INTRODUCTION


- It is estimated that ~50% of the adult population in the US takes some type of dietary supplement, typically to ‘improve/maintain overall health’.
- >75% of products are used without care-provider recommendation.
II. Multivitamins

- It is estimated that ~30% of the adult US population take multivitamins daily.
- A recent clinical trial of male physicians taking multivitamins concluded there was a very modest, but (statistically) significant, reduction in total cancers with daily multivitamin use (*NEJM*, 308:1871 (2012)).
- Do we need to supplement diets with vitamins/multivitamins? Maybe…. in certain circumstances.

III. When are vitamin supplements worthwhile?

- *Inadequate intake* -- alcoholics, poor, elderly, dieters, poor diet
- *Increased needs* -- pregnancy, lactation, infants, smokers, injury, trauma, recovery from surgery, infection
- *Poor absorption* -- elderly, GI disorders, specific GI surgeries, e.g. gallbladder removal, gastric bypass, cystic fibrosis, severe diarrhea, drug-induced vitamin deficiencies – e.g. long term antibiotic use, cholestyramine, mineral oil

IV. Definitions

- Vitamins are *organic compounds* and minerals are *chemical elements* that are required as nutrients in small amounts by an organism.
- Vitamers are different forms of a particular vitamin, e.g. vitamins K1 and K2, vitamins D2 and D3, retinol and retinal, etc.
V. Reference Tables for Intake of Vitamins and Elements Intakes


- Estimated average requirements (EAR): the average daily nutrient intake level estimated to meet the requirements of half of the healthy individuals in a group.
- Recommended Dietary Allowance (RDA): the average daily dietary intake level; sufficient to meet the nutrient requirements of nearly all (97-98%) healthy individuals in a group. Calculated from the EAR.
- Tolerable Upper Limit (UL): maximum adult daily intake unlikely to cause harm.

![Risk of Inadequacy vs. Observed Level of Intake](image)

**RDA = 1.2(EAR)**

Daily Values (DVs) are set by the FDA. [http://ods.od.nih.gov/HealthInformation/dailyvalues.aspx](http://ods.od.nih.gov/HealthInformation/dailyvalues.aspx)

- Two groups: Daily Reference Values (DRVs) for energy-producing nutrients, e.g. fats, carbohydrates, protein etc. and Reference Daily Intakes (RDIs) for vitamins and minerals.
- A DV is often, but not always, similar to one's RDA for that nutrient.
- DV is primarily used for labeling purposes. % DV on label is based on 2,000 calorie/day diet for adults and children over 4 yrs.
VI. Standardization

- Units of biological activity (IU) superseded, where known, by potencies based on weight (µg, mg) of the most active vitamer.
- IoM guidelines use weight.
- FDA labels use both.

VII. History and Discovery

1500 BC  Ancient Egyptians used liver - rich in vitamin A - applied to the eye to treat night blindness.

1536  Jacques Cartier, exploring the St. Lawrence River, uses local native knowledge to save his men from scurvy by boiling the needles from cedar trees to make a vitamin C-rich tea.

1795  British navy adds lemons to sailors' rations, 40 years after a Scottish naval surgeon, James Lind, had urged that citrus fruits be used to prevent scurvy.

1884  Japanese navy eradicates beriberi - vitamin B1 deficiency - by feeding sailors meat and fruit in addition to polished white rice, which lacked the thiamine-rich husks.

1897  Beriberi (a polyneuritis) was induced in birds fed only polished rice and reversed by feeding the rice polishings.

1911  Casimir Funk isolates amine-containing concentrate containing thiamine from rice polishings, which was curative for polyneuritis in pigeons, and names it 'vitamine' for vital amine.
Xavier Mertz – Antarctic explorer – dies of vitamin A poisoning from ingesting sled dog liver after supplies are lost in a crevasse.

<table>
<thead>
<tr>
<th>Year discovered</th>
<th>Vitamin</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1912</td>
<td>Vitamin B1</td>
<td>Rice bran</td>
</tr>
<tr>
<td>1912</td>
<td>Vitamin C</td>
<td>Lemons</td>
</tr>
<tr>
<td><strong>1913</strong></td>
<td><strong>Vitamin A</strong></td>
<td><strong>Milk/egg yolk</strong></td>
</tr>
<tr>
<td>1918</td>
<td><strong>Vitamin D</strong></td>
<td><strong>Cod liver oil</strong></td>
</tr>
<tr>
<td>1920</td>
<td>Vitamin B2</td>
<td>Eggs</td>
</tr>
<tr>
<td><strong>1922</strong></td>
<td><strong>Vitamin E</strong></td>
<td><strong>Wheat germ, Seed oils</strong></td>
</tr>
<tr>
<td>1926</td>
<td>Vitamin B12</td>
<td>Liver</td>
</tr>
<tr>
<td><strong>1929</strong></td>
<td><strong>Vitamin K</strong></td>
<td><strong>Alfalfa</strong></td>
</tr>
<tr>
<td>1931</td>
<td>Vitamin B5</td>
<td>Liver</td>
</tr>
<tr>
<td>1931</td>
<td>Vitamin B7</td>
<td>Liver</td>
</tr>
<tr>
<td>1934</td>
<td>Vitamin B6</td>
<td>Rice bran</td>
</tr>
<tr>
<td>1936</td>
<td>Vitamin B3</td>
<td>Liver</td>
</tr>
<tr>
<td>1941</td>
<td>Vitamin B9</td>
<td>Liver</td>
</tr>
</tbody>
</table>
VII. WATER SOLUBLE VITAMINS

A. Generalities

1. **Metabolism and storage** -- only B12 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 B1)

1. **Structure**

![Thiamin Structure](image)

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](image)
2. **Function** – used to harvest carbohydrates for energy

![Diagram of carbohydrate metabolism]

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


a) **Oxidative decarboxylation of α-keto acids**

\[
\begin{align*}
\text{e.g. } & \quad \text{CH}_3\text{C}^\text{C}=\text{CO}_2\text{H} \quad \xrightarrow{\text{TPP}} \quad \text{CH}_3\text{C}=\text{SCoA} + CO_2 + \text{NADH} \\
& \quad \text{liptoic acid NAD}^+ \text{CoASH} \\
& \quad \text{pyruvate dehydrogenase complex}
\end{align*}
\]

\[
\begin{align*}
\text{e.g. } & \quad \alpha\text{-ketoglutaric acid} \quad \xrightarrow{\text{TPP NAD}^+ \text{CoASH lipoic acid}} \quad \text{succinyl CoA} + CO_2 \\
& \quad \alpha\text{-ketoglutarate dehydrogenase complex}
\end{align*}
\]
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)

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. $\text{CH}_2\text{OH}$  $\text{CHO}$

\[ \begin{array}{c}
\text{CHO} \\
\text{CHOH} \\
\text{CHOH} \\
\text{CH}_2\text{PO}_3\text{H}_2
\end{array} \] + \[ \text{HOCH} \]

\[ \begin{array}{c}
\text{CHO} \\
\text{CHOH} \\
\text{CHOH} \\
\text{CH}_2\text{PO}_3\text{H}_2
\end{array} \]

\[ \text{CHO} \]

\[ \text{CHOH} \]

\[ \text{CHOH} \]

\[ \text{CH}_2\text{PO}_3\text{H}_2 \]

xyulose-5-phosphate  ribose-5-phosphate

c) **Non-coenzyme function** – TPP 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.

```
\[
\begin{align*}
\text{N}^3 & \text{C}^2 \text{S}^2 \\
\text{H} & \\
\rightarrow & \\
\text{N}^2 & \text{C}^1 \text{S}^1 \\
\text{H} & \\
\text{CH}_3 & \text{C} \text{COOH} \quad \text{pyruvate} \quad \text{H}^+ \\
\text{H} & \\
\rightarrow & \\
\text{N}^2 & \text{C}^1 \text{S}^1 \\
\text{H} & \\
\text{CH}_3 & \text{C} \text{COOH} \\
\text{OH} & \\
\end{align*}
\]
```

‘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 \(\rightarrow\) 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 \(\rightarrow\) institutionalization for a significant number of patients. Symptoms: confusion, memory loss, confabulation, psychotic behavior; maybe irreversible in part.

e) Factors \(\rightarrow\) B\(_1\) deficiency
   (i) ↑ carbohydrate intake -- TPN, alcoholics
   (ii) ↓ absorption -- ulcerative colitis, etc., alcoholism
   (iii) ↓ intake -- poor diet, geriatrics, breast fed infant from B\(_1\) 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.

\[
\begin{array}{c}
R \downarrow \text{CH}_2 - \text{N} \\
\text{C} \text{S}
\end{array}
\]

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</td>
<td></td>
</tr>
<tr>
<td>megaloblastic anemia</td>
<td></td>
</tr>
<tr>
<td>Hyperalanemia</td>
<td></td>
</tr>
<tr>
<td>Hyperpyruvate acidurea</td>
<td></td>
</tr>
<tr>
<td></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 biodynametic enzymes in fungi or bacteria. These genetically engineered organisms may appear bright yellowish-orange, which is the color of Riboflavin.

1. **Structure**

![Riboflavin Coenzymes](image)

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

riboflavin → gut mucosa → FMN → liver → FAD

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

![Flavin group diagram]

oxidized – yellow
reduced - colorless

Examples of enzymes having flavin groups:
succinate dehydrogenase (-succinate → fumurate in TCA cycle)
fatty acid acyl CoA dehydrogenase (β-oxidation of lipids)
glutathione reductase – important in antioxidant activities

NADPH → FAD → 2GSH
NADP → FADH₂ → GSSG → H₂O₂ or ROOH

glutatione peroxidase

The following are important flavoproteins (containing FMN): Cytochrome C reductase (electron transport); NADP⁺ -- 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 B₂ if dairy intake is low
d) Low B₂ 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) \( \text{DV} = 1.7 \text{ mg} \)
   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 B\(_6\)**

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 B\(_6\) is a better term to use.

   Three phosphorylated forms are present also:

   \[
   \text{P} \xrightarrow{\text{PO}_4} \text{FMN} \hspace{1cm} \text{PLP} \xrightarrow{\text{FMN}} \text{PNP}
   \]
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.

\[
\text{R} - \text{NH}_2 + \text{HO-CH}_2\text{CHOP} \rightleftharpoons \text{HO-CH}_2\text{CHOP} + \text{PLP dependent enzyme}
\]

PLP dependent enzyme

\[
\text{holoenzyme}
\]

a) **Transamination**

\[
\text{R} - \text{CH} - \text{COOH} + \text{R} - \text{CH} - \text{COOH} \rightarrow \text{HO-CH}_2\text{CHOP} \rightleftharpoons \text{HO-CH}_2\text{CHOP} \rightleftharpoons \text{HO-CH}_2\text{CHOP} + \text{PLP}
\]

\[
\text{NH}_2 \quad \text{NH}_2
\]

\[
\text{CH}_3 \quad \text{CH}_3
\]

\[
\text{PNP}
\]

\[
\text{transaminase}
\]

\[
\text{aspartic acid}
\]

\[
\text{pyruvic acid}
\]

\[
\text{oxaloacetic acid}
\]

\[
\text{alanine}
\]

\[
\text{PLP}
\]

\[
\text{e.g. glutamate-aspartate transaminase}
\]
b) Decarboxylation

\[
\text{R} - \text{CH} - \text{COOH} + \text{NH}_2 \xrightarrow{\text{decarboxylase}} \text{R} - \text{CH} - \text{NH}_2 + \text{CO}_2
\]

e.g.

\[
\text{HOOC}\text{CH}_2\text{CH}_2\text{C} - \text{COOH} \xrightarrow{\text{PLP}} \text{HOOC}\text{CH}_2\text{CH}_2\text{C} - \text{H} \xrightarrow{\text{PLP}} \text{NH}_2
\]

\[
\gamma\text{-amino butyric acid (GABA)}
\]

\[
\text{HO} - \text{C} - \text{COOH} \xrightarrow{\text{PLP}} \text{HO} - \text{C} - \text{NH}_2
\]

\[
\text{(5-hydroxytryptophan)}
\]

\[
\text{HO} - \text{C} - \text{COOH} \xrightarrow{\text{PLP}} \text{HO} - \text{C} - \text{NH}_2
\]

\[
\text{(5-hydroxytryptamine (serotonin))}
\]

\[
\text{CH}_2 - \text{C} - \text{COOH} \xrightarrow{\text{PLP}} \text{CH}_2 - \text{C} - \text{NH}_2
\]

\[
\text{(histidine)}
\]

\[
\text{CH}_2 - \text{C} - \text{COOH} \xrightarrow{\text{PLP}} \text{CH}_2 - \text{C} - \text{NH}_2
\]

\[
\text{(histamine)}
\]

\[
\text{HO}\text{C} - \text{CH}_2\text{NH}_2 \xrightarrow{\text{PLP}} \text{HO}\text{C} - \text{CH}_2\text{NH}_2
\]

\[
\text{(DOPA)}
\]

\[
\text{HO}\text{C} - \text{CH}_2\text{NH}_2 \xrightarrow{\text{PLP}} \text{HO}\text{C} - \text{CH}_2\text{NH}_2
\]

\[
\text{(DOPAMINE)}
\]

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\textreg;(Roche) contains no pyridoxine and can be used if multivitamin supplementation is desired for patient on l-DOPA. The anti-Parkinsons’s drug Sinemet\textreg; 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.)

\[
\begin{align*}
\text{methionine} & \xrightarrow{\text{ATP}} \text{S-adenosylmethionine} \\
\text{homocysteine} & \xrightarrow{\text{PLP, serine}} \text{cystathionine} \\
\text{cystathionine} & \xrightarrow{\text{PLP, cystathionine } \gamma\text{-lyase}} \text{α-ketobutyrate} + \text{cysteine}
\end{align*}
\]

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.

f) Other reactions requiring B₆:

(i) Glycogen phosphorylase (release of glucose in muscle)
(ii) Heme biosynthesis
(iii) Nucleic acid biosynthesis (via SAM)

SUMMARY of Pyridoxal/pyridoxamine reactions

hydrolysis of Imine leads to incorporation of ‘oxygen atom’

$\text{H}_2\text{O}$ attacks carbon atom of the imine, that carbon gets an oxygen

PLP enzymes control which carbon atom gets the oxygen atom by switching between the external imine and the internal imine.
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.

\[
\text{Isoniazid} \quad \xrightarrow{\text{C-NH-NH}_2} \quad \text{PLP}
\]

(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>Cystathionurea</td>
<td>Mental retardation</td>
<td>25-500 mg/day</td>
<td>Defective cystathionase</td>
</tr>
<tr>
<td>d)</td>
<td>PMS (50-500 mg/d) -- evidence is uneven. PLP is known to bind to steroid receptors.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e)</td>
<td>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>
</tr>
<tr>
<td>f)</td>
<td>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>
<td></td>
<td></td>
</tr>
<tr>
<td>g)</td>
<td>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>
<td></td>
</tr>
</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 B₆.

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 B₁₂ and folic acid in high homocysteine.

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