotransmitter systems in schizophrenia; this concept, along with the present study finding of a biopterin deficit, suggests that further study of the BH4 system in schizophrenia is warranted and desirable.”

- Summary: Low BH4 causes hypofunction of DA, NE, SE and glutamate. It is linked to Schizophrenia and might be part of the cause of it.

Low BH4 Causing Damage to NMDA Receptor: https://www.sciencedirect.com/science/article/pii/S0197018601000146

- “Our data support the hypothesis that functional activity and number of NMDA receptors are regulated by strength of the glutamatergic input. Thus, reduced glutamate uptake resulting in increased concentration of ambient glutamate initiate a series of adaptive responses manifested as a gradual down-regulation of the functional activity and expression of NMDA receptors.”

The link between Nitric Oxide and BH4:

- "BH4 is crucial for manufacturing Dopamine, as well as NO. If BH4 is low there can be a break in the NO/OONO-cycle (think NO and its arch enemy peroxynitrite, a NO scavenger) which causes a vicious cycle of inflammation, more peroxynitrite, less BH4, more inflammation, more peroxynitrite, less BH4 and on and on… By raising NO you can reduce inflammation and peroxynitrite and thus indirectly raise BH4."

Negative effects of dysfunctional NO/ONOO-cycle: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3856065/

- "Here is a study discussing the NO/ONOO-cycle and what it involves: NF-κB, inflammatory cytokines, iNOS, nitric oxide (NO), superoxide, mitochondrial dysfunction (lowered energy charge, ATP), NMDA activity, intracellular Ca2+, TRP receptors and tetrahydrobiopterin (BH4) depletion."

Nitric Oxide and dopamine receptors: https://www.ncbi.nlm.nih.gov/pubmed/22034069, https://www.ncbi.nlm.nih.gov/pubmed/19816675

- “Apparently, NO has a negative effect on D2, and a positive effect on D1.”

- Note: This help explains some of the ADHD symptoms that are experienced, and part of the reason my thinking is somewhat psychotic.

Selegiline massively increases Nitric Oxide: https://www.ncbi.nlm.nih.gov/pubmed/10867219, https://www.ncbi.nlm.nih.gov/pubmed/9721939

- Note: This in part explains many of its beneficial effects on ADHD, Depression, Alheimerz's, etc

Info on NO/ONOO-cycle and how it relates to diseases such as chronic fatigue: http://www.townsendletter.com/FebMarch2010/cureNO0210.html

Folinic Acid for BH4/Neurotransmitter production: http://wesa.fm/post/experimental-new-therapy-shows-promise-treating-severe-depression

- Check out the study at the end of the article. Basically folinic acid should work if it is a deficiency of folate in the brain.

- Discusses Low BH4 as a treatment of treatment resistant depression.

Experiences:

Alpha-2 Agonists: Alpha-2 agonists have been beneficial for myself and others with this issue. They decrease norepinephrine at the site where it competitively binds with BH4. My experience with Alpha-2 agonists is that they decrease my blood pressure during exercise but not when resting, which is consistent with the effects of supplementing BH4.

Red wine & BH4: My experience during my first red wine afterglow, which lasted about five days, had many similarities with the experiences people have reported from taking BH4.

Red wine, blood flow: Drinking red wine massively improves my blood flow the following morning.

Exercise: Exercise increases BH4. Exercise can clear my mind for a few hours after.

Support for Overmethylation/Methylation Problems:

Methylation, schizophrenia and ADHD:

- I think I am an overmethylator: hypofunction of NMDA part of schizo, half of schizos are overmethylators when only 8% of pop. are overmethylators, I identify with many traits of overmethylators, overmethylators have higher chance of ADHD. In clinical studies, about 45% of persons diagnosed with schizophrenia were found to be severely overmethylated.

Possibly why only red wine works for me:

- Red wine is extremely high in histamine, over methylation is a histamine deficiency (Histapenia). Explains why only red wine, not cheap beer, works.

I respond poorly to methyl donors and I seemed to respond poorly to 5-MTHF.

Support for Too Many MAO's:

Red wine: Red wine uses up MAO's so there is less of them.

Experience: I have responded well to Curcumin."

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~> Area-1255 (area-1255.forumotion.info):

“**Mechanism would probably be blockade-induced Upregulation of NMDA-receptors.**

You can try DAA + Sarcosine + Pregnenolone + 1 teaspoon of Cinnamon per day.

That should do the trick.

Pregnenolone Sulfate Restores the Glutamate-Nitric-Oxide-cGMP Pathway —> (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3930995/)

Up-regulation of neurotrophic factors by cinnamon and its metabolite sodium benzoate —> (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3930995/)

Sodium benzoate (Cinnamon) trialed for Schizophrenia (Adult-onset Autism) —> (https://epiphanyasd.blogspot.com/2014/12/sodium-benzoate-cinnamon-trialed-for.html)
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