PHARMASUITABLES FEBRUARY 2016

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DISCLOSURES

- Steve and Phil work for Rocky Mountain Health Plans. Phil is an employee of the Mesa County Health Department
- We do not have any financial interest in the medications we are discussing today.
- We have no intention to malign any person, business or product.

THREE DRUGS TO THINK TWICE ABOUT

RECOMMENDING VITAMIN D

ORDERING VITAMIN D LEVELS

USPSTF, Feb 2013, Vitamin D and Calcium to Prevent Fractures
Applies to asymptomatic community dwellers, with no history of fractures or osteoporosis

Population	Recommendation	Grade
Premenopausal Women	Insufficient evidence to assess the balance of the benefits & harms	I
Men	Insufficient evidence to assess the balance of the benefits & harms	I
Community dwelling Postmenopausal Women	Insufficient evidence to assess the balance of the benefits & harms	I
Community dwelling Premenopausal Women	Daily supplementation of vitamin D3 400 IU or less and 1,000 mg of calcium or less has no effect on fractures and increases the risks of renal stones	D
Community dwelling >adults 65 and at increased risks for falls	Vitamin D (800 IU) supplementation is effective in preventing falls.	B

QUIT RECOMMENDING VITAMIN D

And what's new with elderly adults with a fall?

Bischoff-Ferrari (JAMA Int Med Feb 2016) performed a randomized controlled trial study of 200 men and women >70 years who had experienced a fall.

58% were vitamin D deficient (< 20 ng/ml) at baseline.

The participants were randomized to two one of two high dose regimens (60,000 IU D3 per month or 24,000 IU D3 plus 300 ug calcifediol per month) or a low dose control group (24,000 IU of D3 per month.)

QUIT RECOMMENDING VITAMIN D

Results:

Guess what?

Serum vitamin D levels went up more in the high dose groups than with the low dose group. (82% > 30 ug/ml vs 55% >30ug/ml).

After 12 months the high dose participants did not have any better lower extremity function and had a **greater** chance of falling (66% vs 48%) NNH =6

QUIT ORDERING VITAMIN D LEVELS

- No consensus exists on the definition of vitamin D deficiency.
- The accuracy of the tests to determine vitamin D deficiency is difficult to determine because of the lack of studies that use an internationally recognized reference standard.
- The USPSTF found no studies that evaluated the direct benefit of screening for vitamin D deficiency in adults. Grade **I**
- The American Society for Clinical Pathology **recommends against** screening for vitamin D deficiency in the Choosing Wisely campaign.

HYALURONIC ACID INJECTIONS FOR KNEE OSTEOARTHRITIS

- Meta-analysis of 19 trials (Jevsevar et al J Bone Joint Surg Am 2015 Dec 16) that included only studies of > 30 patients and at least 4 weeks follow-up that used either the WOMAC (Western Ontario and McMasters Universities Arthritis Index) or a visual log pain scale.
- In these double blind sham-controlled trials, hyaluronic acid (HA) statistically improved function and decreased pain scores, but the treatment effects WERE NOT CLINICALLY SIGNIFICANT.

Pain Scale of 100 points: 8 points is clinically significant. Studies showed 2.3 points difference.

Function Scale 100 mm: 20 mm is clinically significant. Studies showed 9.6 mm difference.

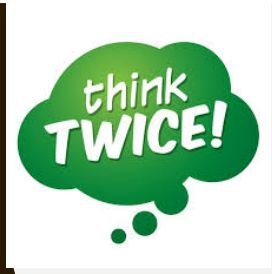
HYALURONIC ACID INJECTIONS FOR KNEE OSTEOARTHRITIS

- In contrast, in non-blinded trials that compare HA with usual care, the treatment effect exceeded the minimum important difference (ie.. HA is clinically significant).
- Ladies and gentlemen,

"Hyaluronic acid injections are a potent placebo." And the longer the needle, the better it works.

The 2013 Guidelines for knee arthritis of the American Academy of Orthopaedic Surgeons

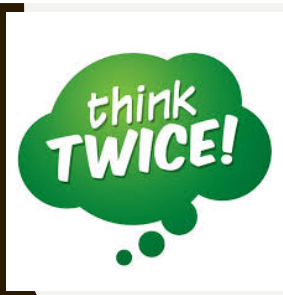
recommends against the use of hyaluronic acid injections.



HOME ALLERGY HOT

There is now an industry promoting allergy injections be given at home. The process involves:

- # Allergy testing in a primary care physician's office by a allergy technician employed by the allergen company. (Doc bills the patient for allergy testing)
- # Allergy tech employed by the allergen company prepares the extracts. (Doc bills the patient for having "supervised" that mixing.)
- # Allergen company representative trains the patient or parent to administer the extracts at home.
- # The patient or parent administers the sub q injections at home.



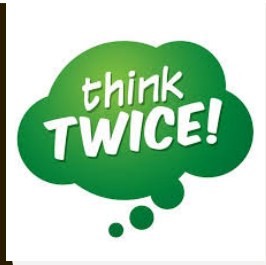
HOME ALLERGY HOT

❖ Proposed Mechanism of Action:

The allergen company promotes "a slow buildup of the dose of the subcutaneous immunotherapy, designed to obtain recommended allergen concentrations on a cumulative basis." (International Forum of Allergy and Rhinology, Vol oo, No.o, xxxx 2015)

❖ Tolerability:

The home protocols call for 2-6 times as many doses as standard office based protocols, with as many as 300 doses given in the first year. Standard office based regimens typically involve 40-150 doses administered in the first year. Doing injections at home would save lots of time and hassle.



HOME ALLERGY HOT

❖ Cost

Insurers, other than Medicaid, may limit the number of doses of immunotherapy or do not pay for home shots at all (Aetna, Blue Cross Blue Shield NC, Capital Blue Cross, WellCare Health plans). Thus, depending on insurance, home immunotherapy may cost more than twice that of conventional office based shots.

Efficacy:

I cannot find any long term data to support or refute this technology's efficacy. The study quoted above was not randomized, but allowed allergic rhinitis patients to opt for the active treatment (60 patients) or the no treatment control group (56 patients). The patients in the active treatment group improved more over their own baselines than the control (no immunotherapy) patients improved over their own baselines. The patients were followed for one year.

HOME ALLERGY HOT

❖ Safety:

There is a very small, but real risk of experiencing a dangerous, potentially fatal reaction with allergy shots.

The following organizations **recommend against** home allergy shots:

Mayo Clinic World Allergy Organization National Jewish Hospital

Children's Hospital University of Colorado

American College of Allergy Asthma & Immunology

European Academy of Allergy and Immunology

National Institutes of Health

ANOTHER LOUSEY TALK

PEDICULUS HUMANUS CAPITIS
AAP GUIDELINE UPDATE 2015

Devore et al Pediatrics 2015;135;e1355, published online April 27, 2015

PEDICULUS HUMANUS CAPITIS LIFE CYCLE

- Head lice treatment costs $1 Billion/year
- Not a health hazard or sign of poor hygiene, but stigma and kids are ostracized.
- Adult 2-3 mm long (sesame seed), 6 legs, tan to grayish white. Female lives up to 3-4 weeks and when mature lays 8-10 eggs per day.

PEDICULUS HUMANUS CAPITIS LIFE CYCLE

- Eggs attached to hair follicle within 4 mm of scalp and incubated by body heat. They hatch in 8-9 days.
- Nymphs become adults in 9-12 days.
- The louse feeds by injecting small amounts of saliva which has vasodilatory and anti-coagulant properties into the scalp, allowing the louse to suck small amounts of blood every few hours.

PEDICULUS HUMANUS CAPITIS TRANSMISSION

- Lice can't fly, hop or jump. They can only crawl.
- Pets DO NOT play a role in the transmission of human lice.
- In most cases, transmission occurs by direct head to head contact. Indirect spread through contact with personal belongings of an infected individual (combs, brushes, hats) is much less likely to occur.

PEDICULUS HUMANUS CAPITIS TRANSMISSION

- There are case reports that combing dry hair can build up enough static electricity to eject a louse from an infected scalp for a distance up to a meter.
- Lice found on combs are likely to be injured or dead.
- In one study, live lice were found on only 4% of pillowcases used by infected volunteers.

PEDICULUS HUMANUS CAPITIS DIAGNOSIS

- Diagnosis by direct observation.
- Difficult at times because lice avoid light and can crawl rapidly.
- Studies show that the diagnosis of infestation is easier using a louse comb.

PEDICULUS HUMANUS CAPITIS DIAGNOSIS

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- Using water, oil or a conditioner slows down the lice and eliminates static electricity.
- Smaller eggs are easier to see near the nape of the neck or behind ears.
- Many presumed "lice" submitted by physicians, nurses and parents to labs have been found to be artifacts …dandruff, hairspray droplets, scabs, dirt or other insects like aphids.

PEDICULUS HUMANUS CAPITIS TREATMENT

- Resistance patterns?
- Think safety, ease of use, costs, efficacy and recurrence.
- Cochrane review of head lice treatment in the works.

PERMETHRIN (1%)

- Most studied pediculicide in US and least toxin to humans.
- Apply the Nix lotion to **damp** hair after shampooing with a non-conditioning shampoo. Leave on 10 minutes, rinse and towel dry. Conditioners interfere with permethrin adhering to the hair shaft and reduce its residual effect.
- Retreatment at 9 days (new evidence based on the life cycle) whether you can see lice or not, is now thought optimal.

PERMETHRIN (1%)

- Adverse effects: pruritis, erythema and edema. Less allergenic than pyrethrins.
- 5% permethrin (Elimite) not approved for lice and does not work any better in those lice resistant to 1% permethrin.
- 1% permethrin (Nix) available in 60 cc, 2 bottles for $13.97 from Amazon or 2 bottles and a comb for $18.33 from Safeway.

PYRETHRINS

- Manufactured from chrysanthemums, formulated with piperonyl butoxide
- Neurotoxic to lice, but newly laid eggs do not have a nervous system so 20%-30% of eggs remain viable after treatment..
- Pyrethrins available in shampoo and mousse formulations.
- Apply to **Dry** hair, leave on for 10 minutes., then rinse out. Retreat in 9 days.
- RID 45 available OTC at Safeway, $22 for 8 oz.

MALATHION

- Malathion is an organophosphate (cholinesterase inhibitor)
- Reintroduced in 1999, after being taken off the market twice because of long application time, flammability and odor.
- Apply lotion to dry hair, allow to air dry and then wash off after 8-12 hours, although some studies suggest that leaving on for only 20 minutes is effective.
- Malathion has high ovicidal activity and a single application is adequate for most patients.

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MALATHION

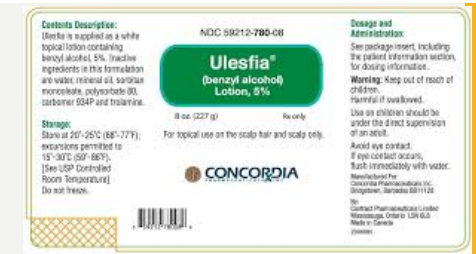
- The high alcohol content of malathion (78% isopropyl alcohol) makes it highly flammable. Do not use blow dryer, curling iron or a flat iron. Do not smoke around a child being treated.
- Little data for use in kids under 6 years and contra-indicated in kids under 2 years.
- Generic malathion, 59 ml of 0.5% lotion available at a wide range of prices in GJ:

  $107 at Walgreens; $150 at Walmart; $221 at Albertsons.

BENZYL ALCOHOL 5% ULESFIA

- Approved by FDA in 2009 in kids older than 6 months.
- Kills lice by asphyxiation.
- 2 RCTs showed ~75% no live lice 14 days after last application. Inert vehicle success was 5%-26%.

BENZYL ALCOHOL 5% ULESFIA



- Apply to dry hair in adequate quantities to saturate the scalp and the entire length of the hair. Leave on for 10 minutes and wash out. Repeat in 9 days as benzoyl alcohol is not ovicidal.
- Common adverse reactions: pruritus (12%), erythema (10%) and pyoderma (7%).
- Cost in Happy Valley: Ulesfia $59-$65 in multiple pharmacies for 227 gm of 5% lotion. Concern is need to treat at least twice and with long hair (>22") might need 3 bottles per treatment.

SPINOSAD (0.9% SUSPENSION)

- This compound is derived from natural fermentation of a soil bacterium, *Saccharopolyspora spinose* and contains benzoyl alcohol.
- Activity is neurotoxin against both adults and ova.
- Superior to permethrin in one study: Spinosad 84%-87% treatment success vs 43%-45% for permethrin.

SPINOSAD (0.9% SUSPENSION)

- Apply to dry hair, starting at scalp and working to ends of hair. Rinse after 10 minutes. Repeat in 7-9 days only if live lice are seen.
- Adverse reactions: local erythema 3%; eye irritation 2%.
- Cost of generic Spinosad: 120ml bottle for $102 at Walgreens and $211 at Safeway.

IVERMECTIN (0.5%)

- Sklice lotion approved by FDA for head lice in 2012 for kids 6 months and older.
- In a study comparing Sklice with its vehicle, 74% vs 18% were lice free at day 15.
- Topical ivermectin lotion is applied to dry hair and scalp and is rinsed after 10 minutes. Only one application is required, because when the treated eggs hatch, the lice are unable to feed as a result of pharyngeal muscle paralysis.

IVERMECTIN (0.5%)

- Adverse effects: rare, skin or eye irritation.
- Sklice lotion, 117 gm tube 0.5% : Range: City Market $279; Safeway $300.
- Oral ivermectin (Stromectol) not FDA approved for lice. Oral ivermectin may cross blood/brain barrier in humans and block neural transmission.

ALTERNATIVE TREATMENTS

- Prescriber's Letter says avoid all natural products. Essential oils widely used in traditional medicine, but variability of their constitution affects outcomes.
- Ylang ylang oil is associated with contact sensitization.
- Lavender oil, tea tree oil and Andiroba oils are not required to jump through FDA hoops.
- One study showed HairClean 1-2-3 (anise, ylang ylang, coconut oils and isopropyl alcohol) was found to be at least as effective as Nix.

OCCLUSIVE AGENTS DESICCATION

- Petrolatum shampoo, mayonnaise, butter or margarine, and olive oil have all been applied to suffocate the lice. Although widely used, there have been no RCTs to evaluate effectiveness.
- A non-randomized, uncontrolled 2004 study reported a 96% cure rate with Cetaphil cleanser. The lotion is applied to the hair, dried on with a hair dryer, left on overnight and washed out the next morning. This process is repeated weekly x 3.

OCCLUSIVE AGENTS DESICCATION

The AirAlle is a custom built machine that uses one 30 minute application of hot air to desiccate the lice. Need expensive machine and a trained operator.

- Don't try this at home with a hair dryer as studies have shown that live lice may become airborne.

BEING "NIT-PICKY"

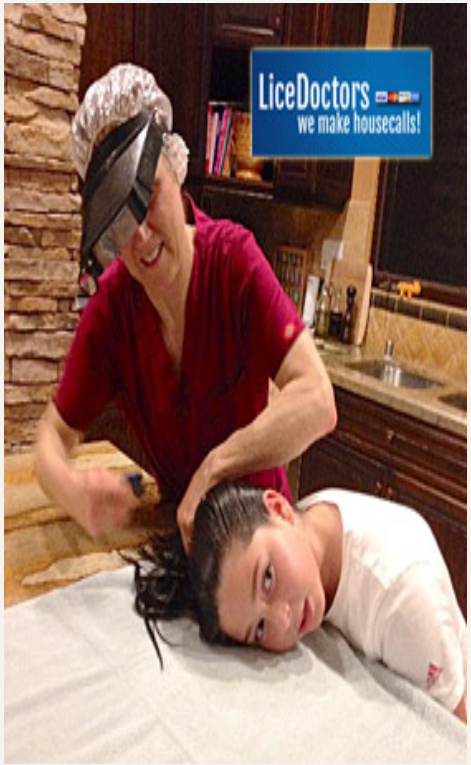
- Manual removal is safe, cheap and tedious.
- The AAP guideline promotes nit-picking as an opportunity for parent and child to have "some close extended time together."
- Battery powered MagiComb with oscilating teeth claims to kill live lice and nits. A bug zapper like device, Robi-Comb claims to kill live lice. No RCTs and warnings not to use in kids with seizures or pacemakers.

BEING "NIT-PICKY"

- Vinegar, WD-40, vodka and bleach have been promoted to facilitate loosening the "glue" that attaches the nit to the hair shaft. There are no evidence based data to support use of any of these products.

BEING "NIT-PICKY"

- Finally, if you are affluent and want to focus the quality time with your kids to more pleasant activities, there are lice salons.
- Lice Clinics of America: $175 buys you a 30 minute AirAlle treatment and a professional comb out. Budget minded: the 30 minute AirAlle, but you do the comb out at home goes for $119.



ENVIRONMENTAL INTERVENTIONS

- Treat family members who share a bed with an infested person, even if no live lice are found.
- Only items that have been in contact with the head of the person with the infestation in the 24-48 hours before treatment should be considered for cleaning. Think clothing, headgear, furniture, carpeting and rugs.
- Washing, soaking or drying items at >130 degrees will kill stray lice and nits. Vacuum furniture, carpets and rugs.

LICE AND SCHOOLS

AAP Guidelines:

- "Because a child with an active case of head lice likely has had the infestation for a month or more by the time it is discovered, and poses little risk to others, he or she should remain in class." Confidentiality is crucial and **sending the kid home "stat" compromises confidentiality.**
- Do "ALERT letters" to all parents in a class violate privacy laws? No studies to show if these letters are efficacious.
- "No nit" policies that exclude children from school until all nits are removed may violate a child's civil liberties. "No nit" policies should be abandoned.


FEAR
THE
HAWK

1954

Oct. 2010

July 2011

2015

Savaysa™
(edoxaban) tablets

Dec. 2012

DABIGATRAN (PRADAXA)

- Direct Thrombin Inhibitor
- Use
  - Prevent thromboembolism in nonvalvular afib
    - NNT = 200 vs. warfarin for one year
  - Prevent VTE after hip/knee replacement
    - Non-inferior to enoxaparin in VTE, death, and maj. Bleeding
  - Treat DVT/PE
    - Non-inferior to warfarin in preventing recurrent VTE/death, major bleeding
- Dosing
  - 150mg BID
  - 75mg BID if CrCl <30

DABIGATRAN (PRADAXA)

- Reversal
  - ~~No reversal agent is available for DTI's~~
  - As with rivaroxaban, supportive care and control of bleeding site are first line
  - Administration of clotting factors (FFP, PCC) not wholly effective as the thrombin is inactivated in these products
  - Empiric FFP not advised as there is not a deficiency of clotting factors, but inhibition of Factor IIa
  - Activated charcoal w/in 2 hours of last dose
  - Dialysis will remove 60% of drug after 2-3 hours, 70% after 4 hours

ENTER PRAXBIND (IDARUCIZUMAB)

- Manufacturer: Boehringer Ingelheim
- Indication: when reversal of anticoagulant effects of Pradaxa is needed for emergency surgery or life threatening/uncontrolled bleeding
- MOA: humanized monoclonal antibody fragment, binds to dabigatran and rapidly neutralizes it's effects

ENTER PRAXBIND (IDARUCIZUMAB)

- Efficacy
  - 3 randomized DB placebo trials
  - N=283, 224 got at least one dose
  - One trial treated 14 patients with 220mg BID x 3 days, then single 220mg dose
    - Praxbind was administered 2 hours later, 5g IV infusion

Table 1. **Change in Coagulation Parameters in 14 Dabigatran-exposed Subjects Treated with 5g Praxbind** *(from Praxbind prescribing information)*

Clotting Assay (Mean and Standard Deviation)	Pre-Idarucizumab (N=14)	End of infusion of Idarucizumab (N=14)	24 hours after Idarucizumab (N=14)
dTT [s]	66.6 (12.0)	32.1 (1.38)	33.0 (1.69)
aPTT [s]	67.8 (14.5)	29.2 (4.74)	31.9 (5.71)
ECT [s]	122 (42.2)	34.7 (1.92)	38.8 (2.86)
TT [s]	127 (62.6)	12.5 (0.786)	19.3 (5.14)
ACT [s]	236 (47.6)	116 (7.71)	140 (10.1)

Table 2. **Change in Coagulation Parameters in 14 Dabigatran-exposed Subjects Treated with Placebo** *(from Praxbind prescribing information)*

Clotting Assay (Mean and Standard Deviation)	Pre-Placebo (N=14)	End of infusion of Placebo (N=14)	24 hours after Placebo (N=14)
dTT [s]	64.7 (9.82)	65.3 (12.1)	36.1 (2.48)
aPTT [s]	65.2 (14.0)	66.5 (13.2)	37.0 (7.10)
ECT [s]	117 (29.8)	122 (32.9)	44.7 (5.39)
TT [s]	132 (35.4)	147 (46.7)	39.5 (11.8)
ACT [s]	219 (44.7)	216 (50.5)	148 (15.1)

ENTER PRAXBIND (IDARUCIZUMAB)

- Efficacy
  - Another study administered Praxbind to dabigatran patients presenting with serious bleeding (n=66) or requiring urgent procedure (n=57)
    - Reversal of the anticoagulant effect was measured by ECT or dTT in the first 4 hours
    - Maximal effect on reversing anticoagulation by 4 hours was 100%
    - 89% achieved complete reversal which was evident immediately after administration

ENTER PRAXBIND (IDARUCIZUMAB)

- Safety
  - >5% incidence:
    - Hypokalemia
    - Delirium
    - Constipation
    - Pyrexia
    - Pneumonia

ENTER PRAXBIND (IDARUCIZUMAB)

- Administration
  - 5 gram IV infusion
  - Provided as 2 vials with 2.5mg/50mL each
  - Infusion or bolus injections given consecutively
  - Pradaxa therapy can be restarted by 24 hours
- Cost
  - AWP=$42/mL, so $4200 for one dose
  - (PCC is about $15,000)

THE FUTURE

- Andexanet
  - Binds to and reverses the effects of the Factor Xa inhibitors (rivaroxaban, apixaban, …)
  - May also reverse fondaparinux and the LMWH

TRESIBA (INSULIN DEGLUDEC)

- New Ultra long acting insulin
- Manufactured by Novo Nordisk
- Duration of action
  - About 42 hours
  - Lantus, Levemir, and Toujeo last about 24 hours
- Dosing
  - Unlike other basal insulins, Tresiba can be dosed at any time of the day due to long DOA

TRESIBA (INSULIN DEGLUDEC)

- Storage
  - Can be stored at room temp for 56 days
  - Lantus can be stored for 28 days, and Levemir for 42 days
- Efficacy
  - Nine open label trials compared Tresiba to either insulin glargine or insulin detemir, non-inferiority design.
  - One study compared to sitagliptin to show superiority

TRESIBA (INSULIN DEGLUDEC)

- **Type 1 diabetes:**
  - **Study B**: 26 week, open label, MC, n=455. Pts randomized to Tresiba or insulin detemir QHS. After 8 weeks, 33% of pts were using detemir twice daily. By end of trial, difference in HbA1c was -0.09% which met the non-inferiority setpoint of 0.4%. Other studies with glargine had similar results.

TRESIBA (INSULIN DEGLUDEC)

- **Type 2 diabetes:**
  - **Study D:** 52 week, open label, MC, n=1030. Pts randomized to Tresiba or glargine once daily, with background of metformin +/- DPP4i oral therapy. At week 52, different in HbA1c was 0.09% which met the non-inferiority setpoint of 0.4%.
  - **Study I:** 26 week, open label, MC, n=447. Pts randomized to Tresiba or sitagliptin once daily. Up to two OAD drugs comprised background therapy (metformin, SU, or pioglitazone). At week 26, A1c reduction with Tresiba was a statistically significant 1.52 vs. 1.09 for sitagliptin. Not a surprising result.

TRESIBA (INSULIN DEGLUDEC)

- **Pro's:**
  - Very long duration of action affords more flexibility in timing of dose each day as compared to the other basal insulins.
    Studies indicate non-inferiority to other basal insulins in lower A1c. May cause less nocturnal hypoglycemia, although overall risk of hypoglycemia is the same.
  - May benefit patients needing to inject a basal insulin twice daily such as those needing more than 80 units daily, since the U200 pen can deliver up to 160 units per dose.
  - Can be stored at room temp for a longer period of time than other basal insulins.

TRESIBA (INSULIN DEGLUDEC)

- **Con's:**
  - No efficacy benefit vs. other basal insulins
  - Insulin glargine will be available as a generic insulin some time in 2016 and will represent a less costly option than Tresiba or insulin detemir (Levemir). Higher cost than Lantus, Levemir, or Toujeo (approximately $50 more per month).

ENTRESTO (SACUBITRIL/VALSARTAN)

- Manufactured by Novartis
- New(ish) drug for CHF
- FDA Indication
  - To reduce risk of death and hospitalization in patients with CHF (NYHA II-IV) and reduced EF
- MOA
  - FDC of valsartan and a new class of drug, sacubitril.
  - Sacubitril is a neprilysin inhibitor
  - Neprilysin breaks down bradykinin and natriuretic peptides. Inhibiting this enzyme leads to higher levels of these peptides, leading to vasodilation, excretion of sodium, and possibly has a reduces cardiac remodeling.
  - Since neprilysin inhibition leads to an increase in the RAAS, an ACEI or ARB must be used concurrently.

ENTRESTO (SACUBITRIL/VALSARTAN)

- Dosing
  - 1 tablet BID
    - Start with 49mg/51mg, titrate up every 2-4 weeks to 97mg/103mg target dose

ENTRESTO (SACUBITRIL/VALSARTAN)

- Efficacy
  - One clinical trial was conducted to bring Entresto to market - PARADIGM-HF
  - n=8442, DB trial that compared treatment with valsartan/sacubitril (97mg/103mg BID) to enalapril 10mg BID in patients with class II-IV systolic HF with an EF < 40%. Other therapies were continued.
  - Primary endpoint was composite of CV death or HF hospitalization.
  - Study was stopped early after 27 months due to benefit of the valsartan/sacubitril combination vs. enalapril.

ENTRESTO (SACUBITRIL/VALSARTAN)

- Efficacy
  - 1° outcome occurred in 21.8% of valsartan/sacubitril vs. 26.5% for enalapril, NNT=21 over 27 months.
  - 13.3% experienced CV death in the valsartan/sacubitril arm vs. 16.5% in the enalapril arm, NNT=31
  - **A run in phase** ensured patients could tolerate the target dose. 20% (2079 patients) withdrew during this phase, 13% due to adverse effects, abnormal labs, or death. These adverse effects were not included in the study analysis or results.

ENTRESTO (SACUBITRIL/VALSARTAN)

- Adverse effects
  - Hypotension
    - 18% vs. 12% on enalapril, NND =16
  - Angioedema
    - 1 in 200 with Entresto, 1 in 300 with enalapril
  - Hyperkalemia
  - Cough
  - Dizziness
  - Renal failure

ENTRESTO (SACUBITRIL/VALSARTAN)

- Comments
  - The new drug here is sacubitril, not valsartan
    - Why didn't they compare valsartan to valsartan + sacubitril?
    - Or enalapril to enalapril + sacubitril?
  - Only one study. It was not replicated.
  - Dose of enalpril was same as SOLVD and CONSENSUS trials with enalapril, but clinicians were not allowed to titrate to max CHF dose of 20mg BID if warranted. This puts the comparison at unfair advantage to Entresto cohort.

ENTRESTO (SACUBITRIL/VALSARTAN)

- Pros
  - More effective in reducing CV death and HF related hospitalization than enalapril 10mg BID.
    In theory may reduce HF related cardiac remodeling as a result of the novel mechanism of action.

ENTRESTO (SACUBITRIL/VALSARTAN)

- Cons
  - The contribution of sacubitril to the improvement in CHF outcomes is unclear.
  - There was no comparison made between valsartan alone and valsartan plus sacubitril.
  - There was no comparison made between enalapril alone and enalapril plus sacubitril.
  - The comparison made in PARADIGM-HF provokes questions as to whether the result was due to the combination or simply reflects the efficacy of valsartan over enalapril.

ENTRESTO (SACUBITRIL/VALSARTAN)

- Cons
  - Marketing slogans such as "ushers in a new paradigm in treating CHF" may lead to unwarranted overuse.
  - Expensive at $385 per month and may lead to lower compliance rates since this drug will have to replace the ACEI or ARB therapy.
  - Neprilysin breaks down beta amyloid plaques in the brain. These plaques are well known contributors to Alzheimer's disease. No link has (yet) been shown between neprilysin inhibition and Alzheimer's incidence, but this would take a long term trial. Unclear what the long term effects of treatment with sacubitril might be.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WARNING! SCARY COMMERICAL

- With a background of ominous sounds, including a beating heart and the dog's whines, a narrator darkly intones:
  - With heart failure danger is always on the rise. Symptoms worsen because your heart isn't pumping well. About 50% of people die within 5 years of getting diagnosed. But there's something you can do. Talk to your doctor about heart failure treatment options. Because the more you know the more likely you are to keep it pumping.
- http://us.keepitpumping.com/index.jsp