

# The Surprising Health Benefits of Methylene Blue

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## STORY AT-A-GLANCE

- › Methylene blue helps mitochondrial respiration and improves brain energy metabolism. By doing that, it can improve cognitive performance and prevent neurodegeneration
- › Methylene blue is the parent molecule for hydroxychloroquine and chloroquine, off-patent drugs commonly used to treat not only malaria but also COVID-19
- › Emergency rooms around the world use it, as it's the only known antidote for metabolic poisons causing methemoglobinemia, which is when a metabolic poison interferes with the transport of oxygen in hemoglobin
- › Methylene blue is a hormetic drug, so low doses have the opposite effect of high doses
- › Low doses, 0.5 mg to 1 mg per kilo of bodyweight, are recommended for nonacute, longer-term treatments. Uses include the prevention and treatment of dementia, post-stroke and other brain injuries, cognitive enhancement, and the general optimization of health if you're already healthy

In this interview, Francisco Gonzalez-Lima, Ph.D., discusses a really powerful strategy to improve your mitochondria, which generate the vast majority of the energy your cells produce from food.

Gonzalez-Lima is an expert on methylene blue, which helps mitochondrial respiration and improves brain energy metabolism. By doing that, it can improve cognitive performance and prevent neurodegeneration.

*“With methylene blue, we have been able to show all of those [benefits],” Gonzalez-Lima says. “Our group was the first to map the effects of methylene blue in the brain of humans and show its effects on improving brain metabolism, blood flow and memory function.”*

## **What Is Methylene Blue?**

Methylene blue is the parent molecule for hydroxychloroquine and chloroquine, off-patent drugs commonly used to treat not only malaria but also COVID-19. Best known as a fish tank antiseptic and textile dye for blue jeans, it was actually the first synthetic drug in modern history, developed in 1876. Since then, we’ve discovered it has many really important medicinal benefits.

The first medical application of methylene blue was for malaria. In 1890, Paul Ehrlich, a scientist at the famous Charité Hospital in Berlin, Germany, discovered methylene blue inhibits an enzyme that weakens the malaria parasite.

One of the first antipsychotic medications was also made from methylene blue. Other drugs developed from or with it include antibiotics and antiseptics. In the past, it was commonly used to treat urinary tract infections. It’s also been used as an antiviral agent in blood used for transfusions.

To this day, methylene blue is found in every hospital in the world, as it’s the only known antidote for metabolic poisons (any poison that interferes with oxygen transport or displaces oxygen, either from the blood or from the mitochondria).

For example, if you’re admitted for carbon monoxide poisoning, they’ll give you methylene blue intravenously. Cyanide is another example. The only known antidote for cyanide poisoning is methylene blue. It’s also been speculated that methylene blue might be useful in the treatment of acute lung infections such as SARS-CoV-2.

Importantly, methylene blue is a hormetic drug, which means that low doses have the opposite effect as high doses. For example, it’s primarily used in emergency rooms at the upper dosage limit (3 milligrams to 4 mg per kilo of bodyweight) for

methemoglobinemia, which is when a metabolic poison interferes with the transport of oxygen in hemoglobin, by the iron in hemoglobin being oxidized to +3 rather than its normal reduced +2 state.

However, if you take too high a dose, you produce methemoglobinemia. At dosages in between, there's no effect. Likewise, while low dosages have an antioxidant effect, high doses are pro-oxidative and can kill bacteria and tumor cells.

## **Methylene Blue, an Antioxidant and Energy Producer**

Gonzalez-Lima's research has primarily focused on low-dose benefits for nonacute purposes over the longer term — such as neuroprotective benefits and cognitive enhancement. While it has several mechanisms of action, a unique feature is that it acts on the level of electrons. He explains:

*“Our body uses electrons as part of the electron transport chain that happens inside mitochondria, and these electrons, moved along through the mitochondria, are generated from electron donors that we produce by the foods that we eat.*

*All the foods that we eat, the only way they contribute to energy is by producing electron donors. They donate these electrons to the electron transport inside the mitochondria. The ultimate electron acceptor in nature is oxygen. That's why the process of removing electrons from a compound is referred to as oxidation.*

*In mitochondria, this process is called oxidative phosphorylation. The electron transport is coupled with the phosphorylation of adenosine to eventually produce the adenosine triphosphate molecule (ATP). Methylene blue is an electron cyler. It's an autooxidizing compound.*

*So, methylene blue donates its electrons directly to the electron transport chain, it obtains electrons from surrounding compounds, and maintains oxygen*

*consumption and energy production. By doing this, it helps oxygen to be fully reduced into water.*

*So, it becomes two things that are often not found together. It acts as an antioxidant, because oxygen is neutralized into water by donating electrons to the electron transport, and it produces energy, because when the electron transport pumps are moving along oxidative phosphorylation, you have an increase in ATP formation.*

*Oftentimes, we have things that improve energy metabolism, but then they lead to oxidative stress. In the case of methylene blue, that's not the case.*

*You can increase oxygen consumption rates, increase ATP production for energy metabolism, and at the same time reduce oxidative stress which, of course, will lead to reduction in oxidative damage at the level of mitochondria, then at the level of the other parts of the cells, and eventually membranes of the cells, and reactions that are cascades of this oxidative damage.”*

Basically, as an electron cyler, methylene blue acts like a battery, but unlike other compounds that do the same thing, it doesn't cause damaging oxidation in the process. If anything interferes with oxygenation or cellular respiration, such as cyanide, methylene blue is able to bypass that point of interference through electron cycling, thus allowing mitochondrial respiration, oxygen consumption and energy production to function as it normally would.

## **Improved Mitochondrial Respiration Improves Health, Cognition**

Methylene blue can also be helpful in instances where you have impaired blood flow that prevents the delivery of oxygenated hemoglobin to the tissues. In this case, methylene blue helps counteract the reduced blood flow by optimizing the efficiency of mitochondrial respiration.

Healthy blood flow is particularly important for brain function, and many older people have chronic hypoperfusion that contributes to neurodegeneration and memory

problems. These issues, Gonzalez-Lima says, can be prevented by methylene blue.

In summary, inside the electron transport chain in your mitochondria are five complexes, the primary purpose of which is to conduct the electrons generated from food, primarily carbohydrates and fat, in the form of acetyl CoA. Sometimes the electron transport chain gets blocked or impaired, and methylene blue is able to bypass such blockages.

**“ When you’re perfectly healthy, low doses of methylene blue will enhance oxygen consumption, mitochondrial respiration and ATP production above baseline, basically optimizing the whole system. So, it acts as a metabolic enhancer and not just an antidote for metabolic poisons and other inhibitory processes.”**

The most important complex, Cytochrome c Oxidase, which catalyzes the reaction of oxygen becoming water, is blocked by cyanide. But methylene blue can insert electrons wherever there is a blockage.

What’s more, when you’re perfectly healthy, low doses of methylene blue will enhance oxygen consumption, mitochondrial respiration and ATP production above baseline, basically optimizing the whole system. So, it acts as a metabolic enhancer and not just an antidote for metabolic poisons and other inhibitory processes.

Methylene blue’s action on mitochondrial respiration is also coupled with biochemical upregulation of your oxygen consumption machinery in general, and hemodynamic processes that increase local blood supply to tissues.

And, as detailed by Gonzalez-Lima in the interview, this upregulation remains even after the methylene blue is expelled from your system (primarily through urination unchanged as your body minimally metabolizes it), and over time, it can actually increase the

number of mitochondria. In your brain, this will benefit cognition, as your brain is the most energy-dependent organ in your body.

Methylene blue also activates the Nrf2 pathway. Nrf2 is a transcription factor that, when activated, goes into the cell's nucleus and binds to the antioxidant response element (AREs) in the DNA. It then induces the transcription of further cytoprotective enzymes such as glutathione, superoxide dismutase catalase, glutathione peroxidase, phase II enzymes, heme-1 oxygenase and many others.

## **Methylene Blue for Brain Health**

Perhaps one of the most revolutionary benefits of methylene blue is for the prevention and treatment of dementia, neurodegenerative diseases such as Alzheimer's and Parkinson's, and neural injuries caused by stroke and traumatic brain injuries (TBIs). This is particularly important as the COVID jabs have radically increased strokes. As explained by Gonzalez-Lima:

*"Any process where increasing oxygen-based energy production plays a major role, methylene blue will have a role to play. One of the first studies we did that was very impressive [was on] a model in the eye. The reason we used the eye was because the retina in animals is readily accessible so that we can inject into the retina.*

*Rotenone [a broad-spectrum pesticide and Complex 1 inhibitor] inhibits mitochondrial respiration, subsequently there is atrophy and degeneration of the retinal layer, which is very dramatic. If methylene blue is on board, we can prevent this process because the mitochondrial respiration can continue, so the tissue is not affected.*

*This was a model called an optic neuropathy due to mitochondrial defects. It's the most common form of blindness in younger people, so we did this to verify in vivo that [methylene blue] could have this neuroprotective effect. Then we did it in other things like brains. We found a similar phenomenon ...*

*Methylene blue can be protective in ischemic and hemorrhagic strokes. We've also published a study with a hypoxia. In other words, we reduced the amount of oxygen delivered to the animals, and we could use an fMRI, noninvasively, in the animals to see that we were able to increase the amount of cerebral metabolic rate for oxygen consumption in the presence of methylene blue under hypoxic conditions.*

*With respect to dementia, by the time you see the tau protein inside neurons, those neurons are metabolically, essentially, dead, so it is too late. By acting on that, you cannot recover the metabolic machinery and the health of the neurons.*

*So, those neurons are not rescued in any way that is functionally meaningful. Generally speaking, biomarkers are not good therapeutic targets because they may or may not have any causal relationship with the disease."*

In biohacker circles, low-dose methylene blue is used as a nootropic, meaning a compound that helps improve cognitive function. However, while some promote sublingual or buccal application (under your tongue or on the inside of your cheek), the best way is to swallow it, as the acid in your stomach makes it more bioavailable.

## **Urinary Tract Infections in the Elderly**

In my mind, this is one of the most important uses: It is a highly effective agent against urinary tract infections (UTIs). Many elderly are put on antibiotics, which disrupts their microbiome. Methylene blue was used for many decades at a dose of 65 mg per day and was even sold in pharmacies as Urolene Blue.

Since your body doesn't really metabolize it, it is excreted by your kidneys into your bladder where it reaches very high concentrations over time and becomes a potent oxidant stress that kills virtually any pathogen in the bladder. Plus, it has the additional "side effect" of improving brain health and reducing dementia. In my mind, it is reprehensible medical malpractice not to use methylene blue in UTIs in the elderly. It clearly is the safest and most effective drug of choice.

## Contraindications

While methylene blue is very safe, there are some contraindications. One is G6PD deficiency, which is also a contraindication for high-dose ascorbic acid treatments, which could be deadly. Methylene blue is also a mild monoamine oxidase (MAO) inhibitor, so taking high doses with a selective serotonin reuptake inhibitor (SSRI) antidepressant could potentially lead to serotonin syndrome, which is not good. The risk of this, however, is very small. Gonzalez-Lima explains:

*“With respect to the warning about the SSRIs, the problem is not methylene blue but the amount of SSRI. The problem was in a specific application of methylene blue where they use it for parathyroid surgery as a stain ...*

*To my knowledge, there’s never been more than five cases, where the patients were anesthetized, and they still had SSRIs [in their system], and they did repeated flushing in the open neck with methylene blue, which exceeded these doses that we have been talking about.*

*The U.S. FDA reacted with this warning. But this has been reviewed by both surgeons and pharmacologists at the Mayo Clinic, and they wrote a rebuttal paper where they indicate that there is no evidence to suggest oral methylene blue has any interaction with the therapeutic dosing of serotonergic compounds, especially SSRIs, and that this was something that happened under these specific [surgical] conditions.*

*Canada limits the warning to that particular application, but our FDA went beyond that to any kind of serotonergic drug. I think there is absolutely no evidence for oral methylene blue having interactions in this low-dose range with any SSRIs.*

*And when they talk about the MAO inhibitor function, it really only works as an MAO inhibitor in the higher concentration of the higher dose range, not the low-dose range. So, the effects of methylene blue as an antidepressant – only to a*

*very limited extent, if you repeat it cumulative treatments – can be due to any kind of a MAO inhibitor role.*

*In addition, it is due to its metabolic enhancing function, so it antagonizes some of the depression symptoms like the low energy that is experienced with depression. So yes, it is effective to reduce symptoms of depression.*

*Unfortunately, this warning is going to make some physicians scared of using it in combination with SSRIs.”*

## **Dosing Suggestions**

As mentioned, methylene blue is a hormetic, so low dosages have the opposite effect of high dosages. While every possible dose response has not been tested, as a general guideline, the benefits Gonzalez-Lima discusses in this interview are based on dosages between 0.5 milligram per kilogram of bodyweight to 4 mg per kg. He admits lower doses may work but he hasn't tested them.

For an acute treatment, the upper limit is between 3 mg to 4 mg per kg, which is typically the range given as an IV antidote for methemoglobinemia. For nonacute, more long-term treatment, 0.5 mg to 1 mg per kg per day works better. It has a half-life of 12 to 13 hours, so once-a-day dosing is fine. He gives the following example of how methylene blue has been used in the treatment of fears and phobias:

*“One of the processes in which a memory formation can be used therapeutically is when you form a memory to extinguish fear. Individuals who have a phobia, you can expose them to the specific situation that is involved in the phobia, and there is a learning called extinction learning that happens that you extinguish your response.*

*In that situation, we only give methylene blue once after this extinction learning to facilitate the process of memory consolidation. What happens after you go through the learning is the process of consolidation, which requires energy.*

*So, by facilitating the energy availability during the consolidation phase, which happens over a number of hours, then the next time [you're exposed to fear-evoking stimuli, you've] consolidated that extinction memory more effectively.*

*We've done this also with post-traumatic stress disorder (PTSD), where you use prolonged exposure therapy. In that situation, you can give the methylene blue after different sessions where you see that there is a good extinction learning.*

*In other words, where people are learning through exposure to reduce their fear levels, that's when you want to reinforce that therapeutic learning by giving them the methylene blue right after the session."*

For brain health, nootropic effects and the prevention or treatment of dementia, 0.5 mg to 1 mg per kg per day (or when needed) is the dose Gonzalez-Lima recommends and uses.

## **How to Select a High-Quality Product**

Last but not least, selecting the correct product is of crucial importance, in addition to getting the dosing right. There are three basic types of methylene blue: industrial, chemical and pharmaceutical-grade.

The only version you'll want to use medicinally is pharmaceutical-grade. Do not ingest methylene blue from the pet store that is meant for fish tanks. Industrial-grade methylene blue has lots of impurities, and typically contain only 10% to 25% methylene blue.

Chemical or laboratory grade, which is used for staining purposes on laboratories, has a much higher purity, but it's still not suitable for medicinal purposes as it typically has heavy metal contaminants like lead, cadmium and arsenic. Over time, the impurities can accumulate in your body, resulting in toxicity.

Pharmaceutical grade is 99%+ pure. This is the kind used when injected intravenously for antidote purposes, or used orally. These products will be marked USP, which stands

for United States Pharmacopeia.

According to Gonzalez-Lima, USP is better in terms of purity than the European pharmaceutical grade, which has fewer requirements. Taking the methylene blue with some ascorbic acid (vitamin C) facilitates absorption. You won't find methylene blue at your local pharmacy but many compounding pharmacies can obtain the pharmaceutical grade.

"Ascorbic acid is a way to facilitate the cycling of methylene blue by promoting its reduction," he explains. Considering the importance of mitochondrial health, methylene blue appears to be a simple and remarkably effective way to improve your overall health and cognitive function.