II. WATER SOLUBLE VITAMINS

A. Generalities

1. **Metabolism and storage** -- only B\textsubscript{12} and folate are appreciably stored. In general, water soluble vitamins are excreted readily and are not stored. As a result, depletion is more of a problem than toxicity.

2. **Toxicity** -- only niacin and pyridoxine are at all toxic (in high conc.). In general, the water soluble vitamins have few toxicities.

The water soluble vitamins are coenzymes for various common biochemical reactions and their status can be readily determined by measuring the appropriate enzyme activities in blood. Typically, the enzyme activity is measured in the absence and the presence of exogenously added coenzyme, to determine whether the patient needs more of the vitamin.

B. Thiamin -- (Vitamin B\textsubscript{1})

1. **Structure**

![Chemical structure of thiamin]

Chemically, the structure includes a pyrimidine ring and a thiazole ring. The thiazole ring has received enormous attention from mechanistic biochemists - they have pondered the reason for the choice by nature of a sulfur atom in the ring. Imidazole rings and oxazole rings would also, in principle, be capable of catalyzing the relevant chemical reactions.

![Space-filling model of Thiamin]
2. **Function** – used to harvest carbohydrates for energy

![Diagram of metabolic pathways involving thiamine pyrophosphate](image)

**Figure 28.9. Summary of important reactions involving thiamine pyrophosphate.**


- **a) Oxidative decarboxylation of α-keto acids**
  
  e.g. \[ \text{CH}_3\text{C}-\text{CO}_2\text{H} \xrightarrow{\text{TPP, lipoic acid, NAD}^+, \text{CoASH}} \text{CH}_3\text{C}-\text{SCO}_2^+ + \text{CO}_2 + \text{NADH} \]
  
  pyruvate dehydrogenase complex

  e.g. \[ \alpha\text{-ketoglutaric acid} \xrightarrow{\text{TPP, NAD}^+, \text{CoASH}} \text{succinyl CoA} + \text{CO}_2 \]
  
  α-ketoglutarate dehydrogenase complex
The decarboxylation is accomplished by a mitochondrial enzyme complex as shown below. L = lipoic acid, E = enzyme, TPP = thiamin pyrophosphate.

**Pyruvate dehydrogenase complex in detail**

(α-hydroxyethyl TPP)

![Diagram of the pyruvate dehydrogenase complex]

b) **Transfer of α-ketols** (pentose phosphate pathway) -- 10% of carbohydrate metabolized this way. This pathway provides pentoses for RNA and DNA synthesis and NADPH for the biosynthesis of fatty acids and other endogenous reactions.

e.g. \( \text{CHO} \)

\[
\begin{align*}
\text{CHO} &\quad \text{CHO} \\
\text{CHO} &\quad \text{CHO} \\
\text{CHO} &\quad \text{CHO} \\
\text{CHO} &\quad \text{CHO}
\end{align*}
\]

\( \begin{array}{c}
\text{CH}_2\text{OH} \\
\text{HO} \quad \text{CH} \\
\text{CH}_2\text{OPO}_3\text{H}_2 \\
\text{xyulose-5-phosphate}
\end{array} + \begin{array}{c}
\text{CHO} \\
\text{CHO} \\
\text{CHO} \\
\text{CHO}
\end{array} \rightarrow \begin{array}{c}
\text{CHO} \\
\text{CHO} \\
\text{CHO} \\
\text{CHO}
\end{array}
\]

\( \begin{array}{c}
\text{CH}_2\text{OH} \\
\text{HO} \quad \text{CH} \\
\text{CH}_2\text{OPO}_3\text{H}_2 \\
\text{ribose-5-phosphate}
\end{array} + \begin{array}{c}
\text{CHO} \\
\text{CHO} \\
\text{CHO} \\
\text{CHO}
\end{array} \rightarrow \begin{array}{c}
\text{CHO} \\
\text{CHO} \\
\text{CHO} \\
\text{CHO}
\end{array}
\]

\( \begin{array}{c}
\text{CHO} \\
\text{CHO} \\
\text{CHO} \\
\text{CHO}
\end{array} \)

\( \begin{array}{c}
\text{CHO} \\
\text{CHO} \\
\text{CHO} \\
\text{CHO}
\end{array} \)

\( \begin{array}{c}
\text{CHO} \\
\text{CHO} \\
\text{CHO} \\
\text{CHO}
\end{array} \)

\( \text{xyulose-5-phosphate} + \text{ribose-5-phosphate} \rightarrow \text{sedoheptulose-7-phosphate} \)

c) **Non-coenzyme function** – TTP involved in the control of chloride channels in brain and elsewhere in nerve impulse conduction.
3. **Mechanism** – formation of adduct with C2 of thiazole ring.

![Chemical diagram](image)

‘Classic’ experiments support this mechanism, including facile exchange of solvent D2O at the C-2 position.

4. **Deficiency** – thiamin needs are proportional to caloric intake and is essential for carbohydrate metabolism. Usually consider requirement as 0.5 mg/1000 calories plus 0.3 mg during pregnancy and lactation. Studies show laboratory evidence of thiamin deficiency (erythrocyte transketolase assay) in 20-30% of elderly patients and 40-50% of chronic alcoholics. <2% of healthy controls showed evidence of deficiency.

   a) Early signs of deficiency – anorexia, nausea, vomiting, fatigue, weight loss, nystagmus, tachycardia.

   b) Late signs of deficiency – Beriberi cardiac - increased heart size, edema cerebral - depression, irritability, memory loss, lethargy GI tract - vomiting, nausea, weight loss neurological - weakness, polyneuritis, convulsions.

   Signs and symptoms vary with age of patient, rapidity of onset, and severity of deficiency.
c) Thiamine and the alcoholic
   (i) intake low and alcohol blocks conversion of thiamin → TPP
   (ii) ↓ absorption - ↓ active transport
   (iii) ↓ storage
   (iv) increased fluid intake and urine flow causes thiamin washout
   (v) involved in fetal alcohol syndrome.

d) Wernicke-Korsakoff syndrome – seen in some alcoholics; neurological disorder resulting in impaired mental functioning → institutionalization for a significant number of patients. Symptoms: confusion, memory loss, confabulation, psychotic behavior; maybe irreversible in part.

e) Factors → B₁ deficiency
   (i) ↑ carbohydrate intake -- TPN, alcoholics
   (ii) ↓ absorption -- ulcerative colitis, etc., alcoholism
   (iii) ↓ intake -- poor diet, geriatrics, breast fed infant from B₁ deficient mother, etc.
   (iv) alcoholism.

f) Cellular uptake – Intestinal cells contain a thiamin specific receptor/transporter (hTHTR) which appears to specifically pump thiamin and not TPP. After cellular uptake, thiamin is converted to TPP. Polymorphisms in the gene encoding hTHTR are known and may contribute to thiamin-responsive megaloblastic anemia. Once in the circulation specific transport proteins may ‘store’ TPP and control its circulation (hypothesized), but most is bound to Albumin. Most ends up in skeletal muscle, brain, heart, liver.

5. **Source** – present in most tissues (as TPP) and plants (as thiamin); rich sources include: lean meat, especially pork, cereal grains, eggs, yeast, nuts. Thiaminase – in some fish (raw) and shellfish (raw) and ferns. This enzyme can hydrolyze thiamin.

![Thiamin Structure](image)

In the milling or processing or processing of rice and flour, the thiamin is lost. ‘Whole’ wheat or rice contains ~10 times as much Thiamin as white wheat or rice. Today in the USA, most white flour, rice and pastas are "enriched" to bring thiamin levels to near original levels. "Enriched" products also have added riboflavin, niacin, iron, and folic acid.
6. **Stability** – labile at pH > 4 and when heated (especially at alkaline pH values) prolonged cooking levels especially at pH > 4.

7. **Diagnosis of deficiency state**

   a) ↑ pyruvate and lactate in plasma
   b) transketolase activity in RBC – most important technique.

8. **Uses**

   a) deficiency states -- for alcoholics
   b) thiamin responsive inborn errors of metabolism -- see below
   c) mosquito repellent -- efficacy? -- for dogs, for humans 50 mg QID 2d before and during exposure is recommended.
   d) acute alcoholism: give 100 mg IM or IV stat. This is a common practice.
   e) Alzheimer’s disease—little evidence for benefit (huge doses used).

9. **Thiamin responsive inborn errors of metabolism:**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wernicke – Korsakoff</td>
<td>Transketolase</td>
</tr>
<tr>
<td>Maple Syrup urine disease</td>
<td>Failure to decarboxylate branched chain amino acids</td>
</tr>
<tr>
<td>Thiamin responsive megaloblastic anemia</td>
<td>?</td>
</tr>
<tr>
<td>Hyperalanemia</td>
<td></td>
</tr>
<tr>
<td>Hyperpyruvate acidurea</td>
<td>Pyruvate dehydrogenase</td>
</tr>
</tbody>
</table>

10. **Requirement** – 0.5 mg/1000 cal. DV = 1.5 mg. Minimum intake should be at least 1 mg.

11. **Toxicity** – nontoxic on oral administration; No UL value. Anaphylactic reactions have been observed in patients receiving repetitive parenteral doses.

12. **Patient Counseling/ Patient Use Issues**

   a) Needed to drive carbohydrates to energy
   b) Rarely needed as a single supplement. Use a multivitamin to get needed thiamin.
   c) Special benefit in alcoholics at higher doses
   d) Benefit in high doses in rare thiamin-responsive inborn errors of metabolism
   e) Uncertain benefit as a mosquito repellant (if true, 1-2 week onset)
   f) Nontoxic.
C. Riboflavin (Vitamin B₂)

Like Vitamin B₁, Riboflavin is highly water soluble, and it is difficult to achieve toxic levels in the body – excess vitamin is efficiently eliminated renally. It used as an additive in many enriched foods and can be produced in huge, industrial scale, quantities by expression of the biodynthetic enzymes in fungi or bacteria. These genetically engineered organisms may appear bright yellowish-orange, which is the color of Riboflavin.

1. **Structure**

   ![Riboflavin molecule](image)

   \[
   \begin{align*}
   \text{FMN} &= \text{riboflavin monophosphate} \\
   \text{FAD} &= \text{flavin adenine dianucleotide}
   \end{align*}
   \]

   riboflavin coenzymes

   \[
   \begin{align*}
   \text{riboflavin} &\xrightarrow{\text{gut mucosa}} \text{FMN} &\xrightarrow{\text{liver}} \text{FAD}
   \end{align*}
   \]

   ATP  ADP  ATP  ADP
2. **Function** – redox, tissue respiration, H transfer as flavin containing enzyme.

\[
\begin{align*}
\text{oxidized} & \quad \text{yellow} \\
\text{reduced} & \quad \text{colorless}
\end{align*}
\]

Examples of enzymes having flavin groups:
- succinate dehydrogenase (\(-\text{succinate} \rightarrow \text{fumarate} \text{ in TCA cycle}\))
- fatty acid acyl CoA dehydrogenase (\(\beta\)-oxidation of lipids)
- glutathione reductase – important in antioxidant activities

\[
\begin{align*}
\text{NADPH} & \quad \text{FAD} & \quad 2\text{GSH} & \quad \text{H}_2\text{O}_2 \text{ or ROOH} \\
\text{NADP} & \quad \text{FADH}_2 & \quad \text{glutathione reductase} & \quad \text{glutathione peroxidase} \\
\text{GSSG} & \quad 2\text{H}_2\text{O} \text{ or ROH} + \text{H}_2\text{O}
\end{align*}
\]

The following are important flavoproteins (containing FMN): Cytochrome C reductase (electron transport); \(\text{NADP}^+ \rightarrow \text{cytochrome C reductase}\); cytochrome P-450 reductase (drug metabolism), flavin monooxygenase (drug metabolism).

3. **Deficiency state**

   a) Not usually seen in isolation but occurs in combination with other B vitamin deficiencies.
   b) Fatigue, cheilosis, glossitis, vascularization of cornea, dermatitis
   c) Vegans and teenagers may be low in B\(_2\) if dairy intake is low
   d) Low B\(_2\) intake may be a risk factor for cataract development
   e) Alcoholics are at risk due to low intake and low absorption.

4. **Source** – milk, meats, leafy vegetables, eggs, yeast, “enriched” products.

5. **Stability**

   a) Usually > 30% destroyed by cooking
   b) Labile to light
   c) More stable in acid than alkali in absence of light.
6. **Use**
   a) Deficiency states. Is a component of most multivitamin mixtures.
   b) New – may help in migraine headache prevention.
   c) New – high intake associated with lower risk for cataracts and a 3mg supplement reduced risk.

7. **Requirements**
   a) DV = 1.7 mg
   b) “Average” U.S. diet contains 2 mg for males and 1.5 mg for females
   c) Diagnosis – erythrocyte glutathione reductase activity
   d) No UL value

8. **Patient Counseling/ Patient Use Issues**
   a) Routine single dose supplementation not needed. Use a multivitamin to get needed riboflavin.
   b) Possible use in preventing migraine headaches. Use 400 mg/d.
   c) Will turn urine bright yellow in doses higher than the DV.
   d) Nontoxic.

D. **Vitamin B₆**

1. **Structure**

   pyridoxine (P)  pyridoxal (PL)  pyridoxamine (PN)
   ![Structure Diagram]

   Pyridoxine is a commonly used term for this vitamin, but all 3 are equally active so vitamin B₆ is a better term to use.

   Three phosphorylated forms are present also:

   \[
   P \cdot PO_4 \rightleftharpoons PLP \rightleftharpoons PNP \rightleftharpoons FMN
   \]

   Coenzyme = pyridoxal-5-phosphate “PLP”
2. **Function** – participates in over 140 enzymatic reactions by forming a Schiff base with the terminal amino group of lysine in the enzyme. It is estimated that this corresponds to ~4% of all enzymatic reactions known.

\[
R \equiv NH_2 + HO\underline{\text{CH}}CH_2OP \overset{\text{PLP dependent enzyme}}{\rightleftharpoons} HO\underline{\text{CH}}CH_2OP \rightarrow \text{holoenzyme}
\]

---

**a) Transamination**

\[
R\equiv C\equiv COOH + \text{NH}_2\text{H} \overset{\text{enzyme}}{\rightarrow} \text{HO\underline{\text{CH}}CH_2OP} \overset{\text{PLP}}{\rightleftharpoons} \text{HO\underline{\text{CH}}CH_2OP} \overset{\text{H}_2O}{\rightarrow} \text{HO\underline{\text{CH}}CH_2OP}
\]

\[
R\equiv C\equiv COOH + \text{NH}_2\text{H} \overset{\text{PLP}}{\rightarrow} \text{HO\underline{\text{CH}}CH_2OP} \overset{\text{H}_2O}{\rightarrow} \text{HO\underline{\text{CH}}CH_2OP}
\]

---

**e.g. glutamate-aspartate transaminase**

\[
\text{HOOC}CH_2CH\equiv COOH + \text{CH}_3-C\equiv COOH \overset{\text{PLP}}{\rightleftharpoons} \text{NH}_2\text{H} \overset{\text{transaminase}}{\rightarrow} \text{HOOC}CH_2CH\equiv COOH + \text{CH}_3-C\equiv COOH
\]

\[
\text{HOOC}CH_2C\equiv COOH + \text{CH}_3-CH\equiv COOH \overset{\text{transaminase}}{\rightarrow} \text{NH}_2\text{H} \overset{\text{PLP}}{\rightarrow} \text{HOOC}CH_2C\equiv COOH + \text{CH}_3-C\equiv COOH
\]
b) Decarboxylation

\[
\text{R} - \text{CH} - \text{COOH} \quad \text{NH}_2 \quad \text{amino acid} \quad + \quad \text{HO}_2 \text{C} - \text{CH}_2 - \text{CH}_2 - \text{C} - \text{COOH} \quad \text{NH}_2 \quad \text{glutamic acid}
\]

\[
\text{HO}_2 \text{C} - \text{CH}_2 - \text{CH}_2 - \text{C} - \text{COOH} \quad \text{PLP} \quad \text{CO}_2 \quad \text{HO}_2 \text{C} - \text{CH}_2 - \text{CH}_2 - \text{C} - \text{H} \quad \text{NH}_2 \quad \gamma\text{-amino butyric acid (GABA)}
\]

\[
\text{HO} - \text{H} - \text{C} - \text{COOH} \quad \text{PLP} \quad \text{CO}_2 \quad \text{HO} - \text{H} - \text{C} - \text{NH}_2 \quad \text{5-hydroxytryptophan}
\]

\[
\text{HO} - \text{H} - \text{C} - \text{NH}_2 \quad \text{PLP} \quad \text{CO}_2 \quad \text{HO} - \text{H} - \text{C} - \text{NH}_2 \quad \text{5-hydroxytryptamine} \quad \text{(serotonin)}
\]

\[
\text{N} - \text{N} - \text{CH}_2 - \text{C} - \text{COOH} \quad \text{PLP} \quad \text{CO}_2 \quad \text{N} - \text{N} - \text{CH}_2 - \text{C} - \text{NH}_2 \quad \text{histidine}
\]

\[
\text{N} - \text{N} - \text{CH}_2 - \text{C} - \text{NH}_2 \quad \text{histamine}
\]

\[
\text{HO} - \text{OH} - \text{NH}_2 \quad \text{PLP} \quad \text{CO}_2 \quad \text{HO} - \text{OH} - \text{CH}_2 - \text{CH}_2 - \text{NH}_2 \quad \text{DOPA}
\]

\[
\text{HO} - \text{OH} - \text{NH}_2 \quad \text{PLP} \quad \text{CO}_2 \quad \text{HO} - \text{OH} - \text{CH}_2 - \text{CH}_2 - \text{NH}_2 \quad \text{DOPAMINE}
\]

Note: B\textsubscript{6} contraindicated in levo-DOPA therapy because B\textsubscript{6} enhances peripheral decarboxylation of levo-DOPA to dopamine which will not cross Blood Brain Barrier; Larobec\textsuperscript{®} (Roche) contains no pyridoxine and can be used if multivitamin supplementation is desired for patient on l-DOPA. The anti-Parkinsons’s drug Sinemet\textsuperscript{®} contains levo-DOPA and carbidopa (A DOPA decarboxylase inhibitor) -- therefore, no interaction.
c) B₆ and sulfur amino acid metabolism. (Note: elevated homocysteine is an independent risk factor for cardiovascular disease and birth defects.)

\[
\text{CH}_3\text{SCH}_2\text{CH}_2\text{C}^\text{COOH} \quad \text{ATP} \quad \text{H} \quad \text{CH}_3\text{SCH}_2\text{CH}_2\text{C}^\text{COOH} \\
\text{methionine} \quad \text{N}_5\text{-methyl THFA} \quad \text{methyl B}_{12} \quad \text{hydroxy B}_{12} \quad \text{S-adenosylmethionine} \quad \text{methyl acceptor}
\]

\[
\text{HSCH}_2\text{CH}_2\text{C}^\text{COOH} \quad \text{H} \quad \text{HSCH}_2\text{CH}_2\text{C}^\text{COOH} \\
\text{homocysteine} \quad \text{S-adenosylhomocysteine}
\]

\[
\text{PLP} \quad \text{serine} \quad \text{PLP} \quad \text{cystathionine} \quad \text{gamma-lyase}
\]

\[
\text{SCH}_2\text{CH}_2\text{C}^\text{COOH} \quad \text{H} \quad \text{H}_3\text{CCH}_2\text{C}^\text{COOH} \quad \text{H} \quad \text{HSCH}_2\text{CH}_2\text{C}^\text{COOH} \quad \text{NH}_2 \\
\text{cystathionine} \quad \alpha\text{-ketobutyrate} \quad + \quad \text{cysteine}
\]

d) B₆ involvement in methionine formation (and S-adenosyl methionine) makes it indirectly involved in methylation. Hence B₆ is indirectly involved in lipid metabolism and nucleic acid formation and immune function.
e) B₆ involved in tryptophan metabolism to serotonin and niacin.

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Tryptophan</th>
<th>COOH</th>
<th>HO</th>
<th>COOH</th>
<th>PLP</th>
<th>3-hydroxykynurenine</th>
<th>N-formylkynurenine</th>
<th>Kynureninase</th>
<th>3-hydroxyanthranilic acid</th>
<th>Niacin</th>
</tr>
</thead>
</table>

f) Other reactions requiring B₆:

(i) Glycogen phosphorylase (release of glucose in muscle)
(ii) Heme biosynthesis
(iii) Nucleic acid biosynthesis (via SAM)
3. **Deficiency**
   
a) Not seen usually and, if seen, is associated with other vitamin deficiencies or is iatrogenic; symptoms include rash, peripheral neuritis, anemia and possible seizures. Deficiency diagnosed by low plasma PLP and low transaminase activities (±PLP).

b) Iatrogenic B₆ deficiencies
   
   (i) Isoniazid – antituberculosis drug – forms Schiff base with B₆. Can get neuritis and convulsions. 25-300 mg/d B₆ given to prevent B₆ deficiency.

   ![Isoniazid Reaction Diagram]

   Isoniazid

   (ii) 4-Deoxypyridoxine – (experimental only)

       ![4-Deoxypyridoxine Structure]

       Symptoms – Skin lesions on face, glossitis, stomatitis, convulsive seizures (↓ GABA?), anemia (↓ heme synthesis?).

   (iii) Oral contraceptives.- older high dose Ocs can affect B6 but not a problem now.

4. **Source** – milk, meats, legumes, tuna, whole grains, beans.

5. **Stability** – pyridoxine is stable; some loss on cooking, especially with meats, due to Schiff base formation and decrease of the pyridoxal in the foods.

6. **Diagnosis of Deficiency** – measure erythrocyte transaminases.
7. **Use**
   a) Routine use in multivitamin products
   b) In INH therapy
   c) Certain inborn errors of metabolism

<table>
<thead>
<tr>
<th>Name</th>
<th>Symptoms</th>
<th>Dose of B₆</th>
<th>Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>B₆--dependent infantile convulsions</td>
<td>Clonic and tonic seizures</td>
<td>10-25 mg/day</td>
<td>Defective glutamic acid decarboxylase; possible GABA depletion</td>
</tr>
<tr>
<td>B₆--responsive anemia</td>
<td>Microcytic, hypochromic anemia</td>
<td>100 mg/day</td>
<td>Defective hemoglobin synthesis</td>
</tr>
<tr>
<td>Xanthurenic aciduria</td>
<td>Mental retardation</td>
<td>25-100 mg/day</td>
<td>Defective tryptophan metabolism due to faulty kyureninase, xanthurenic acid spills into urine</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>Mental retardation, Early heart disease</td>
<td>25-500 mg/day</td>
<td>Defective cystathionine synthetase homocysteine appears in urine</td>
</tr>
<tr>
<td>Cystathionuria</td>
<td>Mental retardation</td>
<td>25-500 mg/day</td>
<td>Defective cystathionase</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d) PMS (50-500 mg/d) -- evidence is uneven. PLP is known to bind to steroid receptors.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e) Carpal tunnel syndrome -- evidence is uneven. It seems to work for some. A trial of B₆ 100-200 mg/d for 6 mos. may be worthwhile.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f) Use in lowering homocysteine levels (see sulfur amino acid scheme above). High homocysteine may be an independent risk factor for cardiovascular disease but this is now controversial. Combine with folic acid and B₁₂ for optimum lowering action.</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>g) Nausea and vomiting in pregnancy-Helpful in high doses. PremesisRx contains 75mg sustained release B₆ (plus 12ug B₁₂, 1mg folic acid and 200mg calcium) or 25mg of generic B₆ TID is less expensive.</td>
<td></td>
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</tbody>
</table>

8. **Requirement** – DV = 2 mg; UL = 100 mg.

9. **Toxicity**
   a) > 200 mg/day can decrease prolactin levels
   b) > 1-2 g/day can cause serious neuropathy by an unknown mechanism. Recommendation: avoid long term use in doses above 200 mg.
10. **Patient Counseling/ Patient Use Considerations**

a) Routine single dose supplementation usually not needed. Use a multivitamin to get needed B\textsubscript{6}.

b) Sometimes used, with limited evidence, for carpal tunnel syndrome, PMS, and depression on OCs.

c) Rare use in high doses for inborn errors.

d) Sometimes used to prevent neuropathy with isoniazid.

e) For nausea and vomiting of pregnancy, 25 mg TID or use PremensisRx which is FDA approved for this.

f) Used with B\textsubscript{12} and folic acid in high homocysteine.

g) Keep doses < 200 mg/d to avoid neuritis.