

Polypharmacy

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Polypharmacy is inevitable...

- We're living longer with more clinical conditions...multimorbidities
- We have a myriad of medications to choose from...
- Therefore, polypharmacy is an unfortunate consequence of multimorbidity, where several medications are used to treat multiple diseases, syndromes, and conditions in older adults

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Is there a definition of "polypharmacy?"

- The older adult living in the community has an average of 6.5 chronic conditions, and multidrug therapy is the rule rather than the exception.
- One patient may have diabetes, hypertension, coronary artery disease, GERD, Alzheimer disease, depression, and osteoporosis
- An average of 1 to 3 drugs is prescribed per condition—so *it's easy to do the math.* ☺
- Anywhere from 6 to 20 prescription drugs per person and that's *without* asking about any over-the-counter drug use or drugs that they may have "borrowed" from friends—generally, old prescriptions that had a few "left-over" pills.
- (Zurakowski T. The practicalities and pitfalls of polypharmacy. *The Nurse Pract* 2009; 34(4):36-41)

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Choosing appropriate drugs for our older patients—a little help

- Beers criteria is a compilation of medications potentially to avoid or consider with caution because they often present an unfavorable balance of benefits and harms for older people
- First released in 1989; has been revised over the years with the latest revision in 2019—
- It is now known as the American Geriatric Society Beers Criteria
- Two major caveats: 1) The AGS Beers Criteria® should never solely dictate how medications are prescribed and, 2) it should not justify restricting health coverage, but it should be considered when prescribing.

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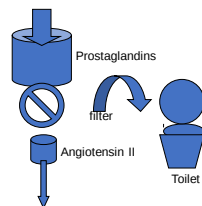
The AGS Beers Criteria-- Consists of five lists of nearly 100 medications or medication classes to avoid or use with caution for some or all older adults

- 1) the list that should be avoided by most older people (outside of hospice and palliative care settings)—opiates, verapamil (highly constipating), anticholinergic drugs
- 2) The list that should be avoided by older people with specific health conditions—NSAIDs with Chronic Heart Failure
- 3) The list that should be avoided in combination with other treatments because of the risk for harmful "drug-drug" interactions—NTG with ED drugs
- 4) The list that should be used with caution because of the potential for harmful side effects—NSAIDs
- 5) The list that should be dosed differently or avoided among people with reduced kidney function, which impacts how the medication is excreted—metformin

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Normal glomerular function...

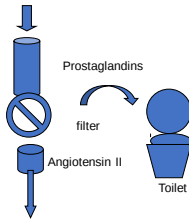
- Afferent arteriole (vasodilated via **(prostaglandins)** – (3 lanes in)
- Blood entering glomerulus
- Glomerulus→filter
- Efferent arteriole (vasoconstricted via **(angiotensin II)** (one lane out)
- Pressure differential = filtration



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NSAIDS, prostaglandin inhibition, and renal function (PG play a bigger role for maintaining renal blood flow in the elderly)

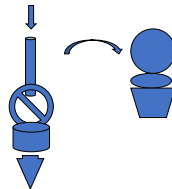
- Afferent arteriole (vasodilated via **(prostaglandins) – NSAIDS –** (1.5 lanes in)—slows sodium, H₂O and potassium excretion...HF issue



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Add an ACE inhibitor or an ARB, or ARNI (ex. HF) combined w/ NSAIDS

- NSAIDS inhibit prostaglandins and vasoconstrict the afferent arteriole (1.5 lane IN)—Reduce filtration (decreased eGFR)



- Angiotensin II inhibitors/blockers:
- Vasodilate the efferent arteriole (3 lanes OUT)
- All of the blood leaves the kidneys, reduced Blood flowing in = reduced input, increased output
- Acute kidney injury

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So, that being said...let's incorporate some of the Beers criteria into 10 general principles of polypharmacy

- The stacking effect
- Acid is necessary for the absorption of drugs
- Lower serum albumin levels for binding drugs
- The liver and drug metabolism
- The CYP 450 enzyme system, grapefruit juice, and the small intestine
- Know the patient's estimated glomerular filtration rate (eGFR)
- The increased permeability of the lipid layer that covers the brain
- The half-life of drugs is important
- Complementary and alternative therapies
- Specific drug-to-drug interactions

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PRINCIPLE #1: The “stacking” effect—

- A single drug with a specific side effect may not be a problem...however, polypharmacy with numerous drugs with the same side effect can be deadly—
- 2 examples: K⁺ retaining drugs and anti-cholinergic drugs and a case study

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The “stacking” effect with anti-cholinergic drugs is all too common—wreaks havoc in the elderly; known as the anti-cholinergic burden

Hundreds of drugs have anti-cholinergic effects—and it's not just the usual suspects

- A refresher on the normal functions of acetylcholine in the Central Nervous System (CNS) and the Peripheral Nervous System (PNS):

- Cognitive function (CNS)
- Pupillary constriction (PNS)
- Decreases heart rate (PNS)
- Increases salivation (PNS)
- Increases peristalsis in the GI tract (PNS)
- Tightens the Lower Esophageal Sphincter (PNS)
- Loosens urinary sphincter (PNS)

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A drug with anti-cholinergic effects have the opposite effects

- Confusion
- Pupillary dilation (blurred vision, glaucoma)
- Tachycardia (angina, possible MI)
- Decreased salivation (dry mouth)
- Opens LES (GERD)
- Decreased peristalsis in GI tract (constipation)
- Tighten urinary sphincter (urinary retention)

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In other words...

- Ya' can't see, ya' can't pee, ya' can't spit, ya' can't sh#t...
- And, you can't remember what you came into the bathroom for

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Anti-cholinergic drugs to tighten the bladder sphincter for urge urinary incontinence?

- Oxybutynin (Oxytrol, Ditropan); tolterodine (Detrol, Detrol LA); fesoterodine (Toviaz)
- Darifenacin (Enablex);
- Solifenacin (VESicare)
- Trospium (Sanctura, Regurin)

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Dry mouth from anti-cholinergic drugs?

- Nitrostat will NOT be absorbed when taken sublingually with a dry mouth
- A comparison of sublingual nitrostat vs. the nitro pump spray in older patients without dry mouths...prescribe the pump spray
Nitrostat vs. Nitro pump spray
- Resolution of chest pain: 120 seconds vs. 92 sec
- Onset of action: 3 minutes vs. 2 minutes
- Duration of action: 10 minutes vs. 15 minutes
- No brainer as long as they can manipulate the spray

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BIG CONCERNS ABOUT USING highly anti-cholinergic drugs at any time in adults—

- Acetylcholine is the neurotransmitter of cognitive function
- Brain atrophy and cognitive decline are observed in geriatric patients receiving anticholinergic medications
- The most **highly** anticholinergic drugs are associated with increased risk for dementia in elders up to 20 years **after** exposure.
- Drugs for urinary problems: (Oxybutynin (Oxytrol, Ditropan); tolterodine (Detrol, Detrol LA); fesoterodine (Toviaz); Trospium (Sanctura, Regurin)
- And two highly anticholinergic antidepressants—paroxetine (Paxil), amitriptyline (Elavil)
- SUMMARY: "As suggested by guidelines, anticholinergics in general should be avoided in older adults."
- (Richardson, K. Anticholinergic drugs and risk of dementia: case-control study. *BMJ* 2018;361:k1315)

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Acetylcholine--the neurotransmitter of cognition and anti-cholinergic drugs

- "The use of anti-cholinergic drugs has been strongly associated with adverse health outcomes, including cognitive impairment, dementia, falls, functional decline, hospitalization and mortality, especially in older adults."
- "The results of the present study showed that approximately half of the residents living in veteran's homes had exposure to anticholinergic drugs, and these residents had a significantly higher risk for short-term cognitive decline."
- (Geriatrics and Gerontology International. April 17, 2017. Suppl. 1)

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And more, more, more drugs with anticholinergic effects...

- Amitriptyline – if ever used (and sometimes is for neuropathy); the higher the dose, the higher the risk of anticholinergic effects;
- Clozapine
- **Cimetidine (1st dose delirium)** (choose famotidine/Pepcid)
- **Haloperidol** (short-term use only)
- Captopril (rarely used ACEI)
- Nifedipine
- Prednisolone
- **Codeine**
- Oxycodone
- Dig (not used much anymore)
- dipyridamole (other platelet inhibitors can be used—clopidogrel, prasugrel)
- **Warfarin (switch to DOACs)**
- **Furosemide**
- Isosorbide dinitrate
- **Diphenhydramine (Benadryl)**
- **The PM versions of OTC analgesics (Tylenol PM)**
- **Paroxetine** (never use this antidepressant in patients who are taking the acetylcholinesterase inhibitors such as donepezil (Aricept)—it negates the benefits of boosting acetylcholine...

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Is there a “best” antidepressant for the older patient?

- Escitalopram (Lexapro in U.S.; Cipralex in Canada) would probably win the contest with its decreased drug interactions and decreased side effects
- Citalopram can prolong the QT interval
- sertraline has the shortest half-life—and the mantra in the elderly is...
“Never give a drug with a half-life longer than their life...”

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Want to reduce the anti-cholinergic burden for urge incontinence in older women?

- Instead of: Oxybutynin (Oxytrol, Ditropan); tolterodine (Detrol, Detrol LA); fesoterodine (Toviaz) ; Trospium (Sanctura, Regurin)
- An estrogen ring for women (Estring 7.5 µg daily) is just as effective as the anti-cholinergic drugs listed above-- same results, less side effects, (Nelken RS, *Menopause* 2011 Sep;18:962; Eckler K. More treatment options for overactive bladder in PMF. *Menopause* 2011 Sep 18:941)
- A “dollop” of estrogen on the urethral opening may also be just as effective (anecdotal evidence) and may reduce post-menopausal UTI's by 50%
- Low-dose estrogen without progestin therapy does NOT increase the risk of VTE, invasive endometrial cancer or breast cancer (*Menopause* 2018)
- How about mirabegron (Myrbetriq)?—stimulates Beta-3 adrenergic receptors in the bladder's detrusor muscle; causes the bladder to relax and reduces urinary urgency symptoms – **expensive, but better option when concerned about cognitive decline**

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BIG CONCERNS ABOUT USING highly anti-cholinergic drugs—

- adverse effects such as brain atrophy and cognitive decline in geriatric patients receiving anticholinergic medications
- Including the drugs listed for urinary problems (Oxybutynin (Oxytrol, Ditropan); tolterodine (Detrol, Detrol LA); fesoterodine (Toviaz) ; Trospium (Sanctura, Regurin)
- Including one highly anticholinergic antidepressant—paroxetine (Paxil, others)
- Richardson, K. Anticholinergic drugs and risk of dementia: case-control study. *BMJ* 2018; 361 doi: <https://doi.org/10.1136/bmj.k1315> (25 April 2018)Cite this as: *BMJ* 2018;361:k1315

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Stacking effect of drugs that retain K⁺ (potassium) causing hyperkalemia

- Hyperkalemia is usually not a problem with a single agent...until OTHER drugs are added that also retain potassium and the K⁺ level can go into the RED ZONE
- What's the big deal about hyperkalemia? Cardiac arrhythmia. Death.

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The "stacking effect" and hyperkalemia

- Taking a careful and thorough drug history can help reduce this potentially dangerous adverse effect in the world of polypharmacy—
- Spironolactone (Aldactone) is an old, tired "mild" K⁺ - sparing diuretic that has taken on a new life; It's part of the triad of drugs used to treat of heart failure with a reduced ejection fraction (HFrEF) —an ACE inhibitor or ARB*, a beta-blocker, and spironolactone
- A newer aldosterone-inhibitor—eplerenone (Inspra)
- Spironolactone or eplerenone inhibit aldosterone resulting in sodium and water *excretion* and potassium *retention*
- The ARNI, sacubitril/valsartan (ENTRESTO) is preferred over an ACE inhibitor or an ARB for NYHA classes II-IV, especially those with a reduced ejection fraction

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Spironolactone (Aldactone) and eplerenone (Inspra)

- obtain a serum potassium level at 1 week and 1 month after initiating therapy and then obtain a potassium level at each visit.
- If less than 5 mmol/L at 1 month, consider increasing the drug
- If is 5.0–5.4 mmol/L, maintain the same dose
- If the level is 5.5–6.0 mmol/L, decrease the dose
- If the level is greater than 6.0 mmol/L, discontinue the drug
- Spironolactone—highly protein bound, lots of drug interactions, food can interfere; CHEAP; 9% risk of gynecomastia
- Eplerenone – less than 50% protein bound, few drug interactions, food doesn't interfere, EXPENSIVE; less than 1% risk of gynecomastia
- (Miller AB. Aldosterone antagonism in heart failure. Vasc Health Risk Manag. 2007 Oct;3(5):605-609)

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What other drugs contribute to hyperkalemia?

- Any drug that blocks angiotensin will also block aldosterone down the line...and K⁺ retention is the final result
- ACE inhibitors—the “PRILS” and Angiotensin receptor blockers (ARBs)(“SARTANS”) come to mind immediately
- ACE inhibitors or ARBs + spironolactone? Some patients w/HF need additional aldosterone antagonism
- Don’t forget the newest ARNI (angiotensin-receptor/ neprilysin inhibitor)—sacubitril/valsartan (Entresto) also increases K⁺ levels and is the preferred choice for HFrEF

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TMP/SMX (trimethoprim/sulfamethoxazole) (Bactrim/Septra) used for urinary tract infections and hyperkalemia

- Trimethoprim **inhibits** distal tubular reabsorption of Na⁺ and subsequent K⁺ secretion, resulting in K⁺ retention
- Trimethoprim-induced hyperkalemia has been reported multiple times in patients with mild renal insufficiency and in otherwise normal patients given TMP-sulfamethoxazole combinations for as short a time as **5 days**.
- Up to 6% of patients on TMP/SMX develop hyperkalemia within the first few days
- Highest risk for hyperkalemia—older than 65, renal insufficiency, diabetes, HF, or those taking other meds that increase K⁺ (the “stacking effect”)

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TMP/SMX and hyperkalemia

- Check K⁺ after 4 or 5 days of TMP/SMX; or hold the ACEI if possible; if needed, switch antibiotics
- Hospitalizations due to hyperkalemia increase by 7-fold or more when elderly patients take TMP/SMX with any other drug that retains potassium
- ~3/1000 seniors will have sudden death within 14 days of taking TMP/SMX with an ACEI or ARB compared with 1 of every 1000 patients taking an ACEI or ARB with amoxicillin
- January 15, 2015 *Prescriber’s Letter*

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How about Nitrofurantoin instead of TMP/SMX or urinary tract infections?

- Nitrofurantoin is also associated with hyperkalemia.
- If an antibiotic is necessary for a symptomatic urinary tract infection in the elderly use fosfomycin (Monurol) or a fluoroquinolone (ciprofloxacin or levofloxacin)*, or beta-lactams (Amoxicillin/clavulanate [Augmentin], cefaclor, etc.)
- *don't use a floxacin if *C. diff* is a high risk or if they are on corticosteroids (acute tendonitis; "risk of aortic dissection or aneurysm in certain patients associated with systemic use of these antibiotics") (FDA warning MAY 2017)
- (Arnold)(Antoniou)

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Just a friendly reminder—Spironolactone is used for other conditions, not just CHF...

- **"go to drug" for treatment-resistant HTN** (Resistant BP is defined as BP not controlled on a 3-drug regimen with a diuretic as one of the agents).
- "It's a pharmaceutical backbone for resistant hypertension treatment."*
(Williams B, et al. Spironolactone vs. placebo, bisoprolol, and doxazosin, to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomized, double-blind, crossover trial. Lancet 2015;386:2059-2068)
- Cirrhosis of the liver (due to liver failure and secondary hyperaldosteronism)
 - PCOS (usually not a problem in Geriatrics)

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We're not finished stacking drugs yet...NSAIDs (non-steroidal anti-inflammatory drugs) also increase K⁺ retention

- NSAIDs for longer than 2 weeks in young adults & adults will result in K⁺ retention
- NSAIDs for any length of time in geriatric patients...why?
- The geriatric kidney is more dependent on prostaglandin-induced renal artery and afferent arteriole vasodilation to maintain renal blood flow than the "younger" kidney...NSAIDs inhibit renal prostaglandins and cause renal arteriole vasoconstriction with Na⁺, K⁺, and water retention
- (ibuprofen, piroxicam (Feldene), and naproxen (Aleve) are the biggest offenders)

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Newest class of oral drugs for diabetes— "FLOZINS"—SGLT2 inhibitors--2013

- Sodium glucose co-transporter 2 inhibitors (SGLT2); lower HbA1c by 1%; Reduce renal glucose reabsorption and increase urinary glucose excretion + natriuresis
 - Retain potassium
 - Canagliflozin (Invokana)
 - Dapagliflozin (Farxiga)
 - Empagliflozin (Jardiance)
 - VERY popular drugs for Type 2 diabetes—decrease serum glucose AND have also been shown to have cardiovascular benefits
- (Medical Letter, December 21, 2015)

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Herbal products that increase K+

- Horsetail (*Equisetum arvense*)
- Alfalfa (*Medicago sativa*)
- Dandelion (*Taraxacum officinale*) (French –Pissenlit)
- Stinging Nettle (*Urtica dioica*)
- *Chan su* (marketed as a topical aphrodisiac)
- Milkweed (*Asclepias* species)
- Lily of the valley (*Convallaria majalis*)
- Siberian ginseng (*Eleutherococcus senticosus*)
- Hawthorn Berry (*Crataegus* species)

(Palmer BF. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. *N Engl J Med* 2004;351:585)

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The stacking effect: Case study

- 28 yo. female presented to ER with petechiae, purpura, nose bleeds, blood in urine, blood in stool, bleeding from her "snuff box" and around her hairline, but she felt "fine" 😊
- Hematology MD called STAT to the ER...asked her about any drugs she was on and she said just a "baby aspirin" a day. Ordered a battery of tests, PT, aPTT, thrombin time, fibrinogen, platelet counts, platelet aggregation assay, lactate (early sepsis? DIC?)

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The stacking effect: Case study

- Everything was normal except platelet aggregation assay—
- Not sensing an emergency the hematologist signed off
- Registered Dietician was in the ER at the time and sat down with the women and asked her a few MORE questions about her health and habits...
- Are you taking any over-the-counter supplements? Alternative therapies in addition to your “baby aspirin”? What do you do for exercise? How’s your diet?

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What was she taking OTC? Exercise?

- She ran 7-10 miles a day—ibuprofen 400-600 QID
- Glucosamine for her joints
- Ginkgo for increased blood flow to brain and legs
- Grapeseed extract for anti-inflammatory purposes
- Garlic and ginseng for general well-being
- Vitamin E for heart health
- Aspirin for joints and heart health
- **ALL OF THE ABOVE INHIBIT PLATELET AGGREGATION (CLUMPING)**
- acupuncture treatments—bleeding from her acupuncture sites
- And, if *Prevention* magazine told her to take something, she took it.

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Bleeding and the stacking effect...

- ASA, NSAIDs (except celecoxib), ticagrelor (Brilinta), clopidogrel (Plavix), prasugrel (Effient)—all inhibit platelets
- direct oral anticoagulants (DOACs)—rivaroxaban/Xarelto, apixaban/Eliquis, and dabigatran/Pradaxa—inhibit clotting factors
- Warfarin (Coumadin)—inhibits clotting factors
- Valproic acid (Depakote, Depakene)—inhibits platelets
- Vancomycin, TMP/SMX, Linezolid/Zyvox, ampicillin, piperacillin--platelets
- OTC—cimetidine/Tagamet--platelets
- SSRIs—inhibit platelets

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Stacking alternative therapies—platelet inhibition

- Vitamin E – greater than 800 mg - 1000 mg/day
- Fish oil (greater than 3 grams/day) can decrease the ability of platelets to aggregate especially if the patient is taking other G's (see below) + ASA and/or NSAIDS and/or Plavix
- SJW (St. John's Wort)
- feverfew (used for migraines)
- If it starts with a G it inhibits platelet aggregation—gingko, garlic, glucosamine, ginseng, ginger, grapeseed extract
- Don't forget alcohol inhibits platelets as well

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Principle #2—you need acid to absorb many drugs

- As we age, gastric acid tends to decrease in the stomach (controversial)
- Proton Pump Inhibitors can wreak havoc with drug absorption due to a 70-90% reduction in gastric acid in patients with GERD—(this is NOT controversial)
- What are some drugs that need acid for absorption?
- Anti-fungal drugs-- ketoconazole (Nizoral), itraconazole (Sporanox)
- Vitamin B₁₂
- cefpodoxime (Vantin)--antibiotic
- Oral iron supplements
- Calcium

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POLYPHARMACY PRINCIPLE #2: Lower serum albumin levels due to decreased synthesis in the older liver, or patients with liver failure

- The older patient may have albumin levels of 3.2 g/dL (slightly below the lower limits of normal—3.5-5.5 g/dL)
- BUT even this slight decrease can be a big problem--albumin is the major serum protein that binds drugs
- protein-bound drugs are inactive vs. "free" drugs are active drugs
- BOTTOM LINE: older patients take the most drugs; drugs will be "competing" for binding sites; some drugs are stronger binders than others so the "weak" binders usually get displaced OFF the binding sites...this can lead to drug toxicity

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Low albumin and competition for binding sites

- Warfarin is “highly protein bound”, but is also a “weak binder”
- Numerous drugs knock warfarin off its binding sites—over 300+
- The biggest bully? Sulfa-based drugs kick warfarin right off of the binding sites
- Examples: Trimethoprim-sulfamethoxazole (Septra, Bactrim), thiazide diuretics (HCTZ), loop diuretics—furosemide/Lasix, celecoxib/Celebrex, sulfasalazine—all sulfa-based
- Other non-sulfa drugs: Metronidazole, erythromycin, ciprofloxacin (“Cipro”) and other “floxacin”

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Warfarin and the anti-fungal drug, miconazole

- Another interaction to mention in the geriatric world—topical Monistat for vaginal yeast infections—“Well, I have this little ‘itch’ down there...”
- 😊
- ...OTC Monistat can double the INR
- SPEAKING OF YEAST INFECTIONS...
- SGLT2 inhibitors are notorious for vaginal (1/14 and scrotal 1/29) yeast infections...all that “sugar down there”
- Another reason to use the estrogen ring for an overactive bladder—to reduce UTIs and yeast infections in older women; or mirabegron (Myrbetriq)

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Other common drugs that can knock warfarin off the albumin binding sites?

- Acetaminophen (yep, and how many elderly patients are on acetaminophen for osteoarthritis?) (p.s. it doesn’t work any better than a placebo*)
- Add a little caffeine + codeine and it works better... “MOM”
- but also start a bowel program at the same time.
- And don’t forget it can increase the INR
- *daCosta BR, et al. Effectiveness of NSAIDs for the treatment of pain in the knee and hip osteoarthritis: a network meta-analysis. *Lancet*, May 21, 2016; 387(10033):2063-2162

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So when should the INR levels be checked in patients on warfarin?

- Any time you add or subtract a drug from the regimen of a patient on warfarin, you should check the INR levels within 72 hours (or sooner)
- Enter the DOACs – hallelujah! Very few drug interactions, no need to monitor, no food interactions

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Who are the DOACs?

- Direct Oral Anti-Coagulants
- Factor Xa inhibitors—rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Savaysa), and betrixaban (Bevyxxa)
- Factor X inhibitor – dabigatran (Pradaxa)

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PRINCIPLE #4: THE LIVER and DRUG METABOLISM

- Hepatic blood flow may be reduced due to atherosclerosis
- Atherosclerosis doesn't just pick on the hepatic artery though—it fills the carotids to the brain, coronary arteries to the heart, the aorta, renal arteries, femoral and popliteal arteries
- WOW...IS THERE ANY ARTERY THAT DOESN'T FILL WITH FAT???? 😊

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YES! The internal mammary artery...seriously?

- Fewer fenestrations in its endothelial layer and lower intercellular junction permeability
- greater anti-thrombotic molecules such as heparin sulfate and tissue plasminogen activator (tPA)
- higher endothelial nitric oxide production (maintaining vasodilation)
- All of the above make the IMA impervious to the transfer of lipoproteins, which are responsible for the development of atherosclerosis. (Otsuka F. et al. *Ann Cardiothorac Surg* 2013 Jul; 2(4): 519–526)

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And that's why we use the the IMA for bypass...results?

- IMA grafts are associated with long-term patency and improved survival vs. saphenous vein grafts.
- IMA graft use has also been shown to be superior at 1-year and at five years compared to percutaneous procedures, including the use of drug-eluting stents for the treatment of coronary artery disease.
- **Any problems with the IMA?** Tends to be a short artery and can use both IMA's for triple vessel disease... or it can only be used for a single LAD bypass...unless... they're old breasts... 😊

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Back to PRINCIPLE #4: THE LIVER and DRUG METABOLISM

- Fat in the hepatic artery + some drugs also reduce hepatic blood flow—example: the OTC H2 blocker cimetidine (Tagamet)—never use cimetidine...if an H2 blocker is necessary, choose famotidine (Pepcid); cimetidine is also highly anti-cholinergic, 1st dose delirium
- Decreasing blood flow to the liver results in the decreased metabolism of drugs resulting in **increased** bioavailability and toxicity—for example:
- Beta blockers ("olols" such as metoprolol; "ilols" such as carvedilol) and bradycardia
- Morphine and bradypnea (we usually don't use morphine in the elderly unless they are in hospice or palliative care)
- Sildenafil (Viagra) toxicity

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Can a man really have too much sildenafil?

- Toxicity???
- Visual effects—blue vision (Pilots and flying)
- A sustained erection...
- Priapism (named appropriately after the Latin god Priapus—the fertility god and the “protector of the male genitalia”)—“*If you have had an erection for more than 4 hours...*”
- 16-year-old kids and their Daddy’s Cialis...YIKES...

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And, of course, the potentially deadly interaction with the ED drugs--NTG

- Can’t take within 24-48 hours depending on the half-life of the ED drug...
- Tadalafil – 36-48 hours
- Sildenafil, vardenafil, avanafil—24 hours
- “*When was your last dose of ____?*”
- “*2 hours ago, but don’t tell my wife...*”
- Women can be on tadalafil for PAH—case study we should ALL remember!!

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Tamoxifen and liver metabolism St. John’s Wort and tamoxifen (Nolvadex)

- First approved as an OC in the early 1970s; Sadly, more women got pregnant on it than the placebo
- AGONIST/ANTAGONIST drug
- Boosts (agonist) estrogen receptors (ER) on the uterine lining (bad—increased risk for uterine cancer) and boosts estrogen receptors in bones (good—prevents osteopenia and osteoporosis)
- Blocks (antagonist) ER on breast cancer patients that are ER+ decreasing the risk of a primary and secondary breast cancer (GOOD); but it blocks estrogen’s effects in hypothalamus—resulting in hot flashes (BAD)
- Prevention: Decreases breast cancer risk in women with dense breasts (63%) (*New Scientist*, November 5, 2011)

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The liver is the major organ for drug metabolism via the CYP450 enzyme system

- CYP 3A4, CYP 2D6, etc.
- **Tamoxifen is the #1 prescribed drug to prevent a recurrence of estrogen receptor positive breast cancer**
- Tamoxifen, is metabolized by the liver enzyme **CYP 2D6** to a more **potent** metabolite, endoxifen.
- In fact, endoxifen is 100 times more potent than tamoxifen and does the lion's share of the work to prevent either a recurrence of breast cancer or prevent primary breast cancer in high- risk patients

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Paroxetine, fluoxetine, sertraline, SJW and tamoxifen

- 30% of patients on tamoxifen also take an SSRI for either depression (from their cancer diagnosis or other reasons) or hot flashes from tamoxifen
- Using either paroxetine (one brand name for hot flashes—Brisdelle, the other brand name for depression—ex. Paxil), fluoxetine, and/or sertraline with tamoxifen is a NO, NO —**strong inhibitors of CYP 2D6**; St. John's Wort also falls into this category
- Inhibiting CYP 2D6 decreases the conversion of tamoxifen to endoxifen
- All of the above drugs in bullet #2 inhibit CYP 2D6 **reducing** the effectiveness of tamoxifen—in some instances by greater than 50%
- Use of any of the above antidepressants can almost double the risk of recurrence (13.9% vs. 7.5% w/placebo) (plasma levels of endoxifen are decreased by 64% with paroxetine)
- (Prescriber's Letter July 2009) (2014 NEJM May 8)

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What to do?

- Switch antidepressants or switch to an aromatase inhibitor (anastrozole) to block estrogen if the patient is a postmenopausal female
- Use citalopram (or escitalopram) for hot flashes if you pick an SSRI
- can also use escitalopram for depression
- Or try gabapentin; pregabalin; clonidine for the hot flashes
- Venlafaxine has also been approved

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PRINCIPLE #5: This hepatic CYP 450 enzyme system is also located along the brush border of the small intestine (extrahepatic)

- CYP 3A4 is the major metabolizing enzyme in the small intestine; CYP 3A4 initiates the metabolism of ~60% of all drugs before they even GET to the liver
- If something inhibits CYP3A4 the drug will be absorbed into the systemic circulation resulting in a higher bioavailability and potential toxicity
- What inhibits this enzyme that makes the headlines constantly?
- GRAPEFRUIT JUICE or GRAPEFRUIT

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Grapefruit juice/grapefruit can wreak havoc with the metabolism of many drugs...

- Simvastatin—grapefruit juice increases the bioavailability of simvastatin by 700% and atorvastatin by 25%—increased risk of myalgias and myositis
- Very high risk of rhabdomyolysis (skeletal muscle breakdown) and subsequent acute renal failure with doses of simvastatin over 80 mg
- ALWAYS QUESTION an 80 mg dose of simvastatin
- The risk of rhabdomyolysis is 25x higher with doses of 80 mg of simvastatin (Medical Letter, October 20, 2008)
- If greater than 40 mg of simvastatin is needed, switch to either 40 mg of atorvastatin or 10-20 mg of rosuvastatin
- Amiodarone also causes muscle aches and pains...can potentiate the risk of rhabdomyolysis with simvastatin

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If a patient is on a statin and complaining of muscle aches and pains... consider all of causes muscle aches and pains before stopping the statin drug

- Just getting out of bed ☹️
 - Vitamin D deficiency
 - Osteoarthritis
 - The ED drug tadalafil
 - Hypo- or hyperthyroidism
- Treating hypothyroidism may relieve or decrease statin-related myalgia (Dr. J. Garber, Harvard Special Report, *Thyroid Disease*, available at www.health.harvard.edu/TD)

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Grapefruit/grapefruit juice, amiodarone and verapamil

- Grapefruit juice inhibits the enzyme (CYP3A4) in the small intestine that metabolizes amiodarone—increased bioavailability and increased toxic side effects (fatal ventricular dysrhythmias)
- **DO NOT PRESCRIBE amiodarone if your patients cannot understand this interaction and refuse to give up their grapefruit products**
- Another anti-arrhythmic that interacts with grapefruit/juice—verapamil (the non-dihydropyridine calcium channel blocker...toxic levels can cause a fatal arrhythmia)

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What does grapefruit (GF) or grapefruit juice (GFJ) do?

- 62 y.o. female found dead on the kitchen floor—...was on verapamil for atrial fibrillation—toxicology studies showed verapamil toxicity; known to drink 4-5 Absolut vodkas with grapefruit juice daily
- Bad ending to this story

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Principle #6—the eGFR (estimated glomerular filtration rate) and chronic kidney disease (CKD)

- **The over-65, “elderly” kidney—the scope of the problem**
- Compared with 30 years ago, today’s patients are older, have a higher incidence of CV disease and diabetes, take **multiple** medications, and are exposed to more diagnostic and therapeutic tests using contrast dyes (CTs of everything with contrast dye, cardiac cath with contrast dye)
- Chronic kidney disease affects nearly 30% of all elderly individuals
- OLD KIDNEYS, lots of drugs, and **drug-induced nephrotoxicity**—may be as high as 66 percent—the newest class of drugs implicated in direct nephrotoxicity (tubulointerstitial nephritis and CKD) are the PPIs (proton pump inhibitors); long-term, high-dose use—omeprazole and friends

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What is the normal glomerular filtration rate? Gender differences?

- GFR is defined as the sum of the filtration rates of all 2.5-3 million functional nephrons
- The peak GFR is ~125 mL/min/1.73 m² in **men** and 100 mL/min/1.73 m² in **women**
- Peak kidney function? – when you are filtering like a champion?...is at age 24
- Basically, all of our body functions peak at age 24—and you have a good 6 years...we're all cookin' on all burners from 24-30 years of age

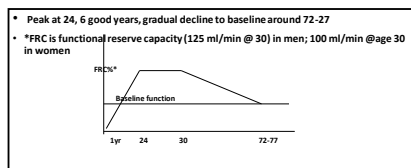
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And then? The party's over...

- Your 30th birthday is a physiologic milestone...almost everything is downhill from there
- It's called senescence...the gradual loss of structure and function of body parts due to aging
- The 1% RULE—a 1% decline in body functions per year after age 30

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Senescence and the Kidney—1% rule; most body functions decrease by 1% per year starting at age 30



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Let's do the math..

- 75-year-old female = loss of 1% per year after age 30—
- Easy math... 45 years after that wild and crazy 30th birthday party she has lost 1 mL/min per year = 45 mL/min
- Her peak at age 30 was 100 mL/min
- Easy math again--100 -45 = 55 mL/min in a HEALTHY 75-year-old female (not taking into account weight, ethnicity, smoking, diabetes, hypertension ☺)

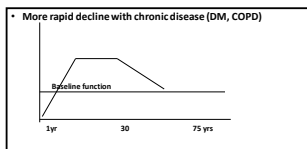
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Where does she fit in the Chronic Kidney Disease schedule?

- CKD-1 = GFR >90 mL/min/1.73 m² or higher
- **CKD-2 = GFR 60-89 mL/min=mild renal insufficiency**
- **CKD-3a = GFR 45-59 mL/min=mild to moderate renal insufficiency; a GFR of less than 60 mL/min/1.73 m² represents a loss of more than half of normal kidney function**
- CKD-3b = GFR 30-44 mL/min—moderate to severe
- CKD-4 = 16-29 mL/min =severe renal insufficiency
- CKD-5 = 0-15 mL/min = failure or ESRD (end-stage renal disease)—
- CKD-5D -- dialysis

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Senescence and chronic disease...reaching baseline earlier



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Clinical significance of mild to moderate renal insufficiency?

- Primarily has to do with drugs and the ability to filter and excrete drugs
- The majority of the 6,000++ drugs are excreted through the kidneys and need an adequate glomerular filtration rate to do so; drug retention and toxicity can result from decreased filtration
- Gabapentin (Neurontin) and pregabalin (Lyrica) should not be used with eGFRs less than 60 mL/min (increased CNS effects)
- Empagliflozin should not be initiated in patients with an eGFR <60 mL/min/1.73 m² or CrCl <60 mL/min. In patients tolerating empagliflozin whose eGFR falls persistently below 60 mL/min/1.73 m² or CrCl below 60 mL/min, the dose of empagliflozin should be adjusted to or maintained at 10 mg once daily.
- OTC H₂ blockers—cimetidine* (Tagamet) or famotidine (Pepcid) should not be used with GFRs less than 50 mL/min (due to increased risk of CNS effects)

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Metformin, eGFR, and dose adjustments

eGFR (mL/min)	Maximum daily dose	Recommended monitoring
≥60	2550 mg	Monitor renal function annually
45-59	2000 mg	Monitor renal function every 3 to 6 months
30-44	1000 mg	2-4 fold risk of lactic acidosis—10/100,000
<30	Do not use	6-7 fold risk of lactic acidosis in this group

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Principle #7—the bilipid layer that covers the brain becomes more permeable to drugs with age

- Lipid-soluble drugs cross the blood brain barrier much more easily as we age...therefore, increased CNS side effects are common
- Confusion and delirium
- problems with coordination and imbalance
- movement disorders (Parkinsonism is the term for drug-induced Parkinson's disease; tardive dyskinesia with dopamine blockers—FGA > SGA)

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Treatment of tardive dyskinesia

- Tetrabenazine (Xenazine)(drug first synthesized for schizophrenia 50 years ago—approved for chorea in 2009); depletes neurotransmitters serotonin, norepinephrine and especially dopamine in the basal ganglia (Medical Letter, January 2009)

NEWER and BETTER...

- Valbenazine/Ingrezza (April 2017)
- Deutetrabenazine/Austedo (June 2017)

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Acetylcholine is the neurotransmitter of cognition

- *"The use of anti-cholinergic drugs has been strongly associated with adverse health outcomes, including cognitive impairment, dementia, falls, functional decline, hospitalization and mortality, especially in older adults."*
- (Geriatrics and Gerontology International, April 17, 2017, Suppl. 1)
- *"The results of the present study showed that approximately half of the residents living in veteran's homes had exposure to anticholinergic drugs, and these residents had a significantly higher risk for short-term cognitive decline."*

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Anti-cholinergic drugs increase the risks of confusion and memory loss

- There are over 500 drugs with anti-cholinergic properties that can wreak havoc with cognitive function in older patients
 - Why would anti-cholinergic drugs be used in older patients?
- Bladder control issues, movement disorders (side effects of dopamine blockade), drooling, diarrhea, colds, sleep, bronchodilators for COPD
- And in many instances these drugs are "added" to their pile of other drugs—many of which also have anti-cholinergic effects—and we're back to the stacking effect

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And more, more, more drugs with anticholinergic effects...

- **Amitriptyline** – if ever used (and sometimes is for neuropathy) the higher the dose, the higher the risk of anticholinergic effects;
- Clozapine (2nd Generation anti-psychotic)
- Haloperidol (1st generation anti-psychotic)
- Cimetidine (1st dose delirium)
- Captopril, nifedipine
- Prednisolone
- **Paroxetine** (potently anti-cholinergic: never use this antidepressant in patients who are taking the acetylcholinesterase inhibitors such as donepezil (Aricept)
- dig, dipyridamole
- **warfarin**
- **Furosemide**
- Isosorbide dinitrate
- Codeine
- Oxycodone
- Diphenhydramine (OTC Benadryl)
- The PM versions of OTC analgesics (Tylenol PM)
- Oxybutynin (Oxytrol, Ditropan); tolterodine (Detrol, Detrol LA); fesoterodine (Toviaz); Darifenacin (Enablex); Solifenacin (VESicare) Trospium (Sanctura, Regurin)

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What are the other BIG CONCERNS ABOUT USING highly anti-cholinergic drugs at any time in an adult—

- Brain atrophy and cognitive decline are observed in geriatric patients receiving anticholinergic medications
- The most **highly** anticholinergic drugs are associated with increased risk for dementia in elders up to 20 years **after** exposure.
- Including the drugs listed for urinary problems (Oxybutynin (Oxytrol, Ditropan); tolterodine (Detrol, Detrol LA); fesoterodine (Toviaz) ; Trospium (Sanctura, Regurin) and, including two highly anticholinergic antidepressants—paroxetine (Paxil), amitriptyline (Elavil)
- SUMMARY: "As suggested by guidelines, anticholinergics in general should be avoided in older adults."
- (Richardson, K. Anticholinergic drugs and risk of dementia: case-control study. *BMJ* 2018;361:k1315)

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Principle #8—know the half-life of a drug before prescribing to the elderly

- **The RULE in GERIATRICS...Never give a drug that has a half-life longer than their life...**
- Fluoxetine (usually 2-9 days, can be up to 16 in the very old patient) vs. sertraline (18-24 hours)
- Fluoxetine—fluoxetine is metabolized by the liver to a more potent, longer-acting drug (norfluoxetine)...increasing its half-life—add this to a kidney that's not filtering adequately due to age and fluoxetine can become toxic as the drug will be retained for longer periods of time. NOT a good choice for an anti-depressant in the older adult; sertraline IS a good choice in teenagers with depression who forget to take their drugs or conveniently flush them down the toilet

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T_{1/2} (half-life) of a drug—how long it takes to get 1/2 of the drug out of the body

- Another example: the benzodiazepine (BZs) known as diazepam (Valium) — the half-life of diazepam is “your age in hours”
- **EXAMPLE: 5 mg of valium for anxiety**
- Valium in an 80-year-old? Half life 80 HOURS – VALIUM in a 20-year-old? 20 HOURS
- So you have to reduce the dose in the 80-year-old and increase the dosing interval if Valium is your only choice—
- Fortunately, shorter-acting BZs are available—including alprazolam (Xanax)(12-15 hours), lorazepam (Ativan)(10-20 hours); really short-acting—midazolam (Versed)1-4 hours); triazolam (Halcion)-1.7-5 hours)

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A few other T_{1/2} notes:

- **Furosemide (Lasix)** a potent diuretic that “lasts six hours” (serum half-life of Lasix is 1.5 hours as an oral drug. It takes 4 half-lives to excrete all of the drug ($4 \times 1.5 = 6$), therefore it only lasts 6 hours.
- **Tadalafil (Cialis)** has a half-life is 17.5 hours in normal healthy men and 21.6 hours in elderly men, while the half-lives of sildenafil and vardenafil are similar at 4 hours (Francis and Corbin 2003). The therapeutic window (fancy way of saying how long it’s active) of 36 hours for tadalafil (Porst et al 2003)—this why tadalafil is called “the weekend warrior”.

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Nocturnal hepatic cholesterol synthesis and statin dosing

- Endogenous hepatic cholesterol synthesis is cyclical in nature with the greatest production during fasting states—nocturnal production via the liver
- Statins inhibit the enzyme (HMG-CoA-reductase) that produces LDL-cholesterol
- The elimination half-life of a statin determines if an agent should be dosed at bedtime.
- To maximize the effects of statins with a short half-life—fluvastatin, lovastatin, and simvastatin—take the prescribed dose at bedtime allowing the greatest drug concentration to be present during peak endogenous cholesterol synthesis. (simvastatin/Zocor (2-3 hours), fluvastatin/Lescol (less than 3 hours), and lovastatin/Mevacor)(1.1 -3 hours)—

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The half-life of individual statins

- The rest of the statins have longer half-lives allowing for flexibility in administration time.
- atorvastatin/Lipitor (15 hours with metabolites 20-30 hours), pitavastatin/Livalo (12 hours), pravastatin (77 hours), and rosuvastatin/Crestor (19 hours)
- (Dulay D. et al. *Can J Cardiol*. 2009 Feb; 25(2): e28–e31)(Luvai A. Rosuvastatin: A Review of the Pharmacology and Clinical Effectiveness in Cardiovascular Disease. *Clin Med Insights Cardiol*. 2012;6:17-33)(Carolyn J. Steber, PharmD, ebmconsult.com)

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Principle #9—Herbal interactions are rampant

- Take a thorough patient history for all of the prescription, OTC herbal/alternative/complementary, illicit and “borrowed-from-friends” drugs
- When taking a history for the use of supplements approach the topic in a non-judgmental way...
- “We know that supplements are very popular today...some of these products can either interfere with some of the drugs, including over-the-counter drugs such as acetaminophen (Tylenol) and ibuprofen that you are taking. These products can make your drugs either more potent or less potent. Are you taking any alternative therapies, over-the-counter supplements that we need to be aware of—multivitamins, single vitamins, melatonin, fish oil, calcium, magnesium?”

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Lots of supplements interact with acetaminophen increasing the potential for hepatotoxic effects

- Asian ginseng (for whatever ails ya’), resveratrol (antioxidant), feverfew (headaches), garcinia (Dr. Oz’s favorite weight loss herbal product—total of 2 lbs–1 kg—really?), boswellia (cold symptoms), St. John’s wort, green tea extracts, cannabidiol, high doses of niacin (B3)(Red Bull, Monster drinks), echinacea, black cohosh, red yeast rice, conjugated linoleic acid (CLA, burns fat for weight loss, at least in mice), noni juice, gotu kola, chaparral, comfrey, coltsfoot, kava (linked to acute liver failure—black box warning in U.S. could potentially increase the blood levels of acetaminophen and **increase the risk hepatotoxic effects**)
- BOTTOM LINE? Unexplained liver enzyme elevations (AST/ALT)? Ask about supplements!

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60% of all drugs interact with St. John's Wort

- St. John's Wort (blossoms on June 24, birthday of St. John the Baptist) is the number one herbal product that interacts with over 60 percent of all prescription drugs. The interaction is to make the drugs LESS effective: Cyclosporine (transplant patients), tamoxifen, HIV Rx, and Combined Oral Contraceptives
- Side effect?

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I'm PREGNANT!!!

- As the old saying goes...
- *"It takes many nails to build a crib; but only one screw to fill it."*

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Principle #10—Other interactions of note

- Now that tramadol has found a new life in pain management
- Hypoglycemic potential (glipizide + glargine/Lantus) + tramadol
- 3-fold higher increase of hypoglycemia-related hospitalizations in patients taking tramadol compared to those on other opiates such as hydrocodone
- Absolute risk is low BUT stay alert with elderly patients, or those with renal disease or taking other meds that can cause hypoglycemia
- Usually occurs within the first 10 days
- Popular OTC herbal product that lowers glucose slightly--berberine
- *Prescriber's Newsletter* (February 2015)

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Other interactions of note...

- Risk of hyponatremia with HCTZ, fluoxetine/Prozac (all SSRIs lower serum sodium), and acetaminophen (can cause SIADH)
- Dandelion is an herbal product that can also lower serum sodium—used as a diuretic; The English folk name for dandelion root is “piss-a-bed” and the French nickname is “pissenlit”
- A serum sodium that drops to less than 120 mg/dl can cause severe brain damage
- Neurological signs of low serum sodium (hyponatremia) are highly variable and depend on the level and rate of fall of the serum sodium:
 - Decreased level of consciousness.
 - Cognitive impairment (short-term memory loss, disorientation, **confusion**, depression).
 - Focal or generalized seizures.
 - Brainstem herniation - seen in severe acute hyponatremia; signs include coma; fixed, unilateral, dilated pupil; decorticate or decerebrate posturing; respiratory arrest.

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Does glucosamine work for osteoarthritis pain? GAIT study

- Moderate-to-severe pain? glucosamine combined with chondroitin sulfate provided statistically significant pain relief compared with placebo—about **79 percent** had a 20 percent or greater reduction in pain versus about **54 percent** for placebo.
- mild pain? glucosamine and chondroitin sulfate together or alone did not provide statistically significant pain relief.
- The chondroitin component provides an additional 8-10% pain relief—some say it's not worth the cost...give the supplement 3 months to work
- (ConsumerLab.com; accessed December 2019) NIH glucosamine/chondroitin arthritis intervention trial primary study (GAIT study). NCCIH—National Institutes of Health; 2016)

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Thank you.

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