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Enhancing fit-for-purpose prescribing in contemporary natural health practice

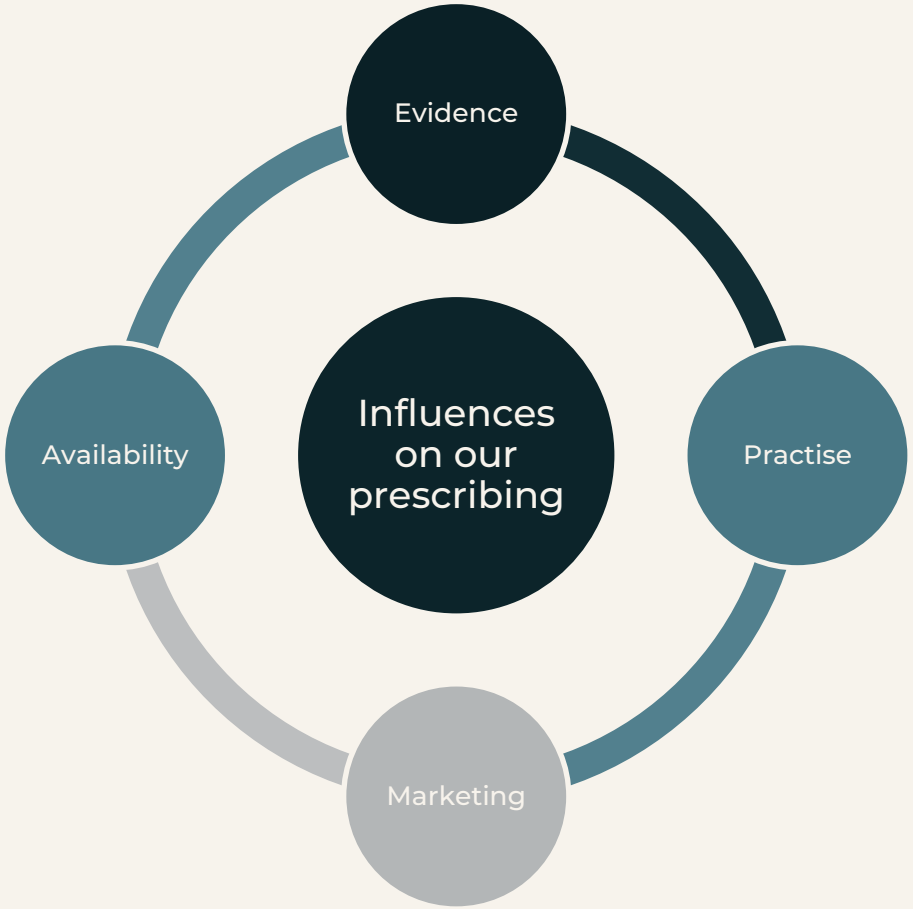
Samuel Peters
Head of Education
BioMedica Nutraceuticals



What is fit-for-purpose prescribing?

Fit-for-purpose prescribing can be defined as:

The intentional selection and application of natural medicines that are evidence-based, clinically relevant, and aligned with the patient's individual physiological needs, therapeutic goals, and stage of healing. It reflects both the integrity of the medicine and its appropriateness within a personalised, naturopathic framework.



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Key clinical considerations in fit-for-purpose prescribing

- Enhancing the action of a compound that is fit-for-purpose
- Efficacy and economics
- Technology that is safe and biocompatible
- Nutrient forms that do not override physiological checkpoints
- Safety in context

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Enhancing the action of a compound that is fit-for-purpose



Curcumin

- Curcumin is a highly pleiotropic molecule that was first isolated from the rhizomes of turmeric in 1815.
- Since this time, thousands of clinical papers have revealed the therapeutic potential of curcumin as an antioxidant, anti-inflammatory, anti-cancer, and antimicrobial agent.
- Curcumin has become the target of human clinical trials due to its diverse biological and pharmacological activities.
- These investigations support curcumin's therapeutic potential in inflammatory, cardiovascular, neoplastic, neurodegenerative and metabolic diseases.



Curcumin Bioavailability

- Curcumin is considered to have a very poor bioavailability. Low aqueous solubility, poor absorption, and rapid metabolism and elimination are the three primary causes.
- Low oral bioavailability is evidenced in clinical trials showing negligible or undetectable serum plasma curcumin levels after oral consumption.
- However, numerous studies utilising concentrated curcuminoid extracts (including Curcumin C3 Complex®) have found clinical benefits and positive effects on relevant biomarkers at doses deemed insufficient to impact plasma curcumin levels.

Delivery mechanism

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ethical | innovative | dedicated

Research Review

The Problem of Curcumin and its Bioavailability, Could its Gastrointestinal Influence Contribute to its Overall Health-Enhancing Effects, *Advances in Nutrition, 2018.*

Key Findings: Curcumin may have therapeutic benefits that extend beyond its well-known and clinically demonstrated anti-inflammatory, antioxidant, anticancer, antiviral and neurotrophic effects. Evidence suggests that a significant proportion of curcumin's therapeutic potential may arise from its effect on the gastrointestinal tract specifically through its ability to modulate; the microbiome, intestinal permeability, and gut inflammation and through controlling pathogenic microbial overgrowth.

Curcumin Bioavailability

- A bioavailability arms race has resulted in numerous curcumin products with larger increases in bioavailability compared to standard curcumin preparations.
- However, these novel ‘bioavailability-enhanced’ preparations can have significant limitations.
- The clinical efficacy of curcumin relates to both delivery mechanisms, dosage and the quality of the raw material.

Curcumin Bioavailability

- **Curcumin C3 Complex®** is a high-quality turmeric extract standardised to a specific compositional ratio of the three primary curcuminoids: curcumin (75%-81%), bisdemethoxycurcumin (2.2-6.5%) and demethoxycurcumin (15-19%).

- Curcumin C3 Complex® has a demonstrated safety and efficacy profile, which is unmatched by any other curcumin preparation available on the market.

- The clinical efficacy of curcumin is thought to be enhanced when administered with the primary curcuminoids bisdemethoxycurcumin and demethoxycurcumin, exerting a synergistic effect.

- From a clinical perspective, it is therefore important to choose a curcumin preparation that maximally increases these curcuminoids.

Table 1: Comparison between pharmacokinetic parameters of parent curcuminoids between clinically relevant doses of Curcumin C3 Complex® and a curcumin phospholipid complex.[6]

	Curcumin C3 Complex®	Curcumin Phospholipid Complex
Curcumin		
C_{max} ng/mL	57	71
C_{24} ng/mL	14	11
AUC_{0-24} ng/mL	731.6	669.4
AUC_{0-48} ng/mL	929	785
Demethoxycurcumin		
C_{max} ng/mL	180	55
C_{24} ng/mL	9	Below level of quantification
AUC_{0-24} ng/mL	674.5	152.5
AUC_{0-48} ng/mL	801	178
Bisdemethoxycurcumin		
C_{max} ng/mL	58	24
C_{24} ng/mL	9	Below level of quantification
AUC_{0-24} ng/mL	593.8	124.5
AUC_{0-48} ng/mL	706	132

C_{max} Maximum serum concentration;
C_{24} Serum concentration at 24 hours;
AUC_{0-24} Area under the curve (0-24hours)
AUC_{0-48} Area under the curve (0-48hours)

Asher, G. N., Xie, Y., Moaddel, R., Sanghvi, M., Dossou, K. S. S., Kashuba, A. D. M., … Hawke, R. L. (2017). Randomised Pharmacokinetic Crossover Study Comparing 2 Curcumin Preparations in Plasma and Rectal Tissue of Healthy Human Volunteers. The Journal of Clinical Pharmacology, 57(2), 185–193. https://doi.org/10.1002/jcph.806

Curcumin C3 Complex®: Literature Review

CONDITION	DOSE/DURATION	STUDY OBJECTIVE/DESIGN	RESULTS
MUSCULOSKELETAL			
Knee osteoarthritis	**Curcumin C3 Complex®:** 1.5g + 15mg piperine/day in three divided doses (n=19) **Control:** Placebo (n=21) **Duration:** 6 weeks	**Objective:** To investigate the efficacy of curcuminoids in reducing inflammatory biomarkers and systemic oxidative burden in patients with knee osteoarthritis (OA) **Design:** Randomised, double-blind, placebo-controlled pilot trial	In the curcuminoid group, there was a significant improvement in three widely used measures of OA severity i.e. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (by 32%), Visual Analogue Scale (VAS) (by 40%) and Lequesne's Pain Functional Index (LPFI) (by 29%). Moreover, subscale analysis of WOMAC scores revealed a significant effect of curcuminoids in reducing all three components of the WOMAC index i.e. physical function, stiffness and pain. There was also a significant reduction in the proportion of subjects using Naproxen in the Curcumin C3 Complex® group (84%) as compared to the placebo group (19%). No serious adverse events were reported, and no dropouts were due to the adverse event of curcuminoid therapy.[1]
	Curcumin C3 Complex®: 1.5g + 15mg piperine/day in three divided doses (n=19) **Control:** Placebo (n=21) **Duration:** 6 weeks	**Objective:** To determine changes in serum levels of inflammatory biomarkers in knee OA patients whose clinical symptoms were improved as a result of supplementation with curcuminoids **Design:** Randomised, double-blind placebo-control parallel-group clinical trial	Serum concentrations of inflammatory markers were significantly reduced in the curcuminoid group i.e., interleukin (IL)-4 (P = 0.001), IL-6 (P = 0.006) and high-sensitivity C-reactive protein (hs-CRP) (P = 0.004). However, serum levels of tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), and mean erythrocyte sedimentation rate (ESR) remained unaltered (P > 0.05). A comparison of the magnitude of changes in the evaluated inflammatory biomarkers did not indicate any significant difference between the study groups (P > 0.05). The authors concluded that the benefit of the curcuminoids is because of a local anti-inflammatory effect in the
REPRODUCTIVE			
cumin C3 nplex®: 500mg + g piperine/day (n=40) **ntrol:** Placebo (n=40) **ration:** 7 days ore until 3 days after nstruation for three es	**Objective:** To assess the effect of curcumin and piperine on IL-10, IL-12 and IgE levels in patients with PD and PMS **Design:** Triple-blind, placebo-controlled clinical trial	Curcumin + piperine treatment was associated with a significant reduction in the mean serum levels of IgE (P = 0.001) but there were no significant changes in the placebo group (P = 0.12). Serum concentrations of IL-10 and IL-12 before and after the trial period did not differ significantly between the two groups (P > 0.05). Curcumin might have a positive effect on serum IgE levels in healthy young women with PMS and PD. Studies with higher doses and longer durations of treatment with curcumin are required to confirm these findings.[42]
ONCOLOGY			
cumin C3 nplex®: 8g/day 21) **ration:** 8 weeks; up to 18 months depending on disease progression	**Objective:** To evaluate the clinical biological effects of curcumin against advanced pancreatic cancer **Design:** Non-randomised, open-label, phase II trial	Curcumin down-regulated expression of NF-κB, cyclooxygenase-2, and phosphorylated signal transducer and activator of transcription-3 in peripheral blood mononuclear cells from patients, most of whom had baseline levels considerably higher than those found in healthy volunteers. Curcumin treatment led to a decrease in constitutive pSTAT3 activation (a molecule implicated in tumorigenesis and chemoresistance) in most patients. No toxicities were observed. In conclusion, oral curcumin was well tolerated and has

59 human clinical trials

Colecalciferol and calcifediol: what's the difference?

- Colecalciferol is the predominant form of vitamin D found in animal products, while calcifediol results from the hydroxylation of colecalciferol in the liver.

- Both agents are inactive precursors that require hydroxylation in the kidneys to produce 1,25-dihydroxyvitamin D3 (calcitriol), the biologically active form of vitamin D.

Table 2: Pharmacokinetics

	Colecalciferol	Calcifediol
Metabolism	Undergoes a two-step enzymatic process	Undergoes a one-step enzymatic process
Polarity	Lipophilic	Hydrophilic
Absorption efficiency	79% (61 – 91%)	93%
Half-life	2 months	15 days

Research

Various studies have investigated the dose-response effects of supplementation with colecalciferol compared with calcifediol in healthy, postmenopausal, or elderly populations.

Although data may vary, evidence suggests that, at equivalent dosages, **calcifediol is approximately three times more effective than colecalciferol in raising serum 25(OH)D levels within four to eight weeks.**

It is important to note that in all comparative studies, the dose of calcifediol shown to be most effective in increasing serum vitamin D levels corresponded to a therapeutic dose often employed in clinical settings (20µg daily). In contrast, the dose of colecalciferol used was substantially lower than what is typically prescribed by natural health practitioners to correct a deficiency or to modify disease (800IU daily). As such, interpreting these results is challenging since the doses of each agent are not comparable and do not reflect what is frequently used in clinical practice.

Research

Interestingly, recent studies have evaluated serum vitamin D levels following the cessation of calcifediol and colecalciferol treatments.

In one trial, **the elimination rate of calcifediol was up to 109% higher** than that observed in the colecalciferol group six months after discontinuing supplementation.

Another study observed that, irrespective of the initial dose, serum concentrations of calcifediol **returned to baseline levels within two months after discontinuation**, highlighting its rapid elimination rate.

This difference may be attributed to the greater retention of colecalciferol in body tissues following supplementation, allowing for its gradual and sustained release into the circulation as needed.

Fast uptake
=
Fast elimination

Slow uptake
=
Slow elimination

Safety

Calcifediol

- One study found that calcifediol was associated with slightly higher levels of serum calcium and 24-hour urine calcium excretion compared to colecalciferol, suggesting this form **may increase the risk of hypercalciuria** in some populations.

- Given its higher potency, dosing errors in the administration of calcifediol have occurred, resulting in serum 25(OH)D levels exceeding the therapeutic range, leading to cases of **overdose or vitamin D intoxication**. However, its short half-life and rapid elimination facilitate a swift response to dose adjustments.

Colecalciferol

- Traditionally been considered a safe substance with a **lower likelihood of causing toxic effects**, even when administered at high doses or for extended periods.

- According to large randomised controlled trials, supplementation with 2000IU of colecalciferol daily for over five years has not been associated with significant safety concerns, even among individuals who have sufficient vitamin D levels at baseline.

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Clinical summary

- **Colecalciferol** is the preferred form of vitamin D for achieving and **maintaining optimal levels in the long-term management** of a deficiency for the majority of patients.

- **Calcifediol** may be the preferred form for certain sub-populations, such as those with malabsorption syndromes, liver disease, obesity, or patients with severe vitamin D deficiency, in order **to elevate serum levels promptly**. Given the limited research on the safety and efficacy of calcifediol across various health conditions, it may be less suitable for long-term maintenance

Coenzyme Q10

- CoQ10 is a lipid-soluble benzoquinone found in nearly all cellular membranes, where it serves as a **crucial electron carrier in the mitochondrial respiratory chain**, facilitating the production of cellular energy.
- CoQ10 exists within the body in the **oxidised form (ubiquinone/ ubidecarenone)** and the **reduced form (ubiquinol)**, which continuously interconvert within cells to support its normal physiological function.
- In its reduced form, ubiquinol acts as a primary scavenger of free radicals and is a potent antioxidant, capable of regenerating tocopherol and ascorbate back to their active, reduced forms.

Does aging reduce CoQ10 interconversion?

- While evidence suggests that ageing may reduce the rate of CoQ10 biosynthesis, **there is no human data to support the hypothesis that ageing also reduces the efficient conversion of ubiquinone to ubiquinol.**
- While studies have observed that older adults tend to exhibit a higher proportion of ubiquinone in circulation, this shift is more likely attributed to increased oxidative stress rather than a diminished enzymatic capacity to convert ubiquinone into its reduced, bioactive form.

The circulating balance of CoQ10 shifts with age

A greater proportion of CoQ10 is present in the **oxidised form (ubiquinone)** as we age, while the reduced form (ubiquinol) tends to be relatively lower.

Younger adult

(e.g. 20–30 years)



Ubiquinol
(reduced, bioactive form)

Ubiquinone
(oxidised form)

Ageing & increasing oxidative load

Associated with a higher proportion of ubiquinone in circulation

Older adult

(e.g. 70+ years)



Ubiquinol
(reduced, bioactive form)

Ubiquinone
(oxidised form)

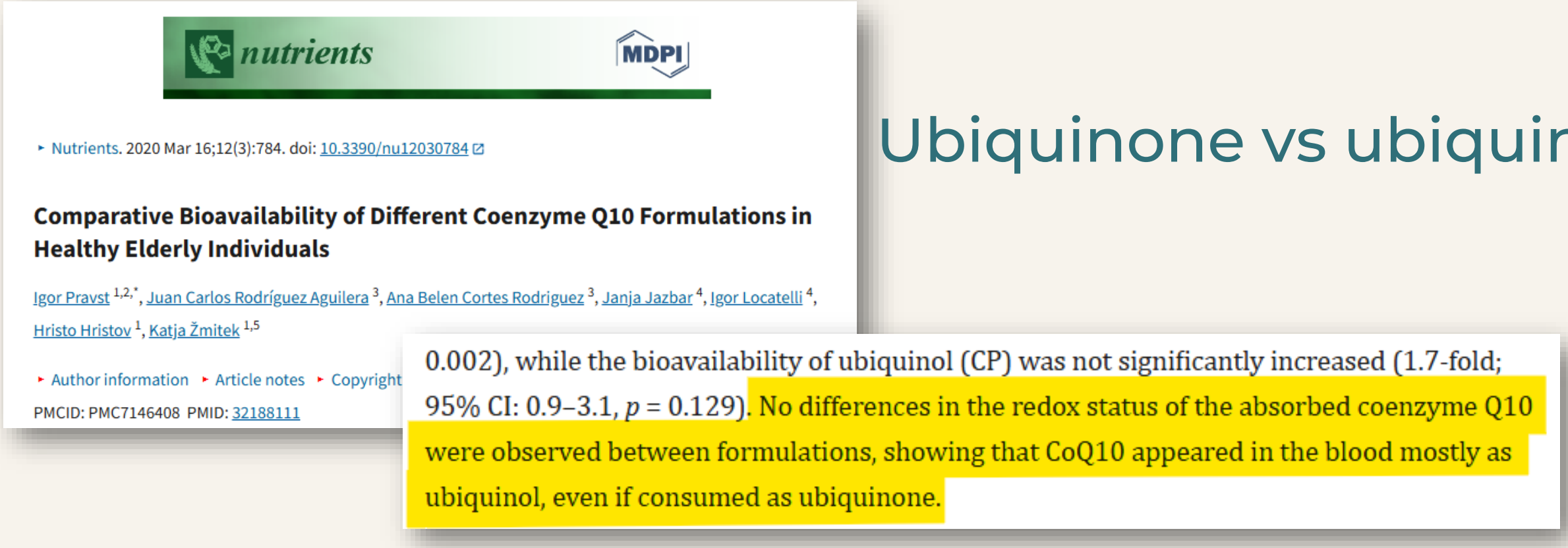
The higher proportion of ubiquinone with age is more likely related to increased oxidative stress, rather than a reduced ability to convert ubiquinone into ubiquinol.

The body retains enzymatic capacity to interconvert ubiquinone and ubiquinol throughout life.

When evaluating CoQ10 status in older adults, it is important to consider oxidative load, not just assume a decline in metabolic conversion efficiency.

Conceptual illustration based on published human data. Relative proportions are not to scale and are for educational purposes only.

Ubiquinone vs ubiquinol



nutrients

MDPI

Nutrients. 2020 Mar 16;12(3):784. doi: 10.3390/nu12030784

Comparative Bioavailability of Different Coenzyme Q10 Formulations in Healthy Elderly Individuals

Igor Pravst [1,2,*], Juan Carlos Rodríguez Aguilera [3], Ana Belen Cortes Rodriguez [3], Janja Jazbar [4], Igor Locatelli [4], Hristo Hristov [1], Katja Žmitek [1,5]

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PMCID: PMC7146408 PMID: 32188111

0.002), while the bioavailability of ubiquinol (CP) was not significantly increased (1.7-fold; 95% CI: 0.9–3.1, $p = 0.129$). No differences in the redox status of the absorbed coenzyme Q10 were observed between formulations, showing that CoQ10 appeared in the blood mostly as ubiquinol, even if consumed as ubiquinone.

Studies in elderly populations suggest that regardless of the form ingested (ubiquinone or ubiquinol), **CoQ10 appears primarily as ubiquinol, indicating efficient reduction after absorption.**

CoQ10 in fertility

Females

- Out of 11 studies, **10 studies have used ubiquinone (200 – 600mg)** to improve various outcomes for infertile women, **while 1 study used ubiquinol (150mg)**

Males

- Out of 14 studies, **9 studies have used ubiquinone (100 – 600mg)** to improve various outcomes for infertile men, **while 5 studies have used ubiquinol (150 – 400mg).**



Balancing the clinical outcomes versus cost – While there is growing interest in using ubiquinol over ubiquinone, clinical decisions should be guided by a balanced consideration of therapeutic efficacy, the strength of supporting evidence, and the cost to the patient. Given that ubiquinol is typically at least 2.5 times more expensive than ubiquinone, it is reasonable to conclude that **ubiquinone remains the most cost-effective option**. Moreover, ubiquinone is the form most consistently used in clinical studies supporting CoQ10's role in female fertility, particularly in improving egg quality, ovarian response, and pregnancy outcomes.

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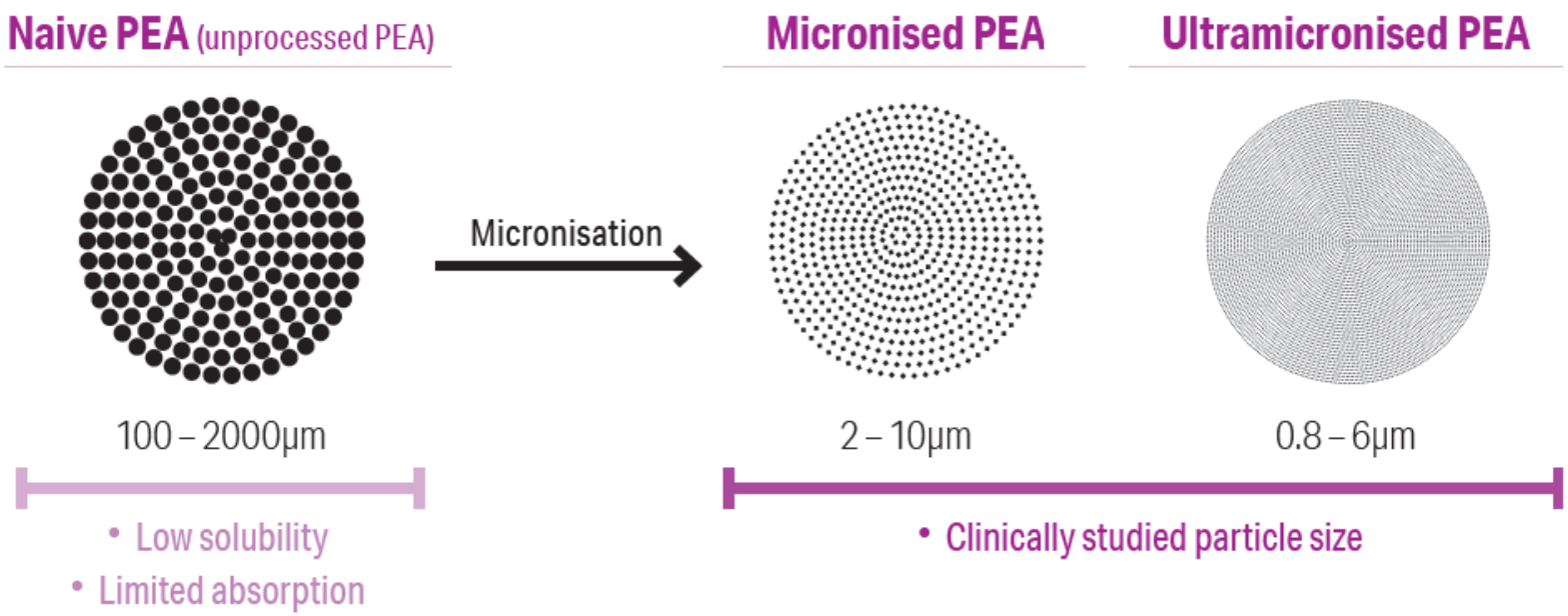
Efficacy and economics

Not all PEA is from the same POD



The clinical impact of particle size

The lipophilic nature of PEA generally results in poor absorption and bioavailability. Specialised manufacturing techniques which reduce the particle size of PEA (micronisation) facilitate absorption.



BioMedica's PEA 600 contains a high quality, pharmaceutical grade palmitoylethanolamide (99% of particle sizes are smaller than 10µm, and 50% are smaller than 3µm), in a pure, low-excipient, PEG-free capsule for superior compliance.

PEA forms

- **Levagen+ is a water-soluble form of PEA, which claims to have 1.7 x better absorption than standard PEA**

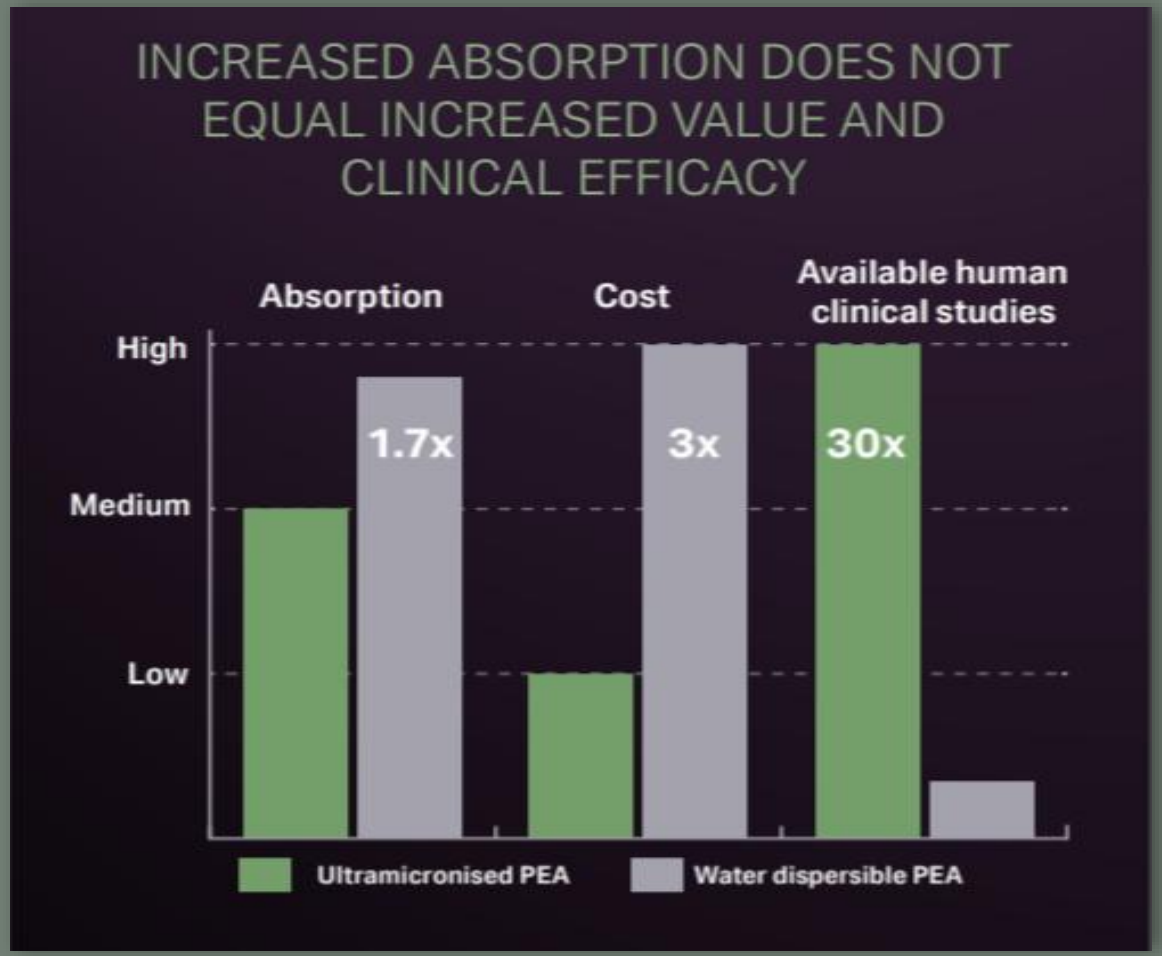
This is based on one clinical absorption study

Study conditions

- Conducted under fasting conditions – regular PEA is better absorbed with a fat-containing meal
- Comparator PEA was not in an ultramicronised form

These conditions are likely to have inflated the differences between the two formulations, compared to if the comparator PEA was given under ideal conditions

Ultramicronised size PEA given with food is the most clinically effective and cost-effective choice


INCREASED ABSORPTION DOES NOT EQUAL INCREASED VALUE AND CLINICAL EFFICACY
Absorption
Cost
Available human clinical studies
High
Medium
Low
1.7x
3x
30x
Ultramicronised PEA
Water dispersible PEA

WEIGHT OF EVIDENCE
Ultramicronised PEA:

- Remains the most cost efficient and clinically effective form of PEA
- Validated by dozens of human clinical studies
- Efficacy supported by multiple meta-analyses
- No known drug interactions

CHOOSING THE RIGHT PEA PRODUCT

- ☑ Pure, low-excipient, high- strength capsule or powder
- ☑ Does not require the use of PEG's to enhance absorption
- ☑ Ultramicronised form
- ☑ Cost-efficient and convenient high-strength delivery for optimal compliance and outcomes

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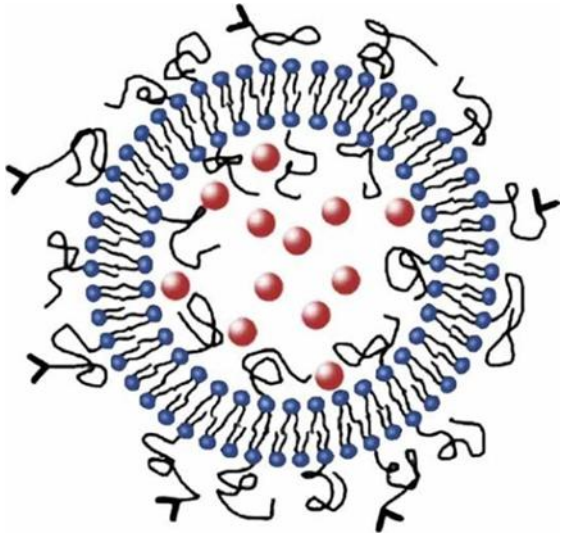
Technology that is safe and biocompatible

Excipients that are safe for short and long-term use



Polyethylene Glycol (PEG)

- What are PEG's?
- To PEGylate or not to PEGylate?



Questions surround both safety and efficacy of PEGylated liposomes

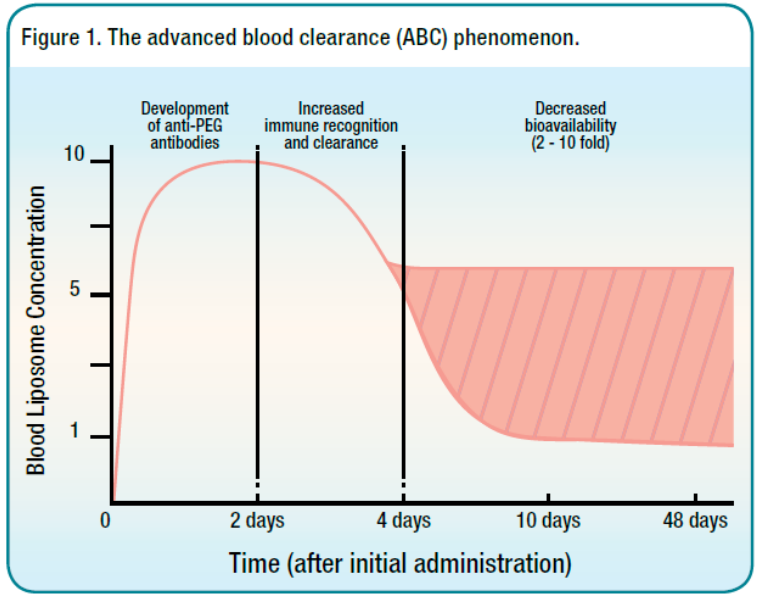
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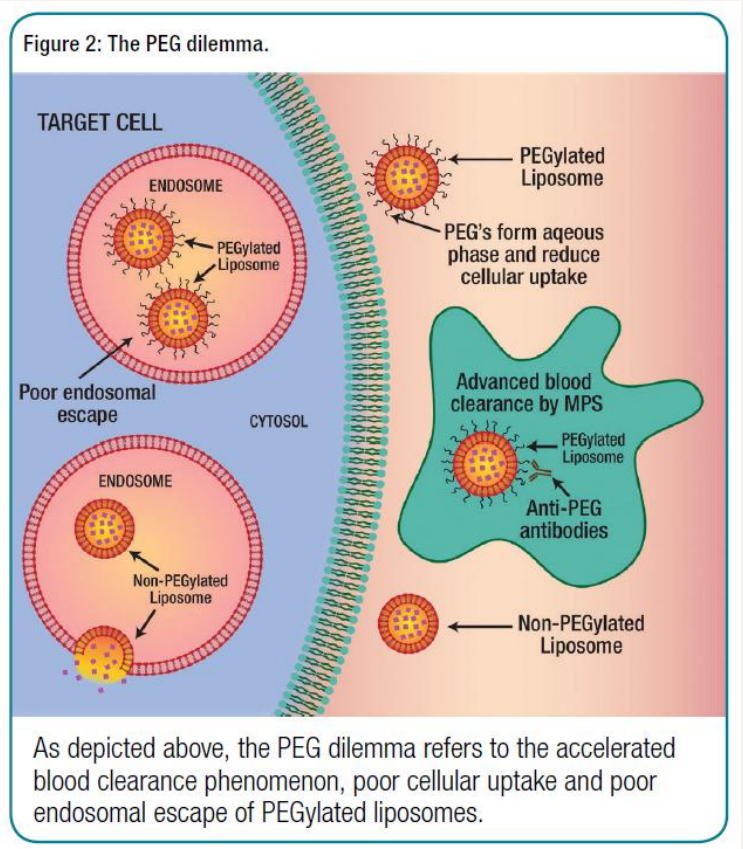
Safety of PEG's

- Primary safety concern relates to the risk of cumulative exposure:
  - Renal toxicity
  - Metabolic acidosis
  - Vacuolation
- The consequences of long-term exposure is hard to predict
- Vitamin E based PEG's

PEG's affect nutraceutical efficacy

- PEGylated liposomes suffer from a phenomenon known as the "PEG dilemma"
  - Advanced blood clearance phenomenon
  - Poor cellular uptake
  - Poor endosomal escape





Hatakeyama, H., Akita, H., & Harashima, H. (2013). The polyethyleneglycol dilemma: advantage and disadvantage of PEGylation of liposomes for systemic genes and nucleic acids delivery to tumors. *Biological & Pharmaceutical Bulletin*, 36(6), 892–9.

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Nutrient forms that do not override physiological checkpoints



Which form of folate is best?

Food folates

Folic acid

Folinic acid

5-Methyl-Folate



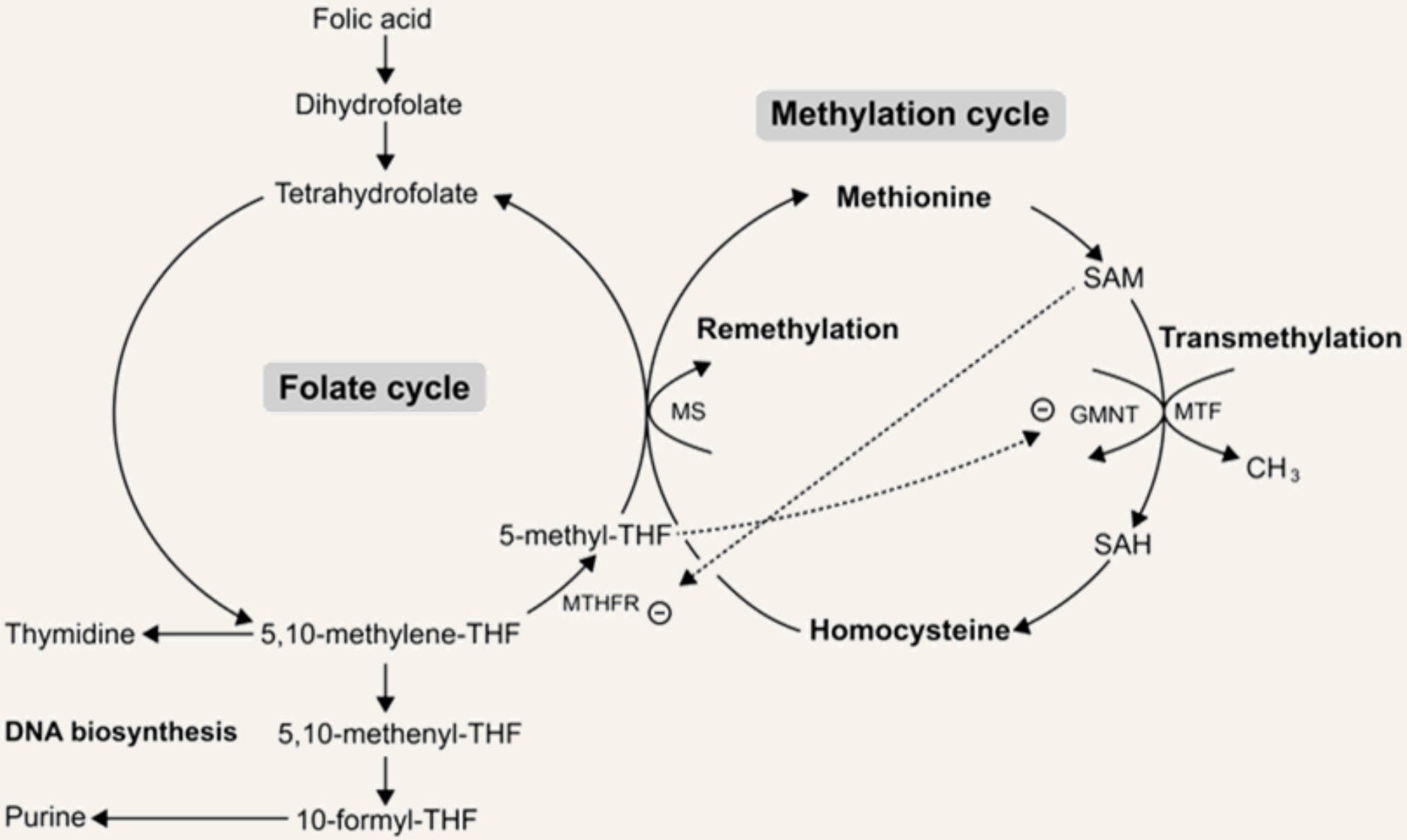
Folate claims

#1 Methyl-folate is superior because it can directly enter the folate cycle

- Is this more likely to be a disadvantage of methylfolate?
- The MTHFR enzyme serves as an enzymatic checkpoint in the regulation of methyl donors in the cell
- Unknown long-term health consequences from overriding these checkpoints?

Crider, K. S., Devine, O., Hao, L., Dowling, N. F., Li, S., Molloy, A. M., … Berry, R. J. (2014). Population red blood cell folate concentrations for prevention of neural tube defects: Bayesian model. *BMJ (Online)*, *349*. https://doi.org/10.1136/bmj.g4554

Yamada, K., Strahler, J. R., Andrews, P. C., & Matthews, R. G. (2005). Regulation of human methylenetetrahydrofolate reductase by phosphorylation. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(30), 10454–10459. https://doi.org/10.1073/pnas.0504786102


Folic acid
Dihydrofolate
Tetrahydrofolate
Methylation cycle
Methionine
SAM
Remethylation
Transmethylation
Folate cycle
MS
GMNT
MTF
CH3
5-methyl-THF
SAH
MTHFR
Thymidine
5,10-methylene-THF
Homocysteine
DNA biosynthesis
5,10-methenyl-THF
Purine
10-formyl-THF

Folate claims

#2 Methyl-folate is just as effective as folic acid for preventing neural tube defects

- No studies exist which prove that alternative forms of folate can prevent NTD's
- We can't assume that alternative forms of folate are bioequivalent, especially for serious conditions
- Listed medicines in Australia must contain folate as folic acid (at least 400mcg) in order to claim that the product is "for the prevention of NTD's".

Other claims relating to folates

- Folic acid is synthetic and oxidised and therefore has negative health consequences
- Unmetabolised folic acid is toxic
- Folic acid can mask a B12 deficiency
- Folic acid can contribute to the development of folate sensitive cancers
- Folic acid and folinic acid are toxic in individuals with MTHFR polymorphisms



Micro Learning

FREE

Folate fundamentals: aligning evidence and practice in the folate debate

Presented by **Samuel Peters**

11TH SEP, 2025

Replay 45 minutes

Watch now

Module 1

Folic acid remains the preferred form of folate in **preconception** and **pregnancy**

Watch now

Module 2

Folic acid and folinic acid are safe and effective in patients with **MTHFR polymorphisms**

Watch now

Module 3

Folic acid and folinic acid are the only safe forms of folate for patients with **cancer**

Watch now

Module 4

Folate does not mask a **B12 deficiency**

Watch now

Module 5

Folic acid is synthetic but **safe**

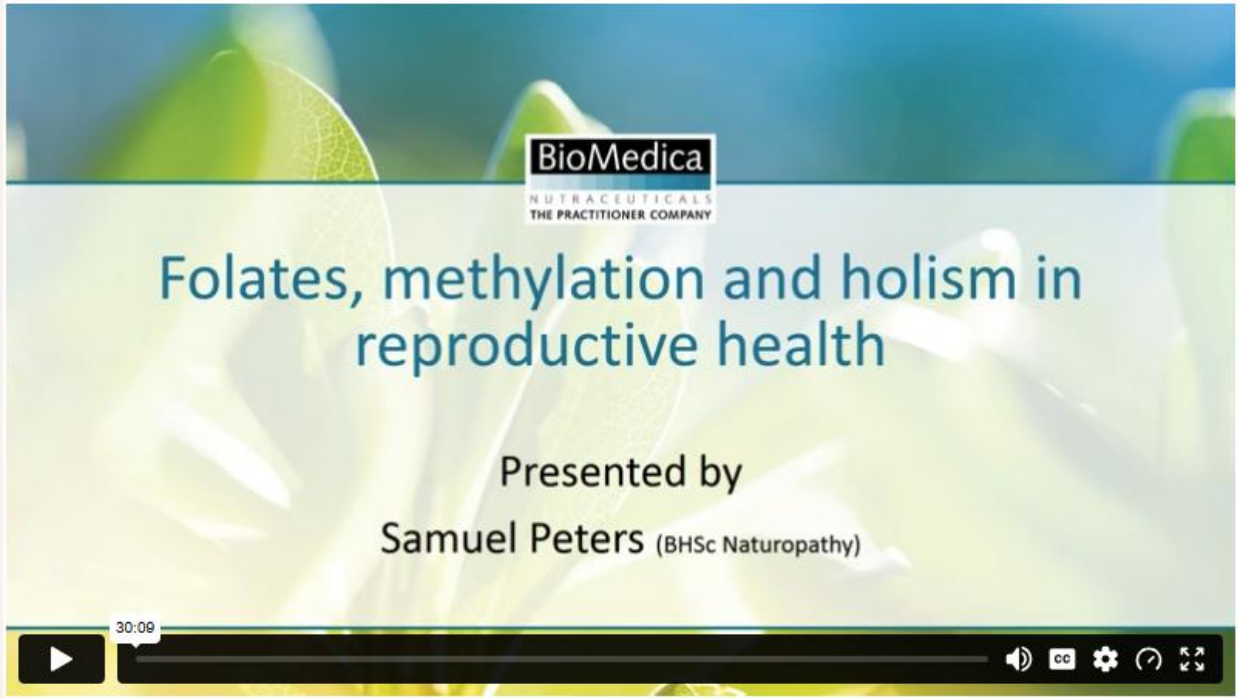
Watch now

Module 6

Clinical outcomes and anecdotes: What is really driving results?

Watch now

Folates, methylation and holism in reproductive health





Samuel Peters BHSc (Nat)

August 2020
30 Minutes

Samuel Peters is the Education and Technical Manager at BioMedica, leading a growing and dedicated team of practitioners and researchers in the delivery of high quality educational material and technical support.

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- Presentation notes
- References

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Safety in context

Vitamin B6



Vitamin B6 adverse affects

- Peripheral neuropathy is a known side effect of excessive vitamin B6 intake and is characterised by tingling, burning, or numbness, typically in the hands or feet.
- **The majority of cases are from supratherapeutic doses >1000mg daily,** often reported from laypersons self-prescribing with over-the-counter supplements.
- The pathogenic mechanisms associated remain elusive, and a lack of consensus over which vitamin B6 vitamer leads to neuropathy is apparent.
- While several opposing theories have been proposed, many aspects of these hypotheses are unexplored, and the basic assumptions they are founded on can be argued, particularly concerning pyridoxine pharmacokinetics, toxicological testing, and metabolism.

Vitamin B6 adverse effects

- The TGA has recently reduced the maximum permissible daily dose of B6 in AUST-L products from 200mg to 50mg.
- The NHMRC has also recommended reducing the Nutrient Reference Values Upper Limit for vitamin B6 from 50mg to 14mg daily.

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

Australian Government

National Health and Medical Research Council

What are safe doses of vitamin B6

Should practitioners limit the daily dose of B6 supplementation to 50mg or 14mg per day?

Are higher doses still safe to prescribe?

Let’s look at the evidence...

The evidence

- The first clinical report regarding potential neurotoxicity was published in 1983 when 7 patients suffered sensory neuropathy while consuming **2,000-6,000mg for 2-40 months.**

- Additional reports describing similar adverse effects were published, generally at doses higher than 500mg daily; however, **none of the studies** in which an objective neurological examination was performed **reported evidence of sensory nerve damage at intakes below 200mg daily.**

- A recent review examining seven case series, one prospective study, and one case-control study, concluded that **neurological side effects due to vitamin B6 intake are rare, consistently reversible, and typically occur after high doses (>500mg) and/or for long durations (>6 months).**

The evidence

- In this review, the reported cases depended on the dose and timeframe:
  - **After 12 months or longer with doses less than 2,000mg daily**
  - **Less than 12 months with doses greater than 2,000mg daily**

- Few publications described neurotoxic symptoms following doses less than 50mg daily; however, due to flaws in the reporting, such as inadequate details of the neurological symptoms, exact product composition, definite daily intakes, and clinical examinations, their reliability has been criticised.

- In adults with vitamin B6 deficiency, subacute or chronic neuropathy may also develop; therefore, it is important to differentiate between deficiency and toxicity.

Evidence of safety

- On the other hand, a plethora of evidence has supported the safe use of vitamin B6 for a wide range of health conditions, including cognitive impairment, mental health concerns, cardiovascular diseases, neuropathy, and premenstrual syndrome.

- In one study, **50mg of vitamin B6** alongside B12 and folic acid for **7.3 years** lowered homocysteine in women with endothelial dysfunction without causing any toxicity concerns.

- An additional study found that large doses of **vitamin B6 (up to 200mg)** can be safely used for **pregnant women** experiencing severe nausea and vomiting during the first trimester.

Selected studies involving **long-term** B6 supplementation

Condition	Dose	Duration	Results/Toxicities
Endothelial dysfunction in women(Christen 2018) **n = 300**	**Treatment:** Vitamin B6 (50mg) + vitamin B12 (1mg) + folic acid (2.5mg) **Control:** Placebo	**Duration:** 7.3 years	**Results:** Findings indicate that long-term, combined treatment with B6, B12, and folic acid lower homocysteine levels. **Toxicities:** No adverse events or toxicities were reported
Homocysteine-lowering therapy(van Dijk 2001) **n = 158**	**Treatment:** Vitamin B6 (250mg) + folic acid (5mg) **Control:** Placebo	**Duration:** 2 years	**Results:** Findings support the hypothesis that homocysteine-lowering treatment with folic acid plus pyridoxine has beneficial vascular effects. **Toxicities:** No adverse events or toxicities were reported
Mild cognitive impairment(Lehmann 2003) **n = 30**	**Treatment:** Vitamin B6 (80mg) + vitamin B12 (2mg) + folic acid (10mg) **Control:** Placebo	**Duration:** mean 270 days (range 110-740 days)	**Results:** By treating patients with MCI and high homocysteine with oral high-dose B vitamins, cognitive stabilisation was achieved. **Toxicities:** No adverse events or toxicities were reported
Homocysteine-lowering therapy in patients with CVD or diabetes(Ray 2007) **n = 5522**	**Treatment:** Vitamin B6 (50mg) + folic acid (2.5mg) + vitamin B12 (1mg) **Control:** Placebo	**Duration:** 5 years	**Results:** Vitamin therapy reduced homocysteine levels; however, it did not reduce the risk of venous thromboembolism, DVT, or pulmonary embolism. **Toxicities:** No adverse events or toxicities were reported

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Selected studies involving **high-dose** B6 supplementation

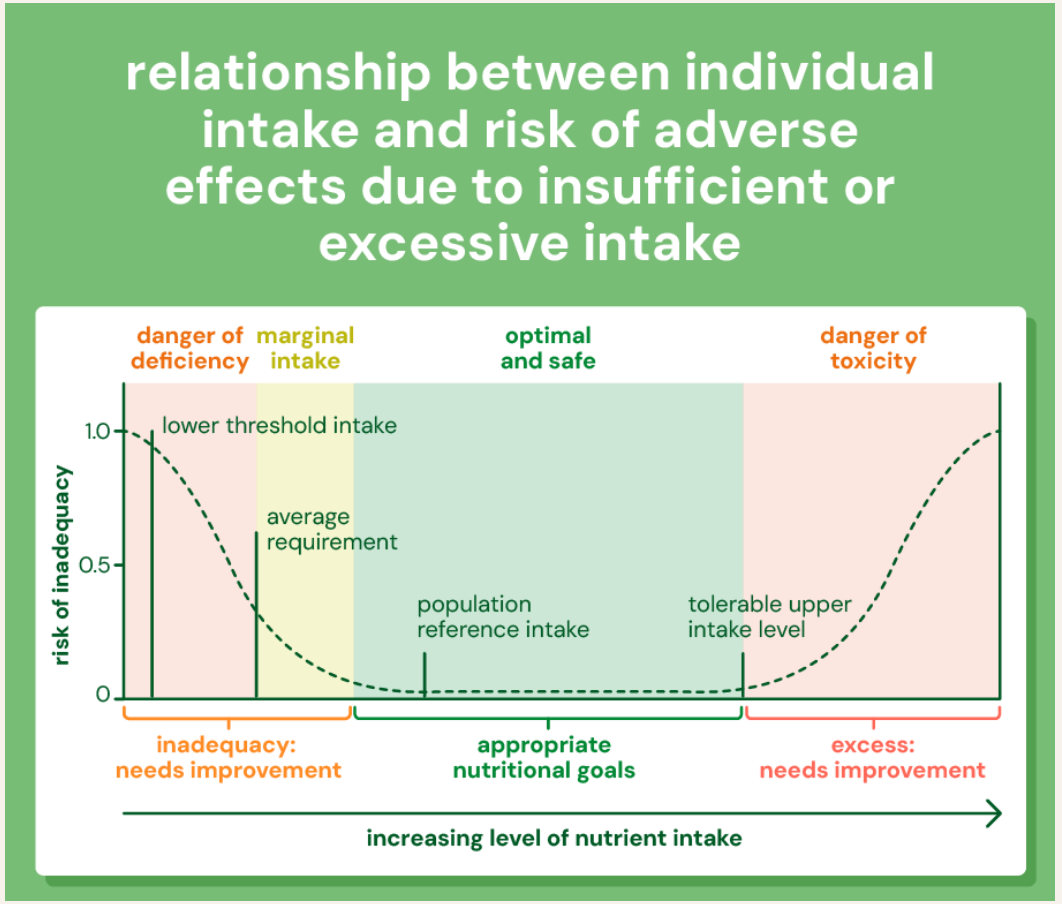
Condition	Dose	Duration	Results/Toxicities
Safety of B6 for nausea and vomiting in pregnancy(Shrim 2006) **n = 96**	**Treatment:** Vitamin B6 (110mg/day median dose; range: 50-510mg/day)	**Duration:** The first trimester of pregnancy	**Results:** The data suggest that women experiencing moderate to severe NVP with a recommended dose of 40 mg/day B6 is insufficient can safely receive larger doses up to 200 mg/day. **Toxicities:** No adverse events or toxicities were reported
Premenstrual dysphoric disorder(Maaroofi 2006) **n = 121**	**Treatment:** Vitamin B6 (80mg daily) **Control:** Placebo	**Duration:** 3 months taken during the luteal phase	**Results:** Vitamin B6 improved emotional but not somatic symptoms of PMDD. **Toxicities:** No adverse events or toxicities were reported
Homocysteine in schizophrenia and schizoaffective disorders(Miodownik 2007) **n = 11**	**Treatment:** Vitamin B6 (1200mg)	**Duration:** 3 months	**Results:** High doses of vitamin B6 lead to a decrease in homocysteine levels in male patients with schizophrenia or schizoaffective disorder. **Toxicities:** No adverse events or toxicities were reported
Tardive dyskinesia and schizophrenia or schizoaffective disorder(Lerner 2007) **n = 50**	**Treatment:** Vitamin B6 (1200mg)	**Duration:** 26 weeks	**Results:** High doses of vitamin B6 significantly reduce symptoms of tardive dyskinesia compared to placebo. **Toxicities:** No adverse events or toxicities were reported
Anxiety(Field 2022) **n = 478**	**Arm 1:** Vitamin B6 (100mg) **Arm 2:** Vitamin B12 (1mg) **Arm 3:** Placebo	**Duration:** 1 month	**Results:** Vitamin B6 supplementation reduced self-reported anxiety and induced a trend towards reduced depression, as well as increased surround suppression of visual contrast detection. **Toxicities:** No adverse events or toxicities were reported

Deficiency or toxicity?

Deficiency signs and symptoms	Toxicity signs and symptoms
• Dermatitis / seborrheic rash	• Peripheral sensory neuropathy
• Weakness, sleeplessness, fatigue	• Dermatoses
• Anaemia	• Dizziness
• Peripheral sensory neuropathy	• Nausea
• Angular stomatitis and glossitis	• Ataxia
• Elevated homocysteine	• Bone pains
• Renal calculi	• Muscle weakness
• Impaired glucose tolerance	• Fasciculations (muscle twitches)
• Confusion	
• Irritability	
• Depression	
• Seizures	

Nutrient Reference Values Upper Limit

- The NRV Upper Limit represents the maximum daily nutrient intake that is unlikely to cause adverse health effects in the general population when consumed over the long term
- It is a population wide health recommendation that does not take into consideration individual needs, deficiency states, disease states or therapeutic goals.



https://www.eufic.org/en/understanding-science/article/dietary-reference-values-a-reference-for-whom

Summary

- For most individuals, vitamin B6 supplementation causes no toxicity concerns when used appropriately, and **the benefits largely outweigh the potential risk** of **reversible** neuropathy.
- **In the majority of the studies assessing safety, neuropathy may develop if vitamin B6 is ingested in doses greater than 500mg and for long durations.**
- While a very small percentage of patients experience symptoms of peripheral neuropathy at doses lower than 50mg, this appears to be a rare reaction, and symptoms generally improve after discontinuation
- Self-prescribing and over-the-counter supplements are the most likely cause of toxicity concerns, which highlights the important role of healthcare practitioners in patient-centred care.
- Every intervention has risk. Not intervening carries risk.

Research Update

Understanding vitamin B6-induced neuropathy: an evidence based assessment

Snapshot

- Vitamin B6 is an essential, water-soluble vitamin that participates in over 140 enzymatic reactions in the body and plays a vital role in the central and peripheral nervous systems.
- However, concern regarding vitamin B6-induced neuropathy has occurred within the healthcare profession due to the TGA-issued label warning on all products containing a daily dose above 10mg.
- According to the literature, neurological side effects of vitamin B6 intake are rare, consistently reversible, and typically occur after ingestion of high doses (>500mg) and for long durations (>6 months).
- On the other hand, a plethora of evidence has supported the safety of vitamin B6 for a wide range of health conditions, including cognitive impairment, mental health concerns, cardiovascular diseases, neuropathy, and premenstrual syndrome.
- Self-prescribing and over-the-counter supplements are the most likely cause of toxicity concerns, highlighting healthcare practitioners' important role in patient-centred care.

Vitamin B6 forms and functions

Vitamin B6 is an essential, water-soluble vitamin found in various sources, such as meat, poultry, fish, legumes, nuts, cereals, vegetables, and bananas.[1] Six different vitamers of vitamin B6 exist, namely pyridoxine, pyridoxal, pyridoxamine, and their phosphorylated derivatives pyridoxine phosphate, pyridoxal-phosphate, and pyridoxamine phosphate.[2] Pyridoxal phosphate (PLP) is the main bioactive form and is a versatile cofactor participating in over 140 enzymatic reactions that perform various functions throughout the body, including the breakdown of food, balancing pathway from pyridoxal, pyridoxamine, and pyridoxine found in food.[5] However, the bioavailability of vitamin B6 in foods is influenced by the extent and type of processing, and quantities are often lost through prolonged heating, milling, refining, and storage.[3] Though complete dietary insufficiency is rare in developed countries, low vitamin B6 status has been reported in various population groups, including contraceptive users, smokers, alcoholism, and in patients with coeliac disease or diabetes.[6,7] Secondary vitamin B6 deficiency may also result from mutations causing defects in the B6 salvage pathway, inborn errors causing an accumulation of intermediates that react with PLP, the intake of pharmaceutical

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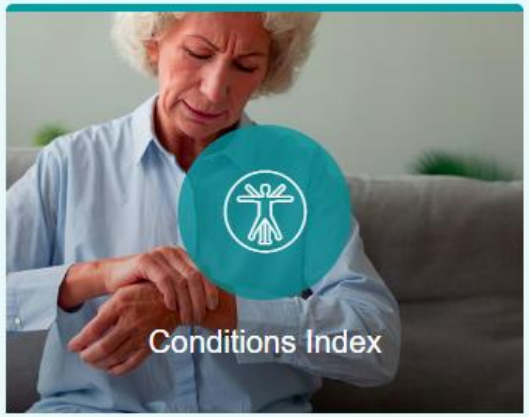
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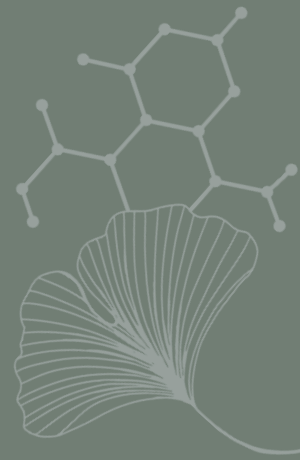
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