Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

DFMO

Evidence Summary

Very low doses have a good safety profile in human trials; laboratory studies suggest possible protection from cancer, Alzheimer's and brain injury, but may negatively impact lifespan.

Neuroprotective Benefit: Preclinical evidence for neuroprotection, but high levels are associated with gastrointestinal toxicity. May benefit in AD where polyamines are elevated but could potentially impair cognitive outcomes in the context of normal brain aging where polyamines are reduced.

Aging and related health concerns: May help reduce cancer risk, but preclinical studies suggest that decreasing polyamines might negatively impact lifespan.

Safety: Clinical trials report that doses below 0.4 g/m²/d have minimal side effects but polyamines serve many essential roles in the brain and body that raise concerns for their chronic depletion by DFMO. Higher doses associated with gastrointestinal events and hearing loss.

What is it? DFMO (α-difluoromethylornithine), also called eflornithine, is an approved drug to treat sleeping sickness (by intravenous injection, CDC) or excessive hair growth (by topical cream). It's ability to treat cancer has been minimal in clinical trials but it has been under testing for chemoprevention (by oral administration) particularly in combination with NSAIDs.
DFMO is most known for irreversible inhibition of ornithine decarboxylase (ODC), which can deplete polyamines including putrescine, spermidine, and spermine. This inhibition is irreversible but in mammals ODC has a rapid turnover rate ($T_{1/2}$ of 10-30 minutes), possibly explaining why DFMO does not successfully treat cancer (Steverding 2010). DFMO can also inhibit arginase to reduce arginine conversion to ornithine (e.g. Selamnia 1998), leading to an increase in arginine levels.

Neuroprotective Benefit: Preclinical evidence for neuroprotection, but high levels are associated with gastrointestinal toxicity. May benefit in AD where polyamines are elevated but could potentially impair cognitive outcomes in the context of normal brain aging where polyamines are reduced.

Types of evidence:

- *4 rodent studies for benefit. 1 rodent study suggesting harm possibly due to toxic dose*
- *1 fly study suggesting harm (worse age-related memory impairment)*
- *autopsy studies provide theoretical support for treatment of Alzheimer's but not brain aging*

No human research has examined whether DFMO can promote brain health in aging or protect against dementia. Animal studies suggest that it might protect against Alzheimer's disease or brain injury with several possible mechanisms of action. However, the doses used in those animal studies is high enough to cause gastrointestinal toxicity, raising doubt on whether the low doses considered safe for chronic use in humans will have similar neuroprotective benefit.

Carol Colton's group at Duke University propose that neurodegeneration in Alzheimer's disease (AD) is caused by an immune suppression that lowers arginine levels in the brain, triggering cellular starvation and eventually cell death. DFMO raises arginine levels and protected against Alzheimer's-like pathology in the CVN-AD animal model (Kan 2015). Specifically, the treatment was 10 mg/kg DFMO plus 1 mg/kg putrescine by oral gavage for 14 weeks, with the putrescine added presumably to avoid polyamine depletion and resulting gastrointestinal toxicity. In the lab of J Fike at the University of Arkansas, DFMO added to the drinking water at 1% protected the brain from radiation and/or traumatic brain injury (Allen Fike 2014, Rosi Fike 2012). The dose may have been too high for safety in humans given that DFMO at a slightly higher dose (1.5% or 2%) caused seizures and a failure to gain weight in

the mice. DFMO impaired memory in rats in another study but that might have been due to toxicity from the high dose (3% in drinking water) (Gupta 2012).

Of note, L-arginine supplementation might possibly increase levels in the brain. Although the polyamines depleted by DFMO cannot pass the blood-brain barrier, intravenous injection of l-arginine at 150 mg/kg increased brain levels of the related neurotransmitter agmatine in monkeys (Piletz 2003). DMFO treatment has not been tested in humans for cognition. Autopsy studies provide theoretical support for the idea that DFMO might protect against Alzheimer's disease, since ODC and polyamines have been found to be increased in brain regions affected by the disease (e.g. Inoue Toyo'oka 2013, Morrison Kish 1995) although this was reported in the temporal cortex but not the hippocampus in one study (Morrison Kish 1998). This may be specific to AD, as similar effects were not seen with another neurodegenerative disease (Morrison Kish 1998). However, the opposite effect has been reported with respect to aging, with decreased rather than increased polyamines (Vivo 2001). For age-related memory impairment, no studies have reported on the effects of DFMO but a study in flies suggests that DFMO could theoretically impair rather than protect. In that study, ODC and related polyamines induced autophagy and protected against age-related memory impairment (suggesting that DFMO inhibition of ODC might harm) (Gupta 2013).

APOE4 interactions: No available evidence suggests that the effects of DFMO are altered by APOE4 status.

Aging and related health concerns: May help reduce cancer risk, but preclinical studies suggest that decreasing polyamines might negatively impact lifespan.

Types of evidence:

- *1 preclinical study in invertebrates and human cell culture*
- *trials and many other studies (but no meta-analyses) suggesting possible chemoprevention*
- *theoretical effects based on biological pathways*
- *Theoretical harm because spermidine, a polyamine depleted by DFMO, may be anti-aging*

The effects of DFMO on aging or lifespan has not been well studied. One study in *Nature Cell Biology* reported that spermidine (one of the polyamines depleted by DFMO) decreases with age and that this reduction "led to hyperacetylation, generation of reactive oxygen species, early necrotic death and decreased lifespan." The study included human cell culture, fruit flies, *c. elegans* worms, and yeast (Eisenberg 2009). Other studies also argue that spermidine may have anti-aging properties (reviewed

in Ingrams & Roth 2015, Minois 2011, & Minois 2014) and spermidine levels are high in centenarian populations (Pucciarelli 2012).

DFMO might reduce the risk of cancer particularly if combined with certain NSAIDs (e.g. Kreul 2012, Jeter 2012). However, the benefit may not extend to all cancers and at least one trial achieved a trend but not overall significance (e.g. Lynch 2015). Epithelial cell tumors like colon cancer and skin cancer are particularly known for high polyamines (Ramani 2014)and the strongest clinical evidence for DFMO is in trials on those conditions. Historically, this mechanism of action has been believed to be polyamine depletion but a 2013 study suggested a different pathway (Witherspoon 2013).

Methionine restriction is an oft-cited alternative protocol to mimic lifespan extension by dietary restriction. DFMO can affect methionine metabolism although whether it might replicate or reverse potential benefits is not clear (Witherspoon 2013). DFMO might also reduce homocysteine levels (Witherspoon 2013) although this has not been clinically studied.

Safety: Clinical trials report that doses below 0.4 g/m²/d have minimal side effects but polyamines serve many essential roles in the brain and body that raise concerns for their chronic depletion by DFMO. Higher doses associated with gastrointestinal events and hearing loss.

Types of evidence:

- Several clinical trials up to 36 months duration

At doses above 1 gram/day, DFMO has clear risks (Table 1 in Meyskens 1999) including diarrhea, abdominal pain/bloating, nausea/vomiting, hematological side effects, and hearing loss that is typically reversible but possibly not always (Lao 2004). Risks are relatively uncommon for doses under 1 g/m²/day (Table 1 in Meyskens 1999). However, ototoxicity has been reported with 0.5 g/m²/day (Love 1998)(Lao 2004) and subclinical hearing loss with 0.4 g/m²/day but not at lower doses (Meyskens 1999). A large trial with 0.5 g/d found no evidence of hearing loss after 36 months (Meyskens 2008). The risk of hearing loss might be caused by cumulative exposure over 150 g, even if the daily exposure is only 1 g/day (Meyskens 1999).

At lower doses, DFMO is well-tolerated with virtually no risks reported in clinical trials up to 36 months. On the other hand, the polyamines that are depleted by DFMO have important functions in the brain and body that raise questions on the safety of very long-term use. For example, polyamines can stabilize DNA conformation, protect DNA from various stressors, and help neuronal axons to

regenerate after injury (Ramani 2014). Spermine can help to resolve inflammation and putrescine modulates immune cell activity. Polyamines can stabilize cellular membranes and play a role in many cellular functions like gene transcription, RNA translation, the formation of cell junctions, and apoptosis (Ramani 2014). The polyamine putrescine may help to control depression and anxiety (Fiori 2008) and DFMO depletion of putrescine caused anxiety-like behavior and memory impairment in rats (Gupta 2009). Polyamines are important for brain development (Ramani 2014) and the levels of ornithine decarboxylase in the brain are particularly high in the first year of life (Morrison 1998). Although no DFMO side effects related to these polyamine functions have been identified in clinical trials, these trials may not have been designed to look for slight changes in anxiety, depression, cumulative long-term DNA damage, or other possible risks based on the normal functions of polyamines.

Dosing and Sources: Oral doses of DFMO are used in chemoprevention trials but, is typically given as an injection for sleeping sickness (CDC). In the USA, neither oral nor injectable versions of DFMO are on the market although the CDC has some stocks available and there is a topical cream (Vaniqa) used to stop hair growth on the face.
The Colton study on mice used 10 mg/kg/d, equivalent to 0.81 mg/kg/d or 48 mg/d for a 60 kg person if multiplying by 3 (mouse Km) and dividing by 37 (human Km) per Reagan-Shaw's 2008 suggested conversion. In a chemoprevention trials, oral doses between 0.075-0.2 g/m^2/day had no observed safety risks (Meyskens 1999).

Future research: Low-dose oral DFMO has been studied in a variety of clinical trials with no overt toxicity noted. Tracking down patients who participated in those trials might allow cost-effective very long-term follow-up of the effects of treatment with DFMO for the duration of the trial.

Search terms:
Pubmed:

- DFMO with the following terms: cancer, brain, senescence, Alzheimer's, cognitive, synaptogenesis, synapse, homocysteine, irreversible, lifespan, methionine, stem, neurogenesis, adverse dose, low-dose
- DFMO with meta-analysis or systematic review filter
- Colton CA
- Ornithine decarboxylase with aging or lifespan or mortality
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