Law: Seniors Self-Diagnosing and Treating: A Brave (and scary) New World

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Disclosure

- The speaker has no financial or nonfinancial disclosures associated with this topic. There will be discussion of dietary supplements, peptides, and counterfeit drugs, none of which are FDA approved products.

2

Objectives

- At the conclusion of this talk the successful participant will be able to

1. Describe the reasons seniors are increasingly diagnosing and treating themselves with therapies
2. Describe the legal and regulatory pathways that provide seniors access to therapies outside the drug supply chain
3. Describe ways that pharmacists can recommend dietary supplements that are free of adulterants and contaminants
4. Describe the risks associated with self-treatment with dietary supplements, "peptides," and counterfeit drugs

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Seniors Take Lots of Meds

- Patients ≥65 years =13% of the population
- They consume ~30% of prescription medications
  - 61% take at least 1 prescription medication with an average of 3-5 chronic prescriptions
- Seniors use ~30% of over-the-counter medications

https://www.aafp.org/pubs/afp/issues/2002/1115/p1917.html#:~:text=Patients%2065%20years%20and%20older%20represent%20approximately%2013,the%20use%20of%20over-the-counter%20medications%20or%20herbal%20therapies
Medscape Registrationhttps://www.medscape.com/viewarticle/501879?form=fpf

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Costs of Prescription Medication for Seniors Are Out of Reach

- More than 1.4 million Medicare enrollees paid more than $2,000 in out-of-pocket costs in 2020
- 3.5 million seniors (6.6%) reported affordability problems with prescriptions in 2019
- 2.3 million seniors did not get needed prescriptions due to cost
  - Millions of others reduced prescribed doses or skipped doses due to costs

https://www.kff.org/medicare/issue-brief/how-will-the-prescription-drug-provisions-in-the-inflation-reduction-act-affect-medicare-beneficiaries/
https://aspe.hhs.gov/sites/default/files/documents/1e2879846aa54939c56efeec9c6f96f0/prescription-drug-affordability.pdf

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Prescribers Limit Controlled Substance Medication Access or Quantities

- Seniors experience more pain-related conditions
- There is a 3X increase in OUD in Medicare enrollees
  - 4.6 cases per 1,000 in 2013 to 15.7 cases per 1,000 in 2018
- The rate of overdose deaths among seniors quadrupled
  - 3 to 12 per 100,000 from 2002 – 2021 according to CDC data
- CDC guidance now limits opioids for chronic pain

https://www.psychologytoday.com/us/blog/some-assembly-required/202406/problematic-substance-use-is-on-the-rise-among-seniors?msockid=3b3a660fabcd6a102f0d7204afcd6448

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Prescribers Limit Controlled Substance Medication Access or Quantities

- From 2010 to 2018, 13.5% of seniors received a benzo and use remained relatively constant from 65 up to 89 years
- From 2002 to 2021, the use of gabapentinoids increased to 9% of all seniors (70+ years)
- The prevalence of low serum total testosterone in seniors is 39% but only 6% meet criteria for symptomatic hypogonadism

https://www.psychologytoday.com/us/blog/some-assembly-required/202406/problematic-substance-use-is-on-the-rise-among-seniors?msockid=3b3a660fabcd6a102f0d7204afcd6448
https://www.annfammed.org/content/22/1/45#:~:text=The%20probability%20of%20gabapentinoid%20users%20increased%20for%20nearly,those%20aged%2070%2B%20was%20around%209%25%20%28Figure%201B%29.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2686341/#:~:text=The%20prevalence%20of%20low%20serum%20total%20testosterone%20among,Massachusetts%20Male%20Aging%20Study%20%28Araujo%20et%20al%202004%29.

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Seniors May Not Want to Discuss "Embarrassing" Health Issues with Doctors

- 75% of men 70+ years experience erectile dysfunction
- 50% of women 60+ years have low sexual desire and/or vaginal atrophy/dryness
- 75% of women 70+ experience periodic urine leakage

https://pubmed.ncbi.nlm.nih.gov/26197627/#:~:text=Erectile%20dysfunction%20%28ED%29%20in%20the%20older%20adult%20male,to%20chronic%20disease%2C%20comorbid%20conditions%2C%20and%20age-related%20changes. https://www.mayoclinichealthsystem.org/hometown-health/speaking-of-health/is-urine-incontinence-normal-for-women
https://agsjournals.onlinelibrary.wiley.com/doi/full/10.1111/jgs.15198#:~:text=Up%20to%20half%20of%20sexually%20active%20older%20women,is%20often%20associated%20with%20a%20partner%27s%20erectile%20dysfunction.

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Question 1

- Don is a 72 year old who is looking online for alternatives. His prescriber told him he would not write any other prescriptions for oxycodone with APAP. He is looking at kratom and for Canadian Pharmacies that don't require a prescription. Which of the following is the motivator for Don to transcend the normal medication supply chain?

a) Cost of prescription options
b) Circumvent prescriber gatekeeping restrictions
c) Embarrassment over his health issue

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Dietary Supplements

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Seniors Take Lots of Supplements

- 40% percent of seniors have used a dietary supplement within the past year
- The average senior takes 2 supplements and 29% take 4 or more

https://www.medscape.com/viewarticle/501879?form=fpf
https://www.health.harvard.edu/staying-healthy/do-you-need-a-daily-supplement

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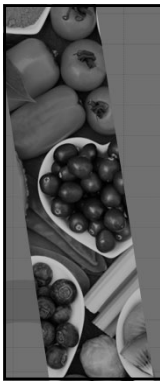

DSHEA Rules and Limitations

- DSHEA Act of 1994:
- Defined dietary supplements (legacy and NDI)
- Required ingredient and nutritional labeling
- Delineated claims and nutritional support statements that could be made
- Empowered FDA to enforce GMP regulations

https://ods.od.nih.gov/About/DSHEA_Wording.aspx

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New Dietary Ingredients (NDIs)

- Products commonly sold before 1994 grandfathered in, others are NDIs
- If you have an NDI, you must notify the FDA and cannot sell a product containing the NDI for 75 days
- If the FDA does not take steps to stop you by proving it is unsafe, you can sell it via interstate commerce thereafter

https://ods.od.nih.gov/About/DSHEA_Wording.aspx

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Real Health Claims

- Petition the FDA for a claim if a published authoritative body (National Academies, NIH, CDC) approves of claim
- Need to give FDA 120-day notice and if FDA does not intervene, can make claim
  - Calcium reduces osteoporosis
  - Fiber reduces cancer
  - Folate reduces neural tube defects

https://ods.od.nih.gov/About/DSHEA_Wording.aspx

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Quasi-Health Claims

- Quasi-Health Claims: supports heart, eye, liver, etc, health
- FDA cannot reject a quasi-health claim unless the FDA ALSO finds no disclaimer that would eliminate the misconception
- Disclaimer: This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease.

https://ods.od.nih.gov/About/DSHEA_Wording.aspx

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Quasi-Health Claims

Must have data to substantiate the quasi-health claim but do not have to send the information to FDA

Must alert the FDA of your intention to use a quasi-health claim at least 30 days prior

FDA can intervene if it chooses and has substantive evidence that the claim is incorrect

https://ods.od.nih.gov/About/DSHEA_Wording.aspx

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GMP

- DSHEA 1994 allows FDA to enforce GMP
  - Facility cleaning & pest control
  - Maintaining & cleaning equipment
  - Quality control procedures
  - Lab and manufacturing operations
- If FDA proves a company's failure to meet GMP, can render the drug product adulterated under 402(g) of the Federal Food Drug and Cosmetics Act

https://ods.od.nih.gov/About/DSHEA_Wording.aspx

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Adverse Event Reporting

- Manufacturers, packers, or distributors name and contact information must be on the product labeling
- Must have a mechanism to collect and assess adverse events
- Must submit serious ADEs to FDA within 15 business days
  - Death, hospitalization, persistent disability, incapacity, or birth defect

https://ods.od.nih.gov/About/DSHEA_Wording.aspx

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FDA Has No Idea How Many Dietary Supplements Exist

The FDA estimates there exists between 55,000 and 80,000 dietary supplement products

If the FDA finds issues with one manufacturer's products, it doesn't automatically know what other products they make

White CM. https://journals.sagepub.com/doi/10.1177/1060028019900504

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FDA Has A High Bar to Meet

- If the FDA believes a product is unsafe because of its ingredients, GMP issues, or other reasons it must prove it
- Innocent until proven guilty

https://ods.od.nih.gov/About/DSHEA_Wording.aspx

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FDA Funding a Barrier to Optimal Safety

- 45% of FDA's funding is through user fees and those units that do not collect user fees are underfunded
- FDA cannot evaluate nearly all dietary supplement products with current funding
- FDA cannot inspect nearly all dietary supplement manufacturing facilities, especially those located outside the US

White CM. https://theconversation.com/why-is-the-fda-funded-in-part-by-the-companies-it-regulates-160444

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Tianeptine a dietary supplement?

- Tianeptine is a tricyclic antidepressant with opioid stimulating effects
- Causes euphoria, addiction and respiratory depression
- Sold as a dietary supplement for almost a year before it was recognized

FEBRUARY 6, 2024 | 5 MIN READ

'Gas Station Heroin' Is a Dangerous and Often Contaminated Supplement

Tianeptine, an addictive drug at high doses, is being sold as a dietary supplement in gas stations and convenient stores. But such products could be contaminated with metals, microorganisms or other undisclosed drugs

BY C. MICHAEL WHITE & THE CONVERSATION US

https://www.nytimes.com/2024/01/10/health/gas-station-heroin-tianeptine-addiction.html

White CM. https://theconversation.com/popularly-known-as-gas-station-heroin-tianeptine-is-being-sold-as-a-dietary-supplement-with-deadly-outcomes-221379

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Selank or Semax a Dietary Supplement?

- Tuftsin is a natural human peptide
- Selank is a synthetic analogue of tuftsin
- Sold as a dietary supplement for cognitive protection and anxiolysis over 6 years
- Now it is sold in the US as a "peptide"

https://enhancedpeptides.com/selank-guide/

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Issues with Dietary Supplements: Microbial Contamination

- Herbal products (alfalfa, coriander, echinacea, garlic, ginkgo, juniper, licorice, psyllium, and St John's wort, CBD, cannabis, kratom) contaminated with fungi and/or bacteria in levels above USP specifications
- Kratom Salmonella issues January 2017 - May 2018 resulted in 199 adverse events & 50 hospitalizations.

White CM. Ann Pharmacother: https://journals.sagepub.com/doi/full/10.1177/1060028019900504

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Issues with Dietary Supplements: Heavy Metal Contamination

- Concentrations of heavy metals in 121 dietary supplements were compared with the concentrations designated for safe daily consumption by the NSF International
- 5% of dietary supplements exceeded the upper limit for arsenic, 1.7% of samples exceeded the levels for lead, cadmium, and aluminum, and 0.8% of samples exceeded the levels for mercury

White CM. Ann Pharmacother: https://journals.sagepub.com/doi/full/10.1177/1060028019900504

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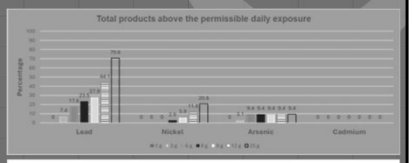
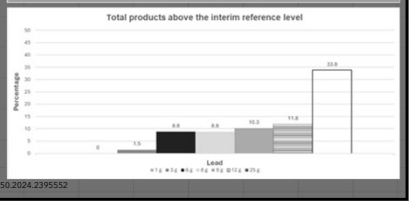
Excessive Heavy Metals in Kratom Products

- The FDA species the acceptable level of lead in drugs and dietary supplements
- The percentage of products that exceeded permissible daily exposure limits for lead (5 µg/day), nickel (200 µg/day), arsenic (15 µg/day), and cadmium (5 µg/day) were determined
- The percentage of products with lead above the interim reference level (12.5 mcg/day) for adult men and post-menopausal women were determined
- IRL is the maximum amount in all orally consumed food, drugs, and dietary supplements





White CM. Clin Toxicol 2024 DOI: https://doi.org/10.1080/15563650.2024.2395552

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Issues with Dietary Supplements: Adulterated with Synthetic Drugs

- From 2007-2016, 6.5 dietary supplement products were adulterated per month as compared to 4.9 products per month from 2017-2021
- From 2007-2016, 619 of 776 products (79.8%) were adulterated by a single API but this was reduced to 138 of 292 products (47.3%) from 2017-2021 ($p<0.0001$).

White CM. J Clin Pharmacol 2022. https://doi.org/10.1002/jcph.2046

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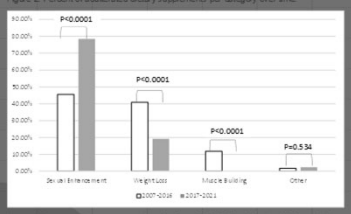
What Products Are Most Adulterated?

From 2007-2016, 6.5 dietary supplement products were adulterated per month as compared to 4.9 products per month from 2017-2021

Figure 2. Percent of adulterated dietary supplements per category over time.



Muscle builders moved to "peptide" market in 2016 after FDA crackdown

Legend: The percentages across categories from 2007-2016 add up to 100% as do the percentages across categories from 2017-2021

White CM. J Clin Pharmacol 2022. https://doi.org/10.1002/jcph.2046

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Sexual Enhancement Products

- Most sexual enhancement products have PDE-5 inhibitors in them
- 39% of products had more than one FDA approved PDE-5 inhibitor in them (sildenafil, tadalafil, and/or vardenafil)
- 14% contained non-FDA approved PDE-5 inhibitors in them
- 2.2% of products had dapoxetine (non-FDA approved drug for premature ejaculation)
- 2.1% of products had three APIs in them

White CM. J Clin Pharmacol 2022. https://doi.org/10.1002/jcph.2046

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Risks of Hidden APIs for Seniors

- PDE5-inhibitors and nitrates are contraindicated
- Higher dose PDE5-inhibitors, unapproved analogues, and multiple PDE5-inhibitors can cause priapism
- Dapoxetine was not effective in clinical trials and has standard antidepressant adverse events

White CM. J Clin Pharmacol 2022. https://doi.org/10.1002/jcph.2046

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Weight Loss Products

- From 2017 through 2021: sibutramine (84.9%), sibutramine analogues (6.3%), phenolphthalein (23.7%), and fluoxetine (5.4%)
- One product (1.8%) contained 1,3-dimethylamylamine, a non-FDA approved API structurally related to ephedrine
- 3.6% of products contained three API while 1.8% contained five of them

White CM. J Clin Pharmacol 2022. https://doi.org/10.1002/jcph.2046

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Risks of Weight Loss APIs for Seniors

- Sibutramine was removed from US market by FDA for risks of ASCVD events
- Phenolphthalein was removed from US market because it is a possible carcinogen
- Fluoxetine can interact with many other drugs metabolized by CYP2D6 and other antidepressants

White CM. J Clin Pharmacol 2022. https://doi.org/10.1002/jcph.2046

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Issues with Dietary Supplements: Little to No Active Ingredients

- In an assessment of cannabadiol (CBD) products, only 12.5%, 25%, and 45% of vaporization liquids, tinctures, and oils were labeled correctly (±10% of the labeled value) and in most cases contained far less CBD than promised
- In two studies using DNA barcoding, many herbal dietary supplement products contained little to no labeled ingredient

White CM. Ann Pharmacother: https://journals.sagepub.com/doi/full/10.1177/1060028019900504

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FDA Action the Last Word?

- In 2018, the FDA identified synthetic stimulants β-methylphenethylamine, methylsynephrine, and octodrine) in dietary supplements for energy and weight loss and issued 31 warning letters
- By January 2022, 9 products were still for sale and 5 still had one or more prohibited stimulant

White CM. https://doi.org/10.1177/10600280241277551
Annals of Pharmacotherapy

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Further Steps to Protect Consumers/Patients

- Stores should only sell products verified for manufacturing quality by independent labs such as USP, NSF, and ConsumerLabs
- Certificates of Analysis on websites may not be accurate and could be a one snapshot in time quality assessment

White CM. Ann Pharmacother:
https://journals.sagepub.com/doi/full/10.1177/1060028019900504

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Question 2

You are a pharmacist at a community pharmacy and a patients asks you which supplements to buy. What is a validated way to assure the dietary supplement you recommend does not have excessive microbial or heavy metal contamination and has the ingredient in the tablets/capsules advertised on the label?

A. USP certification
B. Better Homes and Gardens Certification
C. The most expensive one

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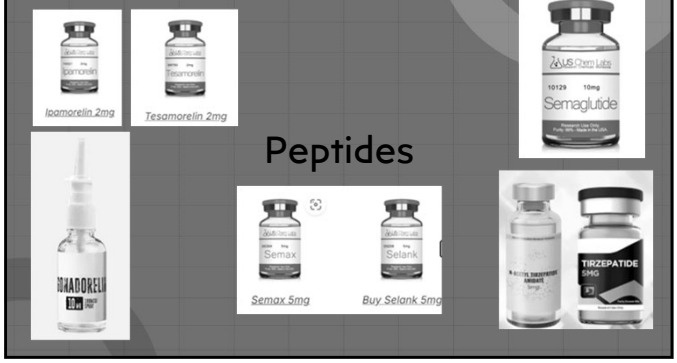

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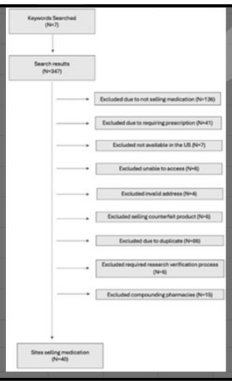
"Peptide Companies"

- Peptide companies sell products under the loophole that it is "For research purposes only" and/or "Not for Human Consumption"
- A host of injectable "research chemicals" can be purchased online
- Testosterone boosters, nootropics, GLP-1s
- We conducted a study looking at the GLP-1 agonists



https://doi.org/10.1177/10600280241277551
Annals of Pharmacotherapy

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Project Results

https://doi.org/10.1177/10600280241277551
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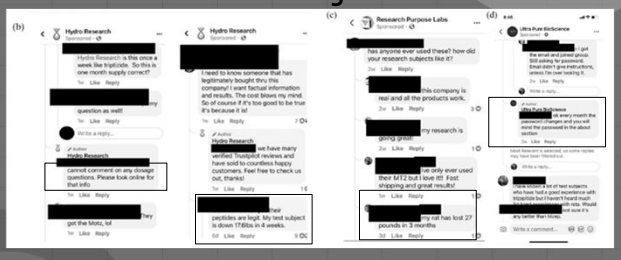
Social Media Marketing



https://doi.org/10.1177/10600280241277551
Annals of Pharmacotherapy

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Quality of Peptides

Several semaglutide products independently tested:

- One product had elevated presence of endotoxin (8.95 EU/mg)
- Product purity levels ranged from 7% to 14% (vs. promised ~99% purity)
- Semaglutide content varied 29% to 39% more or less than promised on the label
- Three products never arrived and purchaser asked to pay additional fee to clear customs

https://doi.org/10.1177/10600280241277551
Annals of Pharmacotherapy

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Question 3

- Sylvia is a 68 year old woman who weighs 120 pounds but wants to weigh 108 pounds like she did when she was 40 years old. Which of the following is NOT a risk she could have if she started using a "peptide" GLP-1 product?

a) She does not have a disease or disorder that requires a GLP-1 product and the risks could outweigh the benefits
b) The products are known to contain lead and arsenic in too high a level
c) The product dosage could vary from the label amount and she could either overdose or underdose as a result

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c) The product dosage could vary from the label amount and she could either overdose or underdose as a result

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Counterfeit Drugs

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Counterfeit Drugs

- The FDA Office of Criminal Investigation keeps a database of press releases about counterfeit drug law enforcement actions
- The FDA counterfeit database contained 130 actions from 1/1/2016 to 12/31/2021
- In 2016, 2017, 2018, 2019, and 2020, and 2021 - fourteen, five, thirty-one, thirty, thirteen, and thirty-seven different law enforcement actions occurred, respectively.

White CM. Ann Pharmacother 2022.
https://doi.org/10.1177/10600280221092482

White CM. JAPhA 2021.
https://doi.org/10.1016/j.japh.2020.04.020

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Where Were The Counterfeit Drugs Purchased?

- 65% of law enforcement actions were for counterfeit products or active ingredients to make counterfeit products sold over the internet
- The rest were sold in stores, person to person, or were used in medical or boutique stores
- In 85% of law enforcement actions, the counterfeit products could be obtained without a prescription

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Which Drug Classes Are Most Implicated

- Erectile dysfunction drugs [sildenafil, tadalafil] were identified 40 times
- Opioids were identified 36 times [tramadol, hydrocodone, oxycodone (Fentanyl a common adulterant)]
- Stimulants were identified 31 times [sibutramine, amphetamine, 3,4-methylenedioxymethamphetamine (MDMA)]
- Anabolic steroids were identified 22 times
- Benzodiazepines were identified 21 times [alprazolam, diazepam, clonazepam, temazepam]

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Size of the Counterfeit Ring

- Six law enforcement actions reported more than a million pills were involved and five reported 200,000 to 999,999 pills
- Four law enforcement actions measured the quantity in kilograms (21.4 kg, 234 kg, and 1,200 kg)
- One was measured in terms of the number of packages shipped each month (~10,000 packages)

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Question 4

- Don finds a "pharmacy" willing to sell him oxycodone with APAP for $7 a pill without a prescription. The site says it is a best seller in Canada. What is the main risk of Don getting his opioids from the unlicensed online site?

a) Fentanyl adulteration and variability of doses could lead to respiratory depression
b) It is more expensive than the prescription version
c) There is no money back guarantee

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Question 4

- Don from question 1 finds a "pharmacy" willing to sell him oxycodone with APAP for $7 a pill without a prescription. The site says it is a best seller in Canada. What is the main risk of Don getting his opioids from the unlicensed online site?

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b) It is more expensive than the prescription version
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Conclusions:

- Seniors can use dietary supplement product, peptide company products, and counterfeit drugs to access (knowingly or not) drugs without a prescription
- Cost, desire to circumvent safeguards, and embarrassment are main reasons seniors go it alone
- The FDA is feebly unable to prevent many of these risks to seniors (and others) even though they are trying really hard
- The dietary supplement laws make it hard for the FDA to take action and the current drug laws allow peptide companies a loophole to directly sell drugs to seniors
- Pharmacists must ask about the use of these nonstandard products and relay the risks to consumers

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