Natural versus Synthetic Chemicals: Regulation and Toxicology of Dietary Supplements

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Instructor:
Toxicology 429 (Fall term): Toxic Substances in Food
Power to help patients meet their lipid goals

When used with diet and exercise

Lipitor®
atorvastatin calcium
tablets

Important information:
Lipitor® (atorvastatin calcium) is indicated as an adjunct to diet to reduce elevated total cholesterol, LDL-C, and triglycerides and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia.

Lipitor® is contraindicated in patients with active liver disease and/or unexplained persistent elevations of serum transaminases. Lipitor® is not recommended for use in women who are or may become pregnant or who are nursing. In patients with hyperhistamine, sensitivity to any component of this medication.

Due to increased risk of myopathy seen with Lipitor® and other statins, physicians should carefully consider combined therapy with fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or isotretin and carefully monitor patients for signs or symptoms of myopathy early during therapy and when changing dose of other drug.

It is recommended that liver function tests be performed prior and at intervals following the initiation of therapy and any elevation of dose, and periodically thereafter. If ALT or AST values ≥3× ULN persist, dose reduction or withdrawal is recommended.

In clinical trials, the most common adverse events were constipation, diarrhea, dyspepsia, and abdominal pain.

Please see brief summary of prescribing information on the next page.

Power you can trust™

Tablets not shown to scale.
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Combine Cardio-Edge™ with world-famous Ultra Preventive® X (rated the #1 multi-vitamin by health professionals), along with CoQ10; our exclusive fast-acting coenzyme Q10 and get the EDGE on cardiovascular health.
Comparing Pharmaceuticals, Dietary Supplements

Pharmaceuticals
- Chemical can be natural or synthetically derived
- FDA regulates as drugs
- Requires regulatory (FDA) pre-market assessment of risk, efficacy
  - Post-marketing surveillance (for adverse reactions)
- System is not perfect
  - Some risks not identified until after marketing

Dietary Supplements
- Chemical is derived from foods or animal tissues
  - Generally, natural chemicals
- FDA regulates as foods (not drugs)
- Pre-market assessment of risk (by FDA) is limited
  - No assessment of efficacy
- System is not perfect
  - Some risks not identified until after marketing
  - Some risks differ from pharmaceuticals

Are Natural Chemicals Safer? Better? What are the risks?
What’s In Our Food?

A complex mixture

- **Nutrients**
- **Non-nutrient substances**
  - Frequently vital for plant or organism survival
    - Plant hormones
    - Naturally occurring pesticides
  - Products of food preparation
    - Additives, coloring agents
  - Natural and unavoidable contaminants
    - Products of microbial contamination
    - Products of environmental pollution
  - Chemicals with pharmacological properties in animals, humans

<table>
<thead>
<tr>
<th>Food</th>
<th>Number of non-nutrient chemicals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheese</td>
<td>160</td>
</tr>
<tr>
<td>Bananas</td>
<td>325</td>
</tr>
<tr>
<td>Wine</td>
<td>475</td>
</tr>
<tr>
<td>Coffee</td>
<td>625</td>
</tr>
<tr>
<td>Beef</td>
<td>625</td>
</tr>
</tbody>
</table>
Example of a Natural, Unavoidable Contaminant of Food

- **Aflatoxins**
  - A chemical produced by certain environmental fungi
  - Can contaminate corn, nuts, cottonseed, tobacco, many other agricultural commodities

- **What are the risks?**  Hazard $\times$ Exposure
  - Depends on the dose
    - U.S.A. (very low dose)
    - China (liver cancer from chronic dietary overexposure)
    - Kenya (acute liver failure from acute dietary overexposure)
Natural Contaminants of Food: Another Example

- Botulinum toxin
  - A chemical produced by *Clostridium botulinum*
  - Can be produced in improperly canned foods, vegetables
  - The most potent neurotoxin known
    - 70 micrograms can be lethal in humans
- What are the risks? Hazard x Exposure
  - Depends on the dose
    - Extremely low dose (nanograms) → Botox
      - Pharmaceutical uses
    - Higher doses
      - Life threatening paralysis in humans
        - Agent of biological warfare
Natural Components of Food: A Final Example

- Solanaceous glycoalkaloids
  - Chemicals that are normally present in tomatoes, potatoes, eggplant
  - Naturally occurring insecticides
    - Similar mechanisms of toxicity as organophosphate, carbamate insecticides (Lorsban, Dursban)

- What are the risks?
- Hazard x Exposure
  - Depends on the dose
    - Modern-day exposure is far below threshold for toxic effects
    - Epidemics of poisoning have been rarely reported throughout human history
Are Natural Chemicals Safer? Better? What are the risks?

- Food is a complex mixture of beneficial and potentially hazardous chemicals.
- Some of the most potent toxic and carcinogenic chemicals known can (and do) occur naturally in foods.
- Health risks are a function of hazard and exposure.
  - The dose makes the poison.
Power to help patients meet their lipid goals

When used with diet and exercise

LIPITOR,
atorvastatin calcium,
cholesterol

POWER YOU CAN TRUST™

Important information:
LIPITOR (atorvastatin calcium) is indicated as an adjunct to diet and other lifestyle changes to reduce total and LDL cholesterol levels and to reduce the risk of stroke in patients with elevated LDL cholesterol levels. LIPITOR is contraindicated in patients with active liver disease or unexplained persistent elevation of serum transaminases. It is not recommended for use in pregnant or lactating women. LIPITOR is used in patients who are receiving or are to become pregnant or are nursing in addition to diet and lifestyle changes. It is unknown if LIPITOR can cause harm to the fetus or if it can cause serious adverse reactions in the nursing mother. The safety and effectiveness of LIPITOR have not been established in children under 10 years of age.

Please see full Summary of Product Characteristics. Potentially common adverse effects are muscle pain and tenderness, injection site reactions, rash, headache, and upper respiratory tract infections.
What is a Dietary Supplement?

- Defined by U.S. Congress in 1994
  - Dietary Supplement Health and Education Act (DSHEA) of 1994, amended Federal Food, Drug, Cosmetic Act
  - product taken by mouth that contains a "dietary ingredient" intended to supplement the diet
    - Includes nutrients and non-nutrients derived from foods
      - Vitamins, minerals, herbal or botanical extracts, enzymes, metabolites
  - DSHEA considers dietary supplements as foods, not drugs
    - Requires labeling to indicate it is a dietary supplement
    - Dietary supplements are not considered food additives
      - Food additives require pre-market toxicology testing and risk assessment by the U.S. FDA

- An industry generating >$17 billion/year
  - Thousands of products are marketed in U.S.
Dietary Supplement versus a Drug?

- Under DSHEA, it is the *intended use* of a product that distinguishes a drug from a dietary supplement
  - Drug: Intended to diagnose, treat, prevent, or cure disease
  - Dietary supplement: **Not** intended to diagnose, treat, prevent, or cure disease
    - Under DSHEA, product label must indicate this
    - DSHEA has other provisions which limit what may be claimed on the product label
Prior to DSHEA, dietary supplements were subject to same requirements as other components of food under FFDCA
- Same regulatory scrutiny as food additives

DSHEA amended FFDCA, providing regulations specific for dietary supplements, including:
- Firms manufacturing or distributing supplements are responsible for determining their safety
- Firms responsible for ensuring that label claims cannot be false, misleading

Burden of ensuring quality, safety, accurate labeling, efficacy placed upon manufacturers
- Contrast scenario of FDA regulatory role with food additives and drugs
DSHEA of 1994

- What is the regulatory standard of safety for dietary supplements under DSHEA?
- Dietary supplement considered “adulterated” (and removed from the market by FDA) if it presents an “unreasonable risk of illness or injury” when used as directed, or under normal conditions of use.
  - Contrast with safety standard for food additives, pesticide residues in foods
    - There must be a reasonable certainty of no harm

- Dietary supplements do not need approval from FDA before they are marketed
- Firms do not need to provide FDA with information regarding safety, efficacy
  - Exception: “New dietary ingredients” *(post-1994)*
- Manufacturers do not need to register their products with FDA before producing, marketing them
  - exception: “New dietary ingredients” *(post-1994)*
- Currently, no regulatory standards exist to ensure quality, purity of dietary supplements
  - FDA proposes to develop regulatory standards in future
    - Currently, the manufacturer is responsible for this
    - Contrast with drugs (Good Manufacturing Practices, Good Laboratory Practices)
Manufacturers have no legal obligation under DSHEA to report data about safety and purported benefits of products

- To FDA or to public
  - Contrast with requirements for food additives, drugs

Under DSHEA, FDA has legal burden to determine a supplement is unsafe before it can restrict production, sale in U.S.

- Needs to be proven harmful prior to legally restricting or prohibiting sale of the product
  - if it presents an “unreasonable risk of illness or injury”
- Post-marketing surveillance for adverse events is under a voluntary reporting system in the United States
DSHEA of 1994 (Product Labeling)

- Certain information must appear on label of dietary supplements
  - manufacturer, packer, or distributor; a complete list of ingredients; and the net contents of the product
  - “Not intended to diagnose, treat, prevent, or cure disease”
- There are no rules on serving size or amounts of ingredients in dietary supplements
  - Decision made by manufacturer, not subject to FDA approval
  - Manufacturer responsible for confirming quality, content of product formulation
    - Not monitored by FDA
    - Proposed rulemaking is currently under consideration by FDA
DSHEA of 1994: Labeling Claims on Dietary Supplements

- Label cannot claim a supplement will treat, diagnose, or cure disease

- Three categories of health claims allowed on label:
  - **Nutrient content claims**
    - Product is a “good source of substance X”
  - **Health claims**
    - relationship between a substance and a disease or health-related condition
    - “diets high in _____ may increase/decrease………”
  - **Structure-function claims**
    - Benefits in context of physiological function
    - “calcium plays an important role in healthy bones”

- Manufacturer (not FDA) responsible for confirming validity of the label claims
Adverse Events Associated with Dietary Supplements: Examples

- L-tryptophan and eosinophilia-myalgia syndrome
  - 1989: 1500 cases, 37 deaths attributed to contaminant in manufacturing process at a single facility in Japan

- Other examples of supplements containing unwanted addition of undesirable contaminants
  - Digitalis poisoning resulting from plantain-derived dietary supplement contaminated by digitalis lantana
  - Kava kava (Piper methysticum) and liver failure
  - Studies have identified other environmental contaminants in dietary supplements
    - Aflatoxins, lead, mercury, DDT as examples
Adverse Events Associated with Dietary Supplements: Examples

- Some dietary supplements may interact with effects of pharmaceutical drugs
- St John’s Wort
  - Can induce as well as inhibit liver enzymes involved in the metabolism of drugs and other chemicals
    - Cyclosporin
    - Indinavir
    - Oral contraceptives
    - Tricyclic antidepressants
    - Benzodiazepenes
Adverse Events and Dietary Supplements: GHB as Example

- Marketed as dietary supplement in 1990’s
  - Active ingredient (GHB) occurs naturally in animal (and human) tissues
    - Sold at health food stores, fitness stores
    - Labeling emphasized “organic” derivation
- Purported euphoric, anabolic, “body building,” other effects
  - Unsuspecting victims
- Became part of club scene
  - Sedative-hypnotic drug of abuse
  - Implicated in date rapes
- Now is a Schedule I Controlled Substance (DEA)
Other Dietary Supplements of Current Concern

- Plant alkaloids containing ephedrine
  - Example of botanical: Ma Huang (ephedra sinica)
  - Contains mixture of mainly ephedrine, other stimulant alkaloids
    - Pseudoephedrine (common OTC decongestant)
- Widely marketed as dietary supplement
  - Weight loss, athletic enhancement
- Pharmacology, toxicology of ephedrine, related alkaloids
  - Increased heart rate, blood pressure (blood vessel constriction), bronchodilator effects
- Some studies have demonstrated poor correlation between product labeling and actual dose of what appears in the product
  - Contrast with regulatory oversight over pharmaceuticals
    - Good Manufacturing Practices (GMP’s)
Dietary Supplements: Observations and Challenges

- Components of dietary supplements can have pharmacological, toxicological effects on healthy individuals
  - What about individuals with disease?
  - Role of chemical interactions?
    - Dietary supplements with pharmaceutical drugs
  - Does the regulatory risk assessment process for dietary supplements take these factors in consideration?
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Questions for Discussion

- Are Natural Chemicals Safer? Better?
- What are the risks?
  - What distinguishes a dietary supplement from a drug?
  - Has this question been answered from a scientific perspective, a regulatory perspective, or both?
  - Are dietary supplements adequately regulated to protect the public from health risks?
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