Update on Herbals and Supplements in the CKD Patient
Landon Dickson, MD; Nephrology Associates; 10/31/14
Confusing for patients
Confusing for doctors
Case #1

- Your 68 year old mother-in-law with CKD Stage 3 (GFR 55 ml/min) comes to you for advice on supplements
- PMH: CKD, HTN, DM2, CAD
- Meds: ASA 81mg daily, Metoprolol XL 25mg daily, HCTZ 25mg daily, Lisinopril 10mg daily, Metformin 500mg BID, and Atorvastatin 10mg daily
- OTC Meds: MVI, Vitamin C, Vitamin D3, Green Tea, Blue Cohosh, Citrus Aurantium, Dandelion Root, and St. John’s Wort
- Wants to add Vital Lady
- Your response?
Case #1 Response

- A. Yes, it is safe, but stop St. John’s Wort as it causes hyperkalemia.
- B. Yes, it is safe, but stop Citrus Aurantium and Green Tea because they lead to oxalate production, worsening the risk of AKI and stones.
- C. No, it's not safe, also stop Blue Cohosh which increases blood pressure.
- D. No, it's not safe, also stop Dandelion Root since it has a mineralocorticoid effect.
- E. Wait a minute. This is your mother-in-law. Take it, take it all!!!!
Case #2

- 55 yo healthy male, co-owner of a large Utah supplement manufacturing company referred for elevated creatinine found on a work health exam (previously normal kidney function in 2013)
- PMH: low back pain, BPH, HTN, skin cancer
- Meds: Advil 800mg BID, flomax 0.4mg daily, amlodipine-benazepril 5-20mg daily, MVI
- BMP: 140/4.8/105/22/38/2.2/9.8
- Urinalysis: pH 5.5, spGv 1.005, TR protein, Hgb -, Nit -, LE –
- Urine microscopy: no crystals, no casts, no RBCs, no WBCs
- What is the cause of his acute kidney injury?
Case #2 Response

- A. AKI d/t hypertensive nephropathy consistent with a bland urine sediment and history of HTN
- B. AKI d/t NSAID nephropathy from high use over time
- C. AKI d/t drug toxicity
- D. AKI d/t obstructive uropathy from his BPH consistent with his mild hyperkalemia and bland urine sediment
Herbal and Supplement Definition

- A group of diverse medical and health care systems, practices, and products that are not presently considered to be a part of conventional medicine.
  - Alternative Medicine: used *in place of* conventional medicine
  - Complementary Medicine: used *together with* conventional medicine
Background

- Dietary Supplement Health and Education Act (DSHEA); 1994; coauthored by Senator Orrin Hatch of Utah
  - No FDA approval process for marketing
  - No FDA requirement for purity or manufacturing standards
  - No FDA review of claims of efficacy
  - Only requirement: “This product is not intended to diagnose, treat, cure, or prevent any disease.”

- NIH: $250 Million dollars annually
  - $122 million to National Center of Complementary and Alternative Medicine (NCCAM)
  - $122 million to Office of Cancer Complementary and Alternative Medicine (OCCAM)
Supplement Facts

Dietary Supplement

100 Capsules

Serving Size: 2 capsules
Servings per container: 50

Amount per Serving % Daily Value

Proprietary Herbal Blend: 500mg *
Boswellia Serrata, Turmeric, Willow Bark,
Natural Dry Collagen, Sarsaparilla Bark, Cat's Claw,
Glucosamina Potassium Sulfate Complex, Cayenne,
Methylsulfonylmethane (MSM), Chondroitin Sulfate,

These Statements have not been evaluated by the Food and Drug Admin. This product is not intended to diagnose, treat, cure or prevent any disease.

Ginseng 400 mg **
(8% Ginsenosides)

**Daily value has not been established.
Background

- >11,000 species of plants known to have medicinal purposes
  - 500 commonly used among various ethnic groups
  - >120 current pharmaceutical medications are plant derived

- 10.2% Americans consulted an herbal provider in 1993; 15.1% did in 1998

- Growing worldwide market
  - $1.6 Billion market in US in 1994 to $3.9 Billion in 1998
  - Europeans spent over $5 Billion in 2003 on herbals and supplements

Distribution of the $4.96 Billion European Market for Over-the-Counter Herbal Medicines in 2003

<table>
<thead>
<tr>
<th>Country</th>
<th>Sales (U.S. dollars)</th>
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<tbody>
<tr>
<td>Germany</td>
<td>2.06 billion</td>
</tr>
<tr>
<td>France</td>
<td>1.13 billion</td>
</tr>
<tr>
<td>Italy</td>
<td>543 million</td>
</tr>
<tr>
<td>Poland</td>
<td>252 million</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>211 million</td>
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<tr>
<td>Spain</td>
<td>170 million</td>
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<tr>
<td>Belgium</td>
<td>127 million</td>
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<tr>
<td>Switzerland</td>
<td>93 million</td>
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<tr>
<td>Austria</td>
<td>88 million</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>81 million</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>76 million</td>
</tr>
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Participants: Community-based survey of 21,169 nonpregnant noninstitutionalized US civilian adults (aged ≥20 years)

Outcome: Self-reported use of dietary supplements containing any of 37 herbs the National Kidney Foundation identified as potentially harmful in the setting of CKD
Results: Duration of Use

**Figure 1.** Frequency of supplement use in the last 30 days among US adults 20 years or older reporting potentially harmful supplement use, NHANES (National Health and Nutrition Examination Survey) 1999-2008.

**Figure 2.** Duration of supplement use among US adults 20 years or older reporting potentially harmful supplement use, NHANES (National Health and Nutrition Examination Survey) 1999-2008.
Dietary Supplements by Race

- Caucasian: 57.3
- Black: 36.1
- Hispanic: 30.6
Complementary and Supplement Use by Age Group

<table>
<thead>
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<th>2007</th>
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Complementary and Supplement Use by Age Group

Purchased by parents for their children!

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Supplements in CKD  (Grubbs, V. Am J Kid Dis 2013)

- No CKD: 48.9%
- CKD Stages 1-2: 50.2%
- CKD Stage 3-4: 65.1%
Supplements in CKD (Grubbs, V. Am J Kid Dis 2013)

To relieve sx, slow progression, find a cure

- No CKD: 48.9
- CKD Stages 1-2: 50.2
- CKD Stage 3-4: 65.1
Demographics

- Caucasian
- Female >> Male
- College Education
- Higher Income (> $50,000)
- Ages 35-49
Herbals with Potassium

- Alfalfa
- American Ginseng
- Bai Zhi (root)
- Bitter Melon (fruit, leaf)
- Black Mustard (leaf)
- Blessed Thistle
- Chervit (leaf)
- Chicory (leaf)
- Chinese Boxthorn (leaf)
- Coriander (leaf)
- Dandelion (root, leaf)
- Dulse
- Evening Primrose
- Feverfew
- Garlic (leaf)
- Genipap (fruit)
- Goto Kola
- Japanese Honeysuckle (flower)
- Kelp
- Kudzu (shoot)
- Lemongrass
- Mugwort
- Noni
- Papaya (leaf, fruit)
- Purslane Sage (leaf)
- Safflower (flower)
- Sassafras
- Scullcap
- Shepherd's Purse
- Stinging Nettle (leaf)
- Turmeric (rhizome)
- Water Lotus
Herbals with Phosphorous (www.kidney.org/atoz/content/herbalsupp)

- American Ginseng
- Bitter Melon
- Borage (leaf)
- Buchu (leaf)
- Coriander (leaf)
- Evening Primrose
- Feverfew
- Flaxseed (seed)
- Horseradish (root)
- Indian Sorrel (seed)
- Milk Thistle
- Onion (leaf)
- Pokeweed (shoot)
- Purslane
- Shepherd's Purse
- Silk Cotton Tree (seed)
- Stinging Nettle (leaf)
- Sunflower (seed)
- Turmeric (rhizome)
- Water Lotus
- Yellow Dock
Herbals That Have Diuretic Properties
(www.kidney.org/atoz/content/herbalsupp)

- Bunch Leaves
- Juniper Berries
- Uva Ursi
- Parsley Capsules
Herbals That Interfere With Other Medications (www.kidney.org/atoz/content/herbalsupp)

- St. John’s Wort
- Echinacea
- Ginkgo Biloba
- Garlic
- Ginseng
- Ginger
- Blue Cohosh
NKF’s Herbals to Avoid in CKD

- Astragalus
- Barberry
- Cat's Claw
- Apium
- Graveolens
- Creatine
- Goldenrod
- Horsetail
- Huperzinea
- Java Tea Leaf
- Licorice Root
- Stinging Nettle
- Oregon Grape Root
- Parsley Root
- Pennyroyal
- Ruta Graveolens
- Uva Ursi
- Yohimbe
Purity of Herbals (not regulated)

- Contamination or Adulteration
  - Heavy metals
  - Sibutramine (appetite suppressant)
  - Fenproporex – not approved in the US
  - Fluoxetine
  - Bumetanide
  - Furosemide
  - Rimonabant – not approved in the US
  - Cetilistate – not approved in the US
  - Anabolic steroids

- 32% of OTC herbals in California have ephedrine, **lead**, **arsenic**, **mercury**, methyltestosterone, phenacetin (Wojcikowski K. et al. Nephrology 9;313,2004)

- 72 herbal weight loss products have been banned by the FDA d/t containing **amphetamines**
Ephedra

- Alpha-adrenergic stimulant; cocaine-like
- In MaHuang
- Use: energy supplement (stimulant), weight loss (thermogenesis), asthma
- Side Effects: HTN (vasoconstriction), kidney stones (precipitates)
- Banned 4/12/2004
Ephedra Substitutes

- Bitter Orange (Citrus Aurantium) – synephrine 525mg
  - Hypertension

- Blue Cohosh – multiple sympathomimetic alkaloids
  - Coronary vasoconstriction, hypertension

- DMMA (dimethylamylamine)
  - Amphetamine analog, alpha agonist
  - Used by weight lifters for energy
  - Sold under 10 different names
  - Heat stroke, acute myocardial infarction, hypertension
  - 86 reports of complications including fatalities
Licorice

- From *glycyrrhiza glabra*
- Sweetener for herbals, 50X sweeter than sugar
- Present in 2/3 of Chinese herbal formulations; present in candy, gum, tobacco, throat lozenges
- Active ingredient is glycyrrhizin (in US, remove glycyrrhizin and use anise instead)
- Blocks 11beta-hydroxysteroid dehydrogenase type 2
  - Increases access of cortisol to MCR
    - Sodium retention and potassium loss
      - Apparent Mineralocorticoid Excess (AME)
        - HTN, hypokalemia, metabolic alkalsosis, low aldosterone, low renin
St. John’s Wort

- Antidepressant, antiviral, treats wounds
- Induces P-450 pathway
  - CYP3A4, CYP2E1, CYP2C19 (involved in >50% of medications)
- Induces intestinal P-glycoprotein/MDRPI
  - Increases export of drug from blood to intestinal lumen
St. John’s Wort

- Decreased bioavailability, decreased drug levels
  - Theophylline (→ pulmonary decompensation)
  - Warfarin (→ clots)
  - Digoxin (→ CHF exacerbations)
  - Thyroid hormone
  - Lipid-lowering agents
  - Oral contraception (→ pregnancy)
  - NNRTIs (→ uncontrolled HIV)
  - Protease inhibitors
  - Calcineurin inhibitors (→ transplant rejection)
  - SSRIs (→ worsening depression)
  - Tyrosine kinase inhibitors
Remember

- St. John’s Wort INDUCES P-450
  - -> decreased drug levels

- Grapefruit Juice INHIBITS P-450
  - -> increased drug levels
Aristolochic Acid Nephropathy (AAN)

- **Chinese Herb Nephropathy**
  - Ingredients containing Aristolochic Acid used in traditional medicine in China, Japan, and India

- **Balkan Nephropathy**
  - Plants in farming communities in Bulgaria, Bosnia, Croatia, Romania, and Serbia along the Danube River basin

- Causes tubulointerstitial nephritis that rapidly progresses to fibrosis and ESRD over months

- 40-45% get renal and urinary tract cancers

- No proven treatment
Cases of CHN/AAN Reported in the Literature Around the World

- USA: 2
- Belgium: 128
- Germany: 1
- UK: 4
- France: 4
- Spain: 1
- China: 116
- Korea: 1
- Japan: 6
- Taiwan: 33

Ginseng
Ginseng

- Ginseng – support nervous system, decrease stress, regulate blood sugars, adrenal health
  - Asian -> no drug interactions
  - American -> reduces effectiveness of warfarin
  - Siberian -> increases digoxin levels, hyperkalemia (inhibits Na-K ATPase)
Others

- Garlic – to reduce blood pressure
  - Inhibits CYP2E1
    - Reduces protease inhibitor activity
    - Avoid in HIV patients

- Ginkgo Biloba – to enhance memory (elderly)
  - Induces CYP2C19
    - Reduces valproic acid and dilantin levels
      - Decreased threshold for seizures
    - Potentiates the effects of ASA and plavix
      - Increased risk of bleeding (elderly!)
Others

- Alfalfa -> triggers lupus, hyperkalemia
- Aloe -> albuminuria, AKI
- Buckthorn -> albuminuria
- Cascara -> albuminuria
- Cranberry juice -> oxalate -> kidney stones
- Hawthorn berry -> lowers BP, but hyperkalemia
- Nettle -> AKI, hyperglycemia
- Wormword -> AKI, rhabdomyolysis
- Yohimbe -> AKI, triggers lupus
Beware

- “Proprietary Blend” – often undisclosed ingredients
  - More and more AKI being seen with newer agents
- Transfer factors: from cow colostrum and chicken egg yolks; helps the immune system “recognize, respond, and remember”
  - Have been associated with AKI in some patients
Herbals and Hyperkalemia - AVOID IN CKD!

- High potassium concentration
  - Noni juice
  - Alfalfa
  - Dandelion root
  - Horsetail
  - Nettle

- Inhibition of Na-K ATPase (digoxin effect)
  - Milkweed
  - Lily of the Valley
  - Hawthorne berries
  - Siberian ginseng
Noni Juice

- From fruit of the Noni Tree
  - High in potassium (contraindicated in CKD, esp if ACE/ARB/aldactone)
    - Tomato juice 58 meq/l
    - **Noni juice** 56 meq/l
    - Orange juice 51 meq/l
    - Grapefruit juice 43 meq/l
    - Grape juice 36 meq/l
    - Pineapple juice 34 meq/l
    - Apple juice 32 meq/l
Vital Lady

- Part of ayurvedic medicine in India
- Ayurveda = Science (Veda) of Life (Ayu)
- Heavy metals deliberately placed to cleanse the body

Contains
- Lead
- Copper
- Arsenic
- Gold
- Sulfur

Metals are “detoxified” by process of samskaras
- Prayer + ritual preparation

Digestive wellness, pain, hair, nails, skin
Case #1 Response

A. Yes, it is safe, but stop St. John’s Wort as it causes hyperkalemia.

B. Yes, it is safe, but stop Citrus Aurantium and Green Tea because it leads to oxalate production, worsening the risk of AKI and stones.

C. No, it’s not safe, also stop Blue Cohosh which increases blood pressure.

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E. Wait a minute. This is your mother-in-law. Take it, take it all!!!!
Case #2 Response

- The patient initially denied OTC medications or herbals.
- After urine and serum work up was unimpressive, he was again asked if he takes his own products. He stated he was taking a complex regimen of transfer factors plus proprietary blends, which he had started 8 months prior.
- After much discussion, he finally agreed to stop his herbals (despite ingredients seeming benign).
- Cr was 2.0 at 1 month, 1.7 at 3 months, 1.3 at 6 months and remained stable.
- Patient was subsequently lost to follow-up thereafter.
Case #2 Response

- A. AKI d/t hypertensive nephropathy consistent with a bland urine sediment and history of HTN
- B. AKI d/t NSAID nephropathy from high use over time
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NKF Website on Herbals

- [www.kidney.org/atoz/content/herbalsupp](http://www.kidney.org/atoz/content/herbalsupp)