

Drug Supplements & Drug Discovery and Development

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Lecture Outline

- Speaker Background (5 minutes)
- Supplements (40-50 minutes)
- Break (10 minutes)
- Drug Discovery and Development (20-30 minutes)
- Wrap-up and follow up questions (10-25 minutes)

Speaker Background

- Green Bay native
- 3rd career pharmacist (others: pastoral ministries & public education)
- Went into pharmacy because of familial seeming medication misuse
- Graduated University of Arizona with a Doctor of Pharmacy degree
- Additional community residency done through UW Madison – at Streu's Pharmacy in Green Bay – Transition of Care service developed with Bellin Health
- Two and a half years in Specialty Pharmacy – Certified Specialty Pharmacist
- Ambulatory Care Pharmacist with Bellin Health – at Howard Clinic – Goal of reducing costs through preventative and intervening medication care

Drug Supplements

Supplements – Lecture Outline



- Supplements - Definitions
 - What are they?
 - What are they not?
 - What is a drug?
- Supplements - Do They Work?
 - Where do drugs come from?
 - What is the Placebo Effect – Healthcare Understanding and Nocebo
 - Drug-drug interactions
 - Cost
- Supplements – Looking at Specific Ones I See Commonly

Supplements – What are They?



- Zion Market Research – Jan 2017 publication “Dietary Supplements... Prespective, Comprehensive Analysis and Forecast 2016-2022” Dietary supplements valued globally at \$132.8 Billion in 2016, expected \$220.3 Billion in 2022
- Statistica.com – estimated prescription drug revenue worldwide in 2018 - \$811 Billion
 - *“A billion here, a billion there, pretty soon, you're talking real money.”*
 - Thought to be said by Everett Dirksen on The Tonight Show
- Wish to be viewed as Natural and Safe
 - Pharmacist on record – Never, ever let natural equal safe
 - Amygdalin in certain fruit seeds (peach, apricot, plum, etc.) breaks down to cyanide
 - Was actually marketed as a dietary supplement “Laetrile” also known as “Vitamin B-17”
 - Mercury and Antimony both natural elements, used in past as remedies, very, very toxic
- What many Americans are turning to
 - Healthcare professionals need to understand and work with this

Supplements – What are They Not?

- They are not FDA regulated
 - FDA does have guidelines for the industry, but the industry is the one who is responsible for making sure they abide by the guidelines
 - If a new ingredient* is in the supplement, must notify FDA and demonstrate that it is reasonably safe
 - New ingredient = Not marketed as a dietary supplement prior to October 15, 1994 – however no list exists of this, thus the industry must vouch for it
- Solid-study demonstrated effectiveness
 - Many of the studies are not constructed well, leading to potentially diluted and/or bias outcomes
 - Studies do not have to mean anything – Prescription drugs the study/ies are evaluated by the FDA
 - Think of it in reverse – If the study would be solid enough to get FDA approval as a drug to treat, why would they not? (Example: Lovasa)

Supplements – What is a Drug?

Orange Juice – A delicious beverage,
usually drank for breakfast

Orange Juice – A drug to prevent and
cure scurvy



Supplements – What is a Drug?

- By US law a drug is "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals"
- From a biochemical standpoint any substance to help maintain life is a drug:
 - Water helps prevent and cure dehydration
 - Too much, in the wrong place can be damaging - drowning
 - Carbohydrates prevent and cure hypoglycemia
 - Too much for too long of a time-period can be damaging – diabetes mellitus Type 2
- How does the Supplement Industry get around this rule?

energy that strikes back.

CONSUME RESPONSIBLY—LIMIT 3 BOTTLES PER DAY. NOT
RECOMMENDED FOR CHILDREN, PREGNANT WOMEN OR
PEOPLE SENSITIVE TO CAFFEINE.

THESE STATEMENTS HAVE NOT BEEN EVALUATED BY
THE FOOD AND DRUG ADMINISTRATION. THIS PRODUCT IS
NOT INTENDED TO DIAGNOSE, TREAT, CURE OR PREVENT
ANY DISEASE.

VENOM, MOJAVE RATTLER AND PIERCING ENERGY THAT
STRIKES BACK ARE TRADEMARKS OF DR PEPPER/SEVEN UP,
INC. ©2008 DR PEPPER/SEVEN UP, INC.

CONSUMER COMMENTS? 1-866-228-3666

Supplements – Do They Work?

Where do many of the drugs we have come from?

- Nature:
 - Aspirin – from the bark of a willow tree
 - Warfarin – from fermented Coumadin clover leaves
 - Lovastatin – from *Monascus purpureus* in Red Yeast Rice
 - Captopril – from studying pit viper venom in S. America
- Laboratory:
 - Once active moiety is determined, then manipulate
 - Enhance benefit, reduce side effects

Supplements – What is the Placebo Effect?

Healthcare Understanding – What We as Providers Need to Get:

- As humans we are not simple cause and effect creatures, we are relationship creatures
 - Not take a pill and get a change
 - Numerous studies show if trust or expectation is there, the outcome will happen without the active ingredient (about 30% of the time)
 - I've personally run into this with guaifenesin and docusate sodium
 - Does not mean an active ingredient is not active
- Time spent with patients listening and incorporating the patients into their therapy greatly increases outcomes
- Failure to do this is a reason patients turn to supplements

Supplements – What is the Placebo Effect?

History of the Placebo Effect:

- *Placebo Domino* (Psalm 116:9) – “I will please the Lord” Latin Vulgate
 - Jerome decided to translate instead of *Ambulabo coram Domino* “I will walk before the Lord”
 - Not necessarily a mistake, but a word choice
- Was chanted repeatedly during recitation of Office of the Dead
- Became a secular mock word for anyone who would please at any cost
- In 1500’s became associated with exorcisms, specifically fake demon possessions:
 - When individual who was possessed was examined by the cleric, the cleric would use a fake holy relic and give it to the individual
 - Believed if individual had seizures it wasn’t a true possession
- In 1752 Dr. James Lind performed a seeming placebo control trial with scurvy
- 1785 “placebo” was in Motherby’s New Medical Dictionary meaning “a trite medication”
- Not till 1958 is modern definition showing up in dictionaries

Supplements – Nocebo?

- When something has no active ingredient, yet still produces harm
- One aspect of this we will discuss when we get to cost
- Not Needing to Treat: Another aspect is the given item does have an active ingredient, but it is for something entirely else:
 - Antibiotics for bacteria given for a viral infection

Supplements – Do They Work?

Short Answer:

- Yes and No
 - Everything has the potential of a placebo effect
 - Some dietary supplements, if you get what is advertised, are active and will have an effect
 - Many are marketed just to part you from your money

Supplements – Drug-Drug Interactions

- If the supplement has an active ingredient, possibly even if it doesn't, you run the risk of drug-drug interactions
 - Just some examples:
 - St. John's Wort and pretty much anything else – especially blood thinners and anti-depressants
 - Red Yeast Rice and another statin – duplicate medications in the same class

Supplements - Cost

“You could try it, since it won’t hurt you”

- Opportunity Cost – Every choice you make has a cost, whether that be time, money, mental energy, pills to swallow, etc.
 - Example: Patient spending \$30/month on supplements (\$360 a year)
- Lack of regulation means you may not get what you think you are
 - Too little
 - Too much or too many other things
- You may just be paying for a placebo effect
- Not wrong to try, but best to get information first

Popular Supplements

Supplement – Red Yeast Rice

- Pros
 - Where we found the active ingredient lovastatin (prescription cholesterol medication)
- Cons
 - No regulation – have to trust the manufacturer



Curcumin (Turmeric)

- Pros:
 - National Cancer Institute is looking into it
 - Many other possible benefits – antidiabetic, anti-depressive, anti-inflammation
- Cons:
 - Limited Bioavailability – We can eat it, but very little gets absorbed into our system
 - The studies used to determine some benefit with cancer (in combination with other medications) had patients taking up to 8 grams per day. At 800 mg per capsule, that's 10 large capsules per day.



Supplement – St. John's Wort

- Pros
 - Does have anti-depressive properties
- Cons
 - No regulation – have to trust the manufacturer
 - Interacts with pretty much every other medication

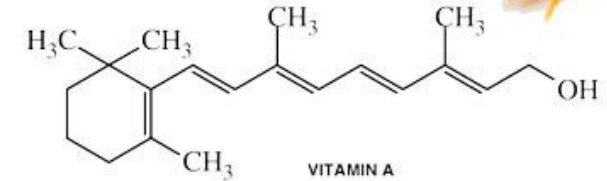


Vitamin-A



Vitamin A – retinyl palmitate

beta-carotene is precursor to Vitamin A from plant sources



- Pros

- Vitamin A is very important for ocular development and maintenance – deficiency can/does lead to loss of eye-sight
- Large ingestion of beta-carotene from plant sources does not produce Vitamin A toxicity, but can produce yellow-tinged skin (carotenemia)

- Cons

- Large ingestion of non-plant source precursor Vitamin A can lead to toxicity including damage to liver



Vitamin B-1 - Thiamine



- Pros
 - Vitamin assists in brain uptake of glucose
 - In Thiamine deficiency (typically alcoholism) assists in helping individual back to normal regulation
 - Does come as a prescription injection
- Cons
 - Another pill to take and if supplement, must trust manufacturer for content

VITAMIN B2

Vitamin B-2 - Riboflavin

- Pros
 - Evidence of 400 mg daily as prevention of migraines
 - Great as a non-toxic phosphorescing (glowing under black light) agent for Halloween parties
- Cons
 - Somewhat pricey to get 400 mg daily dosing
 - Must trust manufacturer if correct amount, albeit, you can test if Vitamin B-2 is in the tablet by using a black light



Vitamin B-3 - Niacin

- Pros
 - May have some level of lipid lowering effect
- Cons
 - Not really recommended anymore as studies don't really show beneficial outcomes
 - Side effects include flushing



Vitamin B-12 – Cyanocobalamin



- Pros
 - Comes as a prescription only (injection) or tablets (supplement) manufactured by producers of other prescription medications
 - Long term metformin use may be associated with Vitamin B-12 deficiency, thus should monitor periodically and is easy to replace if needed
 - Plays a part in peripheral neuropathy and if so, deficiency should be checked
- Cons
 - Some people don't like injections, and if so, is another pill to take

Vitamin C - ascorbic acid

- Pros:
 - Is required by the body for prevention of scurvy
 - Is added to most foods and advertised as such
 - Aids in Iron absorption?
 - Commonly cited
 - Based off of older and/or smaller studies – newer smaller studies yes/no
 - October 2017 study suggests spacing out iron dosing, due to hepcidin development, to every-other-day dosing may increase overall absorption
- Cons:
 - Has been proposed as a vitamin aide in curing or preventing everything from the common cold to cancer – the evidence continues to come back as these claims not having any validity
 - Is added to most foods and advertised as such



Vitamin D



- Pros

- Vitamin D does help prevent rickets and low levels are linked to osteoporosis
- It has been associated with multiple biological functions
- As it is most commonly synthesized in the skin due to sun exposure, many individuals are Vitamin D low, but not deficient

- Cons

- Most people are not Vitamin D deficient
- Little evidence Vitamin D supplementation improves outcomes

Vitamin E



- Pros

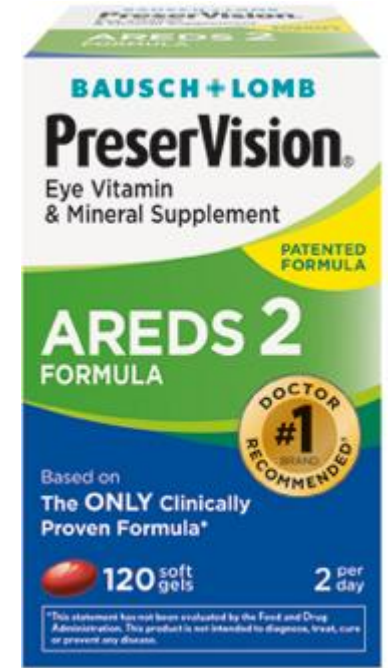
- Deficiency of Vitamin E have been associated with cardiovascular events
- Fat-soluble vitamin, likely get sufficient amount (15 mg) in daily diet

- Cons

- Unclear benefit of more than recommended daily amount
- Higher doses above ~1,000 mg daily have concerns for hemorrhagic effects

Eye Vitamins

- Pros
 - Age-Related Eye Disease Study (AREDS) did support a certain vitamin combination “could slow the progression in patients with either intermediate age-related macular degeneration or with advanced macular degeneration in only one eye” (500 mg Vit C, 400 IU Vit E, 15 mg beta-carotene/25K IU Vit A, 80 mg zinc oxide, 2 mg cupric oxide (copper))
- Cons
 - Many manufacturer’s don’t follow the study’s combination
 - AREDS was published in stages (reports), and results flip-flopped from one publication to the next
 - Positive results appear to be from sub group analysis, which may be a false positive



Echinacea & Zinc

- Pros

- Both have demonstrated reduction in overall time of symptoms of influenza by about 0.5 to 1.5 days (unclear of additive effects)
 - Caveat: Must be started at the first signs of illness
- Main form of zinc demonstrating benefit – throat lozenges, unclear if other forms give same improvement

- Cons

- Cost, taste, continual dosing – do these give more benefit over hydration, sleep and current OTC medications to treat symptoms?



Magnesium

- Pros
 - Magnesium supplementation associated with:
 - Reduced blood pressure
 - Reduced migraine headaches (via reduced blood pressure?)
 - Decreased constipation – works as a cathartic
 - Possibly improved mood
- Cons
 - Which version is best?
 - Another pill to swallow
 - Do you get what manufacturer advertises?



Oncovite for Bladder Cancer

- Pros
 - One 1994 study of 65 patients demonstrated benefit in prevention of reoccurring cancer
- Cons
 - Other studies showed no difference, not all studies were on humans
 - Preventative studies, including recent 2017 Korean study, showed no difference
 - American Cancer Society considers vitamins as complimentary or alternative methods for treatment of cancer



Glucosamine/Chondroitin

- Pros

- Glucosamine might help reduce osteoarthritis knee pain

- Cons

- Large, meta-analysis studies do not show much benefit beyond placebo for other joints, alone or in combination



Omega 3 Fatty Acids – Fish Oil

α-linolenic acid (ALA) plant oils, eicosapentaenoic acid (EPA) & docosahexaenoic acid (DHA) – marine oils



- **Pros**

- Available in prescription form (Lovaza, Epanova, Vascepa)
- May help reduce triglycerides and improve cardiovascular outcomes
 - 2017 American Heart Association (AHA) update – can assist with secondary prevention of coronary heart disease (CHD) and sudden cardiac death in patients with prevalent CHD and in patients with heart failure
 - Still not recommended for primary prevention

- **Cons**

- Supplements show inconsistent benefit in studies
- Non-prescription supplements may contain oxides which counteract benefits of omega-3
- AHA does recommend 2 servings of fatty fish (salmon, mackerel, herring, lake trout, sardines and albacore tuna) per week, as this does have evidence of benefit (albeit \$\$\$)

Supplements - Summary

- Supplements are a big and growing industry which wishes to market supplements as natural and safe – be vigilant not to mix the two
- Supplements are not FDA regulated and typically do not have solid studies to back them up
- Supplements teeter on the gray area between FDA's definition of a drug and biochemical definition
- Nature is a predominate source for drugs, which do have active ingredients
- The Placebo Effect is very real, and typically has about a 30% chance with anything where trust or anticipation can be generated, be careful for nocebo effects
- Supplements with active ingredients have potential for drug-drug interactions so check with physician or pharmacist before starting
- There is always a cost to any choice - \$ and pill burden

10 Minute Break

Discovery & Drug Development

Discovery & Drug Development - Outline

- Drug discovery
- Phases of Drug Development
- Drug Development – How Many Make It & Special Designations

Drug Discovery

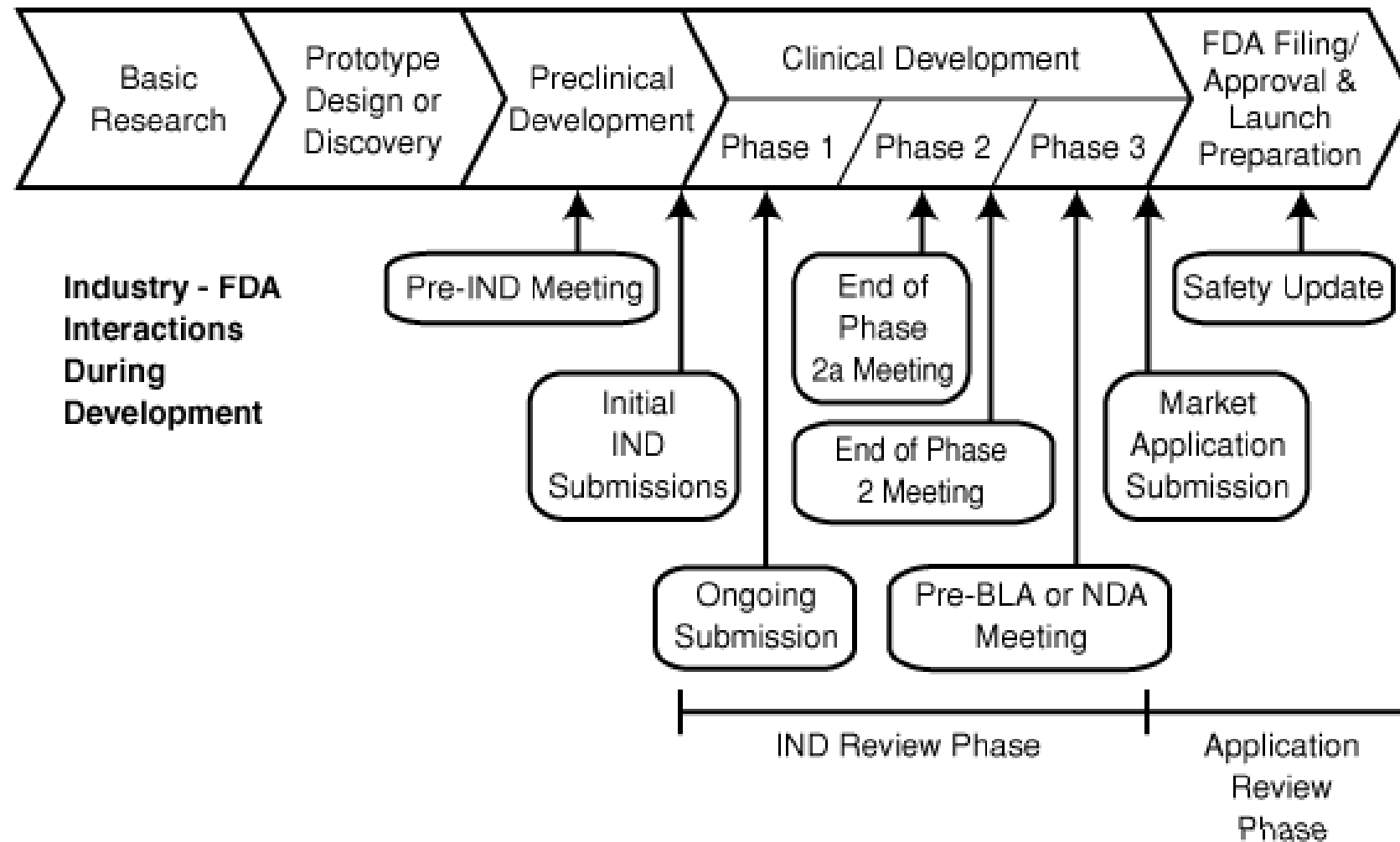
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Phases of Drug Development

- There are 4 phases of development, but other steps as well:
 - Pre-clinical trials – animals/test tubes – does the drug do anything?
 - Investigational New Drug (IND) application - Request ability to do clinical trials from Food and Drug Administration (FDA)
 - IND review– FDA allows it to proceed
 - Phase 1 – Safety (healthy volunteers)
 - Phase 2 – Efficacy (individuals with condition)
 - FDA & Drug Sponsors decide how phase 3 will proceed
 - Phase 3 – Confirmation of Safety & Efficacy
 - FDA & Drug Sponsors meet to craft and submit a New Drug Application
 - FDA reviews application, labeling and facility development
 - FDA approval
 - Phase 4 – Post-marketing surveillance

Phases of Drug Development



Drug Development – How Many Make It?

- On average, total time from discovery to market is about 10 years
- Typically:
 - 66% make it from phase 1 to 2
 - 33% from phase 2 to 3
 - 44% from phase 3 to market
 - Overall about $\leq 10\%$ get through
- Pharmaceutical patents typically are 20 years long, and have to be patented right at the beginning
- Tying into increasing drug costs:
 - Realize the cost to make the medication now is not equal to market price since the market price is helping pay for development of multiple drugs and a 90% failure rate

Drug Development – Special Designations

Review Designations:

For possibly any medication (must meet criteria):

- Priority Review
 - FDA promises to give review attention and take action within 6 months

For medications used to treat life-threatening or serious illness:

- Breakthrough Status
 - The FDA works more integrated with drug developer to speed process, help make trials as efficient as possible, and incorporate cross-disciplinary work on project.
- Fast Track Designation
 - Medication has potential to address an unmet medical need. Drug developer may submit parts of application as information becomes available.
- Accelerated Approval
 - Medication appears to have superiority over current therapy on a “surrogate endpoint.”

Drug Discovery & Development Summary

- Many drugs have their discovery in nature, then utilizes laboratory chemistry to improve effect and decrease side effects
- Drug development is a long and costly process, with only a few making it to market
- There are special designations which help speed the process along, but only some drugs get these designations

Thank You
What additional Questions do you Have?



Brian Barkow, PharmD, CSP